DOLRB File No.: 1228-20-HS, 1236-20-HS 1239-20-HS, 1240-20-HS

ONTARIO LABOUR RELATIONS BOARD

ONTARIO SECONDARY SCHOOL TEACHERS' FEDERATION, ONTARIO ENGLISH CATHOLIC TEACHER'S ASSOCIATION, ELEMENTARY TEACHERS' FEDERATION OF ONTARIO and L'ASSOCIATION DES ENSEIGNANTES ET DES ENSEIGNANTS FRANCO-ONTARIENS

The Applicants

-and-

A DIRECTOR UNDER THE OCCUPATIONAL HEALTH AND SAFETY ACT, HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO (MINISTRY OF LABOUR, TRAINING AND SKILLS DEVELOPMENT) and HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO (MINISTRY OF EDUCATION)

The Responding Parties

-and-

CANADIAN UNION OF PUBLIC EMPLOYEES, and COUNCIL OF TRUSTEES' ASSOCIATION

The Intervenors

EXPERT REPORT OF DR. AMY GREER

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Lawyers for the **OSSTF**

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TAB DESCRIPTION

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Reference 7 Hamner, L. *et al.* High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice. *Morb. Mortal. Wkly. Rep. High* **69**, 606–610 (2020)

Reference 8 Lu, J. *et al.* COVID-19 Outbreak Associated with Air Conditioning in Restaurant, Guangzhou, China, 2020. *Emerg. Infect. Dis.* **26**, 1628–1631 (2020)

Reference 9 Jang, S., Han, S. H. & Rhee, J. Y. Cluster of Coronavirus Disease Associated with Fitness Dance Classes, South Korea. *Emerg. Infect. Dis.* **26**, 1917–1920 (2020)

Reference 10 Morawska, L. & Milton, D. It is Time to Address Airborne Transmission of COVID-19. *Clin. Infect. Dis.* 1–23 (2020).

Reference 11 Zheng, S. *et al.* Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: Retrospective cohort study. *BMJ* **369**, 1–8 (2020)

Reference 12 Guan, W. *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* **382**, 1708–1720 (2020)

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Reference 14 He, J., Guo, Y., Mao, R. & Zhang, J. Proportion of asymptomatic coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J. Med. Virol.* 1–11 (2020). doi:10.1002/jmv.26326

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Reference 18 Stall, N. M. *et al.* Sex- and Age-Specific Differences in COVID-19 Testing, Cases, and Outcomes: A Population-Wide Study in Ontario, Canada. *J. Am. Geriatr. Soc.* 6–11 (2020). doi:10.1111/jgs.16761

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Reference 20 Ontario Ministry of Education. Operational Guidance During COVID-19 Outbreak - Child Care Re-Opening Version 2 (July 2020). (2020). Available at: http://www.edu.gov.on.ca/childcare/child-care-re-opening-operational-guidance.pdf. (Accessed: 15th September 2020)

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Reference 27 Jones, E. *et al. School for Health: Risk Reduction Strategies for Reopening Schools*. *Harvard T.H. Chan School of Public Health Healthy Buildings program* (2020). doi:10.1201/9780203497081.ch7

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https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/medical-devices/personal-protective-equipment/medical-masks-respirators/face-covering-classifications-notice.html. (Accessed: 17th September 2020)

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Reference 34 Phillips, B., Browne, D. T., Anand, M. & Bauch, C. T. Model-based projections for COVID-19 outbreak size and student-days lost to closure in Ontario childcare centres and primary schools. *medRxiv* 2020.08.07.20170407 (2020). doi:10.1101/2020.08.07.20170407

Reference 35 The Hospital for Sick Children. COVID-19 Safe School Simulation. (2020). Available at: https://safeschoolcovid19.ca/updates/. (Accessed: 15th September 2020)

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Reference 37 Zhang, Y. *et al.* How should our testing behaviour change with time in children in current COVID-19 pandemic? *Eur. J. Clin. Invest.* 1–6 (2020). doi:10.1111/eci.13351

Reference 38 Stein-Zamir, C. *et al.* A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. *Euro Surveill.* **25**, 1–5 (2020)

Reference 39 Mossong, J. *et al.* Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases. *PLOS Med.* **5**, 1 (2008)

Reference 40 Salathe, M. *et al.* A high-resolution human contact network for infectious disease transmission. *Soc. Sci*

TAB 1

Dr. Amy L. Greer, BSc, MSc, PhD.

Department of Population Medicine,
University of Guelph, Guelph, ON. Canada.
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Email: agreer@uoguelph.ca
Website: www.mathepilab.org

1. EXPERTISE

I have broad theoretical and practical knowledge in infectious disease ecology, epidemiology, mathematical modeling, and public health. My research program explores the introduction, spread, dynamics, and control of infectious diseases in populations. I use epidemiological data to develop models that can be used to examine the effectiveness of health interventions in order to make informed decisions regarding health policy. I am a highly effective knowledge translator who has extensive experience communicating modeling methods and findings to both technical and non-technical audiences.

2. APPOINTMENTS

Canada Research Chair in Population Disease Modeling and Associate Professor.
2018 - present (Awarded tenure in July 2018)
Department of Population Medicine
University of Guelph
Guelph, ON

Adjunct Associate Professor. 2019- present
School of Public Health and Health Systems
University of Waterloo
Waterloo, ON

Adjunct Associate Professor. 2019- present
Division of Epidemiology, Dalla Lana School of Public Health, Faculty of Medicine
University of Toronto
Toronto, ON

Canada Research Chair in Population Disease Modeling and Assistant Professor. 2014 - 2018
Department of Population Medicine
University of Guelph
Guelph, ON

Director, Math.Epi.Lab Inc. 2013 – 2019.
The Math.Epi.Lab Inc. provides mathematical modeling and epidemiology consulting services to a wide range of companies, government departments, and other organizations.

Assistant Professor. 2010 – 2014.
Division of Epidemiology, Dalla Lana School of Public Health, Faculty of Medicine
Associate Member, School of Graduate Studies
University of Toronto
Toronto, ON

Senior Scientist, 2009 – 2014.
Modeling and Projection Section, Professional Guidelines and Public Health Practice Division
Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada
Ottawa, ON

3. EDUCATION

Research Institute of the Hospital for Sick Children, Child Health Evaluative Sciences, Toronto, ON. Postdoctoral Research Fellow, 2007 – 2009.

Arizona State University, Tempe, AZ, PhD, Biology (Infectious Disease Ecology), 2007.

Trent University, Peterborough, ON, MSc, Biology (Infectious Disease Ecology), 2003.

Mount Allison University, Sackville, NB, BSc (Honours), Biology, 2000.

4. GRANTS AWARDED

University of Guelph, $20,000
Role: primary investigator
Project: Quantifying Canadian physical distancing measures for COVID-19

National Collaborating Centre for Infectious Diseases (NCCID), $8,000
Role: primary investigator
Project: Quantifying Canadian physical distancing measures for COVID-19

Public Health Agency of Canada (PHAC), $20,000
Role: primary investigator
Project: Quantifying Canadian physical distancing measures for COVID-19

NSERC Discovery Grant, $200,000
Role: primary investigator
June 2020 – May 2025 (5 years)
Project: Disease dynamics across complex agricultural networks

Agriculture Canada, Agri-Risk Initiatives Program – Research and Development Stream, $281,374
Role: primary investigator
September 2019 – March 2022 (2.5 years)
Project: Equine Disease Financial Risk Transfer Options

NSERC Collaborative Research and Development Grant, $97,000
Role: Co-applicant with Dr. Shayan Sharif (PI)
April 2019 – April 2022 (3 years)
Project: Is it possible to control transmission of avian influenza virus?

Canada First Research Excellence Fund – University of Guelph, Food from Thought, $41,000
Role: primary investigator
January 2019 – January 2021 (2 years)
Project: The use of big data to predict the emergence of foodborne outbreaks

Canada First Research Excellence Fund – University of Guelph, Food from Thought, $45,000
Role: primary investigator
January 2019 – January 2021 (2 years)
Project: Is it possible to control transmission of avian influenza virus?

Canada Research Chairs Program (renewal), $500,000
Role: primary investigator
January 2019 – January 2024 (5 years)
Project: Population disease modeling.

CIHR Operating Grant, $248,624
Role: Co-applicant with Dr. Julie Arsenault and Dr. Andre Ravel
January 2018 – January 2022 (4 years)
Project: Modelling campylobacteriosis risk in Canada through the various environmental and foodborne sources of exposure in a climate change perspective

Joint Programming Initiative in Antimicrobial Resistance (JPIAMR), through the Canadian Institutes for Health Research (CIHR), $1,500,000.00 ($450,000 to ALG)
Role: Co-applicant with Dr. Derek McFadden (PI)
January 2018 – January 2021 (3 years)
Project: OPEN Stewardship – my team is responsible for the veterinary component of this project.

Canada First Research Excellence Fund – University of Guelph, Food from Thought, $320,000
Role: Collaborator
January 2017 – January 2020 (3 years)
Project: Production Limiting Diseases: Streptococcus suis

CIHR Operating Grant, $100,000
Role: Co-primary investigator with Dr. David Fisman
May 2015 – May 2016 (1 year)
Project: One Health In Action: Mathematical and Epidemiological Tools to Prevent Illness at the Human-Animal Interface in Ontario

OMAFRA – University of Guelph Partnership, $119,588
Role: Co-primary investigator with Dr. Terri O'Sullivan
May 2015 – May 2018 (3 years)
Project: Using network analysis and dynamic models to develop an understanding of the opportunities and challenges for disease control in equine populations.

Equine Guelph, $52,354.00
Role: Co-primary investigator with Dr. Terri O'Sullivan
September 2014-August 2016 (2 years)
Project: Using network analysis and dynamic models to develop an understanding of the opportunities and challenges for disease control in equine populations.

NSERC Discovery Grant, $125,000
Role: primary investigator
August 2014 – August 2020 (5 + 1 years)
Project: Threshold theory as a framework for understanding infectious disease dynamics in livestock populations: implications for the control of agriculturally important pathogens.

Medicago, Unrestricted Research Funds, $36,982
Role: primary investigator
May 2014 – May 2015
Project: Seasonal influenza vaccine modeling.

Canada Research Chairs Program, $500,000
Role: primary investigator
January 2014 – January 2019
Project: Population disease modeling.

Canadian Institutes of Health Research, $300,000
Role: Co-primary investigator with Dr. David Fisman
October 2011 – October 2014
Project: Untangling the web: Understanding the abrupt increase in Chlamydia risk in Ontario through applied epidemiology and mathematical modeling

Canadian Institutes of Health Research, $315,260
Role: Co-primary investigator with Dr. Seyed Moghadas
October 2011 – October 2013
Project: Strategies for protecting vulnerable Canadian populations from emerging infectious diseases

Public Health Agency of Canada, $25,000
Role: Co-primary investigator with Dr. David Fisman
2009-2010
Project: Using individual based models to identify novel interventions for the control of *Chlamydia trachomatis*

Ontario Ministry of Research and Innovation & University of Toronto, $25,000
Role: primary investigator
2009-2010
Project: Using individual based models to identify novel interventions for the control of *Chlamydia trachomatis* 2009

5. MATH.EPI.LAB CONSULTING SERVICES

Public Health Agency of Canada, November 2018 – January 2019 ($9,000)
Provide modeling support to the Centre for Immunization and Respiratory Infectious Diseases (CIRID) related to plant based, pandemic influenza vaccines.

Inuit Tapiriit Kanatami (ITK), December 2017 – April 2018 ($25,000)
Provide modeling support to the Canadian Inuit TB elimination work group. Provide scientific support to the setting of interim TB elimination goals to be announced jointly by the Federal Minister of Indigenous Affairs, Dr. Jane Philpott and ITK President Natan Obed in March 2018 (on World TB Day).

Public Health Agency of Canada, May 2016 – September 2016 ($9,000)
Provide modeling support to the Canadian Pandemic Influenza Plan Task Group (CPIP-TG) related to the renewal of the National Antiviral Stockpile.

Medicago Inc., July 2014 – December 2014 ($46,104)
This engagement was to develop a Java applet "front-end" to the existing pandemic influenza vaccine model we developed in 2013 for knowledge translation purposes.

Medicago Inc., March 2013 – July 2013 ($55,935)
This engagement was to evaluate the potential impact of the novel Medicago pandemic influenza vaccine candidate on pandemic influenza morbidity and mortality within the Canadian population compared to existing pandemic influenza vaccine and under different assumptions regarding pandemic severity.

6. FELLOWSHIPS AND AWARDS

- Award of Excellence, Ontario Ministry of Colleges and Universities. For dedication to my local community, students, and the broader postsecondary education sector during the COVID-19 pandemic. September 2020.
- Research Excellence Award, University of Guelph. August 2019.
- Guelph Life Magazine, 40 under 40 Award. September 2016.
- Research Excellence Award, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada. 2011.
- Senior Lupina Prize for Dynamic Modelling in Health Policy. 2011.
- Beverly Antle Outstanding Trainee Award, Hospital for Sick Children, Child Health Evaluative Sciences. 2009.
- Hospital for Sick Children, Travel Award to attend a meeting at the Pasteur Institute, France. 2008.

7. PEER-REVIEWED PUBLICATIONS

* denotes trainee under my direct supervision
+ denotes trainee collaborator

75. Fisman, DF, **A.L. Greer**, M. Hillmer, and A.R. Tuite. (In press). Derivation and validation of a clinical prediction rule for COVID-19 mortality in Ontario, Canada. Open Forum Infectious Diseases.

74. A.R. Tuite, and **A.L. Greer.** (2020). Shaping the future of the COVID-19 pandemic in Canada. Canadian Medical Association Journal.

73. Fisman, D.N., **A.L. Greer**, and A.R. Tuite. (2020). Age is Just a Number: A Critically Important Number for COVID-19 Case Fatality. Annals of Internal Medicine.

72. Fisman, D.N, **A.L. Greer**, and A.R. Tuite. (2020). Bidirectional Impact of Imperfect Mask Use on Reproduction Number of COVID-19: A Next Generation Matrix Approach. Infectious Disease Modelling 5:405-408.

71. Tuite, AR, **A.L. Greer**, S De Keninck, and DN Fisman. (2020). Risk of COVID-19-Resurgence Related to Duration of and Effectiveness of Physical Distancing in Ontario, Canada. Annals of Internal Medicine.

70. Ogden, N.H., A. Fazil, J. Arino, P. Berthiaume, D.N. Fisman, **A.L. Greer**, A. Ludwig, V. Ng, A.R. Tuite, L.A. Waddell, and J. Wu. (2020). Non-pharmaceutical interventions to control COVID-19 in Canada; modelling scenarios. Canadian Communicable Disease Report 46 (6):198-204.

69. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and **A.L. Greer.** (2020). A within-host mathematical model of H9N2 avian influenza infection and type-I interferon response pathways in chickens. Journal of Theoretical Biology 499: 110320

68. Tuite, A.R., D.N. Fisman, and **A.L. Greer** (2020). Mathematical modelling of COVID-19 transmission and mitigation strategies in the population of Ontario, Canada. Canadian Medical Association Journal. April 09, 2020 cmaj.200476; DOI: https://doi.org/10.1503/cmaj.200476

67. *Cousins, M. D.N. Fisman, J. Sargeant, and **A.L. Greer**. (2020). Identifying environmental drivers of *Campylobacter* infection risk in Ontario, Canada using a One Health approach. Zoonoses and Public Health https://doi.org/10.1111/zph.12715

66. *Brankston, G., **A.L. Greer**, Q. Marshall, B. Lang, K. Moore, D. Hodgins, and J. Beeler-Marfisi. (2020). Air Quality Health Index and Temperature do not Predict Exacerbation of Mild Equine Asthma in Ontario Horses. Frontiers in Veterinary Science. https://doi.org/10.3389/fvets.2020.00185

65. *Khan, S.U., N. Ogden, A. Faizel, P. Gachon, G. Deuymes, **A.L. Greer**, and V. Ng. (2020). Current and projected distributions of *Aedes aegypti* and *Ae. albopictus* in Canada and the US. Environmental Health Perspectives 128(5).

64. *Rossi, T., R.M. Milwid, A. Moore, T. O'Sullivan, and **A.L. Greer**. (In press). Descriptive network analysis of a Standardbred training facility contact network: implications for disease transmission. Canadian Veterinary Journal.

63. +Perret, J., C. Best, , J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. (In press). Resilience in veterinarians in Canada: associations with personal factors and mental health outcomes. JAVMA.

62. *Giang, E., B.M. Hetman, J.M. Sargeant, Z. Poljak, and **A.L. Greer**. (2020). Examining the Effect of Host Recruitment Rates on the Transmission of *Streptococcus suis* in Nursery Swine Populations. Pathogens 9 (174):1-16.

61. +Melmer, D., T. O'Sullivan, **A.L. Greer**, L. Moser, and Z. Poljak. (2020). An investigation of transportation practices in an Ontario swine system using descriptive network analysis. PLoS ONE 15 (1): e0226813.

60. +Perret, J., C. Best, J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. (2019) Prevalence of mental health outcomes among a sample of Veterinarians. Journal of the American Veterinary Medical Association 256 (3): 365-375.

59. *Rossi, T., A. Moore, T. O'Sullivan, and **A.L. Greer**. (2019) Risk factors for duration of Equine Rhinitis A Virus

respiratory disease. Equine Veterinary Journal. doi: 10.1111/evj.13204

58. *Gardner, E.G., S. Kiambi, R. Sitawa, D. Kelton, J. Kimutai, Z. Poljak, Z. Tadesse, S. von Dobschuetz, L. Wiresma, and **A.L. Greer.** (2019). Force of infection of Middle East respiratory syndrome in dromedary camels in Kenya. Epidemiology and Infection 147, e275, p1-6. https://doi.org/10.1017/S0950268819001663

57. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer.** (2019). Descriptive analysis of horse movement networks during the 2015 equestrian season in Ontario, Canada. PLoS ONE 14(7): e0219771. https://doi.org/10.1371/journal.pone.0219771

56. Mihaljevic, J.R., **A.L. Greer**, and J.L. Brunner. (2019). Evaluating the within host dynamics of Ranavirus infection with mechanistic disease models and experimental data. Viruses 11 (5):396.

55. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer**. (2019). Comparing the effects of non-homogenous mixing patterns on epidemiological outcomes in equine populations: A mathematical modelling study. Scientific Reports 9 (1): 3227.

54. *Rossi, T., A. Moore, T. O'Sullivan, and **A.L. Greer**. (2019). Equine Rhinitis A Virus Infection at a Standardbred Training Facility: Incidence, Clinical Signs, and Risk Factors for Clinical Disease. Frontiers in Veterinary Science. https://doi.org/10.3389/fvets.2019.00071

53. *Cousins, M. D.N. Fisman, J. Sargeant, and **A.L. Greer**. (2019) Modelling the transmission dynamics of Campylobacter in Ontario, Canada assuming house flies, *Musca domestica*, are a mechanical vector of disease transmission. Royal Society Open Science. https://doi.org/10.1098/rsos.181394

52. †Hughes, S.L., **Greer, A.L.,** Elliot, A.J., McEwen, S.A., Young, I. and A. Papadopoulos (2019) Monitoring telehealth vomiting calls as a potential public health early warning system for seasonal norovirus activity in Ontario, Canada. Epidemiology and Infection 147 (e112).

51. *Gardner, E.G., D. Kelton, Z. Poljak, S. von Dobschuetz, and **A.L. Greer**. (2019) A case-crossover analysis of the impact of weather on primary cases of Middle East respiratory syndrome. BMC Infectious Diseases 19:113.

50. *Gardner, E.G., D. Kelton, Z. Poljak, S. von Dobschuetz, and **A.L. Greer**. (2019) A rapid scoping review of Middle East respiratory syndrome coronavirus in animal hosts. Zoonoses and Public Health 66(1):35-46

49. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer**. (2019). Validation of modified radio-frequency identification tag firmware, using an equine population case study. PLOS ONE 14(1): e0210148.

48. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer**. (2019). Comparison of the dynamic networks of four equine boarding and training facilities. Preventive Veterinary Medicine 162: 84-94. https://doi.org/10.1016/j.prevetmed.2018.11.011

47. *Coffey, M, **A.L. Greer,** and H.Eberl. (2018). Model Based Economic Assessment of Avian Influenza Vaccination in an All-in/All-out Housing System. Recent Advances in Mathematical and Statistical Methods for Scientific and Engineering Applications.

46. *Brunn, A., D.N. Fisman, J.M. Sargeant, and **A.L. Greer**. (2018). The influence of climate and livestock reservoirs on

human cases of giardiasis. EcoHealth https://doi.org/10.1007/s10393-018-1385-7

45. *Kisiel, L.M., A. Jones-Bitton, J.M. Sargeant, J.B. Coe, D.T.T. Flockhart, A. Reynoso Palomar, E. Canales Vargas, and **A.L. Greer.** (2018). Modeling the effect of surgical sterilization and confinement on owned dog population size in Villa de Tezontepec, Hidalgo, Mexico, using an agent-based computer simulation model. PLoS ONE 13 (6): e0198209.

44. +Farrell, A., J.P. Collins, **A.L. Greer**, and H.R. Thieme. (2018). Do fatal infectious diseases eradicate host species? Journal of Mathematical Biology. https://doi.org/10.1007/s00285-018-1249-3

43. +Farrell, A., J.P. Collins, **A.L. Greer**, and H.R. Thieme. (2018). Times from infection to disease-induced death and their influence on final population sizes after epidemic outbreaks. Bulletin of Mathematical Biology 80 (10): 1937-1961.

42. *Brankston, G., C. *Boughen, V. Ng, D.N. Fisman, J.M. Sargeant, and **A.L. Greer.** (2018). Assessing the Impact of Environmental Exposures and *Cryptosporidium* Infection in Cattle on Human Incidence of Cryptosporidiosis. PLoS ONE 13(4): e0196573.

41. +Mallia, G., Van Toen, J., Rousseau, J., Jacob, L., Boerlin, P., **A.L. Greer**, Metcalf, D., and J.S Weese. (2018). Examining the epidemiology and microbiology of *Clostridium difficile* carriage in elderly patients and residents of a health care facility in southern Ontario, Canada. Journal of Hospital Infection Control 99(4): 461-468.

40. *Khan, S.U., T. O'Sullivan, Z. Poljak, J. Alsop, and **A.L. Greer**. (2018). Modeling livestock population structure: a geospatial database for Ontario swine farms. BMC Veterinary Research 14:31.

39. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. (2018). A longitudinal study describing horse characteristics and movements during a competition season in Ontario, Canada in 2015. Canadian Veterinary Journal 59 (7): 783-790.

38. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. (2018). Using a computer simulation model to examine the impact of biosecurity measures during a facility-level outbreak of equine influenza. Canadian Journal of Veterinary Research 82 (2):89-96.

37. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. (2018). Estimating the potential for disease spread in horses associated with an equestrian show in Ontario, Canada using an agent-based model. Preventive Veterinary Medicine 151: 21-28.

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7. **Greer, A.L.** and D.N. Fisman. (2009). Punching above their weight: Males, reinfection and the limited success of Chlamydia screening programs. Sexually Transmitted Diseases 36(1): 9-10.

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2. Fox, S.F., **A.L. Greer**, R.Torres-Cervantes and J.P. Collins. (2006). First case of ranavirus associated morbidity and mortality in natural populations of a South American frog, *Atelognathus patagonicus*. Diseases of Aquatic Organisms 72 (1):87-92.

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8. In Review

1.⁺Bienentreu, J-F, D.M. Schock, **A.L. Greer**, and D. Lesbarrères. Host identity matters: ranavirus prevalence and infection severity in multi-host amphibian communities**.** Ecology.

2. ⁺Perret, J., C. Best, , J. Coe , **A.L. Greer**, D. Khosa, and A. Jones-Bitton. Veterinarian mental health outcomes and client-centred communication. Veterinary Record.

3. ⁺Melmer, D, T. O'Sullivan, **A.L. Greer**, D. Novosel, D. Ojkic, and Z. Poljak. Understanding the Evolution of PRRS Virus in Ontario using Bayesian Phylogenetics. Viruses.

4. *Milwid, R.M., T.L. O'Sullivan, Z. Poljak, M. Laskowski, and **A.L. Greer**. Use of network analysis to quantify the effect of human-equine interactions on contact network characteristics with a focus on disease transmission potential. BMC Veterinary Research.

5. *Acharya, KR, G. *Brankston, J-PR. ⁺Soucy, A. ⁺Cohen, A. Hulth, S. Löfmark, N. Davidovich, M. Ellen, D. Fisman, J. Moran-Gilad, A. Steinman, D.R. MacFadden, and **A.L. Greer**. Evaluation of an OPEN Stewardship Generated Feedback Intervention to Improve Antibiotic Prescribing Among Primary Care Veterinarians in Ontario, Canada and Israel: Protocol for Evaluating Usability and an Interrupted Time-Series Analysis. BMJ Open.

6. ⁺Plishka, M. J.M. Sargeant, **A.L. Greer**, C. Winder, and S. Hookey. The Prevalence of Campylobacter in Live Cattle, Turkey, Chicken, and Swine in the United States and Canada: A Systematic Review and Meta-analysis. Foodborne Pathogens and Disease.

7. *Brankston, G., E. Merkley, D.N. Fisman, A.R. Tuite, Z. Poljak, P.J. Loewen, and **A.L. Greer**. Sociodemographic disparities in knowledge, practices, and ability to comply with COVID-19 public health measures in Canada. Nature Human Behaviour.

9. PEER-REVIEWED GOVERNMENT PUBLICATIONS

Ogden, N**,** L. R. Lindsay, M.A. Drebot, V. Ng, A. Ludwig, C. Bouchard, G. Brankston, D.N. Fisman, **A.L. Greer**, E. Galanis, H. Wood, A. Dibernardo, P. A. Leighton, P. Corrin, L. Waddell, A-M Lowe, L. Vrbova, and E. Jenkins. (In Press). Health of Canadians in a Changing Climate: Advancing our Knowledge for Action.

10. NON PEER-REVIEWED PUBLICATIONS

Greer, A.L., N. Thampi, and A. Tuite. We can get children back to school full time, if we put the right strategy in place. Globe and Mail Opinion. July 10, 2020. https://www.theglobeandmail.com/opinion/article-we-can-get-children-back-to-school-full-time-if-we-put-the-right/

Greer, AL. What I've learned about being a mom in a pandemic – just let go. The National Post Special Edition. May 8, 2020. https://nationalpost.com/life/covid-19-mothers-day

11. CONFERENCE PRESENTATIONS

127. *Acharya, K.R, G. Brankston, J. Brownstein, R. Chorney, E. Cohn, N. Davidovitch, M. Ellen, D. Fisman, A. Hulth, S. Löfmark, J. Moran-Gilad, D. MacFadden, and **A.L. Greer**. Evaluating the usability, utility, and impact of feedback reports, generated by the OPEN Stewardship platform, as a tool to promote antibiotic stewardship in veterinary clinics. Canadian Association of Veterinary Epidemiology and Preventive Medicine. June 2020. Oral (event cancelled due to COVID-19)

126. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and **A.L. Greer.** A within-host mathematical model to assess the chicken immune response to influenza A (H9N2) virus vaccination and infection. 19th International Congress on Infectious Diseases. Kuala Lumpur, Singapore. February 2020. Poster. (event cancelled due to COVID-19)

125. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and **A.L. Greer.** A within-host compartmental model of influenza A (H9N2) virus infection dynamics and immune response in chickens. Seventh International Conference on Infectious Disease Dynamics. Charleston, SC. December 2019. Poster.

124. +Sadeghieh, T., J. Sargeant, **A.L. Greer**, O. Berke, and V. Ng. Investigating the risk for importation of Zika virus into Canada under current and future climate. Seventh International Conference on Infectious Disease Dynamics. Charleston, SC. December 2019. Poster.

123. *Rossi, T., R. Milwid, A. Moore, T. O'Sullivan, and **A.L. Greer.** Reducing the transmission of infectious respiratory disease in horses by identifying opportunities for improved biosecurity at a Standardbred training facility. Seventh International Conference on Infectious Disease Dynamics. Charleston, SC. December 2019. Poster.

122. *Acharya, K.R, G. Brankston, J. Andre, J. Brownstein, R. Chorney, E. Cohn, N. Davidovitch, M. Ellen, D. Fisman, A. Hulth, S. Löfmark, J. Moran-Gilad, J-P.R Soucy, D. MacFadden, and **A.L. Greer**. Expanding antibiotic stewardship among veterinary prescribers using an OPEN Stewardship platform. Conference for Research Workers in Animal Disease. Chicago, IL. November 2019. Oral.

121. +Plishka, M., J. Sargeant, **A.L. Greer**, and C. Winder. The prevalence of *Campylobacter* in live chicken, swine, turkey, and cattle: a systematic review and meta-analysis. Conference for Research Workers in Animal Disease. Chicago, IL. November 2019. Poster.

120. +Berry, I., P. Mangtani, M. Rahman, **A.L. Greer**, S. Morris, T. Naureen, M. Azad, D. Fisman, and M.S. Flora. Live Poultry Exposure in Urban Bangladesh: evaluating poultry purchasing and contact patterns to identify avenues for avian influenza transmission at the human-poultry interface. Options X for the Control of Influenza. SUNTEC, Singapore. August 2019. Poster.

119. Mihaljevic, J.R., E.M. Hall, E.J. Crespi, **A.L. Greer**, and J.L. Brunner. Mechanistic disease models reveal important drivers of epizootic patterns in the amphibian-*Ranavirus* system. Ecological Society of America Annual Conference. Louisville, KY. August 2019. Oral.

118. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and A.L. Greer. A within-host model of H9N2 avian influenza virus infection and type-I interferon dynamics in chickens. V AMMCS International Conference. Waterloo, ON. August 2019. Oral.

117. *Khan, S.U., T. O'Sullivan, Z. Poljak, J. Alsop, and **A.L. Greer**. Simulating a Classical Swine Fever Introduction into Commercial Pig Farms in Ontario. V AMMCS International Conference. Waterloo, ON. August 2019. Oral.

116. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer.** Assessing the impact of empirical contact patterns on disease dynamics within an equine population. Society for Mathematical Biology. Montreal, QC. July 2019. Oral.

115. *Giang, E., J. Sargeant, Z. Poljak, and **A.L. Greer**. A model for assessing management-driven alternatives for disease control: A case-study on Streptococcus suis disease in nursery pigs. International Conference on Production-Limiting Diseases. Bern, Switzerland. June 2019. Oral.

114. Mihaljevic, J.R., E.M. Hall, E.J. Crespi, **A.L. Greer**, and J.L. Brunner. Mechanistic disease models reveal drivers of divergent epizootic patterns in the amphibian-*Ranavirus* system. Ecology and Evolution of Infectious Diseases, Princeton, NJ. June 2019. Oral.

113. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and A.L. Greer. A within-host model of H9N2 avian influenza virus infection and type-I interferon dynamics in chickens. Ontario Veterinary College Graduate Research Symposium. Guelph, ON. June 2019. Oral. ***X-T Xie was awarded the first place student prize for the best oral presentation for this presentation.

112. +Perret, J., C. Best, , J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. Mental Health of Canadian Veterinarians. Ontario Veterinary College Graduate Research Symposium. Guelph, ON. June 2019. Poster.

111. *Giang, E., B. Hetman, J. Sargeant, Z. Poljak, and **A.L. Greer**. The impact of continuous birth rates on *Streptococcus suis* disease transmission and persistence in nursery swine. Ontario Veterinary College Graduate Research Symposium. Guelph, ON. June 2019. Poster.

110. *Hovdey, R., J. Sargeant, D. Fisman, and **A.L. Greer.** Examining the impact of person-person transmission on VTEC outbreaks in Ontario. Ontario Veterinary College Graduate Research Symposium. Guelph, ON. June 2019. Poster.

109. Mihaljevic, J.R., **A.L. Greer**, and J.L. Brunner. Evaluating the within-host dynamics of *Ranavirus* infection with mechanistic disease models and experimental data. International Symposium on Ranaviruses. Townsville, Australia. June 2019. Oral.

108. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and A.L. Greer. A within-host model of H9N2 avian influenza virus infection and type-I interferon dynamics in chickens. Centre for Public Health and Zoonoses Annual Symposium. Guelph, ON. May 2019. Poster.

107. +Perret, J., C. Best, , J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. Mental Health of Canadian Veterinarians.

Centre for Public Health and Zoonoses Annual Symposium. Guelph, ON. May 2019. Poster.

106. *Khan, S.U., T. O'Sullivan, Z. Poljak, J. Alsop, and **A.L. Greer**. Simulating a Classical Swine Fever Introduction into Commercial Pig Farms in Ontario. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Oral.

105. +Melmer, D., T. O'Sullivan, **A.L. Greer**, L. Moser, and Z. Poljak. Incidence and clinical impact of Porcine Reproductive and Respiratory Syndrome (PRRS) in Ontario sow herds. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Oral.

104. *Giang, E., J. Sargeant, Z. Poljak, and **A.L. Greer**. The impact of continuous birth rates on *Streptococcus suis* disease transmission and persistence in nursery swine. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Oral.

103. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and A.L. Greer. A within-host model of H9N2 avian influenza virus infection and type-I interferon dynamics in chickens. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Poster.

102. *Khan, S.U., N. Ogden, A. Faizel, P. Gachon, G. Deuymes, **A.L. Greer**, and V. Ng. Scouring Through Overwhelming Volume of Climate Data to Project Ecological Niche of *Aedes Albopictus* and *Aedes Aegypti* Mosquitoes' in Canada and the United States, 2020 – 2100. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Oral.

101. *Hovdey, R., J. Sargeant, D. Fisman, and **A.L. Greer.** Examining the impact of person-person transmission on VTEC outbreaks in Ontario. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Oral.

100. +Perret, J., C. Best, , J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. Mental Health of Canadian Veterinarians. Canadian Association for Veterinary Epidemiology and Preventive Medicine. St-Hyacinthe, QC. May 2019. Oral.

99. +Melmer, D., T. O'Sullivan, **A.L. Greer**, L. Moser, and Z. Poljak. Incidence and clinical impact of Porcine Reproductive and Respiratory Syndrome (PRRS) in Ontario sow herds. Swine Research Day, Guelph, ON. May 2019. Poster.

98. +Sadeghieh, T., J. Sargeant, **A.L. Greer**, O. Berke, and V. Ng. Investigating the potential for importation of Zika virus and yellow fever into Canada from Brazil. Annual Meeting of the Canadian Public Health Association. Ottawa, ON. April 2019. Poster.

97. +Perret, J., C. Best, , J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. Mental and Emotional Health in Veterinarians: Impacts on Client and Patient Care. Crossroads Interdisciplinary Health Research Conference. Halifax, NS. March 2019. Oral.

96. +DeCaluwe-Tulk,E., T. *Rossi, **A.L. Greer**, E. +Luo, and T. L. O'Sullivan. Clinical validation of an infrared thermometer in periparturient sows. American Association of Swine Veterinarians. Lake Buena Vista, FL. March 2019. Oral. ***E. DeCaluwe-Tulk was awarded the third place student prize for the best oral presentation for this presentation.

95. Hulth, A., S. Lofmark, J. Andre, R. Chomey, E. Cohen, M. Ellen, N. Davidovitch, J. Moran-Gilad, **A.L. Greer**, D. Fisman, J. Brownstein, and D. MacFadden. A tool for promoting responsible antibiotic prescribing across setting and

sectors. International Society for Disease Surveillance. San Diego, CA. January 2019. Oral.

94. *Xie, X-T, A. Bekele-Yitbarek, S.U. Khan, Z. Poljak, S. Sharif, and **A.L. Greer.** A within-host model of H9N2 avian influenza virus infection kinetics in chickens. Conference for Research Workers in Animal Disease. Chicago, IL. December 2018. Oral.

93. *Hovdey, R., J. Sargeant, D. Fisman, and **A.L. Greer**. Investigating acute environmental drivers of human verocytotoxigenic *Escherichia coli* infections in Ontario. Conference for Research Workers in Animal Disease. Chicago, IL. December 2018. Oral.

92. *Giang, E., J. Sargeant, Z. Poljak, and **A.L. Greer**. Estimating the Basic Reproduction Number (R0) of a *Streptococcus suis* outbreak within a swine herd in Ontario, Canada. Conference for Research Workers in Animal Disease. Chicago, IL. December 2018. Oral.

91. +Melmer, D., T. O'Sullivan, **A.L. Greer**, L. Moser, and Z. Poljak. Understanding the Evolution of PRRS Virus in Ontario Using Bayesian Phylogenetics. Conference for Research Workers in Animal Disease. Chicago, IL. December 2018. Oral.

90. +Melmer, D., T. O'Sullivan, **A.L. Greer**, L. Moser, and Z. Poljak. Development of a system to monitor incidence and clinical impact of PRRS virus in Ontario sow herds. Conference for Research Workers in Animal Disease. Chicago, IL. December 2018. Oral.

89. +Sadeghieh, T., J. Sargeant, **A.L. Greer**, O. Berke, and V. Ng. A Framework for Modelling the Transmission of Yellow fever within Brazil in an Outbreak Situation under Current and Projected Climate. International Meeting on Emerging Diseases. Vienna, Austria. November 2018. Poster.

88. *Gardner, E.G., D. Kelton, Z. Poljak, S. von Dobschuetz, and **A.L. Greer**. The influence of weather on primary Middle East respiratory syndrome coronavirus (MERS-CoV) cases in Saudi Arabia. International Society for Veterinary Epidemiology and Economics (ISVEE 15). Chiang Mai, Thailand. November 2018. Poster.

87. *Rossi, T., T. O'Sullivan, and **A.L. Greer**. Use of proximity loggers to establish contact patterns in a multi-barn standardbred training facility. International Society for Veterinary Epidemiology and Economics (ISVEE 15). Chiang Mai, Thailand. November 2018. Oral.

86. *Rossi, T., T. O'Sullivan, and **A.L. Greer**. Infectious respiratory disease in a Standardbred training facility: incidence, clinical signs, and risk factors for infection. International Society for Veterinary Epidemiology and Economics (ISVEE 15). Chiang Mai, Thailand. November 2018. Oral.

85. +Perret, J., C. Best, , J. Coe **, A.L. Greer**, D. Khosa, and A. Jones-Bitton. Prevalence of Mental Health Outcomes in Canadian Veterinarians. International Society for Veterinary Epidemiology and Economics (ISVEE 15). Chiang Mai, Thailand. November 2018. Oral.

84. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer.** Using a disease transmission model to examine the projected efficacy of Equine Influenza intervention strategies. Calgary International Equine Symposium. Calgary, AB. September 2018. Poster.

83. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer.** Use of radio-frequency identification (RFID) technology to identify high traffic areas within equine facilities. Calgary International Equine Symposium. Calgary, AB.

September 2018. Poster.

82. *Rossi, T., T. O'Sullivan, and **A.L. Greer**. Infectious respiratory disease in a Standardbred training facility: incidence, clinical signs, and risk factors for infection. Calgary International Equine Symposium. Calgary, AB. September 2018. Oral.

81. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. Dynamic network analysis of horse movements during the 2015 equestrian season in Ontario, Canada. Calgary International Equine Symposium. Calgary, AB. September 2018. Oral.

80. *Xie, X.T., S.U. Khan, Z. Poljak, S. Sharif, and **A.L. Greer**. Modeling in-host dynamics of H9N2 avian influenza virus in poultry. OVC Graduate Student Research Symposium. Guelph, ON. June 2018. Poster.

79. +Perret, J., C. Best, **A.L. Greer**, D. Khosa, J. Coe, and A. Jones-Bitton. Mental Health and Wellness in Veterinarians: Impacts on Client and Patient Care. Centre for Public Health and Zoonoses Annual Symposium. Guelph, ON. June 2018. Poster.

78. +Perret, J., C. Best, J. Coe **,** D. Khosa, **A.L. Greer**, and A. Jones-Bitton. Cross-sectional study of the association between veterinarian mental wellness and veterinarian-client interaction outcomes. OVC Graduate Student Research Symposium. Guelph, ON. June 2018. Poster.

77. *Khan, S.U., N. Ogden, A. Faizel, **A.L. Greer**, and V. Ng. Environmental Suitability and Predicted Distribution of *Aedes albopictus* and *Aedes aegypti* Mosquitoes in Canada and the United States: Assessing Arboviral Risks in North America. International Conference on Emerging Infectious Diseases (ICEID), Atlanta, GA, USA, August 2018. Poster.

76. *Gardner, E.G., D. Kelton, Z. Poljak, S. von Dobschuetz, and **A.L. Greer**. A scoping review of Middle East respiratory syndrome coronavirus in natural animal hosts. Centre for Public Health and Zoonoses Annual Symposium. Guelph, ON. June 2018. Poster.

75. *Hovdey, R., J. Sargeant, D. Fisman, and **A.L. Greer**. Using a One Health approach to examine environmental drivers of human verocytotoxigenic *Escherichia coli* infections in Ontario. Centre for Public Health and Zoonoses Annual Symposium. Guelph, ON. June 2018. Poster.

74. *Khan, S.U., **A.L. Greer**, A. Faizel, N.Ogden, and V. Ng. Climate Change and Emerging Viral Threats in Canada: Modeling the Transmission Dynamics of Chikungunya Virus. Centre for Public Health and Zoonoses Annual Symposium. Guelph, ON. June 2018. Oral.

73. *Cousins, M. D.N. Fisman, J. Sargeant, and **A.L. Greer.** Modelling multiple transmission routes of campylobacteriosis in Ontario using a One Health perspective. Centre for Public Health and Zoonoses Annual Symposium. June 2018. Oral.

72. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. Using longitudinal questionnaire data to create networks of horse movements in Ontario, Canada**.** International Conference on Network Science (NetSci 2018) satellite symposium: Integration of Empirical data in network epidemiology. Paris, France. June 2018. Oral.

71. *Milwid, R., T. O'Sullivan, Z. Poljak, M. Laskowski, and **A.L. Greer**. From network analysis to network models: comparing the epidemiological outcomes from 4 equine facilities in Ontario. International Conference on Network Science (NetSci 2018) satellite symposium: Integration of Empirical data in network epidemiology. Paris, France. June 2018. Oral.

70. *Kisiel, L.M., A. Jones-Bitton, J.M. Sargeant, J.B. Coe, D.T.T. Flockhart, A. Reynoso Palomar, E. Canales Vargas, and **A.L. Greer.** Modeling the effect of surgical sterilization and confinement on owned dog population size in Villa de Tezontepec, Hidalgo, Mexico, using an agent-based computer simulation model. 6th International Symposium on Non-Surgical Contraceptive Methods of Pet Population Control. Boston, MA. July 2018. Invited Oral.

69. *Cousins, M. D.N. Fisman, J. Sargeant, and **A.L. Greer.** Modelling multiple transmission routes of campylobacteriosis in Ontario using a One Health perspective. International One Health Congress. Saskatoon, SK. June 2018. Poster.

68. *Garder, E.G., D. Kelton, Z. Poljak, S. von Dobschuetz, and **A.L. Greer**. A scoping review of Middle East respiratory syndrome coronavirus in natural animal hosts. International One Health Congress. Saskatoon, SK. June 2018. Poster.

67. *Khan, S.U., **A.L. Greer**, A. Faizel, N.Ogden, and V. Ng. Climate Change and Emerging Viral Threats in Canada: Modeling the Transmission Dynamics of Chikungunya Virus. International One Health Congress. Saskatoon, SK. June 2018. Poster.

66. *Khan, S.U., **A.L. Greer**, A. Faizel, N.Ogden, and V. Ng. Environmental Suitability and Predicted Distribution of Aedes Albopictus Mosquitoes in Canada and the United States: Assessing Arboviral Risks in North America. International One Health Congress. Saskatoon, SK. June 2018. Poster.

65. +Perret, J., C. Best, **A.L. Greer**, D. Khosa, J. Coe, and A. Jones-Bitton. Mental Health and Wellness in Veterinarians: Impacts on Client and Patient Care. International Conference on Communications in Veterinary Medicine. Barrie, ON. March 2018. Oral

64. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer**. Quantifying the heterogeneity in contact patterns within an Ontario equine facility: a pilot study. Conference for Research Workers in Animal Disease. Chicago, IL. December 2017. Oral.

63. *Milwid, R., O'Sullivan, T.L., Poljak, Z., Laskowski, M., and **A.L. Greer**. Using modified radio frequency identification tags to quantify contact patterns within an Ontario equine facility: a validation study. Conference for Research Workers in Animal Disease. Chicago, IL. December 2017. Poster.

62. *Cousins, M., Fisman, D.N., Sargeant, J., and **A.L. Greer**. Using a dynamic infectious disease model to examine multiple transmission pathways for Campylobacteriosis. Conference for Research Workers in Animal Disease. Chicago, IL. December 2017. Oral.

61. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. A longitudinal study describing horse characteristics and movements during a competition season in Ontario, Canada in 2015. Conference for Research Workers in Animal Disease. Chicago, IL. December 2017. Oral.

60. +Hughes, S.L., **A.L. Greer** , A.J. Elliot**,** S.A. McEwen, I. Young, and A. Papadopoulos. Viral gastroenteritis and prevalence of norovirus and norovirus-like illness in Ontario, Canada - 2009-2014. [abstract]. In: the European Journal of Public Health; 2017, Nov 1-4; Stockholm, Sweden. Oxford University Press, 2017.

59. +Hughes, S.L., **A.L. Greer** , A.J. Elliot**,** S.A. McEwen, I. Young, and A. Papadopoulos. Viral gastroenteritis and prevalence of norovirus and norovirus-like illness in Ontario, Canada -- 2009-2014. Sixth International Conference on

Infectious Disease Dynamics. Spain. November 2017. Poster.

58. +Hughes, S.L., A.J. Elliot**, A.L. Greer**, S.A. McEwen, I. Young, and A. Papadopoulos. Surveillance of norovirus-like illness in Ontario: Using Telehealth Ontario data to detect the onset of community activity. Sixth International Conference on Infectious Disease Dynamics. Spain. November 2017. Poster.

57. *Coffey, M., **A.L. Greer**, and H. Eberl. A model of highly pathogenic avian influenza in boilers with environmental reservoir and vaccine intervention over finite time. Interdisciplinary International Conference on Applied Mathematics, Modeling and Computational Science. Waterloo, ON. August 2017. Poster

56. *Brunn, A., D.N. Fisman, J. Sargeant, and **A.L. Greer**. Temporal associations between environmental conditions and pathogen colonization of livestock on human cases of Giardia duodenalis in Waterloo region. Canadian Association of Veterinary Epidemiology and Preventive Medicine. Calgary, AB. June 2017. Oral.
***A. Brunn was awarded the first place student prize for the best oral presentation for this presentation.

55. *Khan, S.U., T. O'Sullivan, Z. Poljak, J. Alsop, and **A.L. Greer**. Generating A Synthetic Animal Population Structure: A Geospatial Database for Ontario Swine Farms. Canadian Association of Veterinary Epidemiology and Preventive Medicine. Calgary, AB. June 2017. Poster.

54. *Milwid, R., T.L. O'Sullivan, Z. Poljak, M. Laskowski, and **A.L. Greer**. Using proximity logging technology to quantify equine contact patterns within Ontario Equine facilities. Canadian Association of Veterinary Epidemiology and Preventive Medicine. Calgary, AB. June 2017. Oral.

53. *Cousins, M. D.N. Fisman, J. Sargeant, and **A.L. Greer**. Identifying environmental drivers of *Campylobacter* infection risk in Ontario, Canada using a One Health approach. Canadian Association of Veterinary Epidemiology and Preventive Medicine. Calgary, AB. June 2017. Oral.
***M. Cousins was awarded the second place student prize for the best oral presentation for this presentation.

52. *Spence, K.L., T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. Dynamic network analysis of equine travel patterns during the 2015 competition season in Ontario, Canada. Canadian Association of Veterinary Epidemiology and Preventive Medicine. Calgary, AB. June 2017. Poster.

51. *Cummings, J., A. *Olpin, R. *Milwid, M. Laskowski, Z. Poljak, T.L. O'Sullivan, and **A.L. Greer.** Developing a framework for quantifying real-time contact patterns in agricultural animals using OpenBeacon proximity sensing hardware. Modeling in Animal Health Conference. Nantes, France. Abstract. June 2017. Poster.

50. *Milwid, R., T.L. O'Sullivan, Z. Poljak, M. Laskowski, and **A.L. Greer**. Use of proximity loggers to quantify contact patterns within an Ontario equine facility: A pilot study. Modeling in Animal Health Conference. Nantes, France. Abstract. June 2017. Poster.

49. *Khan, S.U., T. O'Sullivan, Z. Poljak, J. Alsop, and **A.L. Greer**. Generating A Synthetic Animal Population Structure: A Geospatial Database for Ontario Swine Farms. Modeling in Animal Health Conference. Nantes, France. Abstract. June 2017. Poster.

48. *Spence, K.L., T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. Using an agent-based model to describe the potential spread of equine influenza within a network of horses attending an equestrian show. Modeling in Animal Health Conference. Nantes, France. June 2017. Oral.

47. *Khan, S.U., T. O'Sullivan, Z. Poljak, J. Alsop, and **A.L. Greer**. Generating A Synthetic Animal Population Structure: A Geospatial Database for Ontario Swine Farms. University of Guelph Swine Research Day. Guelph, ON. May 2017. Poster.

46. *Cousins, M. D.N. Fisman, J. Sargeant, and **A.L. Greer**. Identifying environmental drivers of *Campylobacter* infection risk in Ontario, Canada using a One Health approach. Centre for Public Health and Zoonoses Research Day. Guelph, ON. May 2017. Poster.

45. *Brunn, A., D.N. Fisman, J. Sargeant, and **A.L. Greer**. Temporal associations between environmental conditions and pathogen colonization of livestock on human cases of Giardia duodenalis in Waterloo region. Centre for Public Health and Zoonoses Research Day. Guelph, ON. May 2017. Poster.

44. +Farrell, A., J.P. Collins, **A.L. Greer**, and H.R. Thieme. Do fatal infectious diseases eradicate host species? Epidemic perspective. Joint Mathematics Meetings - Mathematical Association of America and the American Mathematical Society. Atlanta, GA. January 2017. Oral.

43. *Spence, K.L., T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. Estimating potential disease spread at an equestrian show in Ontario, Canada using an agent-based network model. Conference of Research Workers in Animal Disease (CRWAD), Chicago, IL. Abstract. December 2016. Oral.
***K. Spence was awarded the student prize for the best oral presentation in the Biosecurity section for this presentation.

42. +Hughes, S., I. Young, R.V. Ackford, A.J. Elliot, S.A. McEwen, **A.L. Greer,** and A. Papadopoulos. Essential elements of human infectious disease syndromic surveillance systems: a scoping review. International Society for Disease Surveillance. Atlanta, GA. December 2016. Poster.

42. *Milwid, R., T.L. O'Sullivan, Z. Poljak, M. Laskowski, and **A.L. Greer**. Using of proximity logging technology to quantify equine contact patterns within Ontario Equine facilities. OVC Graduate Student Symposium. Guelph, ON. November 2016. Poster.

41. *Spence, K.L., T.L. O'Sullivan, Z. Poljak, and **A.L. Greer**. Mathematical modeling of potential disease spread within a network of horses attending an equestrian event. OVC Graduate Student Symposium. Guelph, ON. November 2016. Poster.

40. *Gardner, E., M. Ali, G. Kayali, D. Kelton, and **A.L. Greer**. Using the Incidence Decay and Exponential Adjustment (IDEA) model to understand MERS-CoV transmission dynamics in a camel herd. International Meeting on Emerging Diseases. Vienna, Austria. November 2016. Poster.

39. *Kisiel, L.M., A. Jones-Bitton, J.M. Sargeant, J.B. Coe, D.T.T. Flockhart, A. Reynoso Palomar, E. Canales Vargas, and **A.L. Greer.** Domestic dog ecology in Villa de Tezontepec, Hidalgo, Mexico and implications for canine rabies transmission. International Conference on Diseases in Nature Communicable to Man. Guelph,

ON. Abstract. August 2016. Oral.

38. **Greer, A.L**. K. Spence*, and E. Gardner*. Using the Incidence Decay and Exponential Adjustment (IDEA) model to understand the early dynamics of the 2014 porcine epidemic diarrhea virus (PEDV) outbreak in Ontario. Canadian Association for Veterinary Epidemiology and Preventive Medicine. Guelph, ON. Abstract. May 2016. Oral.

37. *Milwid, R., T.L. O'Sullivan, Z. Poljak, M. Laskowski, and **A.L. Greer**. Use of novel proximity logging technology to quantify equine contact patterns in Ontario equine facilities. Canadian Association for Veterinary Epidemiology and Preventive Medicine. Guelph, ON. Abstract. May 2016. Poster.

36. *Kisiel, L.M., A. Jones-Bitton, A. Reynoso-Palomar, E. Canales-Vargas, and A.L. Greer. Domestic dog population dynamics in Villa de Tezontepec, Hidalgo, Mexico: towards improved canine population and rabies control. Canadian Association for Veterinary Epidemiology and Preventive Medicine. Guelph, ON. Abstract. May 2016. Oral.

35. *Spence, K.L., T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. Describing the Ontario equine movement network to understand the risk of disease introduction and spread. Canadian Association for Veterinary Epidemiology and Preventive Medicine. Guelph, ON. Abstract. May 2016. Oral.

34. *Brankston, G., C. Boughen*, and **A.L. Greer**. Assessing the Impact of Environmental Exposures and *Cryptosporidium* Infection in Cattle on Human Incidence of Cryptosporidiosis. Canadian Association for Veterinary Epidemiology and Preventive Medicine. Guelph, ON. Abstract. May 2016. Poster.

33. *Spence, K.L., T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. An agent-based modeling approach to determine the impact of control strategies on a facility-level equine influenza outbreak. Canadian Association for Veterinary Epidemiology and Preventive Medicine. Guelph, ON. Abstract. May 2016. Poster.

32. *Spence, K.L., T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. Preventing equine disease epidemics using mathematics. Ontario Ministry of Agriculture, Food and Rural Affairs Expo. Abstract. December 2015. Poster.

31. *Spence, K.L., B. Goh*, T.L., O'Sullivan, Z. Poljak, and **A.L. Greer**. Characterization of the equine contact network at a single equestrian show. Graduate Student Research Symposium. Guelph, ON. Abstract. December 2015. Oral.

30 *Gardner, E., D. Kelton, K. Hand, Z. Poljak, and **A.L. Greer.** Using an agent-based model to compare between two diagnostic tests for *Staphylococcus aureus* bovine mastitis. 5th International Conference on Infectious Disease Dynamics. Clearwater Beach, FL. Abstract. December 2015. Poster.

29. *Spence, K., T. O'Sullivan, Z. Poljak, and **A.L. Greer**. Identifying factors influencing the probability of an equine influenza outbreak in an equine training facility. 5th International Conference on Infectious Disease Dynamics. Clearwater Beach, FL. Abstract. December 2015. Poster.

28. **Greer, A.L**. K. Spence*, and E. Gardner*. Using the Incidence Decay and Exponential Adjustment (IDEA) model to understand the early dynamics of the 2014 porcine epidemic diarrhea virus (PEDV) outbreak in Ontario. 5th International Conference on Infectious Disease Dynamics. Clearwater Beach, FL. Abstract. December 2015. Poster.

27. +Beswick, A, Z. Poljak, **A.L. Greer**, A. Papadopolous, and C. Dewey. Social Media Surveillance: Using Twitter to track Influenza in Canada. Centre for Public Health and Zoonoses Annual Conference. Guelph, ON. Abstract. May 2015. Oral.

26. *Kisiel, L., A. Jones-Bitton, and **A.L. Greer**. The application of Computational Agent-Based Modelling to identify and evaluate dog population management strategies. Centre for Public Health and Zoonoses Annual Conference. Guelph, ON. Abstract. May 2015. Oral.

25. +Walczak, K., Z. Poljak, R. Friendship, **A.L. Greer**, A. Weersink. Factors associated with the antimicrobial treatment rates for swine dysentery during the grower-finisher phase of production. Centre for Public Health and Zoonoses Annual Conference. Guelph, ON. Abstract. May 2015. Poster.

24. Poljak, Z., K. Walczak+, R. Friendship, Brockhoff, **A.L. Greer**, A. Weersink. Insight into epidemiology of swine dysentery by using analysis of treatment records and simulation modeling. International Society for Veterinary Epidemiology and Economics (ISVEE), Merida, Mexico. Abstract. November 2015. Oral.

23. +Arruda, A.G., Z. Poljak, **A.L. Greer**, R. Friendship, and J. Carpenter. Evaluation of porcine reproductive and respiratory syndrome control methods using agent-based modeling. International Society for Veterinary Epidemiology and Economics (ISVEE), Merida, Mexico. Abstract. November 2015. Oral.

22. *Tuite, A., V. Gallant, E. Randell, and **A.L. Greer.** Controlling Tuberculosis Transmission in Canada's North: A Mathematical Modeling Study. Canadian Society for Epidemiology and Biostatistics, Toronto, ON. Abstract. June 2015. Oral.

21. *Kisiel, L., A. Jones-Bitton, and **A.L. Greer**. The application of Computational Agent-Based Modelling to identify and evaluate dog population management strategies. 2nd International Conference on Dog Population Management, Istanbul, Turkey. Abstract. March 2015. Poster.

20. *Spence, K., *B. Goh, T. O'Sullivan, and **A.L. Greer**. Using social network analysis to understand epidemic potential in equine populations: a pilot study. Conference of Research Workers in Animal Disease (CRWAD), Chicago, IL. Abstract. December 2014. Oral.
***K. Spence was awarded the student prize for the best oral presentation in the Biosecurity section for this presentation.

19. *Goh, B. and **A.L. Greer.** Mathematical disease transmission models for livestock populations: A scoping review. Conference of Research Workers in Animal Disease (CRWAD), Chicago, IL. Abstract. December 2014. Oral.

18. **Greer, A.L.** and D. Schanzer. Using a dynamic model to consider optimal antiviral stockpile size in the face of pandemic influenza uncertainty. Epidemics 4, Amsterdam, The Netherlands. Abstract. 2013. Poster.

17. *Hauck, T., A.R. Tuite, D.N. Fisman and **A.L. Greer.** A simple model for Ro generation and short-term outbreak projection. Epidemics 3. Boston, MA. Abstract 2011. Poster.

16. **Greer, A.L.** and D.N. Fisman. Using models to identify cost effective interventions:
pertussis vaccination for pediatric healthcare workers in Canada. American College of Epidemiology. San Francisco, CA. Abstract 2010. Oral.

15. Sander, B., C. Bauch, D. Fisman, **A.L. Greer**, and M. Krahn. Impact of mathematical modeling on health policy decision-making in the context of the recent novel swine-origin influenza A virus (SOIV) outbreak response in Ontario. Society for Medical Decision Making. Hollywood, CA. Abstract 2009. Poster.

14. **Greer, A.L.** and D.N. Fisman. Keeping vulnerable children safe from pertussis: preventing nosocomial pertussis transmission in the neonatal intensive care unit (NICU). Epidemics. Asilomar, CA. Abstract 2008. Poster.

13. **Greer, A.L.** and D.N. Fisman. Keeping vulnerable children safe from pertussis: preventing nosocomial pertussis transmission in the neonatal intensive care unit (NICU). Understanding and controlling infectious diseases: an agenda for the 21st century. Insitut Pasteur, Paris, France. Abstract 2008. Poster.

12. **Greer, A.L.**, S.J. Drews and D.N. Fisman. Why does the "Winter Vomiting Disease" happen in winter? Unravelling the seasonality of Norovirus outbreaks in Toronto, Canada. Annual meeting of the Infectious Diseases Society of America. Washington, DC. Abstract 2008. Poster.

11. **Greer, A.L.** and J.P. Collins. Testing a key assumption of host pathogen theory: density- dependent disease transmission. Annual meeting of the Ecological Society of America. San Jose, CA. Abstract 2007. Oral.

10. **Greer, A.L.** and J.P. Collins. Habitat fragmentation affects disease transmission throughout a population. Annual meeting of Arizona State University Graduates in the Earth Life and Social Sciences. Tempe, AZ. Abstract. 2007. Oral.

9. **Greer, A.L.** and J.P. Collins. Is ATV transmission in tiger salamanders density dependent? Annual Meeting of the IRCEB Amphibian Decline and Disease Group, Tempe, AZ. Abstract. 2006. Oral.

8. **Greer, A.L**. and J.P. Collins. Spatial and temporal variation in *Ambystoma tigrinum* virus (ATV) infection prevalence in a persisting *Ambystoma tigrinum* population on the Kaibab Plateau, AZ. Annual Meeting of the Ecological Society of America. Memphis, TN. Abstract 2006. Oral.

7. Collins, J. P., J. Brunner, **A.L. Greer**, V. Miera, A. Picco, R. Retallick, and D. Schock. A comparison of two emerging infectious diseases caused by chytrid fungus and ranaviruses in tropical and temperate habitats. Annual meeting of the American Society of Ichthyologists and Herpetologists, New Orleans, LA. Abstract 2006. Oral.

6. **Greer, A.L**. and J.P. Collins. Mechanisms of disease transmission influence host persistence or extinction. Annual meeting of Arizona State University Graduates in the Earth Life and Social Sciences. Tempe, AZ. Abstract. 2006. Oral.

5. Fox, S.F., R.J. Torres-Cervantes, A.T. Storfer, G. Parra, **A.L. Greer**, and J.P. Collins. Ranavirus and *Batrachochytrium dendrobatidis* in endangered and diseased populations of the frog *Atelognathus patagonicus* in northern Patagonia, Argentina. Annual meeting of the American Society of Ichthyologists and Herpetologists, New Orleans, LA. Abstract 2006. Oral.

4. **Greer, A.L**. and J.P. Collins. Evaluation of a PCR diagnostic test for ranaviruses using whole carcasses and tail clips as comparison standards. Annual Meeting of the IRCEB Amphibian Decline and Disease Group, Tempe, AZ. Abstract. 2005. Oral.

3. **Greer, A.L**., S.F. Fox, E.W. Davidson and J.P. Collins. Evidence for a ranavirus pathogen in the endangered frog, *Atelognathus patagonicus*, in Patagonia, Argentina. Annual meeting of the Research and Analysis Network for Neotropical Amphibians, San Juan, Puerto Rico. Abstract. 2004. Oral.

2. **Greer, A.L**., M. Berrill and P.J. Wilson. The occurrence of ranavirus in wood frog and leopard frog populations in Ontario. Ontario Ecology and Ethology Conference, McMaster University. Abstract. 2003. Oral.

1. **Greer, A.L**., M. Berrill and P.J. Wilson. The epizootiology of six amphibian mortality events in south central Ontario,

Canada. Annual Meeting of the Canadian Society of Zoologists Conference, Wilfred Laurier University. Abstract. 2003. Oral.

12. INVITED PRESENTATIONS

- Invited speaker, COVID-19 in children – implications for schooling systems. European Society of Clinical Microbiology and Infectious Diseases (ESCMID). September 24, 2020.
- Invited speaker, Pandemic: the biology and mathematics of COVID-19 in Canada, Third Age Learning Seminar. September 23, 2020.
- Invited speaker, Risk of COVID-19 amplification in school settings. Global Research Collaboration for Infectious Disease Preparedness (GLoPID-R), COVID Research synergies – transmission. July 20, 2020.
- Invited speaker, Risk of COVID-19 chains of transmission associated with summer camp settings. Ontario Ministry of Health. May 13, 2020.
- Invited speaker, HIVE 2020 a Conference for Women in STEM, University of Guelph. March 28, 2020 (cancelled due to COVID-19)
- Invited speaker, Preparing Equine Facilities for Shelter in Place Orders. Equestrian Canada. March 25, 2020.
- Invited speaker, COVID-19 Pandemic planning for summer camp settings. Go Camp Pro Webinar. Online. March 6, 2020.
- Invited speaker, Borders in Public Health and Mathematical Epidemiology. Fields Institute, University of Toronto, Toronto, ON October 21-25, 2019.
- Invited speaker, American Society of Microbiology (ASM) Microbe 2019. San Francisco, CA. June 20-24, 2019.
- Invited speaker, Swine Research Day. Guelph, ON. May 9, 2019.
- Invited speaker, Ontario Livestock and Poultry Council. Guelph, ON. February 15, 2019.
- Invited Panelist, Café Mathematique, Fields Institute, University of Toronto, Toronto, ON (declined). November 2019.
- Invited speaker, Equestrian Canada Health and Welfare Committee. October 3, 2018.
- Invited speaker, 11th annual CRIPA Symposium, Faculté de médecine vétérinaire of the Université de Montréal, St-Hyacinthe, QC. May 15-16, 2018.
- Invited speaker, Department of Biology Seminar Series, Laurentian University, Sudbury, ON. April 6, 2018.
- Invited speaker, ITK TB elimination planning meeting, Ottawa, ON. February 26-27, 2018.
- Invited speaker, Nunavut TB Long Term Planning Meeting, Ottawa, ON. October 4-5, 2017.
- Invited speaker, Canadian Food Inspection Agency (CFIA) equine disease surveillance group. August 2017.
- Invited speaker, 2017 China-Canada International Conference on Disease Modelling (CCICDM). Shanghai University, China. June 2-6 2017.
- Invited speaker, Centre for Public Health and Zoonoses Research Day. Guelph, ON. May 23 2017.
- Invited speaker, Ontario Veterinary College, Disease Modeling Club. Guelph, ON. February 28, 2017.
- Invited speaker, Ontario Veterinary College – Hebrew University Collaboration Workshop. Guelph, ON. January 5-6, 2017.
- Invited speaker, Canadian Pandemic Influenza Plan – Task Group. Ottawa, ON. November 14-15, 2016.
- Invited speaker, Public Health Challenges for Modelling and Infectious Diseases: From "Communities of Practice" to "Communities of Health" hosted by National Collaborating Centre for Infectious Diseases (NCCID) and the International Centre for Infectious Diseases (ICID), York University, Toronto. October 2016.
- Invited speaker, International Workshop on Applied Probability, Toronto, ON (declined). June 2016.
- Invited Panelist, Café Mathematique, Fields Institute, University of Toronto, Toronto, ON. November 2015.

- Invited speaker, Workshop on the Mathematical Mobilization of Vaccine Discovery & Development, Fields Institute, University of Toronto. March 2015.
- Invited Speaker, University of Toronto Special Seminar Series on Ebola. Topic: The Ecological Context of the West African Ebola Outbreak. January 2015.
- Invited speaker, International Meeting on Emerging Diseases and Surveillance (IMED), Vienna, Austria. 2014.
- Invited speaker, National Collaborating Centre for Infectious Diseases (NCCID), Winnipeg, MB. 2014.
- Invited Speaker, Mathematics and Informatics for Public Health Conference. Jointly hosted by the Chern Institute of Mathematics and the Chinese Centre for Disease Control. Tianjing, China. 2014.
- Invited Working Group Participant, National Institute for Mathematical and Biological Synthesis (NimBios), Knoxville, TN. Theme: Modeling microbial contamination of fresh produce along the post-harvest supply chain. 2014.
- Invited Speaker, Biomathematics and Biostatistics Symposium, University of Guelph. 2014.
- Departmental Seminar, Department of Mathematics and Statistics, University of Guelph. 2014.
- Departmental Seminar, Department of Population Medicine, Ontario Veterinary College, University of Guelph. 2014.
- Public Health Network Council / Committee of Canadian Medical Officers of Health Meeting, Halifax, NS. 2011.
- Modelling and analysis of options for controlling persistent infectious diseases, Banff International Research Station for Mathematical Discovery and Innovation, Banff, AB. 2011.
- Ontario Agency for Health Protection and Promotion pH1N1 Workshop, Toronto, ON. 2011.
- Canada – China International Conference on the Dynamics of Climate Impact and Infectious Diseases, Nanjing Normal University, Nanjing, China. 2010.
- Pandemic Planning Division, Public Health Agency of Canada, Ottawa, ON. 2010.
- Workshop in dynamic modelling for health policy: infectious and chronic disease interactions. University of Saskatchewan, Saskatoon, SK. 2010.
- Panel on Mathematical Modeling in Epidemiology. American College of Epidemiology Annual Meeting. San Francisco, CA. 2010.
- Yukon Department of Health and Social Services, Chlamydia planning meeting. 2010.
- MITACS annual meeting, Edmonton, AB. 2010.
- Considerations for pH1N1 Planning to Respond to a "Third Wave" in 2010. Ontario and Nunavut Regional Pandemic Planning Meeting, Toronto, ON. 2009.
- Tools for Linking Human and Animal Models of Infectious Disease. Canadian Food Inspection Agency meeting, Montreal, QC. 2009.
- SickKids, CIHR Café Scientifique, It's getting hot in here: climate change and infectious disease dynamics, Toronto, ON. 2009.
- Mitigating the spread of influenza A (H1N1), Part II (Hosted by the British Columbia Centre for Disease Control), Vancouver, BC. 2009.
- Canadian Pandemic Vaccine Task Group, National Vaccine Prioritization meeting, Toronto, ON. 2009.
- H1N1 Mathematical Modeling Workshop (Hosted by the Public Health Agency of Canada), Toronto, ON. 2009.
- Canadian Pandemic Preparedness Meeting: H1N1 Outbreak Research Response (Hosted by CIHR), Toronto, ON. 2009.
- Mitigating the Spread of A H1N1 Flu: Lessons Learned From Past Outbreaks, Arizona State University, Tempe, AZ. 2009.
- Plenary speaker, Annual Meeting of ICC-AMMI-CACMID, Toronto, ON. 2009.
- MITACS Center for Disease Dynamics, York University, Toronto, ON. 2009.
- Toronto Invasive Bacterial Diseases Network education day, Mount Sinai Hospital, Toronto, ON. 2008.
- McMaster University, Mathematical Biology Seminar. 2008.

- Sunnybrook Health Sciences Centre, Toronto, ON. 2008.
- Sanofi Pasteur, Toronto, ON. 2008.
- Harvard School of Public Health, Freeman Symposium, Boston, MA. 2008.
- Department of Mathematics and Statistics. University of Guelph, Guelph, ON. 2007.
- State of Arizona Education Fair, Gilbert, AZ. 2006.

13. HIGHLY QUALIFIED PERSONNEL

Primary supervision (current)

30. Gabrielle Brankston, PhD student - Epidemiology	May 2020 -
29. Lindsay Obress, MSc (thesis) - Epidemiology	September 2019-
28. Thivya Naganathan, MSc (thesis) - Epidemiology	September 2019-
27. Dr. Tanya Rossi, Postdoctoral Fellow	September 2019-
26. Dr. Kamal Acharya, Postdoctoral Fellow	January 2019 -
25. J. Reilly Comper, doctoral student - Epidemiology	January 2019 -
24. Haley Weber, doctoral student (P/T) – Epidemiology	September 2017 – Parental leave: Jan – Dec 2020
23. Wendy Xie, doctoral candidate - Epidemiology	September 2017 -
22. Dr. Emma Gardner, doctoral candidate - Epidemiology	January 2015 – LOA: Jan – Sept 2017 Parental leave: Apr 2019 - Mar 2020

Primary Supervision (completed)

21. Elissa Giang, MSc (thesis) – Epidemiology, University of Guelph	2019
20. Roksolana Hovdey, MSc (thesis) – Epidemiology, University of Guelph	2019
19. Dr. Salah Uddin Khan, Postdoctoral Fellow, University of Guelph/Public Health Agency of Canada	2019
18. Dr. Tanya Rossi, Postdoctoral Fellow, University of Guelph	2019
17. Rachael Milwid, PhD – Epidemiology, University of Guelph	2018
16. Melanie Cousins, MSc (thesis) – Epidemiology, University of Guelph	2018
15. Meagan Coffey, MSc (thesis) – Biophysics, University of Guelph	2017
14. Kelsey Spence, PhD – Epidemiology, University of Guelph	2017
13. Ariel Brunn, MSc (CW) – Epidemiology, University of Guelph	2017
12. Kamel Omer, undergraduate, University of Guelph	Summer 2017
11. Luz Maria Kisiel, MSc (thesis) – Epidemiology, University of Guelph	2017
10. Beatrice Hai, undergraduate, University of Guelph	Summer & Fall 2016
9. Enise Decaluwe-Tulk, undergraduate, University of Guelph	Summer & Fall 2016
8. Cyndi Boughen, undergraduate, University of Guelph	Winter 2015
7. Kelsey Spence, undergraduate, University of Guelph	Summer 2014
6. Beverly Goh, undergraduate, University of Guelph	Summer 2014
5. Christina Chan, MPH, University of Toronto	2011
4. Marcella Jones, MPH, University of Toronto	2010
3. Tanya Hauck, MD, University of Toronto	2012
2. Eva Wong, MPH, University of Toronto	2010
1. Karolina Machalek, MPH, University of Toronto	2010

Graduate Committee membership (current)

17. Lia Humphrey, MSc thesis, Department of Mathematics and Statistics, University of Guelph
September 2019 -
16. Armin Orang, MSc thesis, Department of Population Medicine, University of Guelph
September 2019 -
15. Melanie Cousins, PhD candidate, Department of Public Health and Health Systems, University of Waterloo.
September 2018 -
14. Mikayla Plishka, MSc thesis, Department of Population Medicine, University of Guelph
September 2018 -
13. Isha Berry, PhD candidate, Department of Epidemiology, Dalla Lana School of Public Health, University of Toronto.
September 2018 -
12. Dylan Melmer, PhD candidate, Department of Population Medicine, University of Guelph.
September 2017 -
11. Tara Sadeghieh, PhD candidate, Department of Population Medicine, University of Guelph.
September 2017 -

Graduate Committee membership (completed)

10. Matthew Wong, MSc (thesis), Department of Animal Bioscience, University of Guelph. 2020.
9. Jennifer Perret, PhD, Department of Population Medicine, University of Guelph. 2020.
8. Gabriella Mallia, PhD, Department of Pathobiology, University of Guelph. 2018.
7. Reilly Comper, MSc (thesis), Department of Biophysics, University of Guelph. 2018.
6. Stephanie Hughes, PhD, Department of Population Medicine, University of Guelph. 2018.
5. Ashleigh McGirr, PhD, Dalla Lana School of Public Health, University of Toronto. 2016.
4. Jordan Minigan, MSc (thesis), Department of Environmental Science, University of Guelph. 2016.
3. Adam Beswick, MSc (thesis), Department of Population Medicine, University of Guelph. 2016.
2. Krysia Walczak, MSc (CW), Department of Population Medicine, University of Guelph. 2016.
1. Ashleigh Tuite, PhD, Dalla Lana School of Public Health, University of Toronto. 2015.
***Awarded the Institute of Medical Science (IMS) Siminovitch-Salter Award (2016). This award is given annually to a graduating IMS doctoral student who has made outstanding scholarly contributions.

Examination and Defense Committees

28. Reilly Comper - Qualifying examination committee. Department of Population Medicine, University of Guelph. May 2020.
27. Xuezhen Ge – Dissertation proposal defense committee. Department of Integrative Biology, University of Guelph. January 2020.
26. Melanie Cousins – Dissertation proposal defense committee. Department of Public Health and Health Systems, University of Waterloo. December 2019.
25. Elissa Giang - MSc thesis defense committee. Department of Population Medicine, University of Guelph. December 2019.
24. Roksolana Hovdey - MSc thesis defense committee. Department of Population Medicine, University of Guelph. October 2019.
23. Kaushalya Kuruppu – MSc thesis defense committee Chair. Department of Population Medicine, University of Guelph. August 2019.
22. Jamie Imada - Qualifying examination committee. Department of Population Medicine, University of Guelph. June 2019.
21. Nadine Vogt - Qualifying examination committee. Department of Population Medicine, University of Guelph. June 2019.

20. Amanda Perri – PhD defense examination committee. Department of Population Medicine, University of Guelph. December 2018.
19. Rachael Milwid – PhD defense examination committee. Department of Population Medicine, University of Guelph. August 2018.
18. Melanie Cousins - MSc thesis exam committee. Department of Population Medicine, University of Guelph. August 2018.
17. Reilly Comper – MSc thesis exam committee. Department of Biophysics, University of Guelph. June 2018.
16. Stephanie Hughes – PhD defense examination committee. Department of Population Medicine, University of Guelph. April 2018.
15. Tara Sadeghieh, Qualifying examination committee. Department of Population Medicine, University of Guelph. January 2018.
14. Dylan Melmer – MSc thesis exam committee. Department of Population Medicine, University of Guelph – external examiner. August 2017.
13. Kelsey Spence – PhD defense examination committee. Department of Population Medicine, University of Guelph. August 2017.
12. Ariel Brunn – MSc (CW) defense examination committee. Department of Population Medicine, University of Guelph. August 2017.
11. Aaron B. Langille – PhD defense examination committee. Department of Environmental Sciences, University of Guelph. April 2017.
10. Rachael Milwid – PhD Qualifying examination. Department of Population Medicine, University of Guelph. February 2017.
9. Luz Maria Kisiel – MSc thesis exam committee. Department of Population Medicine, University of Guelph. January 2017.
8. Emma Gardner – PhD Qualifying examination. Department of Population Medicine, University of Guelph. October 2016.
7. Sovit Chalise – MSc (thesis). Department of Biology, Memorial University, St. John's NL – external examiner. July 2016.
6. Kelsey Spence – PhD Qualifying examination. Department of Population Medicine, University of Guelph. June 2016.
5. Vanessa Morton – MSc (CW), defense examination committee. Department of Population Medicine, University of Guelph. July 2014.
4. Jue (Julie) Tang – MSc (thesis), defense examination committee. Department of Population Medicine, University of Guelph. June 2014.
3. Shannon Collinson – PhD dissertation (Department of Mathematics, York University, Toronto, ON) – external examiner. 2013.
2. Kevin Brown – PhD protocol defense examination committee. Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto. 2011.
1. Marija Zivkovic Gojovic – PhD dissertation (Department of Mathematics, York University, Toronto, ON) - external examiner. 2010.

14. INSTITUTIONAL SERVICE

- Research Advisory Committee, Ontario Veterinary College, University of Guelph. 2014 – current.
- Technical advisor, University of Guelph and Ontario Veterinary College Emergency Preparedness Committee for COVID-19. March 2020 – June 2020
- Invited Speaker, Data, COVID-19, and Food. Arrell Food Institute. April 30, 2020.
- Invited speaker, Ontario Veterinary College - Graduate Student Wellness Seminar. Topic: Planning your semester for success. January 2020.
- Search Committee Member, Dept. of Population Medicine, assistant professor tenure-track position in

Epidemiology/One Health. 2020.

- Committee member, University of Guelph, Public Health Curriculum Committee. 2019-2020.
- Committee member, Department of Population Medicine, Graduate Program Committee. 2019-2020.
- Reviewer, University of Guelph – OMAFRA Emergency Management Grant Review Committee, Winter/Spring 2019
- Invited participant, OVC Horse Trust meeting. November 2018.
- Search Committee Member, Ontario Veterinary College, Director, Centre for Public Health and Zoonoses. 2018-2019.
- Search Committee Member, Dept. of Population Medicine, associate/full professor tenure-track position in One Health. 2018.
- Search Committee Member, Dept. of Population Medicine, assistant/ associate professor tenure-track position in One Health. 2018.
- Search Committee Member, Department of Integrative Biology, Department Chair. Spring 2018.
- Reviewer, OVC College Review Committee, OVC Scholarships. Summer 2017.
- Reviewer, OVC College Review Committee, OVC Scholarships. Spring 2017.
- Interviewer, OVC admissions committee, multiple mini interviews (MMI). May 2017.
- OVC College Review Committee, OVC Scholarships/Fellowships. March 2017.
- Ontario Veterinary College collaboration workshop with Hebrew University. January 3-4, 2017.
- Steering committee member, Ontario Veterinary College, Canada Excellence Research Chair proposal. 2017.
- Poster judge for the Annual OVC Graduate Research Symposium. November 2016.
- Participant, OVC Strategic Planning Committee. Fall 2016.
- Interviewer, OVC admissions committee, multiple mini interviews (MMI). 2015.
- OVC College Review Committee, Ontario Graduate Scholarships. 2015.
- Poster judge for the Annual OVC Graduate Research Symposium. November 2014.
- Dean's Advisory Council, Ontario Veterinary College, University of Guelph. 2014 – 2016.
- Data Boot camp Committee, Department of Population Medicine, Ontario Veterinary College, University of Guelph. 2014-2015.
- Master of Public Health (MPH) Program Committee, Ontario Veterinary College, University of Guelph. 2014-current.
- Research Methods 2 Curriculum Committee, Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto. 2011-2012.
- Infectious Disease Curriculum Committee, Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto. 2011-2012.
- MPH Admissions Committee, Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto. 2011-2012.
- Annual review committee for doctoral student progress, Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto. 2009-2011.

15. PROFESSIONAL SERVICE

- Advisor, COVID-19 Task Force, Ontario Camping Association. March – May 2020.
- Member, Public Health Agency of Canada, COVID-19 Modelling Technical Advisory Committee. February 2020 - current
- Committee Member, New Frontiers in Research Fund. Tri-agency Institutional Programs Secretariat. 2019-2020.
- Advisory Board Member (invited), National Collaborating Centre for Infectious Disease (NCCID). 2019- 2024.
- Mentor, 500 Women Scientists, Guelph, ON Pod. 2019-2020.

- Invited speaker (volunteer), Let's Talk Science, Science of Witchcraft and Wizardry at the University of Guelph. November 2, 2019.
- Chair, NSERC Site Visit Committee (SVC). University of Saskatchewan Industrial Research Chair evaluation. June 2019.
- Evaluator, Graduate student oral presentation scoring. Canadian Association for Veterinary Epidemiology and Preventive Medicine. May 2019.
- Team Member, Mathematics for Public Health Lab at York University (Fields CQAM lab). https://www.cqam.ca/mathematics-for-public-health 2019 - current.
- Scientific Merit Reviewer, Canadian Nuclear Laboratories, Chalk River, ON. 2018-current.
- External Reviewer, Tenure and Promotion file for the Department of School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa. Winter 2019.
- Participant, Institut de Recherche en Sante Publique at Universite de Montreal - Delphi consultation on Zoonoses, Winter 2018.
- External reviewer, UK Medical Research Council (MRC) funding proposals. November 2017.
- Member, Community for Emerging and Zoonotic Diseases (CEZD), Canadian Animal Health Surveillance System (CAHSS).
- External reviewer, Discovery Grants (Mathematics and Statistics and Biological Sciences), Natural Sciences and Engineering Research Council (NSERC). December 2017.
- Moderator, Modeling and Network Analysis Section, Conference of Research Workers in Animal Disease (CRWAD). December 2017.
- Invited member, Federal Inuit TB Elimination Task Force (Modeling and health economic sub-group). 2017 – 2018.
- Advisory Group Member, ESRC funded pump-priming research project: "Antimicrobial resistance as a social dilemma: Approaches to reducing broad-spectrum antibiotic use in acute medical patients internationally". Led by the University of Leicester (UK). January 2017 – current.
- External reviewer, Discovery Grants (Mathematics and Statistics), Natural Sciences and Engineering Research Council (NSERC). December 2016.
- Invited member, Equestrian Canada (EC) and Canadian Animal Health Surveillance System (CAHSS) working group for equine disease surveillance. November 2016 - current
- Workshop Organizer, Mathematical Biology for Understanding Emerging Infectious Diseases at the Human-Animal-Environment Interface: a "One Health" Approach. Banff International Research Station for Mathematical Discovery and Innovation. November 2016.
- Technical advisor, Canadian Pandemic Influenza Plan Task Group (CPIP-TG). 2016 – current.
- Certified EpiCore member (www.epicore.org), providing timely input and expertise to speed up early detection of global outbreaks in collaboration with Health Map and ProMed mail. 2016 – current.
- Strategic advisor, Serecon/Canadian Agricultural Health Coalition /Canadian Food Inspection Agency project on Domestic Livestock Movement Demographic Study. 2014-2015.
- Reviewer, Wellcome Trust Sustaining Health Fund. 2015
- Moderator, Modeling for Public Health Group– National Collaborating Centre for Infectious Diseases, Winnipeg, MB. 2014-2016.
- Organizer, Community of Interest in Disease Modeling, University of Guelph. 2014 – 2016.
- Session Moderator, Global Development Symposium. University of Guelph. May 2014.
- Consultant, United States Institute of Medicine (IOM) SMART vaccines beta tester on behalf of the Public Health Agency of Canada, 2013-2015.
- Founding Co-Director, Decision Centre for Infectious Disease Epidemiology (DeCIDE). 2011-current.
- Associate Editor, BMC Public Health. 2011-2016.
- Core Investigator, York University, Centre for Disease Modeling. 2010 - current

- Technical Advisor, Canadian Pandemic Influenza Plan (CPIP), Surveillance Annex Expert Advisory Group. 2013-2014.
- Scientific Advisory Group Member, FitzGerald Seminar Series, University of Toronto. 2011-2014.
- Technical Advisor, Canadian Sustainable Antiviral Stockpile Working Group. 2011-2013.
- Organizing Committee, Canadian Pandemic Influenza Planning Meeting: Assumptions. Public Health Agency of Canada, Winnipeg, Manitoba, February 2-3, 2011.
- Technical Advisor, Canadian Antiviral Scientific Advisory Group. 2010-2014.
- Organizing Committee, "One Health One Model: Modeling at the Animal-Human Interface". 4 day meeting on applying mathematical modeling to the "One Health" paradigm. University of Guelph, November 1-4, 2010.
- Co-organizer, Infectious Disease Epidemiology Afficionados Seminar Series. Hosted by the Fields Institute, University of Toronto. 2009-2011.
- Ontario Agency for Health Protection and Promotion Medical Officers of Health "Scientific Webinar" on Mathematical Modeling and Influenza, May 6, 2009.
- Technical Advisor, Canadian Pandemic Vaccine Task Group. 2009.
- Commentator on pandemic H1N1 waves for the Association of Public Health Epidemiologists in Ontario (APHEO). 2009.
- Workshop organizer, Keeping vulnerable populations safe from pertussis: using modeling tools to identify cost-effective interventions for whooping cough. International Society for Pharmacoeconomics and Outcomes Research (ISPOR). 2009
- Contributor, Symposium on Disaster Modeling for Public Health and Emergency Preparedness. 2008.
- Co-organizer, Ontario Agency for Health Protection and Promotion --- University of Guelph Center for Public Health and Zoonosis meeting on collaborative efforts in human-veterinary health research, Ontario Central Public Health Laboratory. 2008.
- Rounds Working Group, Child Health Evaluative Sciences. The Hospital for Sick Children. 2008.
- Coordinator, School of Life Sciences, See ASU (a community outreach program). 2006-2007.

Manuscript Reviewer: Journal of Infectious Diseases, Infectious Diseases and Therapy, Journal of Swine Health and Production, Clinical Infectious Diseases, Annals of Epidemiology, BMC Public Health, European Journal of Internal Medicine, Copeia, Emerging Infectious Diseases, Journal of Wildlife Disease, Epidemiology, Trends in Parasitology, Vaccine, American Journal of Epidemiology, Nature Scientific Reports, Infection Control and Hospital Epidemiology, Psychology, Health & Medicine, PLoS ONE, Canadian Veterinary Journal, CMAJ Open, Journal of Infection and Public Health, Epidemics, BMC Veterinary Research, BMC Medicine, International Journal of Modern Physics B, Diseases of Aquatic Organisms, Herpetological Revie, Frontiers in Ecology and Evolution, Equine Veterinary Journal

16. MEDIA

- "You want kindergarteners to social distance?". Toronto Star. August 22, 2020. https://www.thestar.com/news/gta/2020/08/22/opening-kindergarten-classes-present-a-myriad-of-problems-physical-and-emotional.html
- "What Ontario schools can learn from elsewhere about making schools safer from COVID-19. CBC News. July 17, 2020.https://www.cbc.ca/news/canada/toronto/ontario-covid-19-school-return-class-september-coronavirus-1.5649529
- "As Ontario heads into Stage 3, pressure grows for full-time school plan amid COVID-19". CBC News. July 15, 2020. https://www.cbc.ca/news/canada/toronto/covid-19-ontario-stage-3-school-reopening-1.5648796
- "Medical experts open letter to government: balance needed in COVID restrictions". Radio Canada International. July 9, 2020. https://www.rcinet.ca/en/2020/07/09/medical-experts-open-letter-to-government-balance-needed-in-covid-restrictions/
- "Health experts press Ottawa for a more 'balanced approach' to tackling COVID-19 pandemic". The Globe and Mail.

July 7, 2020. https://www.theglobeandmail.com/canada/article-health-experts-press-ottawa-for-a-more-balanced-approach-to-tackling/
- "Here we go: Reopening is upon us. But just remember there's still a pandemic". Toronto Star. June 22, 2020. https://www.ourwindsor.ca/opinion-story/10039656-bruce-arthur-here-we-go-reopening-is-upon-us-but-just-remember-there-s-still-a-pandemic/
- "How 'superspreading' helps drive the coronavirus pandemic". Global News. June 14, 2020. https://www.vice.com/en_ca/article/ep44ne/bryan-adams-is-the-latest-vegan-to-falsely-blame-the-pandemic-on-meat
- "The COVID-19 pandemic is remapping childhood- and the effects may linger". Maclean's. June 11, 2020. https://www.macleans.ca/society/health/covid-19-pandemic-coronavirus-canada-children-effects/
- "COVID reopening: hoping it goes right- watching carefully how it might go wrong". CBC Radio Quirks and Quarks. May 29, 2020. https://www.cbc.ca/radio/quirks/may-30-swearing-makes-pain-more-tolerable-mt-st-helens-40-years-later-and-more-1.5589125/covid-reopening-hoping-it-goes-right-watching-carefully-how-it-might-go-wrong-1.5589127
- "Infection rate continues to slide despite broader COVID-19 testing. CBC News. May 19, 2020. https://www.cbc.ca/news/canada/ottawa/covid-19-tuesday-report-1.5575679
- "Bryan Adams is the latest vegan to falsely blame the pandemic on meat". Vice. May 12, 2020. https://www.vice.com/en_ca/article/ep44ne/bryan-adams-is-the-latest-vegan-to-falsely-blame-the-pandemic-on-meat
- "Everything you need to know about her immunity. Hint: we're a long way off". Maclean's. May 8, 2020. https://www.macleans.ca/opinion/everything-you-need-to-know-about-herd-immunity-hint-were-a-long-way-off/
- "Periodic physical distancing for COVID-19 control: new modelling study". Science Daily. April 8, 2020. https://www.sciencedaily.com/releases/2020/04/200408125523.htm
- "2 new deaths, 29 new COVID-19 cases identified in Ottawa" Global News. April 9, 2020. https://globalnews.ca/news/6801078/new-deaths-covid-19-cases-ottawa-april-9/
- "What the COVID-19 'new normal' could look like" Toronto Star. April 12, 2020. https://www.toronto.com/news-story/9940057-what-the-covid-19-new-normal-could-look-like/
- "Coronavirus: Supply squeeze creates dilemma for doctors on who to test". NOW magazine. March 23, 2020. https://nowtoronto.com/news/coronavirus-testing/
- "Stopping COVID-19 could require eight months of 'aggressive social distancing,' outbreak modelling shows. National Post. March 21, 2020. https://www.thechronicleherald.ca/lifestyles/health/stopping-covid-19-could-require-eight-months-of-aggressive-social-distancing-outbreak-modelling-shows-427703/
- "Nail and Hair salons are beginning to close. How will this affect workers?" Teen Vogue. March 20, 2020. https://www.teenvogue.com/story/nail-and-hair-salon-workers-coronavirus
- "Containment if futile: is the COVID-19 coronavirus the pathogen of the century 'everyone is waiting for'? National Post. March 7, 2020. https://www.thechronicleherald.ca/lifestyles/health/containment-is-futile-is-the-covid-19-coronavirus-the-pathogen-of-the-century-everyone-is-waiting-for-420760/
- "Coronavirus testing ramps up as Ontario searches for missed cases". Toronto Star. March 5, 2020. https://www.thestar.com/news/gta/2020/03/05/coronavirus-testing-ramps-up-as-ontario-searches-for-missed-cases.html
- "COVID-19 and pandemic preparedness" CBC Kitchener Waterloo. March 5, 2020.
- "COVID-19 and pandemic preparedness" Guelph Politico podcast. March 5, 2020.
- "COVID-19 and pandemic preparedness" CTV's Your Morning. March 3, 2020. https://www.youtube.com/watch?v=1Oh49QE2vis&feature=youtu.be
- "Preparing for COVID-19" The Ryan Jespersen Show on 930 CHED (Edmonton). March 2, 2020.
- "Canada could move to more active surveillance of COVID-19. Here's what that means". Global News. February 28, 2020. https://globalnews.ca/news/6611251/coronavirus-surveillance-canada/

- "COVID-19 How to prepare at home for potential quarantine" CTV News. February 28, 2020. https://www.ctvnews.ca/mobile/health/covid-19-how-to-prepare-at-home-for-potential-quarantine-1.4832097
- "Are we prepared for a pandemic?" The Bill Kelly Morning show on 900CHML. February 27, 2020.
- "Coronavirus testing ramps up as Ontario searches for missing cases". Toronto Star. March 5, 2020. https://www.thestar.com/news/gta/2020/03/05/coronavirus-testing-ramps-up-as-ontario-searches-for-missed-cases.html
- "Containment is futile: Is the COVID-19 coronavirus the pathogen of the century everyone is waiting for?" National Post. March 7, 2020. https://nationalpost.com/health/coronavirus-covid-19-pandemic
- "Canada could move to more active surveillance of COVID-19. Here's what that means". Global News. February 28, 2020. https://globalnews.ca/news/6611251/coronavirus-surveillance-canada/
- "Social distancing could go a long way toward slowing down COVID-19, researchers say". March 11. Toronto Star. https://www.thestar.com/news/gta/2020/03/10/social-distancing-could-go-a-long-way-toward-slowing-down-covid-19-researchers-say.html
- "The landscape of One Health". Summer/Fall 2019. The Crest. https://ovc.uoguelph.ca/sites/default/files/users/k.mantel/files/CREST_SF2019_webversion_a.pdf
- "The Super Awesome Science Show podcast". August 6, 2019. https://curiouscast.ca/podcast/321/super-awesome-science-show-sass/
- "Tools to help predict disease spread". April 19, 2019. Harness Link Magazine. http://www.harnesslink.com/News/Guelph-research-looks-at-tools-to-help-predict-disease-spread-in-horse-population
- "Guelph research looks at tools to help predict disease spread in horse populations". March 2019. Equine Guelph News. https://www.equineguelph.ca/news/index.php?content=609
- "Warming climate implies more flies – and disease". February 20, 2019. Scientific American Podcast. https://www.scientificamerican.com/podcast/episode/warming-climate-implies-more-flies-mdash-and-disease/
- "Climate change could increase foodborne illness by energizing flies". February 14, 2019. Science News. https://www.sciencenews.org/article/climate-change-increase-campylobacter-infections-flies
- "Study suggests global warming could cause more cases of food poisoning". February 13, 2019. Medical Xpress. https://medicalxpress.com/news/2019-02-global-cases-food-poisoning.html
- "Food poisoning cases could surge as climate change brings swarms of flies, scientists warn". February 13, 2019. The Independent. https://www.independent.co.uk/news/science/food-poisoning-flies-climate-change-disease-global-warming-insects-campylobacter-a8776001.html
- "University of Guelph studies barn interactions and disease patterns". May 15, 2017. American Farriers Magazine. https://www.americanfarriers.com/articles/9167
- "University researchers studying horse contact patterns". April 28, 2017. The Wellington Advertiser. http://www.wellingtonadvertiser.com/comments/index.cfm?articleID=35530
- "Connectedness of horse world revealed in study of Canadian dressage show" June 27 2017. Horse Talk Magazine NZ. http://www.horsetalk.co.nz/2017/06/23/connectedness-horse-world-dressage-show/#1vFAoTqSe6GA4koU.99
- "RFID unbridles pathogen transmission research". April 2017. RFID Journal. http://www.rfidjournal.com/articles/view?15956
- "Study tracks real-time contact between horses and humans". March 2017. Horse Talk Magazine NZ. http://www.horsetalk.co.nz/2017/03/27/real-time-contact-horses-humans/#axzz4etu2DCZL
- "Using radio frequency identification (RFID) tags to help track horses' movement and interactions". March 2017. Equine Guelph, Equine News. http://www.equineguelph.ca/news/index.php?content=503
- "Researcher wants to learn more about horse flu on PEI". CBC news. October 2016. http://www.cbc.ca/news/canada/prince-edward-island/pei-horse-flu-1.3822529
- "How to prevent the spread of equine disease". Straight from the Horse's Mouth Radio Show. March 2016.

- How a Toronto company used big data to predict the spread of Zika. Toronto Star. 22 February 2016.
- "Infectious diseases in a horse show environment". Equine Guelph Research Radio. June 2015.
- "Fighting epidemics by connecting the dots". The Horse Sport. May 2015.
- " e is for Ebola". The American Mathematical Society (AMS) blog. October 2014. http://blogs.ams.org/blogonmathblogs/2014/10/01/e-is-for-ebola/#sthash.P1SVBdtv.dpbs
- "This math model is predicting the Ebola outbreak with incredible accuracy". October 2014. https://motherboard.vice.com/en_us/article/this-math-model-is-predicting-the-ebola-outbreak-with-incredible-accuracy

17. TEACHING

University of Guelph, Guelph, ON
- Course coordinator, Infectious Disease Modeling (POPM*6800). 2020.
- Course coordinator, Infectious Disease Modeling (POPM*6950-01). 2019.
- Co-course-coordinator, Seminar (POPM*6200). 2018-2019.
- Course coordinator, Infectious Disease Modeling (POPM*6950-01). 2018.
- Course coordinator, Infectious Disease Modeling (POPM*6950-01). 2017.
- Course coordinator, Mathematical Epidemiology (POPM*6950-02). 2015.

Dalla Lana School of Public Health, University of Toronto, Toronto, ON
- Guest lecturer. Topic: Enteric infectious disease epidemiology and outbreak investigation. 2015.

Canadian Society for Epidemiology and Statistics
- Short course on Mathematical Modeling of Infectious Diseases: A practical introduction. 6 hour webinar. 2015

Queen's University, Kingston, ON
- Guest lecturer, Department of Public Health Sciences, Infectious Disease Epidemiology. Topic: A practical introduction to mathematical epidemiology. 2013 & 2014.

North American Congress of Epidemiology, Montreal, QC
- Short course in Mathematical Modeling of Infectious Diseases: Beyond the basics. 2011.

Dalla Lana School of Public Health, University of Toronto, Toronto, ON
- Co-course-coordinator, Infectious disease epidemiology (CHL 5412). 2011
- Group leader, Introduction to Public Health Sciences (CHL 5004). 2011
- Co-course-coordinator, Research methods II (CHL 5408). 2011.
- Co-course-coordinator, Short course in Mathematical Modeling of Infectious Diseases: An Introduction to Agent Based Models. 2010.

Society for Medical Decision Making, Hollywood, CA
- Short course in Mathematical Modeling of Infectious Diseases: An Introduction to Agent Based Models. 2009 & 2010.

Hospital for Sick Children, Toronto, ON
- Reading group co-organizer and leader, Biostatistical Methodology Unit. 2008-2009.

Arizona State University, Tempe, AZ
- Teaching assistant, Introductory biology for majors. 2004-2006.
- Teaching assistant, Introductory biology for non-majors. 2003-2004.
- Scientific curriculum instructor. 2005-2007.
- Lecturer, Learning Resource Centre. 2007.

Trent University, Peterborough, ON
- Sessional lecturer, Population ecology. 2003.

PROFESSIONAL DEVELOPMENT

- Unconscious Bias training module. CIHR. February 2020.
- Introduction to OneNote teacher academy. Microsoft Educator Centre. November 19, 2019.
- OneNote class notebook: a teacher's all-in-one notebook for students. Microsoft Educator Centre. November 13, 2019.
- Certified Microsoft Innovative Educator. Microsoft Educator Centre. November 13, 2019.
- Transform learning with Microsoft Teams. Microsoft Educator Centre. November 1, 2019.
- Crafting a collaborative learning environment with Class Teams. Microsoft Educator Centre. November 1, 2019.
- Participant, Introduction to Ontario's Incident Management System (IMS 100), certificate of successful completion issued by the Ministry of the Attorney General. October 2019.
- Member, National Centre for Faculty Development and Diversity August 2017 – current.
- Project-based learning (PBL) as a vehicle for high impact practices: reinventing courses. Worchester Polytechnic Institute (WPI). November 2019
- Best Practices in Graduate Student Supervision, University of Guelph. April 2017.
- Challenging Traditional Assessments through Team Based Learning**,** University of Guelph. January 2017.
- Media training, University of Guelph. June 2016.
- Making Education Accessible, University of Guelph online module. This course provided an introduction to universal instructional design (UIP). June 2014.
- Learner-Centred Assessment**,** Open Learning and Educational Support, University of Guelph. July 2014.

18. VOLUNTEER EXPERIENCE

- Volunteer, Waverley Drive Public School- "Waverley Weekender" Food Program, Guelph, ON. 2018 – current.
- Member, Waverley Drive Public School Parent Council, Guelph, ON. 2017 – current.
- Partners in Research. 2017 – current.
- Early literacy volunteer, Waverley Drive Public School, Guelph, ON (1 afternoon per week). 2015-2016.
- Guest Speaker, Cobourg District Collegiate Institute West, Department of Biology, Cobourg, ON. 2009
- Volunteer, Paediatric Oncology Playroom, Phoenix Children's Hospital, Phoenix, AZ (4 hours per week). 2003-2007.
- Coordinator, Ask a Biologist Program, Arizona State University. 2005-2007.

TAB 2

Ursel Phillips Fellows Hopkinson LLP

JUSTICE AT WORK

Susan Ursel
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UPDATED

September 10, 2020

Sent via E-mail (agreer@uoguelph.ca)

Dr. Amy Greer
50 Golfview Road
Guelph, Ontario
N1E 1A6

Dear Dr. Greer:

Re: Ontario Secondary School Teachers' Federation- COVID-19 and Health and Safety in Ontario Schools and Other Education Worksites; Our File 2565697

As you know, I am counsel to the Ontario Secondary School Teachers' Federation ("the OSSTF") and I currently represent and advise them with respect to the SARS-CoV-2 virus, commonly referred to as COVID-19, and Health and Safety in Ontario Schools and Other Education Worksites. The OSSTF represents more than 60,000 education workers in Ontario.

Our work in this regard is carried out in cooperation with the Elementary Teachers' Federation of Ontario ("ETFO"), the Ontario English Catholic Teachers' Association ("OECTA") and the Association des enseignantes and des enseignants franco-ontariens ("AEFO").

As you know, our case before the Ontario Labour Relations Board is proceeding, and we expect that you will be called as an expert witness in your capacity as an epidemiological advisor to the OSSTF. Prior to your testimony, we request that you provide us with a written report – that will be shared with both counsel to the unions named above, and with all parties to this matter – that provides your expert opinion on the following questions:

1. Can you explain from an epidemiological viewpoint the transmission and infection mechanisms and rates of, and outcomes of infection by the SARS- CoV-2 virus, commonly referred to as COVID-19?

2. What does the term "cohort" mean to you?

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3. How do you understand the term “cohort” to be used in the Guide to Reopening Ontario’s Schools?

4. What is population disease modelling?

5. What is network epidemiology?

    a. How does network epidemiology relate to the question of assessing the health and safety of education workers in the context of school re-opening in Ontario, during the COVID-19 pandemic?

6. From the perspective of network epidemiology, what is the goal of physical distancing?

7. From the perspective of network epidemiology, what is the goal of mask use? Does that differ with different kinds of masks?

8. From the perspective of network epidemiology, what is the goal of wearing PPE (such as gloves and face shields)?

9. What is the risk that a COVID-19 infected individual (student or staff) will enter a school setting on any given day?

10. What sort of outcomes might we expect if a COVID-19 infected individual transmits their infection within the school setting? For each response, is it possible to visually represent the outcomes, using for example a network epidemiology diagram?

    a. What – if any – are the impacts of different class sizes on these expected outcomes, to the extent that those impacts can be assessed? Please specify what class sizes you considered.

    b. What – if any – are the impacts of differing physical distancing (1 m vs 2 m) on these expected outcomes, to the extent that those impacts can be assessed?

    c. What – if any – are the impacts of a fully-masked classroom (students and education workers) on these expected outcomes, to the extent that those impacts can be assessed?

    d. What – if any – are the impacts of a classroom where only the education workers are masked on these expected outcomes, to the extent that those impacts can be assessed?

e. How – if at all – do the impacts of mask-wearing differ depending on what kind of mask is being worn?

f. What – if any – are the impacts of different sizes of cohort (50 direct and indirect in-school contacts vs 100 direct and indirect in-school contacts, within a 14-day period) on these expected outcomes, to the extent that those impacts can be assessed? Please consider the impact of these cohort sizes on both students and staff.

g. What – if any – are the impacts of layering two or more of the different infection prevention and control strategies on these expected outcomes, to the extent that those impacts can be assessed?

11. From the perspective of network epidemiology, what is the potential role of itinerant workers who work at different workplaces, such as occasional teachers, professionals such as speech pathologists, or educational assistants?

12. Based on the above opinions, what is your professional opinion about the relative importance of each measure or group of measures to control for or reduce the transmission and infection of COVID-19 in a public school setting for:

    a. an elementary school?

    b. a middle school?

    c. a secondary school?

    d. a school bus?

13. Also based on the above, what is your professional opinion on the sufficiency of the health and safety measures required under the Guide measures to control for or reduce the transmission and infection of COVID-19 in a public school setting for:

    a. an elementary school?

    b. a middle school?

    c. a secondary school?

    d. a school bus?

14. Finally, in your professional opinion, what changes, amendments or other requirements would you recommend be made to the Guide in order to protect the health and safety of education workers?

Please set out your expertise as a population disease modeller and epidemiologist at the beginning of your report, and provide us with an updated CV.

Please also clearly set out any assumptions you make in responding to the below questions, as well as specifying where necessary the kind of school or re-opening approach considered.

Please also clarify what types of transmission (droplet, fulmite, or aerosolized) you have looked at in responding to each question.

Finally, please note that we may pose additional questions on masks and mask use.

We look forward to receiving your report, and are available to clarify questions or provide additional factual context as required.

Yours truly,

Ursel Phillips Fellows Hopkinson LLP

Susan Ursel
SU/EFCE/kmc

TAB 3

STATEMENT OF MY EXPERTISE AND EXPERIENCE

1. I am an infectious disease epidemiologist, and mathematical modeler with expertise in population disease dynamics, epidemics, and pandemics. I received my PhD in infectious disease dynamics from Arizona State University in 2007 and completed additional research training as a postdoctoral fellow at the Research Institute of the Hospital for Sick Children between 2007 and 2009. In 2009 I was recruited by the Public Health Agency of Canada (PHAC) as a result of my ongoing contributions to both provincial and federal pandemic response activities during the 2009 influenza A (H1N1) pandemic. Between 2009 and 2014, I held scientific positions in the Centre for Communicable Diseases and Infection Control at PHAC where I was actively involved in a number of public health related projects related to sexually transmitted infections, tuberculosis, and seasonal and pandemic influenza. I was actively involved in the federal response to the 2009 H1N1 influenza A pandemic (specifically related to public health interventions such as non-pharmaceutical, antiviral, and vaccine interventions) during this time. I began my appointment as a Canada Research Chair (Tier 2) in Population Disease Modeling at the University of Guelph in January 2014 and was awarded tenure and promoted to Associate Professor in July 2018. I also currently hold academic appointments in the Division of Epidemiology at the Dalla Lana School of Public Health at the University of Toronto, and the School of Public Health and Health Systems at the University of Waterloo. I have also provided technical input into the Canadian Pandemic Influenza Plan for the healthcare sector (CPIP), specifically the surveillance, vaccine, and antiviral annexes. My full CV is attached as Tab 1.

2. I have spent the last 17 years conducting research to explore the introduction, spread, dynamics, and control of infectious diseases in populations with a specific focus on epidemics and pandemics. I integrate empirical data with mathematical and statistical models to test the mechanisms leading to the epidemic spread of pathogens with the overall goal being to examine the effectiveness of public health interventions in order to make informed decisions regarding public health policy.

3. In the course of my scientific career I have conducted high quality ongoing research activities and have demonstrated significant scholarly activity. I have served in an independent, research leadership role since 2007 as shown in the Sections 2 & 3 of my CV. As shown in Section 4 of my CV, I have acquired independent research funding to pursue research questions, trained graduate students to conduct the research and transferred research outcomes to end users via peer-reviewed publications, presentations at scientific conferences and knowledge translation activities. As shown in Section 7 of my CV, I have been successful in transferring research outcomes from my program of research to the public and scientific community in the form of peer-reviewed publications, conference presentations, and other non-technical communications. As shown in Section 7 of my CV, I have published 75 manuscripts in high-quality, peer-reviewed journals. Twenty-two of these manuscripts relate to pandemics, and seven are specific to the dynamics of COVID-19 in Canada (Section 7 of my CV, manuscripts 68, and 70-75). Based on Google Scholar analytics, my research has been cited 1839 times (905 in the past 5 years: h-index = 22, and i10-index = 26). I also have an additional 7 papers currently under review (as shown in Section 8 of my CV). These include 1 additional paper (Section 8, manuscript 7) that describes Canadian compliance with physical distancing measures.

4. In addition to peer-reviewed manuscripts, my research program has produced 127 conference presentations and abstracts (as shown in Section 11 of my CV). These presentations occurred at conferences including the International One Health Congress, the International Conference on Emerging Infectious Diseases, and the International Conference on Network Science. I have been an invited speaker at 61 other scientific events including local events (e.g. University of Guelph Centre for Public Health and Zoonoses Symposium), national events (e.g. National Collaborating Centre for Infectious Diseases (NCCID)), and international events (International Meeting on Emerging Diseases and Surveillance (IMED)). I have also provided financial and mentoring support for 21 trainees

(including postdoctoral fellows, graduate students, and undergraduate students) at the University of Guelph and at the University of Toronto.

5. I also serve on several Advisory Boards and committees including the National Collaborating Centre for Infectious Diseases (NCCID), and the PHAC Modelling Advisory Group for COVID-19. In addition, I have served on the Federal Inuit Tuberculosis Elimination Task Force organized and led by Inuit Leadership at Inuit Tapiriit Kanatami (ITK) to provide support for the goal of eliminating (WHO definition) TB from Canada's Inuit population by 2025.

6. Based on the above assessment and further supported by additional details which can be found in my attached CV, I believe that I have demonstrated my expertise as an infectious disease epidemiologist and mathematical modeler and that I have made significant contributions in all areas of my research focus specifically in the area of outbreaks and pandemics, including with respect to COVID-19.

7. In this report, I will address a number of different questions as posed to me by counsel to the OSSTF in a letter attached at Tab 2, related to the epidemiology and disease transmission dynamics of SARS-CoV-2, the causative agent of COVID-19 with a specific focus on the Ontario population and the Ontario public education setting.

8. **QUESTION:** Can you explain from an epidemiological viewpoint the transmission and infection mechanisms, and rates of, and outcomes of infection by the SARS- CoV-2 virus, commonly referred to as COVID-19?

9. The current coronavirus (COVID-19) pandemic represents a unique challenge for public health and health care systems. One of the most useful metrics for assessing a novel virus is to understand the basic reproductive number (R0). R0 is the number of secondary infections caused by a single infected individual in a fully susceptible population. It is a measure of epidemic potential. The SARS-CoV-2 virus is highly transmissible [1,2] with an estimated average reproductive number (R0) of 2.5 (range 1.8-3.6) [3]. This makes SARS-CoV-2 more transmissible than SARS-CoV, the 1918 influenza pandemic, MERS-CoV, and the 2009 influenza A (H1N1) pandemic [3]. It also means that if transmission is unmitigated, the epidemic grows rapidly.

10. Since the initial emergence of SARS-CoV-2, the scientific community has learned much more about the possible modes of transmission of this virus and their relative contributions to the overall observed dynamics. The general consensus remains that the primary mode of COVID-19 transmission is through direct, indirect, or close contact with infected people through contact with respiratory droplets which are generated when an infected person cough, sneezes, talks, or sings [4]. These droplets (typically > 5-10 microns in size, where 1 micron = one millionth of a metre) contain virus particles which can then come into contact with the mouth, nose and/or eyes of a person who is susceptible to the virus and result in an infection. Another route of transmission related to droplet transmission is fomite transmission. This is often also called a form of indirect transmission. This refers to the case when the respiratory droplets land on surfaces and/or objects in the environment (e.g. doorknobs, railings, desktops etc.) and contaminate them with virus. These virus particles can remain on these surfaces for hours up to days. The length of time that a virus survives on a surface is related to the environmental conditions (e.g. temperature, humidity, UV exposure etc.) as well as the material that the surface is made of [4]. There is evidence that virus persistence and transmission by contaminated fomites is possible and likely plays a role in transmission but is not the dominant mode of transmission [4,5]. There has been much debate over the last 6 months about the contribution of airborne (aerosol) transmission routes. Aerosol transmission is characterized as the spread of the virus by droplet nuclei (aerosols) which are < 5 microns in diameter. These droplet nuclei can be suspended in the air for longer periods of time due to their small size and travel over greater distances [6]. Aerosol transmission is also sometimes called indirect transmission. It has been accepted that in healthcare settings, certain types of medical procedures are aerosol generating however, more recently the question has been raised about the possibility of SARS-CoV-2 spread via aerosols in non-healthcare related settings, specifically indoor settings with poor ventilation [4]. The role of aerosol spread of SARS-CoV-2 in examples of "super-spreading" events where an infected individual infects many more people than we would expect based on the average R0 has been implicated in outbreaks related to crowded indoor settings like a choir outbreak in Washington [7], a restaurant outbreak in China [8], and an outbreak associated with indoor fitness classes in South Korea [9]. Emerging data now suggests that in some types of settings, specifically in crowded indoor settings with poor ventilation where people congregate for longer periods of time, microdroplet aerosols likely contribute to SARS-CoV-2 transmission [10]. It is also important to note, that the RNA from SARS-CoV-2 has also been detected in other biological samples, including the urine and feces of some patients [11,12] . To date, however, there have been no published reports of known transmission of SARS-CoV-2 through feces or

urine. Therefore, it is the case, that droplet transmission, aerosol transmission, and fomite transmission contribute to the observed transmission dynamics of SARS-CoV-2.

11. SARS-CoV-2 is the causative agent of COVID-19. The virus causes moderate to severe illness in approximately 20% of cases [13]. Children younger than 13 years of age are more likely to have a higher proportion of asymptomatic infection than adolescents or adults [14,15]. In addition, one of the more challenging aspects of COVID-19 biology is the contribution of pre-symptomatic transmission. Pre-symptomatic transmission is defined as transmission from an infected individual (source) to another (secondary) individual before the first (source) individual has developed symptoms and it can range from 1-2 days before symptom onset [16]. The proportion of infections that occur prior to symptom onset or by asymptomatic transmission is a critical component related to our ability to control an infectious disease outbreak. When this value is high (as is the case for COVID-19), disease control becomes more difficult [17]. A population wide cohort study was conducted in Ontario to examine sex-specific differences in COVID-19 testing, cases, and outcomes using data from all Ontario residents who received a nasopharyngeal swab for SARS-CoV-2 between January 23, 2020 and April 28, 2020 [18]. In general, hospitalization rates in Ontario were higher in men than women and rates increased with age [18]. An additional Ontario study using the same dataset drawn from the Ontario integrated public health information system (iPHIS), examined factors associated with mortality for individuals diagnosed with COVID-19 in Ontario between January and May, 2020 [19]. This study demonstrated that age and co-morbidities (specifically, diabetes, renal disease, and immune compromise) were strong predictors of mortality [19].

12. **QUESTION:** What does the term “cohort” mean to you?

13. In the case of COVID-19 and school re-opening plans, many different documents use the term “cohort” to refer to a group of individuals in different ways that are not in the original “spirit” of the term cohort and how it is used in infection prevention and control.

14. The Merriam-Webster dictionary defines a cohort as 1) a group, or 2) as a group of individuals having a statistical factor (such as age or class membership) in common in a demographic study. While the common definition does not specifically indicate the size of the group, the infection prevention and control literature often uses the term “cohort” to describe a smaller subset of individuals from within a larger group. The term is often used to refer to the assignment of dedicated staff to a smaller subset of patients within a hospital ward as a way to reduce the potential for the transmission of an infectious pathogen within a hospital setting or to interrupt ongoing transmission as one might see in a hospital outbreak. It specifically relates to the formation of a small group of individuals who could be at risk of exposure by treating them as a small “unit” or cohort as a way to limit further or more widespread transmission. The term cohort also applies to staff. For instance, staff cohorting in a healthcare setting refers to the assignment of a specific healthcare provider to care for/have contact with only a single small “cohort” of patients. Staff cohorting can be used to limit the number of staff interacting with a small group of patients in order to reduce the potential for transmission of a pathogen between cohorts (Figure 1).

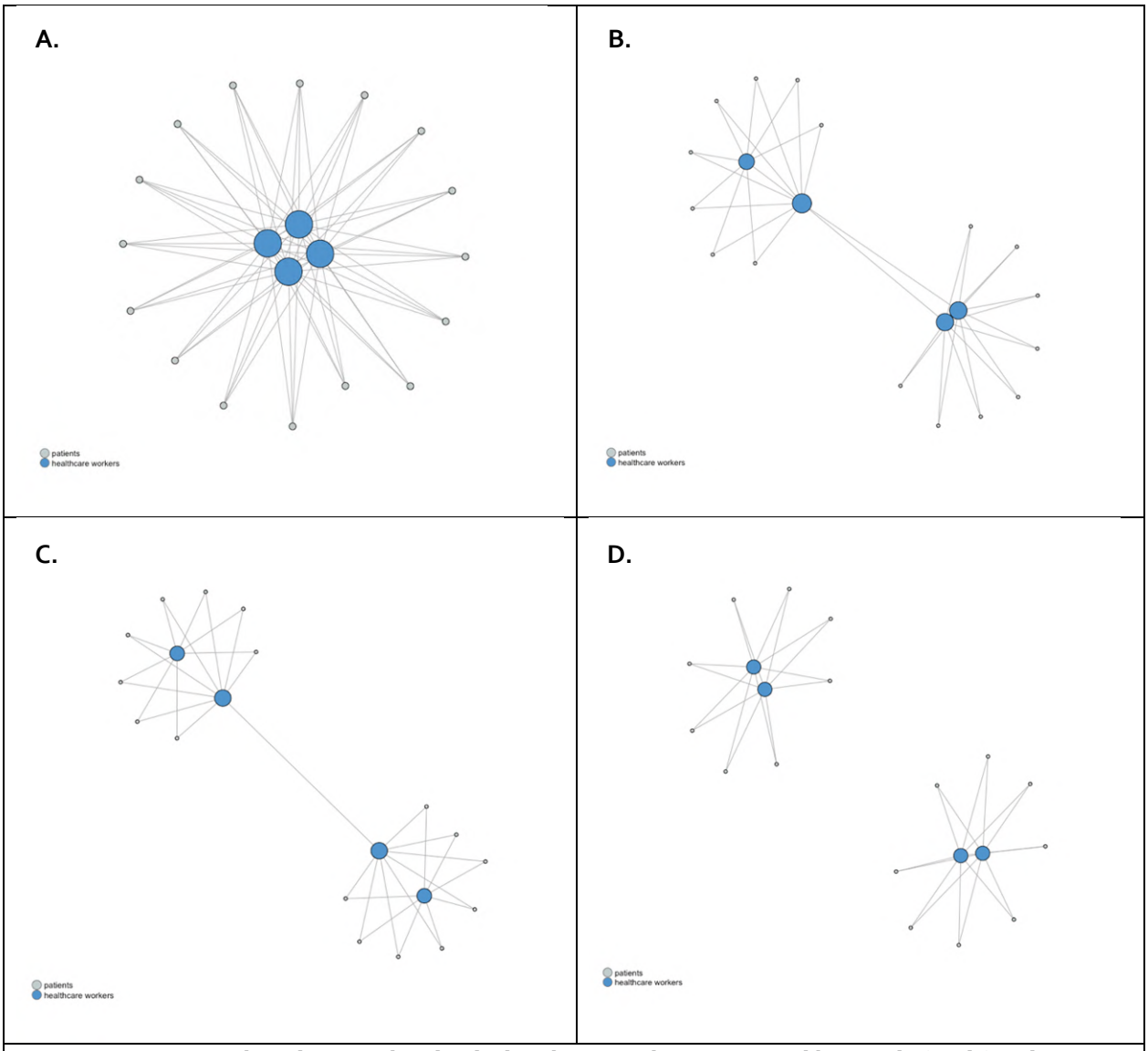

FIGURE 1: In network analysis, each individual in the network is represented by a node (circle) and contact between individual nodes is represented by edges (the lines between nodes). The degree of a node (sometimes called degree centrality) is a count of the number of unique edges that are connected to it. Each panel assumes a hospital ward with 16 patients (grey) and 4 healthcare workers (HCW: blue). We also assume that patients do not have direct contact with one another and only come in contact with the HCW. The node (circle) size in each panel is scaled by the degree metric so larger nodes represent individuals in the network who have more contacts than others. **Panel A**, all 4 HCW care for all 16 patients so HCW have a higher degree (more contacts with patients and other HCW). **Panel B**, HCW are now "cohorted" to smaller groups of patients so the same two HCW only have contact with the same eight patients and do not provide patient care duties to patients in the other cohort. However, the HCW are not cohorted among themselves and so social contact between HCW results in bridge contacts which presents an opportunity for disease transmission between the cohorts. **Panel C** is the same as Panel B but in this case the bridge HCW only has contact with one of the HCW from the other cohort. **Panel D** represents the protective effect of true cohorting between the groups. In this case, HCW have a higher number of contacts (higher degree) but because there is no contact between the groups, if SARS-CoV-2 was introduced to one of the cohorts fewer people would be exposed and the maximum outbreak size would be reduced as there is no bridge to permit the pathogen to spread into the other cohort.

15. In this case, a healthcare worker would be primarily responsible for a small cohort of patients and would have little to no contact with patients or staff from other cohorts. We can view this from the perspective of network epidemiology, where structuring the patient/staff groups into small cohorts means that the network is more fragmented and so the transmission potential of a pathogen is limited as it would not be able to spread between cohorts given an introduction. As soon as we permit any movement or overlap of individuals (e.g. a staff member who interacts with 2 different cohorts of people), you create a transmission bridge between the cohorts which makes it possible for the pathogen to spread much more widely (Figure 1). The goal of "cohorting" is ultimately to reduce the overall number of contacts that any one individual has with other people while at the same time reducing the number of "bridges" that could act to connect otherwise distinct groups or cohorts.

16. When we're thinking about schools, this approach to "cohort" means you cohort an education worker with a smaller group of students, and they only interact in this group. This reduces the number of contacts every individual in the cohort has and therefore reduces the risk of exposure. It is also very important to consider that educators should also be cohorted as well. In this way, direct, in-person close proximity contacts would be minimized between educators with "professional" cohorts of staff in addition to "learning" cohorts that include students. School wide meetings should still be conducted remotely in order to minimize staff contacts. Cohorting in the true sense of the word is also helpful because by creating smaller cohorts of students within the same physical space you concurrently provide improved opportunities for physical distancing within the cohort which reduces the risk of transmission within the cohort given an introduction. It should also be noted that in response to increasing COVID-19 community transmission the Ontario Provincial government announced on September 19, 2020 that they would be reducing private gathering limits to 10 people indoors and 25 people outdoors.

17. It should also be noted, that in July, 2020 the Ministry of Education published the Operational Guidance during COVID-19 Outbreak – Child Care Re-Opening (Version 2) [20]. In this document it outlines a requirement to cap childcare cohorts to 15 children and it also states (on page 6) that although staff are not included in this number they should be considered a part of the cohort that stays together [20]. In late August, 2020, the Ministry updated their Guidance document for child care settings in Version 3 of the document [21]. The revised document from August specifically states that one of the changes to the document is a revised cohort size to maximum group sizes set out under the Child Care are Early Years Act, 2014 (CCEYA) as of September 1, 2020 [21]. Specifically, the updated guidance document now lists maximum child care group sizes on page 8 that exceed the previously documented maximum of 15 children [21].

18. **QUESTION:** How do you understand the term "cohort" to be used in the Guide to Re-opening Ontario's Schools?

19. The term "cohort" is used in the Guide to Re-opening Ontario's Schools as per the Merriam-Webster dictionary definition where it refers to a group of individuals with something in common. In this case, the commonality is that the "cohort" is a group of students who are all students in the same class (this applies to both elementary and secondary schools). On page 3 of the Guide, it states that elementary students will remain in one cohort for the full day. In this case it refers to all of the students assigned to the class. It further states that the "cohorted" classes will stay together with one teacher, where possible. On page 7 of the Guide, it states that "cohorting refers to the practice of keeping students together in a small group throughout their school day, with limited exposure to multiple teachers or a wide variety of classmates". In the current implementation of the Guide in Ontario schools, this is not true. Elementary cohorts do not in fact, refer to small groups of students but rather to regular class sizes and therefore, students have the exact same number of exposures to the number of classmates they would have encountered on a typical school day in their pre-pandemic classroom. For the

Secondary school setting, as described on page 4, it does appear that in "designated" boards that open with an adapted model, the term "cohort" is used in a way that is more in line with infection prevention and control in that class cohorts will be reduced to approximately half the per-pandemic class size (so 15 students in a class cohort rather than 30 students as may have been the case pre-pandemic). In this situation, the "cohorting" of students into smaller groups seems to be implemented in a way that would result in a more limited number of student-to student contacts compared to the pre-pandemic case. However, many secondary schools in non-designated boards are returning to pre-pandemic class sizes that will not reduce the number of exposures that students have within a class and in fact, secondary students in all boards will participate in multiple classes in a single day (and therefore be members of multiple class cohorts and have contact with multiple educators). This means that these classes effectively become a single "cohort" making risk of disease transmission between the groups higher than if they were fully distinct.

20. It becomes confusing because the government is using this term in the Guide in a way that now refers to each individual classroom a cohort, but it really goes against the original use and intention of the word as it is intended in infection control. Cohort means creating a smaller group of individuals in order to reduce the overall number of contacts compared to the pre-pandemic period. If you have the same number of students in a classroom and one teacher (the same as pre-pandemic school), that is not a cohort. That is using the terms cohort and class interchangeably. A class or classroom is not functionally a cohort because it does not reduce the number of pandemic contacts/exposures that a student would have compared to the pre-pandemic setting.

21. **QUESTION:** What is population disease modelling?

22. Population disease modelling is a methodological approach to the study of the introduction and spread of an infectious pathogen within a population. The field is highly interdisciplinary drawing on methods and analytical tools from mathematics, statistics, public health, biology, medicine, and computer science. A mathematical model is a virtual experiment set up to test a hypothesis. It creates a controlled environment where complex relationships between biological, environmental, demographic and behavioural factors can be represented using mathematical constructs.

23. In public health, we are tasked with making decisions about what sort of public health policy will be most beneficial. In an ideal world we would evaluate interventions by measuring the effects directly. However, often times that is just not feasible for a variety of reasons (and certainly not in a pandemic). In this case, mathematical modeling/population disease modeling can be a useful tool for describing a complex system and putting what we know about the natural history of COVID-19 into a mathematical framework, running computer simulations to examine a wide range of "what if" scenarios and then communicate those findings to decision-makers who can use them to help inform the discussion of the next best steps in terms of planning, programs and policies.

24. **QUESTION:** What is network epidemiology?

25. Contact networks (sometimes called social networks) directly influence the opportunities for a pathogen such as SARS-CoV-2 to transmit within a population. The connections that exist between individuals within the population represent a "roadmap" of sorts on which the pathogen is able to travel between different people within the population. For a pathogen such as SARS-CoV-2, which is transmitted by close contact and/or droplets from person to person, the network or web of contacts forms the network structure upon which the pathogen can spread. Network epidemiology is then the study of the relational ties among members of a single bounded community (in this case a school/educational setting) and the networks serve as epidemiological tools to describe the interactions that take place within the population.

26. **QUESTION:** How does network epidemiology relate to the question of assessing the health and safety of education workers in the context of school re-opening in Ontario, during the COVID-19 pandemic?

27. The health and safety of education workers in the context of school re-opening in Ontario depends directly on their "position" in the contact network. Individuals who have a larger number of contacts either with students and/or other staff are at increased risk of being exposed to SARS-CoV-2 during the work period compared to individuals who have very few contacts (Figure 2). In addition, the location of the education worker in the network is also a critical component. Staff who move between groups of individuals/classes/cohorts act as bridges in the network, connecting groups that would not otherwise be connected which generates increased opportunities for the pathogen to spread more widely in the network as a whole (Figure 2). It is also important to clarify the meaning of the term "contact". For pathogens that are primarily transmitted via respiratory droplets we assume that a potential transmission event is possible if individuals are within 2 m of one another. In studies that collect network based data from individuals for the purpose of quantifying "direct contact" the definition in most studies is that this is contact between individuals where you speak directly to the other person or physically touch them (so it would not include passing someone on the sidewalk or having a video conference with someone) [22,23].

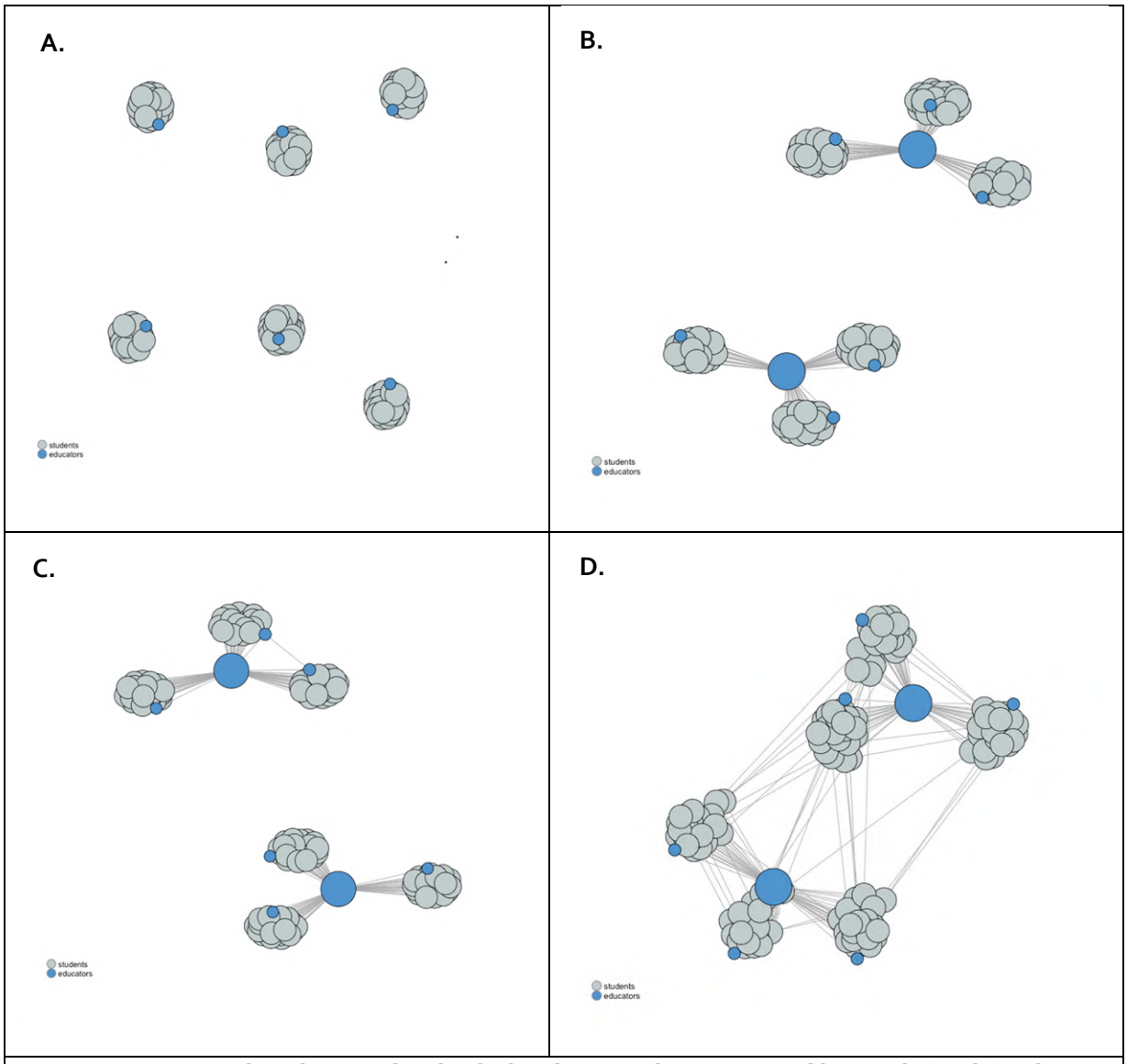

FIGURE 2: In network analysis, each individual in the network is represented by a node (circle) and contact between nodes is represented by edges (the lines between nodes). The degree of a node (sometimes called degree centrality) is a count of the number of unique edges that are connected to it. The node size in each panel is scaled by the degree so larger nodes represent individuals in the network who have more contacts. **Panel A.** assumes six classes with 23 students (grey) and 1 classroom teacher (blue). Classes are assumed to be an exclusive "cohort" (no contact with anyone outside of the class group) and 2 French teachers. French teachers have no contact with anyone else so their degree is 0 so those nodes are very small. Student nodes are large since each student has contact with 23 other students and a classroom teacher. **Panel B**, each French teacher teaches 3 different in-person classes in a day. The French teacher degree metric is now much larger because these educators have contact with 3 classes of students and their teachers. The French teachers now bridge the 3 class cohorts they are associated with. **Panel C** is the same as Panel B but in this case one of the classroom teachers has contact with another classroom teacher from a different cohort and adds an additional bridge to the network **Panel D** represents the 6 class network assuming that 15% of the students ride a bus and therefore by virtue of belonging to a bus "cohort" they have contact with students from other classrooms during their trip to and from school. If SARS-CoV-2 was introduced to the network in Panel D, there is greater potential that the virus could spread between the classes because the network is more connected. Fragmentation is protective and reduces the chance of large outbreaks. It is clear that as we move from Panel A to D that fragmentation of the network decreases.

28. **QUESTION:** From the perspective of network epidemiology, what is the goal of physical distancing?

29. The implementation of physical distancing measures has been shown to reduce the overall incidence of COVID-19 in the community [24]. In both healthcare and non-healthcare settings, physical distancing of less than 1 metre was associated with a 12.8% chance of transmission, compared to 2.6% where 1 metre or more of physical distance was maintained [25]. The protection afforded by physical distancing might double for every additional metre of distancing [25]. In situations where individuals are in a high-occupancy, indoor setting for a prolonged period of time, a 2-metre distance is recommended [26]. The classroom is an example of such an environment. In the community, the current standard in terms of messaging from the Public Health Agency of Canada as well as Public Health Ontario is that individuals should maintain 2 metres of physical distance from non-household/bubble members regardless of the location, occupancy level, or duration of time (e.g. grocery shopping, or picking up a prescription at the pharmacy). In addition, many other school reopening guidance documents including the document from the Harvard School of Public Health specifically, state that 2 metres/6 feet of distance should be maintained[27].

30. The goal of physical distancing is to reduce the number of "close proximity" contacts that an individual has with any other individual outside of their household/social bubble. The contact rate is a key driver of the metric that we use to assess epidemic potential (R0: which is defined and discussed in Section 9). Reducing the contact rate in the population reduces the reproductive number which means that the epidemic slows (e.g. moving towards a slow burn dynamic instead of an epidemic growth dynamic). For this reason, physical distancing is an important component of any infection prevention and control strategy for a school setting. Specifically, physical distancing reduces the intensity and frequency of exposure[27]. Figure 1 from the COVID-19: Guidance for School Reopening outlines the Hierarchy of Controls adapted from the CDC [28]. Physical distancing is placed in the engineering control category making it a more effective intervention than PPE and administrative controls (Figure 3). In terms of network epidemiology, reducing the number of close proximity contacts, acts to fragment the network. Increasing network fragmentation creates "breaks" or barriers in the network which limits the ability of a pathogen to spread (Figure 2).

Figure 1. Hierarchy of Controls (Adapted from CDC)[59]

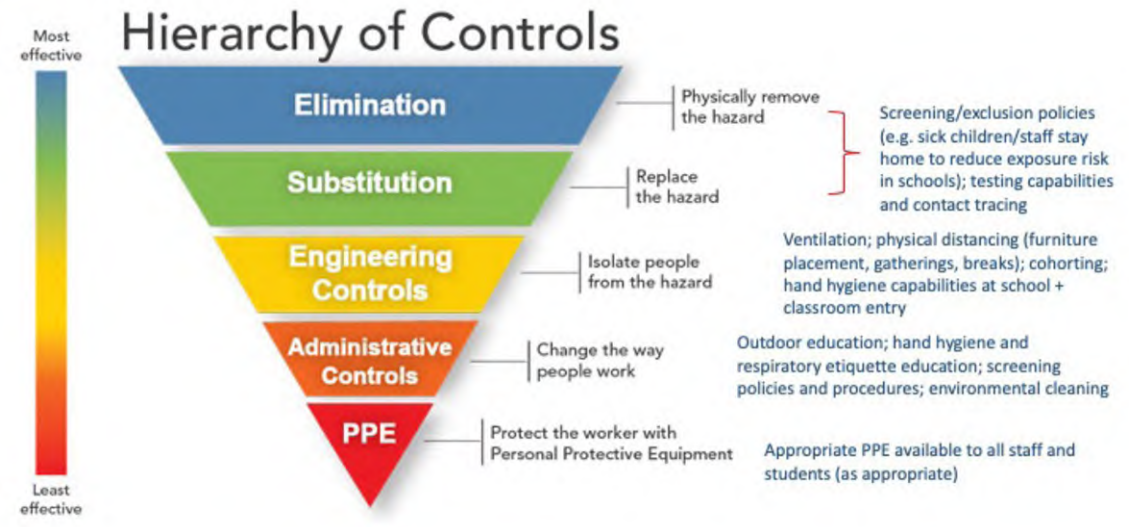

FIGURE 3: The Hierarchy of Controls is an approach to controlling exposures to occupational hazards and is the fundamental method of protecting workers. Traditionally, a hierarchy of controls has been used as a means of determining how to implement feasible and effective control solutions. This approach forms the basis of infection prevention and control strategies.

31. **QUESTION**: From the perspective of network epidemiology, what is the goal of mask use? Does that differ with different kinds of masks?

32. The main purpose of wearing a mask is to reduce exposure intensity to people nearby. Masks help reduce the probability of a transmission event occurring given a sufficient close proximity contact. This is why masks are required in many public spaces and especially when 2 metres of physical distance is not possible to maintain. The other important reason for mask use is related to the issue of pre-symptomatic transmission of SARS-CoV-2 [14,17]. When infected individuals are able to transmit their infection to others before they develop symptoms, adding masks into our public health intervention toolbox can help to reduce the probability of a transmission event occurring when the infected individual is unaware of their infection status.

33. Again, mask use reduces the probability of transmission given a contact which directly impacts our metric of epidemic potential, R0. In fact, even imperfect mask use has the ability to reduce the reproductive number [29]. In our recent paper published in July 2020, we have demonstrated that even imperfect mask use can have significant impacts on reducing SARS-CoV-2 transmission but that uptake needs to be fairly universal to have a significant effect [29].

34. It is important to remember that there are different types of masks (medical masks and non-medical masks). Due to the potential for shortages of medical masks during the pandemic, members of the public engaging in activities in the community for short periods of time have been encouraged to use non-medical face coverings made out of a double layer of tightly woven cotton. Not all non-medical masks are the same. The major difference between a medical mask and non-medical mask is that a

medical mask has been specifically tested to meet a number of specifications related to the risk of "acquiring" a pathogen.

35. A non-medical mask (homemade double layer cloth mask or paper mask like you might buy at a retail store) prevents droplets from the "wearer" from spreading to others nearby or having those droplets land in the environment and contaminate surfaces. This is the primary purpose of a non-medical mask (to protect others from the wearer's droplets). This form of control is often referred to as "source control". It differs from a medical mask which provides source control but also provides some protection to the wearer. Health Canada specifically says, "…non-medical masks or face coverings have not been tested to meet any standards. Although encouraged, wearing a non-medical mask or face covering is not a substitute for physical distancing and hand washing". Health Canada also says, "…face coverings may not protect the user from external respiratory droplets. As well, the filtration capability of a face covering depends on factors such as design, seams, material, layering and shape"[30]. So, a non-medical mask helps to protect others within 2 m of you but has little benefit in terms of necessarily protecting the wearer.

36. Medical masks come in different forms. Although some of them look similar to a paper "surgical" mask that can be purchased by the public, a medical surgical mask and alternatively a medical respiratory (N95) mask are in fact regulated by Health Canada as medical devices and so have quite specific requirements. Medical masks reduce the risk of or prevent the user from potentially contracting a pathogen (SARS-CoV-2). A medical mask is regulated as a Class 1 medical device. According to Health Canada, a medical mask that is regulated as a Class 1 medical device is able to make medical claims or representations include the following statements:
    - to protect the user from contracting COVID-19
    - for anti-viral or anti-bacterial protection (for example, contains a drug or biologic)
    - for use as a medical mask
    - to provide liquid barrier protection
    - designed as a respiratory protective device (for example, used for particulate filtration)
    - for use in high-risk aerosol generating medical procedures (e.g. N95).

37. All medical masks, regulated as medical devices, must meet specific international standards for Class I medical devices, such as ASTM F2100 (American Society for Testing and Materials). The ASTM biological subcommittee develops and maintains standards that are meant to protect healthcare workers or the healthcare environment from biological hazards that can cause infection. These standards include requirements for bacterial filtration effectiveness, and may include specifications for particle filtration efficiency, flammability and fluid resistance.

38. As per Health Canada, labelling for medical masks in Canada must contain clear statements on their intended use (for instance, the purpose for which the device is manufactured, sold or represented) **and** specific performance specifications for their proper use (for example, filtration efficiency and fluid resistance). Medical masks must come with bilingual labelling, either on the packaging or with the device itself.

39. When we are talking about medical masks, we are not talking about a respirator type medical mask (otherwise known as an N95). An N95 respirator mask would not be necessary in a school setting since they are only necessary for aerosol generating medical procedures which include things like intubating a known COVID-19 patient in a hospital setting. In addition, an N95 respirator requires annual fit-checking by a qualified Infection Prevention and Control specialist to check for fit and sizing for every individual. N95's come in different sizes and there are specific requirements about individual fit etc. (e.g. you cannot wear a properly fit N95 if you have a beard).

40. In terms of non-N95 masks, these do some with slightly different performance levels as described by the American Society for Testing and Materials (ASTM) related to things like level of bacterial filtration, and resistance to penetration by synthetic blood [31]. ASTM describes non-N95 medical masks as having 3 different levels. To the extent that I have been able to gather information about the specifics of these levels, it appears that the primary difference between levels 1,2, and 3 are primarily based on increasing levels of fluid resistance. In a school setting, it is possible that some educational workers who work with very young children or children with special needs who require assistance with toileting etc. may be at risk of coming into contact with bodily fluids. In my opinion, it seems likely that a medical mask of level 1-2 would be appropriate for most educational workers but that a level 3 mask with additional fluid resistance could be necessary for some. Interestingly, it is the case that none of the current guidance available on this topic from the WHO or PHO specifies or distinguishes between the different ASTM levels. They only refer to "medical masks.

41. **QUESTION**: From the perspective of network epidemiology, what is the goal of wearing PPE (such as gloves and face shields)?

42. In Figure 3, it is important to note that personal protective equipment (PPE) appears at the bottom of the Hierarchy of Controls meaning that out of all of our infection prevention and control measures it is the least effective. It is essentially the last resort/last layer of protection. It is assumed that all of the more effective interventions (like elimination, and engineering controls) have already been implemented to the highest standard which provides the greatest reduction in overall risk. There are many different types of PPE including medical and non-medical masks. There are some fundamental differences between medical masks and non-medicals masks. Medical masks have additional claims that they are able to make related to their safety testing so that a medical mask that is a regulated medical device serves as both "source control" as well as personal protection. A non-medical mask can make no claims related to personal protection. Further details about masks are outlined above in Sections 32-40.

43. Other PPE includes gloves, and face shields/googles/eye protection. It is my opinion that easy access to opportunities for hand hygiene (either through hand washing using soap and water or using an alcohol-based hand rub) is a much better approach to infection prevention and control than wearing gloves. Gloves (latex, vinyl, and/or nitrile) are meant to be single use PPE such that an individual in a healthcare setting would don a pair of gloves for a specific purpose and then doff the gloves as a single use item followed by hand hygiene. In a non-medical setting, it tends to be the case that many individuals wear gloves for prolonged periods of time and touch many different surfaces and items. In this case, gloves do not reduce the possible transmission of the pathogen and in fact gloves are not recommended by the WHO, PHAC, or CDC for use unless an individual is directly caring for an infected individual [32] . There may be some instances in which an education worker might require gloves for a specific tasks (such as cleaning with an approved cleaner to protect the skin on the hands, or when performing personal support services for their students such as toileting) but in the course of a regular day, providing easy access to hand hygiene opportunities is the preferred method of reducing opportunities for transmission of the pathogen via the hands.

44. There is evidence that respiratory droplets and aerosols can infect an individual through the eye [33]. This is also the reason for the guidance to not touch your eyes, mouth or nose so as to not transfer potentially infectious virus from your hands to your face. As a result, the use of eye protection such as goggles or face shields as part of the standard personal protective equipment in addition to the wearing of masks should be the standard and in fact, is the current standard for all Ontario childcare settings under the COVID-19 guidelines [20]. On page 7 of the Guide to reopening Ontario's schools it states that "Medical masks and eye protection…will be provided…" However, it does not specifically

state that eye protection is required. It is my professional opinion that eye protection in the form of glasses, googles, or a face shield should be required for all educational workers.

45. **QUESTION**: What is the risk that a COVID-19 infected individual (student or staff) will enter a school setting on any given day?

46. The risk of importing/seeding an infected individual into a school setting is going to vary regionally. The calculation of this risk depends on the amount of community transmission that is happening. My colleague, Dr. Ashleigh Tuite (Dalla Lana School of Public Health, University of Toronto) has made a publicly available app (https://art-bd.shinyapps.io/school_entry/) that estimates the probability that an individual who has contracted COVID-19 in the community would attend a school setting (either as a student or staff member).

47. As an example, I pulled the numbers for my own health unit (Wellington, Dufferin, Guelph Public Health: WDGPH) and our local school boards (Upper Grand & Wellington Catholic) recognizing that the boundaries likely don't overlap perfectly with the public health boundaries and that staff might actually live elsewhere. I was unable to find student of staffing information for the French board but this gives you an idea of how the calculations work so I think it is still a reasonable approximation since the public and catholic boards represent the largest number of students in the area.

48. Basically, what the calculation does is take the number of confirmed cases within the health unit (over the past 7 days) broken down by age (caveat: I pulled these numbers on July 30, 2020 so they are out of date but give you an idea). On July 30, 2020, WDGPH was reporting on average 1.04 cases/day (so 15 cases over the 7 day period). One of these cases was in a child between 10-18 years of age (7% of all reported cases). The health unit population size is 284,460 people and 24% of the population is school aged. In our region, we have ~42,982 students and there are ~6,250 adult staff (teachers, principals, V/P's, ECE, EA's, support staff etc.) within these 2 school systems. I pulled all of these numbers from the board statistics which are publicly available.

49. If we use these numbers and assume that there is some level of underreporting in the community we find that even with low community transmission, in this population, the risk is 75% that 1 or more infected individuals will turn up at a school on any given day (not each school but across all schools within these 2 boards given our population size and community transmission). This assumes that for every case identified through testing there are 3 more that are not identified. I have also assumed that we have a full return to in-person, face to face classes.

50. The most important take home message is that low community transmission is a critical component of keeping schools as safe as possible. This app does not have the ability to project what happens once the infected individual is in the school setting so makes no further predictions about within school spread. However, it is important to consider that physical distancing, smaller educational cohorts of students and smaller professional cohorts of staff, combined with mask use will act synergistically to reduce the risk of transmission within schools when an introduction occurs and contribute to minimizing the risk of that individual spreading their infection to other students and/or staff within the school.

51. The first line of defense in our infection prevention and control is to keep COVID-19 out of schools by keeping community transmission low, as it reduces the chance that an infection acquired in the community will be imported/seeded into a school setting. On September 18, 2020 the province of Ontario reported 407 new laboratory-confirmed cases of COVID-19. This clearly indicates that community transmission is increasing and not decreasing or remaining stable.

52. Figure 4 shows the Ontario case counts (as of September 13, 2020) with the cases back dated to their estimated date of infection (x-axis). In each panel, there are 2 lines of data with one representing GTA cases (red) and the other representing cases from outside of the GTA (blue). There are 3 panels in Figure 4. The far-right panel shows cases associated with known outbreaks. Outbreaks are defined as 2 or more laboratory-confirmed cases that are epidemiologically linked within a 14-day period. The peak in the outbreak panel represents primarily cases associated with long term care outbreaks as well as other occupational workplace outbreaks in spring 2020. As of September 13, 2020, the data do not show an increased number of cases resulting from known outbreaks. The middle panel is labelled "Not outbreak" and represents laboratory confirmed cases that are not associated with an outbreak setting. This means cases acquired in the community and these case counts are clearly beginning to rise and show an upward trend both inside and outside the Greater Toronto Area (GTA). The first panel is all of the cases combined (outbreak and non-outbreak).

53. The probability of importing a case to a school increases as community transmission increases so these data suggest that in the coming weeks, we will continue to be challenged by increasing rates of community transmission which increases the number of school importations we would expect to see. In addition, per-test positivity (Figure 5, bottom panel) is also increasing and most rapidly in the 10-29-year age groups which includes some school aged children. Both of these indicators suggest that the risk for school importations is higher than it was in August or July, 2020 and there is no indication that the trend is slowing.

54. In referring back to the Hierarchy of Controls (Figure 3), we see that the most effective intervention for reducing risk in the school setting is to eliminate the hazard by screening students and staff and having individuals with any symptoms stay home. However, in the case of COVID-19 the effectiveness of screening in children is hampered by the fact that many children will show very mild or no symptoms at all and yet can still be infectious to others. In addition, even for people who do develop symptoms, they are infectious to others for 1-2 days before those symptoms appear making strict compliance with physical distancing, hand hygiene, and masks even more important.

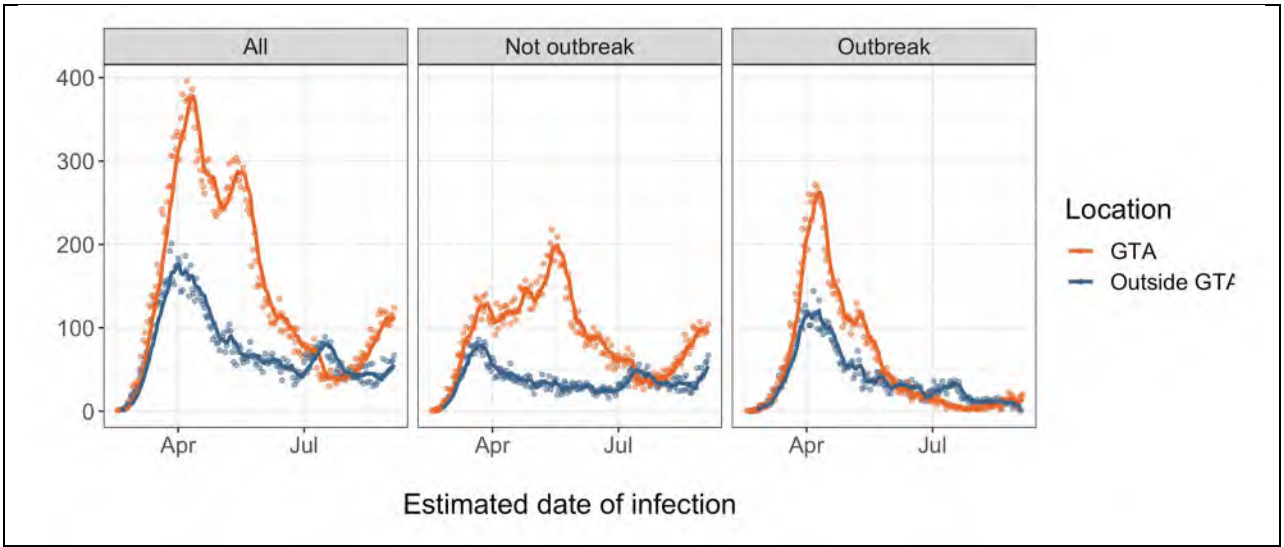

Figure 4. Data from the Ontario integrated Public Health Information System (iPHIS) as of September 13, 2020 showing that community transmission of COVID-19 is increasing in both the GTA and outside of the GTA.

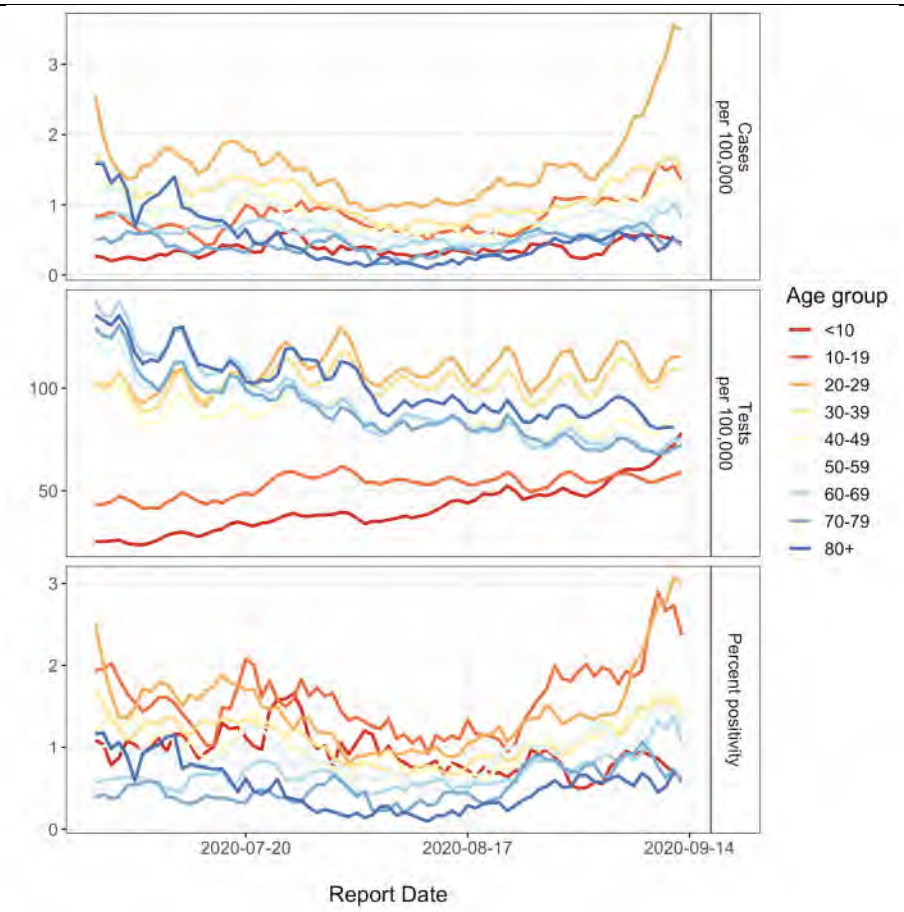

Figure 5. Data from the Ontario integrated Public Health Information System (iPHIS) as of September 13, 2020 showing that the number of laboratory tests per 100,000 population (middle panel) is increasing for school aged children (and this is from a period before schools were fully opened). In addition, per-test positivity has sharply risen in the 10-19 age group.

55. **QUESTION:** What sort of outcomes might we expect if a COVID-19 infected individual transmits their infection within the school setting? For each response, is it possible to visually represent the outcomes, using for example a network epidemiology diagram?

56. If a COVID-19 infected individual transmits their infection within the school setting we might expect somewhat different outcomes depending on a number of factors. The first factor is related to the amount of time this person spent in the school setting during their infectious period. Public Health would work to identify (based on speaking with the laboratory-confirmed case) when the cases infectious period may have started and then look at the school schedule to identify if the person had attended school during the infectious period (this includes the 1-2 day pre-symptomatic period) and if so for how long. The next step would be to identify all of the other people in the school and/or bus who had exposure to the confirmed case during the infectious period. We would then want to evaluate the potential transmission risk for each of the possible exposures. For instance, a short exposure of the infected individual to a susceptible individual in an outdoor setting with physical distance of 2m or more would be considered a low risk exposure. However, a long duration indoor contact that occurred without 2m of physical distance would suggest that person would be at much higher risk of having contracted the virus. The goal of all interventions is to minimize the total number of susceptible people who would be considered a “high-risk” contact.

57. We can think a bit more about the possibilities that exist when an infected individual is introduced into a school network by referring back to Figure 2. If you were to introduce an infected individual randomly into Figure 2 panel A, where each cohort is comprised of 23 students and 1 educator and that group has no contact with any other students or staff, the number of possible transmission events has an upper bound of 23 within the school setting (e.g. in the worst possible scenario an infected individual could transmit to everyone in the cohort before they were identified as infected and the infected individual removed from the group and the remainder of the group dismissed to self-isolate for 14 days). This would be pretty unlikely because the goal is to reduce possibilities for transmission to occur with the addition of the Hierarchy of Control measures of physical distance, hand hygiene, and masks help to minimize the chance that we get such a large chain of transmission. This does not really however represent a complete upper bound because it remains possible that an infected individual from the cohort could transmit to their household and/or bubble resulting in additional, epidemiologically linked cases.

58. When we compare this outcome with the outcomes possible in Figure 2 Panel D, it is clear that additional opportunities for transmission exist in Panel D and transmission opportunities are not confined to any one cohort of individuals. The overlap of bus cohorts with class cohorts combined with staff interactions and teachers who teach across multiple class cohorts means that the final outbreak size in Panel D could be much larger than in Panel A (and again, this does not consider the possible transmission events in households when these students and staff go home).

59. **QUESTION:** What – if any – are the impacts of different class sizes on these expected outcomes, to the extent that those impacts can be assessed? Please specify what class sizes you considered.

60. Class size directly impacts the ability of a school to maintain appropriate physical distancing between students, staff, and students and staff. Higher class sizes combined with limited classroom space means that it is impossible to maintain the recommended 2 m of physical distance to ensure the safest possible return to school for students and staff. It is also the case that in the Guide for Reopening Ontario's Schools that the document states that, "Desks should face forward rather than in circles or groupings". If we consider this to be the case and are interested in seeing the impact of adjusting class sizes (by making smaller "cohorts" of students) we can generate architectural diagrams to visualize the impact on physical distancing.

61. For example, let's assume that the physical floor space of an average portable classroom is 9.8 m by 7.2 m and that there is a standard size for a single elementary school desk and a single secondary school desk (with secondary desks being slightly larger). All student desks will be facing forward (as required by the Guide) and we will assume a best-case scenario which is that the classroom has no built-in features or furniture that cannot be removed so that the entire classroom floor space is useable. It is easy to see that 2 m of physical distance between students and between students and the educator is impossible (Figure 6).

62. These illustrations clearly outline and visually convey support for the fact that the necessary level of physical distancing (2 m) is not possible in an average Ontario school elementary (Figure 6) or secondary school (Figure 7) classroom if class sizes are not reduced. This means that students have a high number of close proximity contacts within their individual class.

63. In designated secondary school boards, the class/cohort size cap of 15 students seems sufficient to achieve appropriate distancing between students and therefore reduce risk to educators. However, in the modified scheduling in the secondary system it is still the case that these secondary students could be part of 2 different classes/cohorts of 15 which likely negates the benefit of the reduced class size in this case, if there are different students to some degree in each class.

64. Another way to examine the impact of class size reductions and the impact that they might have on the risk of transmission within a school setting would be to explicitly examine this question using dynamic infectious disease models. There have been two research projects recently completed that have looked at this question. At this time, neither of these papers have been peer-reviewed. However, these are highly regarded scientists that I know professionally from University of Guelph, University of Waterloo, University of Maryland, Harvard University, and Stanford University. I am confident in their approach and the interpretation of their findings as an expert in this area of research. The findings of these 2 projects are as follows:

65. A new pre-print manuscript by Philips et al. (under review) examines model-based projections for COVID-19 outbreak size and student-days lost to closure in Ontario childcare centers and primary schools [34]. This computer simulation model examined projected outbreak size and student-days lost due to closures in Ontario childcare centers and primary schools. For the purpose of my comments here, I will focus on their approach and findings for schools only (although obviously many schools have childcare centers on site and students attend before and after school programs at these locations which makes it impossible to really fully separate these two types of settings). In the model, they look at the impact of modifying class sizes by examining the impact of different student to educator ratios (30:1, 15:1, and 8:1) including "cohorts" that alternate weekly. In the model, SARS-CoV-2 can transmit in classrooms, school common areas, and also in households where the children and staff live. The model assumes that if a symptomatic individual appears in a classroom, that the class is dismissed for 14 days (this is in line with the current ON public health guidance around management of cases). The authors of the work consider both a high transmission rate scenario (which assumes a "business as usual" scenario with minimal public health interventions in place) and the low transmission rate scenario represents highly effective infection control in the school setting (e.g. consistent use of highly effective masks, social distancing, and disinfection protocols).

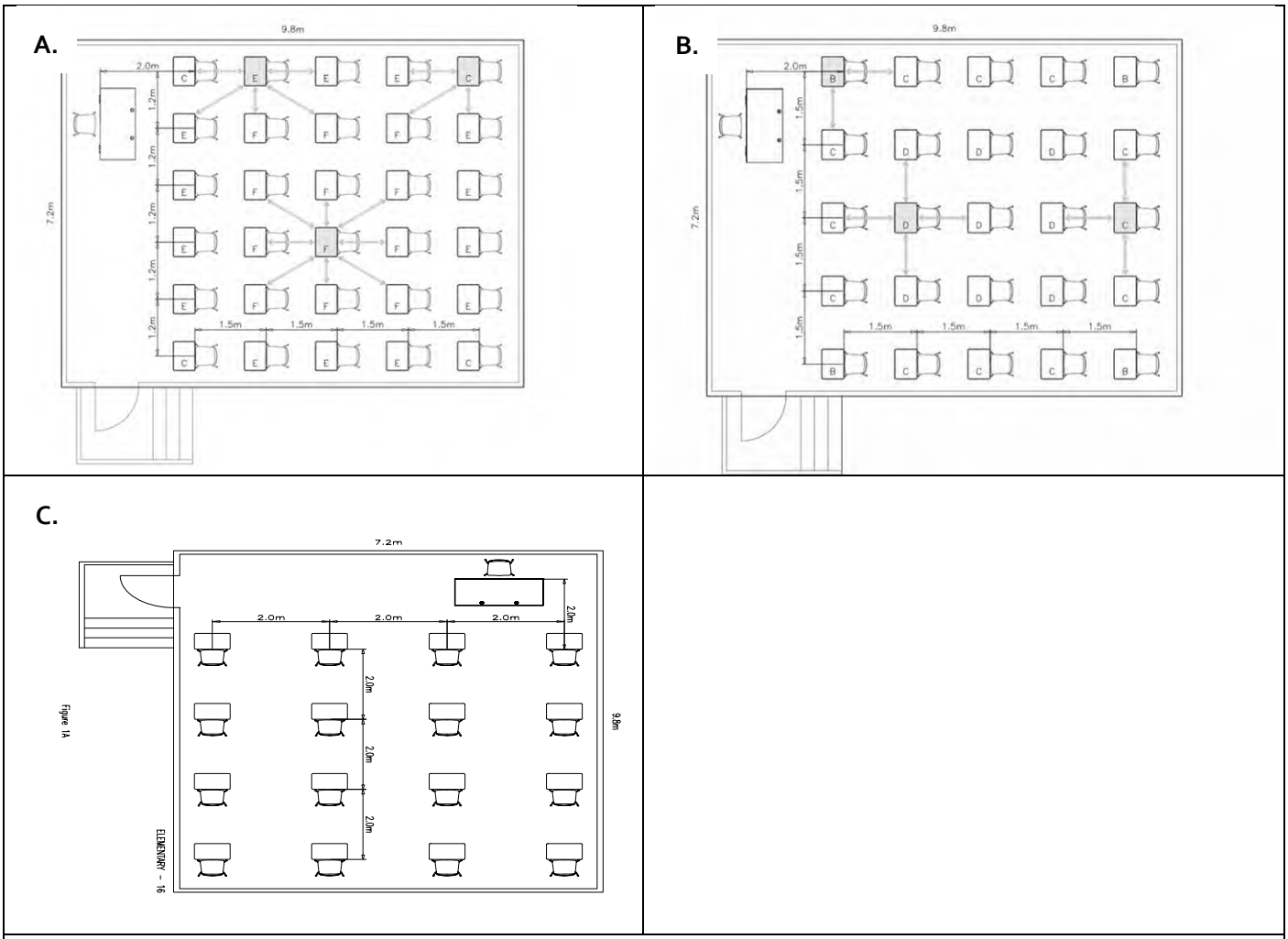

Figure 6. **Panel A** shows when a standard **ELEMENTARY classroom** becomes larger than 25 students, 6 rows of seats are needed, and side-by-side spacing is reduced to 1.2 metres of physical distancing between students. In this arrangement, 100% of the students have at least three close contacts (C), with 87% of students having at least five close contacts (E), and 40% having eight close contacts (F). While the educator's physical desk is located 2m from the student desks in closest proximity, the educator is unable to move anywhere in the classroom without being < 1m from the students. In **Panel B**, a classroom of 25 students and using a 5x5 row arrangement, there is 1.5 metres distance between students, with 36% of students (sitting in the centre) having four close contacts (D), defined as being within 2 metres. 84% of students would have at least three close contacts (C). Those sitting in the corners, 16% of students, would have only two close contacts (B). Although the risk reduction from physical distancing is on a continuum, 2 metres is strongly preferred, and this is not attainable in a classroom of 25 students. In the same classroom with only 16 students (**Panel C**), the 2 m of physical distance that public health strongly recommends for individuals in every other indoor space in the province of Ontario is able to be met with adequate distance between students and also provides a small increase in distance between the educator and the students (although still not 2 m) when the educator must move about the room.

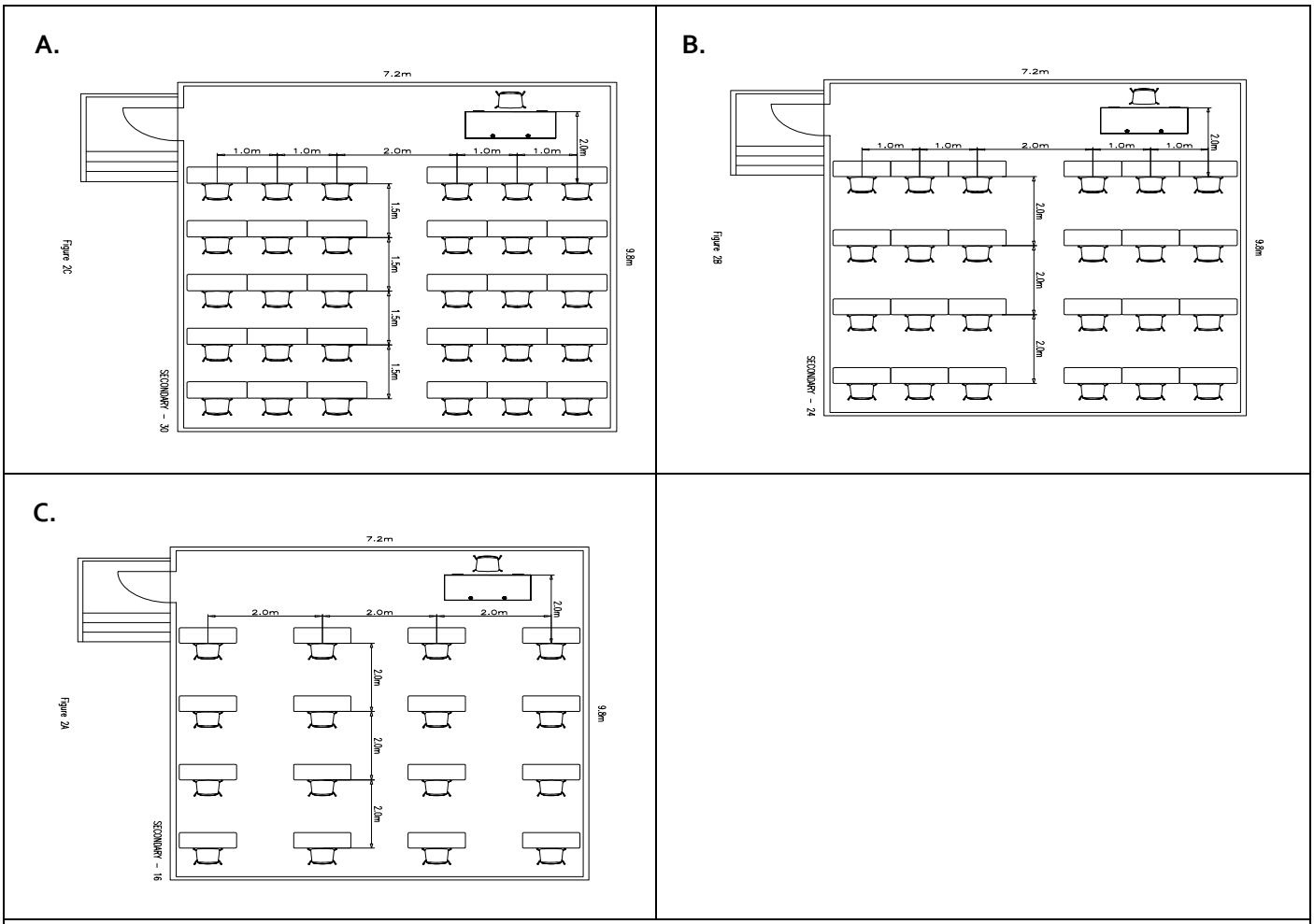

Figure 7. Panel A shows that when a standard **SECONDARY classroom** becomes larger than 25 secondary students who require larger desks, 5 rows of seats are needed, and side-by-side spacing is reduced to 1 metres of physical distancing between students with groups of 3 desks directly touching one another. Each group of 3 students is less than 2 m from at least 1 other group of 3. While the educator's physical desk is located 2m from the student desks in closest proximity, the educator is unable to move anywhere in the classroom without being < 1m from the students. In **Panel B**, a secondary classroom of 24 students and using a 4x4 row arrangement, student desks are in placed in groups of 3 and each desk is touching the desk beside. There is 2 metres of distance between each of the groups of 3. In the same classroom with only 16 students (**Panel C**), the 2 m of physical distance that public health strongly recommends for individuals in every other indoor space in the province of Ontario is able to be met with adequate distance between students and also provides a small increase in distance between the educator and the students (although still not 2 m) when the educator must move about the room.

66. Important Take Home Messages: The school setting scenarios show a cascade of intensifying outbreaks and rapidly mounting student-days of closures as class size increases. This occurs for three reasons. First, as class sizes increase the likelihood that a student tests positive for COVID-19 also increases. Second, when a class is dismissed due to the identification of a positive case more students are affected by the closure, and third, because COVID-19 can be transmitted by individuals during the pre-symptomatic period (before the individual becomes sick) and the increased concern about aerosol dispersal of the virus, there are more individuals infected in the classes that have large class sizes before the case is identified and the class is dismissed. This then results in larger outbreak sizes due to more cases infected before the dismissal, and after the dismissal as the infection continues to spread in households. The metric of student-days missed further supports the benefit of small class sizes as a way to prevent highly disruptive classroom closures. In the model simulations, the majority of

transmission occurred within the classroom setting. This further supports the assertion that physical distancing within the classroom setting is of incredible importance and yet, maintaining 2 m or more of physical distance is impossible when class sizes are large (Figures 6 and 7). Lastly, the model simulations where a 30:1 class was broken down into 2 cohorts of 15:1 that alternated weekly demonstrated significant benefits in terms of reductions in the outbreak sizes observed and student-days missed.

67. A second analysis by Bilinski et al. (unpublished at this time) that was presented to the Public Health Agency of Canada, Modelling Advisory Group on July 7, 2020 focused on preventing COVID-19 transmission in schools using a model-based analysis of safe re-opening strategies.

68. This work was conducted using the State of Maryland as a case study since the senior author is based at the University of Maryland. The model specifically modelled the risk of COVID-19 transmission within an elementary school setting and also considered student and staff households outside of the school setting. Class sizes were assumed to be 23 students with 1 educator and there were assumed to be another 30 adults in the school who served both in class roles and out of class roles. Individuals in the model were assumed to have interactions within their households, within their classrooms, outside of the classroom (e.g. random interactions with other members of the school on the bus, in the hallways etc.), and staff were assumed to have interactions with other staff. A number of different prevention strategies were considered in the model including reducing the in-classroom attack rate (by having good physical distancing and wearing masks), limiting contacts (e.g. cancelling movement of staff between classrooms, no face to face staff meetings, and in class lunches), reducing class sizes by ½, reducing teacher susceptibility (e.g. masks and face shields), and alternate schedules (e.g. having smaller groups of students alternate their face-to-face attendance at school). In the models, 2 different response options were considered. Option 1 was that the symptomatic individual self-isolates and no other action is taken. Option 2 was that when the symptomatic individual was identified as COVID-19 positive, the entire class would be dismissed to isolate for 14 days. Caveat: When this model was developed the State of Maryland (which has a smaller population size) had much higher community transmission than we currently see in Ontario (~350 cases per day). We are currently at ~300 cases per day in Ontario (but in a large population) so this Maryland model may overestimate the risk of importation of a case into a school compared to the current Ontario situation but I would not expect the within school transmission to change once a case is imported.

69. Important Take Home Messages: Outbreak size varies greatly even within a given scenario. Disease transmission is an inherently stochastic process. Stochasticity means that the event (in this case probability of transmission within the school) has a random probability distribution or pattern that can be analysed using statistical tools but may not be predicted precisely. In terms of the probability of disease introduction and spread, this means that there is always a chance that an introduction could lead to no within-school transmission, but that outcome has a lower probability (smaller chance) than the outcome that shows some amount of within-school transmission. Seeding an infection into a school sometimes results in no secondary transmission (no one else gets infected and we dodge a bullet) and sometimes seeding an infection into a school results in an outbreak. The important finding here is that while in many cases the outbreak clusters are relatively small (< 5 individuals) the distribution of possible outbreak sizes has a very long “tail” meaning that in a small number of simulations, the outbreak size is very large (> 20 individuals). Moving to classroom quarantine reduces the overall range of outbreaks sizes observed (more small outbreaks and less large outbreaks).

70. Compared to the base case (24:1 student to educator ratio 5-days per week), the “schedules” that either reduced class sizes by half or adopted a smaller cohort that alternated between in person and remote learning on alternate days/weeks, predicted significant reductions in outbreak sizes. At the upper bound (95th percentile) of the projected outbreak sizes for the different scenarios assuming the

entire class is dismissed when a case is identified, the "worst case" outbreak size was reduced from 16 individuals in the base case to only 6 individuals when class size was reduced by half. Alternating schedules to accommodate smaller class sizes were also able to reduce the outbreak sizes to 5 and 3 individuals depending on the schedule used.

71. So, in short, engineering controls such as class size reduction and cohorting can be implemented to ensure physical distancing and further minimize the likelihood of contact with droplets and/or aerosols from an infectious person. These strategies include furniture placement and physical barriers. The 2-metre distance has been recommended broadly throughout the pandemic following a systematic review on the impact of physical distancing measures on SARS-CoV-2 transmission [25]. Nonetheless, distancing beyond 2 metres has been recommended in the highest-risk settings, which include prolonged contact time, poor ventilation in an indoor environment, and high levels of occupancy. School settings with no class size reductions, represent the near perfect overlap of these highest risk factors with students in crowded, poorly ventilated indoor classrooms over prolonged periods with no possibility of maintaining 2m of distance between students and/or staff. In addition, in the North American setting, there has not been widespread uptake of physical barriers in the classroom (e.g. plexiglas dividers) as has been seen in many Asian countries.

72. **QUESTION:** What–if any–are the impacts of differing physical distancing (1 m vs 2 m) on these expected outcomes, to the extent that those impacts can be assessed?

73. The implementation of physical distancing measures has been shown to reduce the overall incidence of COVID-19 in the community [24]. In both healthcare and non-healthcare settings, physical distancing of less than 1 metre was associated with a 12.8% chance of transmission, compared to 2.6% where 1 metre or more of physical distance was maintained [25]. The protection afforded by physical distancing might double for every additional metre of distancing [25]. In situations where individuals are in a high-occupancy, indoor setting for a prolonged period of time, a 2-metre distance is recommended [26]. The classroom is an example of such an environment. Class size directly impacts the effectiveness of physical distancing measures since classrooms have limited space within which to teach students.

74. It is important to highlight that despite these findings, about the reduced risk of transmission that exists with physical distancing that is 2 m or greater, that a recent school simulation study conducted by scientists at the Hospital for Sick Children has highlighted that "The classrooms used during the simulation resembled a typical public school classroom (i.e. 32 feet by 24 feet). With these room sizes, it was not possible to maintain a two-metre distance between students and accommodate more than 12-15 students in the class even with the desks against all four walls"[35].

75. **QUESTION**: What – if any – are the impacts of a fully-masked classroom (students and education workers) on these expected outcomes, to the extent that those impacts can be assessed?

76. In a research article published in August 2020, Jones and colleagues have clearly described the evidence related to the 1-2 m physical distancing guidelines[26]. This paper includes an incredibly helpful Figure which can help us to understand the spectrum of transmission risk associated with different types of settings when considering the transmission of SARS-CoV-2. With Ontario students returning to full class sizes, classrooms would be considered to be at the high end of occupancy (right hand side of Figure 8). Also, given the duration of the school day, students and staff are in contact for a prolonged period of time and that in many cases, Ontario classrooms are indoor settings with poor ventilation. In this case, one can see that wearing face coverings reduces the risk only if the classroom is well ventilated. A fully masked class reduces risk compared to a scenario where no face coverings/masks are worn but is unlikely to significantly reduce the risk of transmission alone in the absence of other interventions such as physical distancing. Moving to lower occupancy levels (by

reducing class sizes) reduces transmission risk when the group of individuals are wearing masks/face coverings[26]. Since the primary purpose of having students wear masks in the school setting is "source reduction" by reducing the risk that an asymptomatic but infectious individual is spreading droplets into the environment the most effective approach is for near universal masking so that all individuals can obtain some benefit of the masking[29].

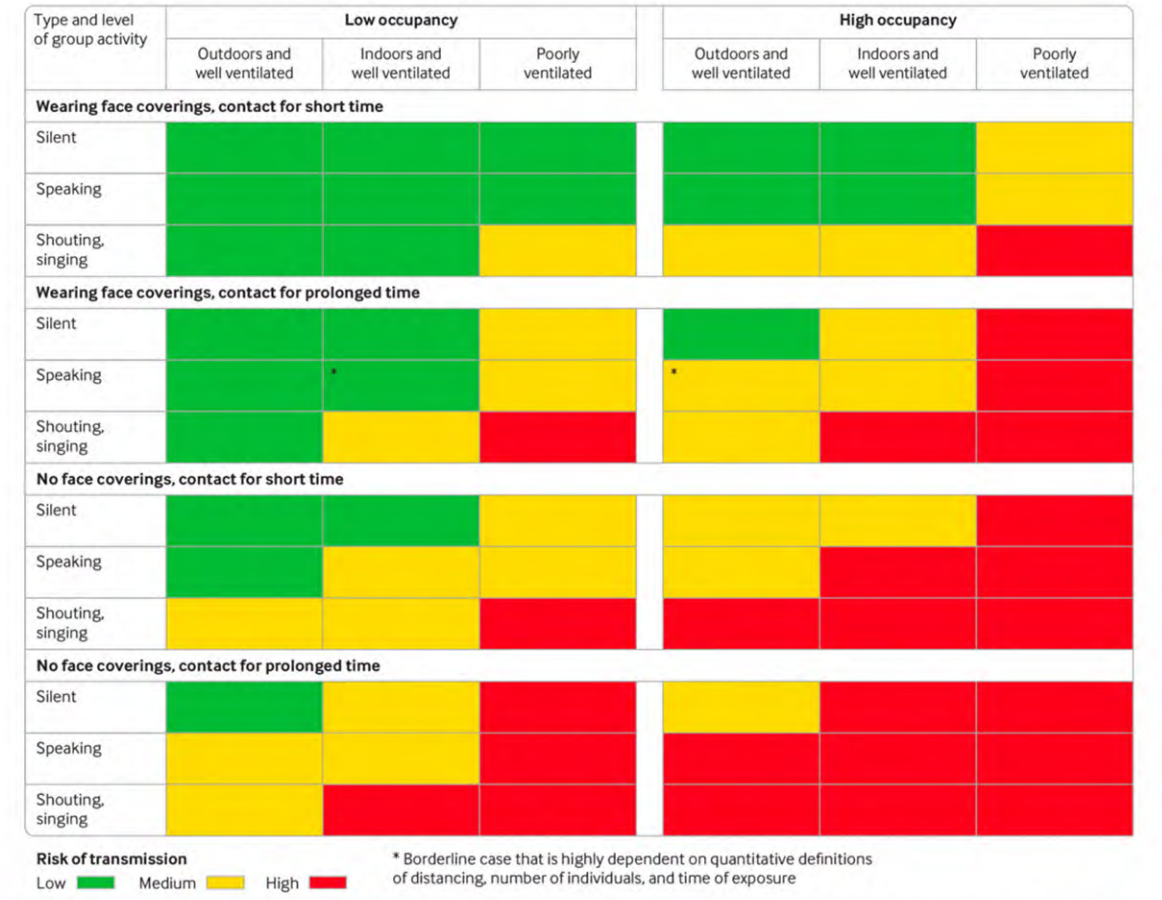

Fig 3 | Risk of SARS-CoV-2 transmission from asymptomatic people in different settings and for different occupation times, venting, and crowding levels (ignoring variation in susceptibility and viral shedding rates). Face covering refers to those for the general population and not high grade respirators. The grades are indicative of qualitative relative risk and do not represent a quantitative measure. Other factors not presented in these tables may also need to be taken into account when considering transmission risk, including viral load of an infected person and people's susceptibility to infection. Coughing or sneezing, even if these are due to irritation or allergies while asymptomatic, would exacerbate risk of exposure across an indoor space, regardless of ventilation

Figure 8. The projected risk of SARS-CoV-2 transmission as described in Jones et al. 2020 with specific focus on high occupancy, indoor settings that are well ventilated or poorly ventilated (as we might expect to see in school classrooms).

77. **QUESTION**: What – if any – are the impacts of a classroom where only the education workers are masked on these expected outcomes, to the extent that those impacts can be assessed?

78. In my opinion, a classroom where only the education workers are masked represents a high risk of transmission potential. This is especially the case since asymptomatic or pre-symptomatic students can transmit the virus to others. In the absence of student "source control" by way of non-medical masking, the risk that education workers are exposed to the virus should an introduction occur is very high. It is the case that the Guide states that education workers will be provided with medical masks (which do confer some protection to the person wearing the mask). However, the extent to which having only education workers wear a medical mask would mitigate transmission potential to the

education worker is not entirely clear but is certainly less effective than having universal masking in my opinion. It should be noted that masking of education workers in the absence of masking of students does not protect the students in any significant way from one another. To my knowledge, there is no evidence to support or refute the idea that fomite transmission from items such as clothing that has been worn in the workplace presents a risk to the health and safety of education workers.

79. **QUESTION**: How – if at all – do the impacts of mask-wearing differ depending on what kind of mask is being worn?

80. I have specifically addressed the different types of masks in Sections 31-40. It is my opinion that even imperfect non-medical mask wearing provides significant benefit in reducing the risk of transmission events by acting as source control and preventing the spread of droplets that could contain infectious virus particles[29]. In addition, education workers who will be provided with medical masks (as per the Guide) will also benefit from some additional protection as medical masks have higher documented levels of filtration as per the details described in Sections 31-40. However, it is important to remember that based on Figure 2, PPE in the form of masks (either medical or non-medical) as a single intervention provide an insufficient level of risk mitigation especially in settings where community transmission is not already very low.

81. **QUESTION**: What – if any – are the impacts of different sizes of cohort (50 direct and indirect in-school contacts vs 100 direct and indirect in-school contacts, within a 14-day period) on these expected outcomes, to the extent that those impacts can be assessed? Please consider the impact of these cohort sizes on both students and staff.

82. In the most general sense, minimizing the total number of in-school contacts is an important way to mitigate the risk of within school transmission should the pathogen be introduced to the school setting. In the current wording of the Guide, it is not clear what exactly is considered a "contact" and there is no specific definition of a direct vs. indirect contact. As a result, these statements are mostly meaningless and therefore explicitly counting contacts to identify if this requirement is being met is not possible.

83. In Section 27 I identified that it is important to clarify the meaning of the term "contact". For pathogens that are primarily transmitted via respiratory droplets we assume that a potential transmission event is possible if individuals are within 2 m of one another. In studies that collect network based data from individuals for the purpose of quantifying "direct contact" the definition in most studies is that direct contact is contact between individuals where you are < 2 m from someone and you speak directly to the other person or physically touch them (so it would not include passing someone on the sidewalk or having a video conference with someone)[22,23]. The term indirect in-school contact as described in the Guide is not clear. The term indirect transmission is used to refer to the transmission of a pathogen to an individual through an indirect route (e.g. the person becomes infected by contact with a contaminated fomite such as touching a contaminated doorknob and then touching their eyes and mouth resulting in transmission). Indirect transmission is also used to describe the aerosol route of transmission. However, these definitions do not appear to translate to the way indirect "contact" is used in the Guide. Another possible way to interpret indirect in-school contacts might be that these would be considered linkages that are created by network bridges which act to "indirectly" connect different groups of individuals.

84. The provincial "social bubble" recommendation is that a "bubble" includes a maximum of 10 people. This intervention works by reducing the number of direct contacts (which are defined as physical distance < 2 m, and/or direct skin to skin contact) that any individual has. Individuals within the bubble are supposed to be "exclusive" to the bubble. We often think about this type of network

structure when we think about sexually transmitted infections. While an individual may be in a relationship with another individual if that contact is not "exclusive" and one member of the relationship has contact with others outside of the primary relationship, it means that the "exclusive" partner is indirectly connected to all of the other individuals that the "non-exclusive" partner has contact with by virtue of having direct contact with the partner. Indirect contacts of this type (if this is in fact, what is meant by the Guide) are very important in terms of the network structure and the risk of disease transmission. In networks where people may not be directly connected, a short average path length (APL) (the number of people you need to go through to get to any other person) means more "distant" people in the network can be reached through a small number of connections. It is a measure of how connected the network is and of the efficiency of potential pathogen transmission on a network. We calculate APL by finding the mean of the lengths of the shortest paths between all pairs of people in the network. The longest path length between any pair of individuals is called the network diameter. Using the network graph in Figure 2, panel D, I have calculated the network diameter to be 4 and the APL to be 2.2789. This means that any individual in the network can be reached with ~2.3 steps/connections. For example, If John (class 1) is in Sally's class (class 1), and Sally (class 1) rides the bus with Trina (class 2), and Trina (class 2) plays with Rose (class 3) at recess than the path length between John and Rose is 3. In the example of the school network in Figure 2, panel D, any person in the network is connected to any other person in the network by 2.3 steps/connections.

85. **QUESTION**: What – if any – are the impacts of layering two or more of the different infection prevention and control strategies on these expected outcomes, to the extent that those impacts can be assessed?

86. It is challenging to specifically quantify the relative reduction in risk that one might expect to see when layering multiple infection prevention and control strategies together in a school setting. We do know that the hierarchy of control represents a well-established approach to minimizing risks (Figure 2). However, we also know that there are a number of SARS-CoV-2 characteristics that make control of the virus much more challenging which means that we need to rely most strongly on the most effective measures in the hierarchy as our first line of defense. Specifically, in Ontario we are currently seeing increasing rates of community transmission. This observation combined with the fact that many children do not have any obvious signs of SARS-CoV-2 infection and that pre-symptomatic transmission occurs before an infected individual develops symptoms means that what is usually considered our most effective intervention in the hierarchy is far less effective in the case of COVID-19. Reducing the risk of importations into school settings will be incredibly challenging under these conditions. Therefore, engineering controls become far more important for implementation in the school setting as ways to manipulate the school environment in ways to ensure 2 m of physical distancing. With a return to full class sizes, 2 m of physical distancing is not possible in many school classrooms which erodes the benefit and value of this intervention which we would typically consider to be on the higher end of effectiveness. There are additional engineering controls which are also implemented in the Ontario school setting such as improving ventilation.

87. In general, while the goal of layering interventions is to help to reduce risk overall, it is my opinion that layering interventions that are not operationalized as intended (e.g. not being able to maintain 2 m of physical distance in a classroom setting) means that the full potential benefit of a layered response is difficult to achieve.

88. **QUESTION**: From the perspective of network epidemiology, what is the potential role of itinerant workers who work at different workplaces, such as occasional teachers, professionals such as speech pathologists, or educational assistants?

89. It's really important to consider itinerant workers such as occasional teachers or other service providers who move within the educational system. We have an existing clear example of why itinerant staff are problematic from a transmission perspective: long-term care (LTC) outbreaks in Ontario, Quebec, and British Columbia.

90. British Columbia represents an especially good example, because early in their outbreak they identified that what made LTC high risk was that staff worked at multiple facilities. This movement of individuals between different locations and systems meant that these individuals acted as "bridges" between different facilities linking infection dynamics across facilities which would have otherwise separate, independent and unlinked (Figures 1 and 2). British Columbia went so far as to require staff be "locked down" to a single facility to minimize risk. In this case, they effectively "cohorted" staff to individual facilities to remove the linkages which existed otherwise.

91. For example, a personal support worker (PSW) with 0.25 FTE contracts at 4 different facilities was now employed full-time at a single facility. Itinerant workers are especially high risk from an occupational risk perspective as they themselves are exposed at multiple locations – which is higher individual risk – but also, they are a potential risk factor to others because that staff person has so many more contacts. That's key here. Everything about communicable disease hinges on the interconnectedness of individuals. A case in an individual is a risk factor to others in the setting. In the Guide to reopening Ontario's schools, it specifically states that some teachers such as French teachers, physical education teachers etc. will still rotate between classes to provide supervision and learning opportunities. This breaks down the class cohorts and indirectly links all cohorts in the school by virtue of these "bridge' staff members.

92. **QUESTION**: Based on the above opinions, what is your professional opinion about the relative importance of each measure or group of measures to control for or reduce the transmission and infection of COVID-19 in a public school setting for:

an elementary school?

93. In an elementary school setting, pre-attendance screening for all adults/educational staff is incredibly important (and all adults in the school should be supported to make good decisions about staying home if there is any question that they might be experiencing symptoms). However, pre-attendance screening for elementary aged children is of far less effectiveness due to the fact that children exhibit very few (if any symptoms) and also can exhibit symptoms that are not typical respiratory symptoms. While the screening tools will catch some likely infected kids and keep them out of school, it is very likely that infected children will pass the screening, attend school but still be infected and able to transmit[36]. In addition, young children require adult supervision if they need to stay home from school and so it is also the case that parents may be less likely to keep children home from school if they "sort-of" pass the screening questions because of the challenge of navigating their work situation.

94. So, because screening is highly imperfect, engineering controls become our best line of defense. These include easy access to hand hygiene and modifying the classroom and school environment to ensure appropriate physical distancing. In addition, improving ventilation is an important part of reducing risk of school transmission.

95. Engineering controls also include "cohorting" however, cohorting students in full pre-pandemic class sizes dilutes the potential benefit of cohorting. While additional cohorting impacts could be seen by using altered school scheduling such as modified recess times to reduce the number of children in the school yard at a time, having children from different classes mix in the school yard also dilutes the benefit of any sort of "cohorting" by permitting bridges to occur between groups. In addition, recess

"cohorts" have been implemented quite differently even in different schools within a single school board such that some schools essentially have any entire grade "cohort" or "division" interacting during the recess period. Again, this dilutes the intention and purpose of creating a smaller "cohort" of students. If cohorts mix in anyway, the cohorts all become one large connected and well mixed group which facilitates opportunities for disease transmission.

96. Moving educational opportunities to outdoor settings (an administrative control) reduces transmission risk because outdoors permits better physical distancing combined with better ventilation.

97. PPE in the form of masks and eye protection is the last line of defense and can help to add an additional level of protection especially since pre-symptomatic transmission occurs but PPE should only be considered in addition to all of the previously described measures. PPE alone is insufficient to make any meaningful contribution to reducing the risk of SARS-CoV-2 transmission in an elementary school setting.

a middle school?

98. My comments about the relative importance of the different measures for elementary schools would be the same for middle schools.

a secondary school?

99. In a secondary school setting, pre-attendance screening for all adults/educational staff is incredibly important (and all adults in the school should be supported to make good decisions about staying home if there is any question that they might be experiencing symptoms). However, pre-attendance screening for secondary school aged children may be slightly more effective than what I have described for elementary and middle school students[36]. In adolescents, infected students may be more likely to exhibit some symptoms but can also exhibit symptoms that are not typical respiratory symptoms[15,37]. In the secondary school setting, the screening tools will catch some likely infected kids and keep them out of school, but it is still the case that some students could pass the screening but still be infected and able to transmit (especially in the pre-symptomatic state). However, many teens could stay home from school independently if necessary and so the issues with household supervision of children who need to stay home is likely less of an issue.

100. Regardless, I would still consider screening to be imperfect, so engineering controls become our best line of defense. These include easy access to hand hygiene and modifying the classroom and school environment to ensure appropriate physical distancing.

101. In addition, improving ventilation is an important part of reducing risk of school transmission.

102. Engineering controls also include "cohorting" however, cohorting students in full pre-pandemic class sizes dilutes the potential benefit of cohorting. Secondary schools have adopted modified schedules to combine in-person learning with remote/virtual learning. This means that students are a part of 2 different "in-class" classes/cohorts each day instead of 3-4 in-class classes/cohorts during the pre-pandemic period as a result of the quadmester/octmester schedule. However, in the secondary setting, this increases the need for within-class physical distancing in order to reduce exposure risks in each individual class/cohort. If classes/cohorts mix in any way, the cohorts all become one large connected and well-mixed group which facilitates opportunities for disease transmission.

103. Moving educational opportunities to outdoor settings (an administrative control) reduces transmission risk because outdoor settings permit better physical distancing combined with better ventilation but are likely more challenging for certain types of secondary classes that require equipment or other resources. It is also the case, that because in some boards, secondary teachers must teach both to their in-class students and remote students at the same time, that an administrative control such as outdoor learning cannot be implemented because of a lack of an ability to implement synchronous remote learning in an outdoor setting.

104. PPE in the form of masks and eye protection is the last line of defense and can help to add an additional level of protection but only in addition to all of the previously described measures. PPE alone is insufficient to make any meaningful contribution to reducing the risk of SARS-CoV-2 transmission in secondary school setting

a school bus?

105. School buses/student transportation represents an additional layer of complexity to the return to school planning. In order to minimize the risk of transmission between students sharing a bus, all of the same school-based interventions need to be implemented. There is nothing magical about a bus that makes it different from a classroom. Buses are indoor, high-occupancy settings where students are in close proximity for periods of time that range from short to quite long, depending on the school bus route. Students and adults should all be completing the screening checklist daily before boarding a bus but as discussed before, screening is not perfect and will miss cases.

106. Engineering controls such as hand hygiene, improved ventilation and physical distancing are all as important on the bus as in the school setting.

107. Physical distancing on the bus is important. Students should be keeping good physical distance from all other students who are not a member of their household. Again, the term "cohorting" has been used to apply to students riding buses. This means that students using school transportation are a part of 2 different "cohorts", the class group and the bus group (Figure 2). If bus contacts are not physically distanced, then this means students on buses are having direct close proximity contact with students from outside of their class cohort (Figure 2, Panel D). This means that students not taking buses are now indirectly linked (through the bus students) to the entire bus cohort. The overlapping and mixing of the cohorts (which is not the intention of using cohorts) means that the school community essentially becomes a well-mixed population (Figure 2, panel D). The introduction of the virus to a contact network with this structure means the virus has opportunities to move between the groups easily.

108. PPE in the form of masks and eye protection is the last line of defense and can help to add an additional level of protection but only in addition to all of the previously described measures. PPE alone is insufficient to make any meaningful contribution to reducing the risk of SARS-CoV-2 transmission in a bus setting.

109. **QUESTION**: Also based on the above, what is your professional opinion on the sufficiency of the health and safety measures required under the Guide measures to control for or reduce the transmission and infection of COVID-19 in a public school setting for:

110. For all settings, screening prior to attending a school setting is necessary and in theory sufficient. However, given the specific biology of COVID-19 (especially in kids), the screening tool has a high chance of false negatives (students screen that they are OK to attend but could still be infected).

Given this, it is even more critical that the other health and safety measures be implemented to the greatest extent possible in order to mitigate risk.

111. Also, for all settings, making hand hygiene easy to access and ensuring appropriate hand hygiene at appropriate times during the school day (or when entering a school bus) seems sufficient as long as it is the case that every class room has access to their own "hand hygiene station" either a sink, soap, and paper towel or alcohol based hand rub.

112. In all settings, non-medical mask use has been deemed "mandatory" for students in grades 4-12 (when indoors). The use of a medical mask has been deemed mandatory and will be provided to all education workers by the province according to the Guide. I would consider both of these measures to be sufficient, but only insofar as they are implemented in those specified grades. See my comments below under the section dealing with elementary schools.

an elementary school?

113. In the elementary school setting it is insufficient to have full class sizes that do not permit 2 m of physical distance. The class/cohort size as currently implemented is insufficient to reduce exposure risk in a meaningful way as it increases the chance that you have an infected student arrive to the class group (because the class group is large), and it also increases the chance that an infection would spread within a class group that is not able to maintain 2 m of physical distance between members.

114. This insufficiency is further exacerbated by the fact that each class contains students who belong to multiple educational setting cohorts (bus cohorts, class cohorts, recess/staggered entry cohorts) Students in multiple cohorts act as "bridges" that indirectly link students from different groups. As a result, it is critical to implement smaller classes and improved physical distancing (that meets the 2 m requirement) in order to attempt to offset the inevitable mixing between "cohorts".

115. It is insufficient that some teachers of special subjects such as French, are expected to move between class groups. This exposes these teachers to MANY different class groups/cohorts (Figure 2, panels B-D). Reducing class size and improving physical distancing would help to offset some of this risk to individual teachers by exposing them to fewer students but the impact of "bridging" between classes/cohorts still remains. It is also the case that there is no mention of cohorting staff within the school setting. Staff should also be "cohorted" into smaller groups such that smaller "professional" cohorts are maintained.

116. It is insufficient that younger students (JK-3) are not required to wear masks. Since asymptomatic and/or pre-symptomatic transmission occurs, non-medical masks for all students is an additional layer of protection that provides source protection for education workers especially in the case where other interventions like smaller cohorts and appropriate physical distancing are not implemented.

a middle school?

117. My perspectives on the sufficiency of health and safety measures as outlined in the Guide are the same as those that I have outlined for elementary schools.

a secondary school?

118. In the secondary school setting it is insufficient to have full class sizes (as seen in non-designated school boards) that do not permit 2 m of physical distance[38]. The class/cohort size as currently

implemented is insufficient to reduce exposure risk in a meaningful way as it increases the chance that you have an infected student arrive to the class group (because the class group is large), and it also increases the chance that an infection would spread within a class group that is not able to maintain 2 m of physical distance between members.

119. This insufficiency is further exacerbated by the fact that each class contains students who belong to multiple educational setting cohorts (bus cohorts, class cohorts). While modifications to the secondary school schedule to combine both in-class and online/virtual learning, and focusing on having students focus on fewer classes at a time do help to reduce the overall number of contacts between students and students and staff, it is still the case that students in multiple cohorts act as "bridges" that indirectly link students from different groups. As a result, it is critical to implement smaller classes and improved physical distancing (that meets the 2 m requirement) in order to attempt to offset the inevitable mixing between "cohorts". It is also important to consider that secondary school settings have significantly more control/independence over the contacts that they have outside of the school setting. Previous research has demonstrated that these "social" contacts are numerous and it is unreasonable to assume that they completely stop[39,40]. Social contacts that occur outside of school which may be of a higher risk (close proximity, and unmasked) are important to consider as they can contribute to further amplification of infections within secondary school student groups.

120. Modifications to the secondary school schedule as put forth in the Guide reduce the total number of students that educational staff have contact with compared to the pre-pandemic period. However, these teachers still have close proximity contact (without 2 m of distance in many cases) with at least two different class groups/cohorts each day. Reducing class size and improving physical distancing would help to offset some of this risk to individual teachers by exposing them to fewer students but the impact of "bridging" between classes/cohorts still remains. It is also the case that there is no mention of cohorting staff within the school setting. Staff should also be "cohorted" into smaller groups such that smaller "professional" cohorts are maintained.

a school bus?

121. The Guide states that school boards may be required to "… operate [buses] closer to capacity". It also states that since physical distancing may not be possible on the bus, that masks for students in grades 4-12 are mandatory while on the bus. This essentially means that despite all of the other possible interventions, none of the other interventions will be sufficiently implemented on the bus which to me is insufficient. Masks in the absence of other higher-level measures are not sufficient on their own. In this case, in the absence of other meaningful implementation of control measures, masks for students in grade K-3 should be required on the bus. Seating charts will not mitigate risk of transmission on the school bus. It is also the case that bus cohorts (with few intervention measures or poorly implemented measures) will be higher risk for transmission events and that risk will then spread into the class cohorts for all students on the bus. Due to the fact that students riding the bus are part of at least two different cohorts (bus cohort and class cohort), and the observation that even with only 15% of students falling into this "2-cohort" group as assumed in Figure 2, Panel D, that this acts to generate a significant amount of connection between all of the classroom groups, it is my opinion that it is necessary to limit the number of riders on a bus to achieve appropriate physical distancing. In addition, buses should not be shared by students who attend different schools.

122. **QUESTION**: Finally, in your professional opinion, what changes, amendments or other requirements would you recommend be made to the Guide in order to protect the health and safety of education workers?

123. There is no specific mention of health and safety measures related to ventilation requirements in schools, classrooms, or buses, and/or emphasizing outdoor learning as much as possible in the Guide. Both of these items are related to engineering and administrative controls that can be beneficial for reducing the risk of transmission given contact with an infected individual.

124. I feel that given the biology of COVID-19, where asymptomatic and/or pre-symptomatic individuals contribute to disease transmission it should be required that all students wear a non-medical mask/face covering when indoors to provide source protection and reduce risk to other students and the education workers.

125. Class sizes/cohort sizes and physical distancing go hand in hand. Based on the available evidence from the Figures presented above, along with the most recent observations from the school simulation study conducted by researchers at the Hospital for Sick Children, it is clear that appropriate physical distancing of 2 metres is not possible with the current class/cohort sizes. There has been no mention or discussion of plexiglass barrier in classroom settings, however we know that this engineering control has been implemented in other countries.

126. There is also no specific mention of staff cohorts etc. It is imperative to consider that staff should also be "cohorted" to some extent in order to reduce risk for broader spread of the pathogen in the school setting (Figures 1 and 2). Having staff that move between classes (e.g. French teachers) should be minimized and more novel modes of delivery should be considered.

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Early dynamics of transmission and control of COVID-19: a mathematical modelling study

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Summary

Background An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to 95 333 confirmed cases as of March 5, 2020. Understanding the early transmission dynamics of the infection and evaluating the effectiveness of control measures is crucial for assessing the potential for sustained transmission to occur in new areas. Combining a mathematical model of severe SARS-CoV-2 transmission with four datasets from within and outside Wuhan, we estimated how transmission in Wuhan varied between December, 2019, and February, 2020. We used these estimates to assess the potential for sustained human-to-human transmission to occur in locations outside Wuhan if cases were introduced.

Methods We combined a stochastic transmission model with data on cases of coronavirus disease 2019 (COVID-19) in Wuhan and international cases that originated in Wuhan to estimate how transmission had varied over time during January, 2020, and February, 2020. Based on these estimates, we then calculated the probability that newly introduced cases might generate outbreaks in other areas. To estimate the early dynamics of transmission in Wuhan, we fitted a stochastic transmission dynamic model to multiple publicly available datasets on cases in Wuhan and internationally exported cases from Wuhan. The four datasets we fitted to were: daily number of new internationally exported cases (or lack thereof), by date of onset, as of Jan 26, 2020; daily number of new cases in Wuhan with no market exposure, by date of onset, between Dec 1, 2019, and Jan 1, 2020; daily number of new cases in China, by date of onset, between Dec 29, 2019, and Jan 23, 2020; and proportion of infected passengers on evacuation flights between Jan 29, 2020, and Feb 4, 2020. We used an additional two datasets for comparison with model outputs: daily number of new exported cases from Wuhan (or lack thereof) in countries with high connectivity to Wuhan (ie, top 20 most at-risk countries), by date of confirmation, as of Feb 10, 2020; and data on new confirmed cases reported in Wuhan between Jan 16, 2020, and Feb 11, 2020.

Findings We estimated that the median daily reproduction number (R_t) in Wuhan declined from 2·35 (95% CI 1·15–4·77) 1 week before travel restrictions were introduced on Jan 23, 2020, to 1·05 (0·41–2·39) 1 week after. Based on our estimates of R_t, assuming SARS-like variation, we calculated that in locations with similar transmission potential to Wuhan in early January, once there are at least four independently introduced cases, there is a more than 50% chance the infection will establish within that population.

Interpretation Our results show that COVID-19 transmission probably declined in Wuhan during late January, 2020, coinciding with the introduction of travel control measures. As more cases arrive in international locations with similar transmission potential to Wuhan before these control measures, it is likely many chains of transmission will fail to establish initially, but might lead to new outbreaks eventually.

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See Online for appendix

Introduction

As of Feb 13, 2020, an outbreak of coronavirus disease 2019 (COVID-19) has resulted in 46 997 confirmed cases.[1] The outbreak was first identified in Wuhan, China, in December, 2019, with most early cases being reported in the city. Most internationally exported cases reported to date have history of travel to Wuhan.[2] In the early stages of a new infectious disease outbreak, it is crucial to understand the transmission dynamics of the infection. Estimation of changes in transmission over time can provide insights into the epidemiological situation[3] and identify whether outbreak control measures are having a measurable effect.[4,5] Such analysis can inform predictions about potential future growth,[6] help estimate risk to other countries,[7] and guide the design of alternative interventions.[8]

However, there are several challenges to such analyses, particularly in real time. There can be a delay to symptom appearance resulting from the incubation period and delay to confirmation of cases resulting from detection

Research in context

Evidence before this study

We searched PubMed, BioRxiv, and MedRxiv for articles published in English from inception to Feb 10, 2020, with the keywords "2019-nCoV", "novel coronavirus", "COVID-19", "SARS-CoV-2" AND "reproduction number", "R0", "transmission". We found several estimates of the basic reproduction number (R_0) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including average exponential growth rate estimates based on inferred or observed cases at a specific timepoint and early growth of the outbreak in China. However, we identified no estimates of how R_0 had changed in Wuhan since control measures were introduced in late January or estimates that jointly fitted data within Wuhan to international exported cases and evacuation flights.

Added value of this study

Our study combines available evidence from multiple data sources, reducing the dependency of our estimates on a single timepoint or dataset. We estimate how transmission has varied over time, identify a decline in the reproduction number in late January to almost 1, coinciding with the introduction of large scale control measures, and show the potential implications of estimated transmission for outbreak risk in new locations.

Implications of all the available evidence

Coronavirus disease 2019 is currently showing sustained transmission in China, creating a substantial risk of outbreaks in other countries. However, if SARS-CoV-2 has Middle East respiratory syndrome coronavirus-like or SARS-CoV-like variability in transmission at the individual level, multiple introductions might be required before an outbreak takes hold.

and testing capacity.[9] Modelling approaches can account for such delays and uncertainty by explicitly incorporating delays resulting from the natural history of infection and reporting processes.[10] Additionally, individual data sources might be biased, incomplete, or only capture certain aspects of the outbreak dynamics. Evidence synthesis approaches, which fit to multiple data sources rather than a single dataset (or datapoint) can enable more robust estimation of the underlying dynamics of transmission from noisy data.[11,12] Combining a mathematical model of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission with four datasets from within and outside Wuhan, we estimated how transmission in Wuhan varied between December, 2019, and February, 2020. We used these estimates to assess the potential for sustained human-to-human transmission to occur in locations outside Wuhan if cases were introduced.

Methods

Data sources

To estimate the early dynamics of transmission in Wuhan, we fitted a stochastic transmission dynamic model[13] to multiple publicly available datasets on cases in Wuhan and internationally exported cases from Wuhan. The four datasets we fitted to were: daily number of new internationally exported cases (or lack thereof), by date of onset, as of Jan 26, 2020; daily number of new cases in Wuhan with no market exposure, by date of onset, between Dec 1, 2019, and Jan 1, 2020; daily number of new cases in China, by date of onset, between Dec 29, 2019, and Jan 23, 2020; and proportion of infected passengers on evacuation flights between Jan 29, 2020, and Feb 4, 2020 (appendix p 3). We used an additional two datasets for comparison with model outputs: daily number of new exported cases from Wuhan (or lack thereof) in countries with high connectivity to Wuhan (ie, top 20 most at-risk countries), by date of confirmation, as of Feb 10, 2020; and data on new confirmed cases reported in Wuhan between Jan 16, 2020, and Feb 11, 2020 (appendix p 3).

Procedures

In the model, we divided individuals into four infection classes, as follows: susceptible, exposed (but not yet infectious), infectious, and removed (ie, isolated, recovered, or otherwise no longer infectious; figure 1). The model accounted for delays in symptom onset and reporting by including compartments to reflect transitions between reporting states and disease states. The model also incorporated uncertainty in case observation, by explicitly modelling a Poisson observed process of newly symptomatic cases, reported onsets of new cases, reported confirmation of cases, and a binomial observation process for infection prevalence on evacuation flights (appendix pp 1–3). The incubation period was assumed to be Erlang distributed with mean 5·2 days[14] (SD 3·7) and delay from onset to isolation was assumed to be Erlang distributed with mean 2·9 days (2·1).[2,15] The delay from onset to reporting was assumed to be exponentially distributed with mean 6·1 days (2·5).[2] Once exposed to infection, a proportion of individuals travelled internationally and we assumed that the probability of cases being exported from Wuhan to a specific other country depended on the number of cases in Wuhan, the number of outbound travellers (assumed to be 3300 per day before travel restrictions were introduced on Jan 23, 2020, and zero after), the relative connectivity of different countries,[16] and the relative probability of reporting a case outside Wuhan, to account for differences in clinical case definition, detection, and reporting within Wuhan and internationally. We considered the 20 countries outside China most at risk of exported cases in the analysis.

We modelled transmission as a geometric random walk process, and we used sequential Monte Carlo simulation to infer the transmission rate over time, as well as the resulting number of cases and the time-varying basic reproduction number (R_t), defined here as the mean number of secondary cases generated by a typical infectious individual on each day in a full susceptible population. The model had three unknown parameters, which we estimated: magnitude of temporal variability in transmission, proportion of cases that would eventually be detectable, and relative probability of reporting a confirmed case within Wuhan compared with an internationally exported case that originated in Wuhan. We assumed the outbreak started with a single infectious case on Nov 22, 2019, and the entire population was initially susceptible. Once we had estimated R_t, we used a branching process with a negative binomial offspring distribution to calculate the probability an introduced case would cause a large outbreak. We also did a sensitivity analysis on the following three key assumptions: we assumed the initial number of cases was ten rather than one; we assumed connectivity between countries followed WorldPop rather than MOBS Lab estimates; and we assumed that cases were infectious during the second half of their incubation period rather than only being infectious while symptomatic. All data and code required to reproduce the analysis is available online.

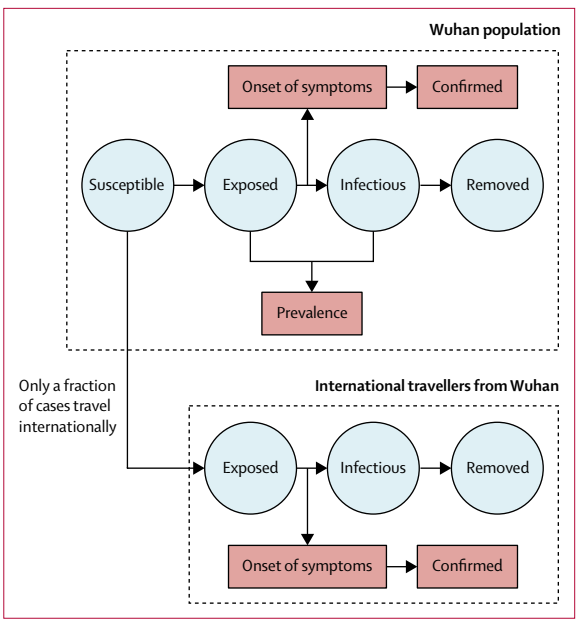

Figure 1: **Model structure**
The population is divided into the following four classes: susceptible, exposed (and not yet symptomatic), infectious (and symptomatic), and removed (ie, isolated, recovered, or otherwise non-infectious). A fraction of exposed individuals subsequently travel and are eventually detected in their destination country.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We estimated that R_t varied during January, 2020, with median values ranging from 1·6 to 2·6 between Jan 1, 2020, and the introduction of travel restrictions on Jan 23, 2020 (figure 2). We estimated a decline in R_t in late January, from 2·35 (95% CI 1·15–4·77) on January 16, 1 week before the restrictions, to 1·05 (0·41–2·39) on January 31.

The model reproduced the observed temporal trend of cases within Wuhan and cases exported internationally. The model captured the exponential growth in case onsets in early January, the rising number of exported case onsets between Jan 15, and Jan 23, 2020, and the prevalence of infection measured on ten evacuation flights from Wuhan to seven countries. We estimated that 94·8% (95% CI 93·1–96·1%) of the Wuhan population were still susceptible on Jan 31, 2020 (figure 2). Our results suggested there were around ten times more symptomatic cases in Wuhan in late January than were reported as confirmed cases (figure 2), but the model did not predict the slowdown in cases that was observed in early February. The model could also reproduce the pattern of confirmed exported cases from Wuhan, which was not explicitly used in the model fitting (figure 2). We found that confirmed and estimated exported cases among the 20 countries most connected to China generally corresponded with each other, with the USA and Australia as notable outliers, having had more confirmed cases reported with a travel history to Wuhan than would be expected in the model (figure 2). There was evidence that the majority of cases were symptomatic. We estimated that 100% (95% CI 51–100) of cases would eventually have detectable symptoms, implying that most infections that were exported internationally from Wuhan in late January were in theory eventually detectable. As a sensitivity analysis, we repeated the analysis with a large number of initial cases, different mobility data, and the assumption that pre-symptomatic cases could transmit. In these analyses, we observed the same result of a decline in R_t from more than 2 to almost 1 in the last 2 weeks of January, 2020 (appendix pp 10–13).

To examine the potential for new outbreaks to establish in locations outside Wuhan, we used our estimates of the R_t to simulate new outbreaks with potential individual-level variation in transmission (ie, so called superspreading events).[17–19] Such variation increases the fragility of transmission chains, making it less likely that an outbreak will take hold following a single introduction. If transmission is more homogeneous, with all infectious individuals generating a similar number of secondary cases, it is more likely than an outbreak will establish.[18]

For **data and code required to reproduce the analysis** see https://github.com/adamkucharski/2020-ncov/

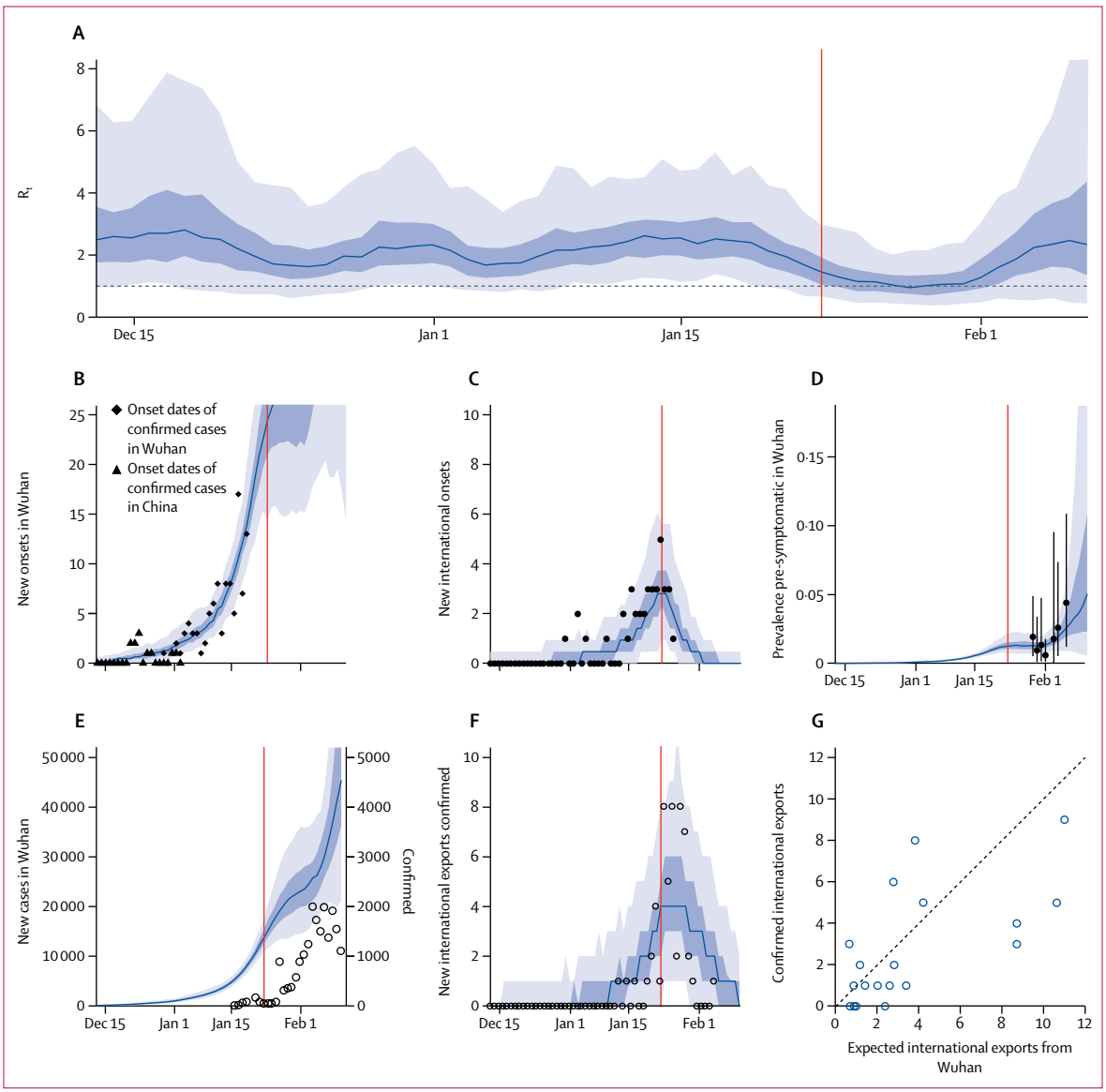

Figure 2: **Dynamics of transmission in Wuhan, fitted up to Feb 11, 2020**

The red line marks travel restrictions starting on Jan 23, 2020. For parts (A) to (F) blue lines represent median, light blue shading represents 50% confidence intervals of the model estimate, and dark blue shading represents 95% confidence intervals of the model estimate. In all panels, datasets that were fitted to are shown as solid points; non-fitted data are shown as empty circles. (A) Estimated R_t over time. The dashed line represents an R_t of 1. (B) Onset dates of confirmed cases in Wuhan and China. (C) Reported cases by date of onset (black points) and estimated internationally exported cases from Wuhan by date of onset (blue line). (D) Estimated prevalence of infections that did not have detectable symptoms (blue line), and proportion of passengers on evacuation flights that tested positive for severe acute respiratory syndrome coronavirus 2 (black points; error bars show 95% binomial CIs). (E) New confirmed cases by date in Wuhan (circles, right hand axis) and estimated new symptomatic cases (blue line, left hand axis). (F) International exportation events by date of confirmation of case, and expected number of exports in the fitted model. (G) Estimated number of internationally exported cases from Wuhan confirmed up to Feb 10, 2020 and observed number in 20 countries with the highest connectivity to China. R_t=daily reproduction number.

Based on the median R_t estimated during January before travel restrictions were introduced, we estimated that a single introduction of SARS-CoV-2 with SARS-like or Middle East respiratory syndrome (MERS)-like individual-level variation in transmission would have a 17% to 25% probability of causing a large outbreak (figure 3). Assuming SARS-like variation and Wuhan-like transmission, we estimated that once four or more infections have been introduced into a new location, there is an over 50% chance that an outbreak will occur (figure 3).

Discussion

Combining a mathematical model with multiple datasets, we found that the median daily R_t of SARS-CoV-2 in Wuhan probably varied between 1·6 and 2·6 in January, 2020, before travel restrictions were introduced. We also

estimated that transmission declined by around half in the 2 weeks spanning the introduction of restrictions.

The estimated fluctuations in R_t were driven by the rise and fall in the number of cases, both in Wuhan and internationally, as well as prevalence on evacuation flights. Such fluctuations could be the result of changes in behaviour in the population at risk, or specific super-spreading events that inflated the average estimate of transmission.[17–19] We found some evidence of a reduction in R_t in the days before the introduction of travel restrictions in Wuhan, which might have reflected outbreak control efforts or growing awareness of SARS-CoV-2 during this period. The uncertainty in our estimates for R_t following the decline in early February, 2020, results from a paucity of data sources to inform changes in transmission during this period.

Comparing model predictions with observed confirmed cases reported in Wuhan, we found that the model predicted at least ten times higher cases than were reported in early February, 2020. The model also did not predict the more recent slowdown in cases, suggesting that transmission might have declined more than our model—which did not fit to this case data—estimated during early February, 2020. Our estimates for international cases in specific countries were broadly consistent with the number of subsequently confirmed exported cases outside Wuhan. However, there were notably more cases exported to France, USA, and Australia compared with what our model predicted. This could be the result of increased surveillance and detection as awareness of SARS-CoV-2 increased in late January, which would suggest earlier exported cases might have been missed, or could be the result of increased travel out of Wuhan immediately before introduction of travel restrictions on Jan 23, 2020.

Based our on estimated reproduction number and published estimates of individual-level variation in transmission for SARS-CoV and MERS-CoV, we found that a single case introduced to a new location would not necessarily lead to an outbreak. Even if the reproduction number is as high as in Wuhan in early January, it could take several introductions for an outbreak to establish, because high individual-level variation in transmission makes new chains of transmission more fragile, and hence it becomes less likely that a single infection will generate an outbreak. This factor highlights the importance of rapid case identification and subsequent isolation and other control measures to reduce the chance of onward chains of transmission.[20]

Our analysis highlights the value of combining multiple data sources in analysis of COVID-19. For example, the rapid growth of confirmed cases globally during late January, 2020, with case totals in some instances apparently doubling every day or so, would have had the effect of inflating R_t estimates to implausibly large values if only these recent datapoints were used in our analysis. Our results also have implications for estimation of transmission dynamics using the number of exported cases from a specific area.[21] Once extensive travel restrictions are introduced, as they were in Wuhan, the signal from such data gets substantially weaker. If restrictions and subsequent delays in detection of cases are not accounted for, this could lead to artificially low estimates of R_t or inferred case totals from the apparently declining numbers of exported cases. Our model estimates benefited from the availability of testing data from evacuation flights, which allowed us to estimate current prevalence. Having such information for other settings, either through widespread testing or serological surveillance, will be valuable to reduce reliance on case reports alone.

There are several other limitations to our analysis. We used plausible biological parameters for SARS-CoV-2 based on current evidence, but these values might be refined as more comprehensive data become available. However, by fitting to multiple datasets to infer model parameters, and conducting sensitivity analyses on key areas of uncertainty, we have attempted to make the best

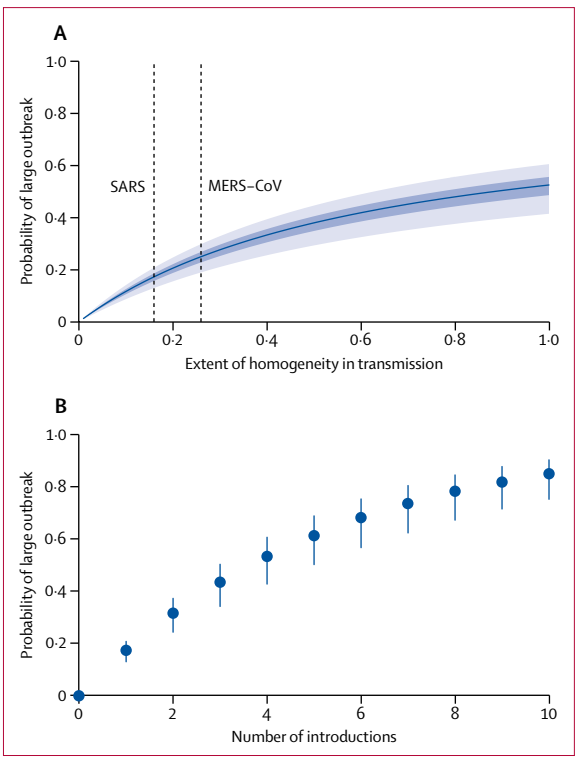

Figure 3: **Risk that introduced infections will establish in a new population**
(A) Probability that a single case will lead to a large outbreak for different assumptions about the extent of homogeneity in individual-level transmission (ie, the dispersion parameter k in a negative binomial offspring process). Results are shown for the median reproduction number estimated for severe acute respiratory syndrome coronavirus 2 in Wuhan between Jan 1, 2020, and Jan 23, 2020. (B) Probability that a given number of introductions will result in a large outbreak, assuming SARS-like superspreading events can occur. Points show the median estimated reproduction number between Jan 1, 2020, and Jan 23, 2020; bars show 95% quantile of the range of median values of R_t during this period. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. R_t=daily reproduction number.

possible use of the available evidence about SARS-CoV-2 transmission dynamics. Furthermore, we used publicly available connectivity and risk estimates based on international travel data to predict the number of cases exported into each country. These estimates have shown good correspondence with the distribution of exported cases to date,[22] and are similar to another risk assessment for COVID-19 with different data.[23] We also assumed that the latent period is equal to the incubation period (ie, individuals become infectious and symptomatic at the same time) and all infected individuals will eventually become symptomatic. However, there is evidence that transmission of SARS-CoV-2 can occur with few reported symptoms.[24] Therefore, we did a sensitivity analysis in which transmission could occur in the second half of the incubation period, but this did not change our overall conclusions of a decline in R_t from around 2·4 to almost 1 during the last 2 weeks of January. We also explored having a larger initial spillover event and using different sources for flight connectivity data, both of which produced the same conclusion about the decline in transmission. In our analysis of new outbreaks, we also used estimates of individual-level variation in transmission for SARS and MERS-CoV to illustrate potential dynamics. However, it remains unclear what the precise extent of such variation is for SARS-CoV-2.[17] If transmission were more homogenous than SARS-CoV or MERS-CoV, it would increase the risk of outbreaks following introduced cases. As more data become available, it will be possible to refine these estimates; therefore we have made an online tool so that users can explore these risk estimates if new data become available (appendix p 4).

Our results show that there was probably substantial variation in SARS-CoV-2 transmission over time, and suggest a decline in transmission in Wuhan in late January, 2020, around the time that control measures were introduced. If COVID-19 transmission is established outside Wuhan, understanding the effectiveness of control measures in different settings will be crucial for understanding the dynamics of the outbreak, and the likelihood that transmission can eventually be contained or effectively mitigated.

Contributors

Data analysis was led by AJK, who programmed the model with help from TWR. AJK, SF, and RME planned the inference framework. CD provided the data from online sources. The CMMID 2019-nCoV working group members contributed to processing, cleaning, and interpretation of data, interpreted the study findings, contributed to the manuscript, and approved the work for publication. All authors interpreted the findings, contributed to writing the manuscript, and approved the final version for publication.

Declaration of interests

We declare no competing interests.

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Rapid communication

Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020

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Since December 2019, China has been experiencing a large outbreak of a novel coronavirus (2019-nCoV) which can cause respiratory disease and severe pneumonia. We estimated the basic reproduction number Ro of 2019-nCoV to be around 2.2 (90% high density interval: 1.4–3.8), indicating the potential for sustained human-to-human transmission. Transmission characteristics appear to be of similar magnitude to severe acute respiratory syndrome-related coronavirus (SARS-CoV) and pandemic influenza, indicating a risk of global spread.

On 31 December 2019, the World Health Organization (WHO) was alerted about a cluster of pneumonia of unknown aetiology in the city of Wuhan, China [1,2]. Only a few days later, Chinese authorities identified and characterised a novel coronavirus (2019-nCoV) as the causative agent of the outbreak [3]. The outbreak appears to have started from a single or multiple zoonotic transmission events at a wet market in Wuhan where game animals and meat were sold [4] and has resulted in 5,997 confirmed cases in China and 68 confirmed cases in several other countries by 29 January 2020 [5]. Based on the number of exported cases identified in other countries, the actual size of the epidemic in Wuhan has been estimated to be much larger [6]. At this early stage of the outbreak, it is important to gain understanding of the transmission pattern and the potential for sustained human-to-human transmission of 2019-nCoV. Information on the transmission characteristics will help coordinate current screening and containment strategies, support decision making on whether the outbreak constitutes a public health emergency of international concern (PHEIC), and is key for anticipating the risk of pandemic spread of 2019-nCoV. In order to better understand the early transmission pattern of 2019-nCoV, we performed stochastic simulations of early outbreak trajectories that are consistent with the epidemiological findings to date.

Epidemic parameters

Two key properties will determine further spread of 2019-nCoV. Firstly, the basic reproduction number R_0 describes the average number of secondary cases generated by an infectious index case in a fully susceptible population, as was the case during the early phase of the outbreak. If R_0 is above the critical threshold of 1, continuous human-to-human transmission with sustained transmission chains will occur. Secondly, the individual variation in the number of secondary cases provides further information about the expected outbreak dynamics and the potential for superspreading events [7-9]. If the dispersion of the number of secondary cases is high, a small number of cases may be responsible for a disproportionate number of secondary cases, while a large number of cases will not transmit the pathogen at all. While superspreading always remain a rare event, it can result in a large and explosive transmission event and have a lot of impact on the course of an epidemic. Conversely, low dispersion would lead to a steadier growth of the epidemic, with more homogeneity in the number of secondary cases per index case. This has important implications for control efforts.

Simulating early outbreak trajectories

In a first step, we initialised simulations with one index case. For each primary case, we generated secondary cases according to a negative-binomial offspring distribution with mean R_0 and dispersion k [7,8]. The dispersion parameter k quantifies the variability in the number of secondary cases, and can be interpreted as a measure of the impact of superspreading events (the lower the value of k, the higher the impact of superspreading). The generation time interval D was assumed to be gamma-distributed with a shape parameter of 2, and a mean that varied between 7 and 14 days. We explored a wide range of parameter combinations (Table) and ran 1,000 stochastic simulations for each individual combination. This corresponds to

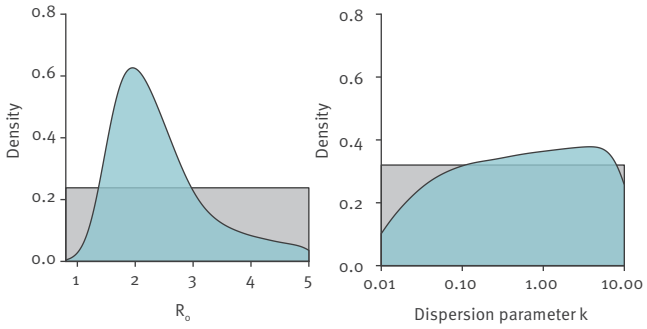
Table

Parameter ranges for stochastic simulations of outbreak trajectories, 2019 novel coronavirus outbreak, China, 2019–2020

Parameter	Description	Range	Number of values explored within the range
Ro	Basic reproduction number	0.8–5.0	22 (equidistant)
k	Dispersion parameter	0.01–10*	20 (equidistant on $\log_{10}$ scale)
D	Generation time interval (days)	7–14*	8 (equidistant)
n	Initial number of index cases	1–50	6 (equidistant)
T	Date of zoonotic transmission	20 Nov–4 Dec 2019	Randomised for each index case

Figure 1

Values of R_0 and k most compatible with the estimated size of the 2019 novel coronavirus epidemic in China, on 18 January 2020



The basic reproduction number R_0 quantifies human-to-human transmission. The dispersion parameter k quantifies the risk of a superspreading event (lower values of k are linked to a higher probability of superspreading). Note that the probability density of k implies a log10 transformation.

a total of 3.52 million one-index-case simulations that were run on UBELIX (http://www.id.unibe.ch/hpc), the high performance computing cluster at the University of Bern, Switzerland.

In a second step, we accounted for the uncertainty regarding the number of index cases n and the date T of the initial zoonotic animal-to-human transmissions at the wet market in Wuhan. An epidemic with several index cases can be considered as the aggregation of several independent epidemics with one index case each. We sampled (with replacement) n of the one-index-case epidemics, sampled a date of onset for each index case and aggregated the epidemic curves together. The sampling of the date of onset was done uniformly from a 2-week interval around 27 November 2019, in coherence with early phylogenetic analyses of 11 2019-nCoV genomes [10]. This step was repeated 100 times for each combination of R_0 (22 points), k (20 points), D (8 points) and n (6 points) for a total of 2,112,000 full epidemics simulated that included the uncertainty on D, n and T. Finally, we calculated the proportion of stochastic simulations that reached a total number of infected cases within the interval between 1,000 and 9,700 by 18 January 2020, as estimated by Imai et al. [6]. In a process related to approximate Bayesian computation (ABC), the parameter value combinations that led to simulations within that interval were treated as approximations to the posterior distributions of the parameters with uniform prior distributions. Model simulations and analyses were performed in the R software for statistical computing [11]. Code files are available on https://github.com/jriou/wcov.

Transmission characteristics of the 2019 novel coronavirus

In order to reach between 1,000 and 9,700 infected cases by 18 January 2020, the early human-to-human transmission of 2019-nCoV was characterised by values of R_0 around 2.2 (median value, with 90% high density interval: 1.4–3.8) (Figure 1). The observed data at this point are compatible with a large range of values for the dispersion parameter k (median: 0.54, 90% high density interval: 0.014–6.95). However, our simulations suggest that very low values of k are less likely. These estimates incorporate the uncertainty about the total epidemic size on 18 January 2020 and about the date and scale of the initial zoonotic event (Figure 2).

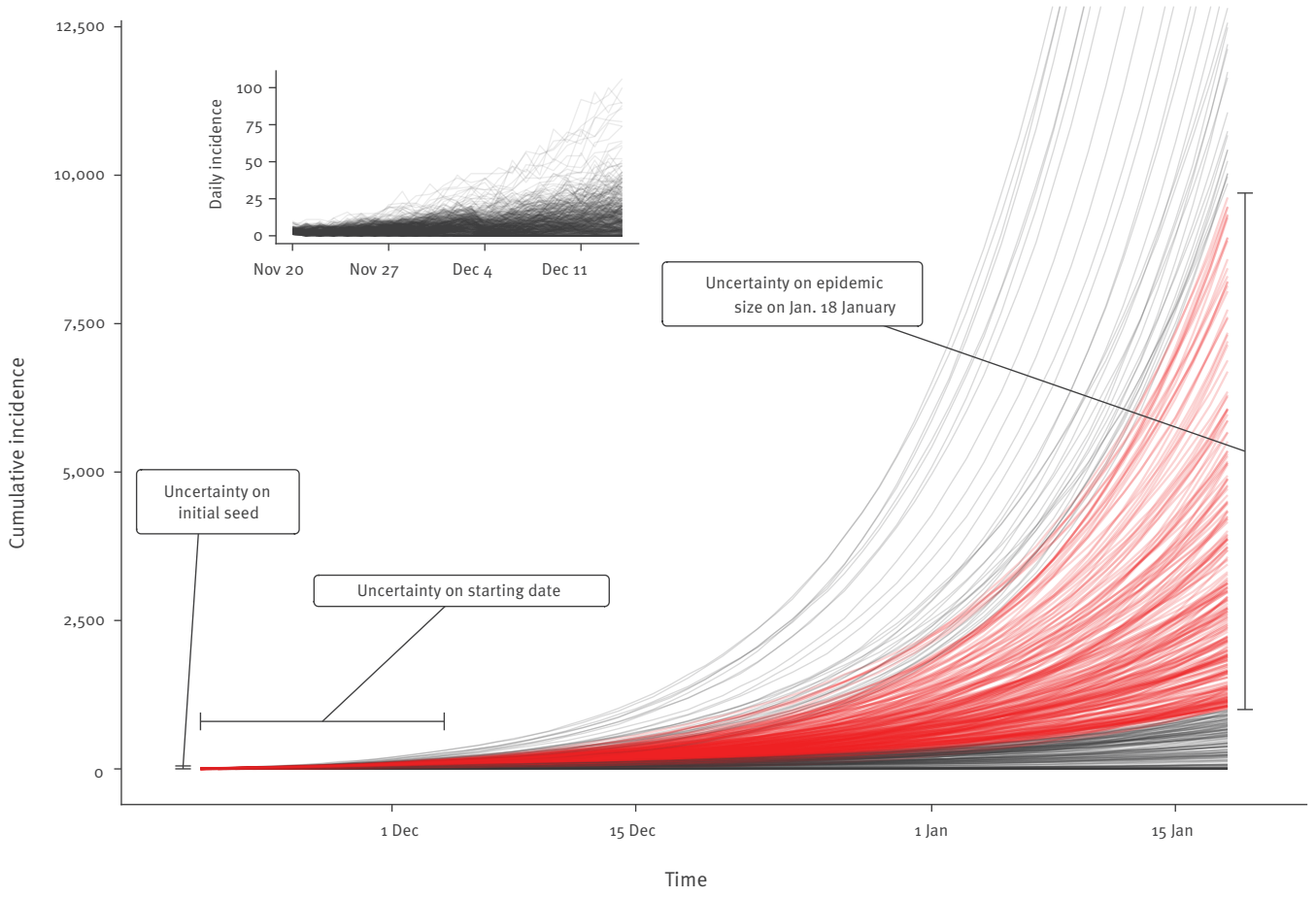
Comparison with past emergences of respiratory viruses

Comparison with other emerging coronaviruses in the past allows to put into perspective the available information regarding the transmission patterns of 2019-nCoV. Figure 3 shows the combinations of R_0 and k that are most likely at this stage of the epidemic. Our estimates of R_0 and k are more similar to previous estimates focusing on early human-to-human transmission of SARS-CoV in Beijing and Singapore [7] than of Middle East respiratory syndrome-related coronavirus (MERS-CoV) [9]. The spread of MERS-CoV was characterised by small clusters of transmission following repeated instances of animal-to-human transmission events, mainly driven by the occurrence of superspreading events in hospital settings. MERS-CoV could however not sustain human-to-human transmission beyond a few generations [12]. Conversely, the international spread of SARS-CoV lasted for 9 months and was driven by sustained human-to-human transmission, with occasional superspreading events. It led to more than 8,000 cases around the world and required extensive efforts by public health authorities to be contained [13]. Our assessment of the early transmission of 2019-nCoV suggests that 2019-nCoV might follow a similar path.

Our estimates for 2019-nCoV are also compatible with those of 1918 pandemic influenza, for which k was

Figure 2

Illustration of the simulation strategy, 2019 novel coronavirus outbreak, China, 2019–2020



The lines represent the cumulative incidence of 480 simulations with $R_0 = 1.8$ and $k = 1.13$. The other parameters are left to vary according to the Table. Among these simulated epidemics, 54.3% led to a cumulative incidence between 1,000 and 9,700 on 18 January 2020 (in red).

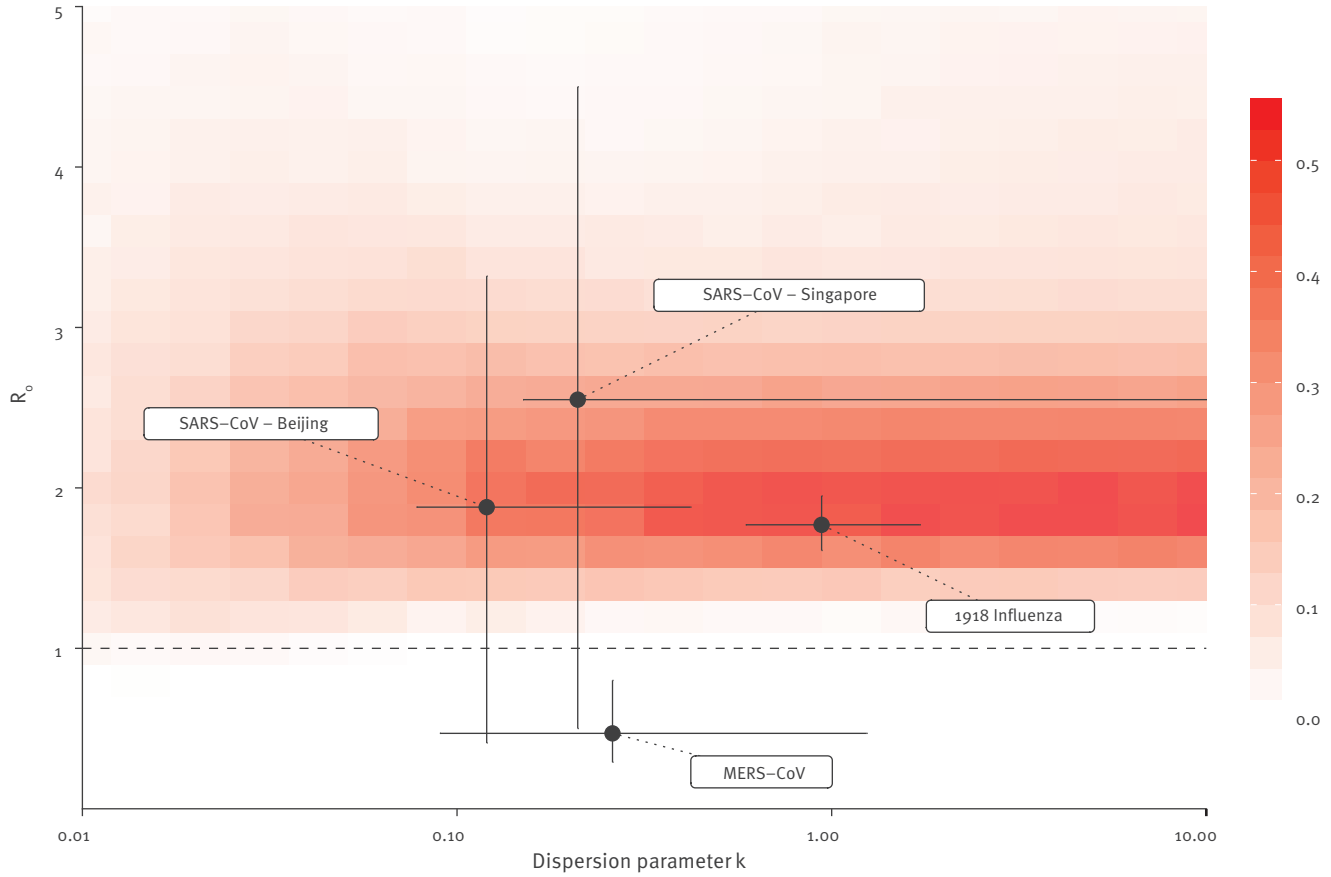
estimated [14]. Human-to-human transmission of influenza viruses is characterised by R_0 values between 1.5 and 2 and a larger value of k, implying a more steady transmission without superspreading. The emergence of new strains of influenza, for which human populations carried little to no immunity contrary to seasonal influenza, led to pandemics with different severity such as the ones in1918, 1957 1968 and 2009. It is notable that coronaviruses differ from influenza viruses in many aspects, and evidence for the 2019-nCoV with respect to case fatality rate, transmissibility from asymptomatic individuals and speed of transmission is still limited. Without speculating about possible consequences, the values of R_0 and k found here during the early stage of 2019-nCoV emergence and the lack of immunity to 2019-nCoV in the human population leave open the possibility for pandemic circulation of this new virus.

Strengths and limitations

The scarcity of available data, especially on case counts by date of disease onset as well as contact tracing, greatly limits the precision of our estimates and does not yet allow for reliable forecasts of epidemic spread. Case counts provided by local authorities in the early stage of an emerging epidemic are notoriously unreliable as reporting rates are unstable and vary with time. This is due to many factors such as the initial lack of proper diagnosis tools, the focus on the more severe cases or the overcrowding of hospitals. We avoided this surveillance bias by relying on an indirect estimate of epidemic size on 18 January, based on cases identified in foreign countries before quarantine measures were implemented on 23 January. This estimated range of epidemic size relies itself on several assumptions, including that all infected individuals who travelled from Wuhan to other countries have been detected [6]. This caveat may lead to an underestimation of transmissibility, especially considering the recent reports about asymptomatic cases [4]. Conversely, our results do not depend on any assumption about the existence of asymptomatic transmission, and only reflect the possible combinations of transmission events that lead to the situation on 18 January.

Figure 3

Proportion of simulated epidemics that lead to a cumulative incidence between 1,000 and 9,700 of the 2019 novel coronavirus outbreak, China, on 18 January 2020



MERS: Middle East respiratory syndrome-related coronavirus; SARS: severe acute respiratory syndrome-related coronavirus.

This can be interpreted as the combinations of R_0 and k values most compatible with the estimation of epidemic size before quarantine measures were put in place. As a comparison, we show the estimates of R_0 and k for the early human-to-human transmission of SARS-CoV in Singapore and Beijing and of 1918 pandemic influenza [7,9,14].

Our analysis, while limited because of the scarcity of data, has two important strengths. Firstly, it is based on the simulation of a wide range of possibilities regarding epidemic parameters and allows for the full propagation on the final estimates of the many remaining uncertainties regarding 2019-nCoV and the situation in Wuhan: on the actual size of the epidemic, on the size of the initial zoonotic event at the wet market, on the date(s) of the initial animal-to-human transmission event(s) and on the generation time interval. As it accounts for all these uncertainties, our analysis provides a summary of the current state of knowledge about the human-to-human transmissibility of 2019-nCoV. Secondly, its focus on the possibility of superspreading events by using negative-binomial offspring distributions appears relevant in the context of emerging coronaviruses [7,8]. While our estimate of k remains imprecise, the simulations suggest that very low values of $k < 0.1$ are less likely than higher values < 0.1 that correspond to a more homogeneous transmission pattern. However, values of k in the range of 0.1–0.2 are still compatible with a small risk of occurrence of large superspreading events, especially impactful in hospital settings [15,16].

Conclusions

Our analysis suggests that the early pattern of human-to-human transmission of 2019-nCoV is reminiscent of SARS-CoV emergence in 2002. International collaboration and coordination will be crucial in order to contain the spread of 2019-nCoV. At this stage, particular attention should be given to the prevention of possible rare but explosive superspreading events, while the establishment of sustained transmission chains from single cases cannot be ruled out. The previous experience with SARS-CoV has shown that established practices of infection control, such as early detection and isolation, contact tracing and the use of personal protective equipment, can stop such an epidemic. Given the existing uncertainty around the case fatality rate

and transmission, our findings confirm the importance of screening, surveillance and control efforts, particularly at airports and other transportation hubs, in order to prevent further international spread of 2019-nCoV.

*Authors' correction

On request of the authors, the ranges for the generation time and the dispersion parameter in the Table were corrected on 17 February 2020.

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Conflict of interest

None declared.

Authors' contributions

JR and CLA designed the study, JR performed model simulations, JR and CLA analysed and interpreted the results and wrote the manuscript.

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Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics

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The objective of this Personal View is to compare transmissibility, hospitalisation, and mortality rates for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with those of other epidemic coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), and pandemic influenza viruses. The basic reproductive rate (R_0) for SARS-CoV-2 is estimated to be 2·5 (range 1·8–3·6) compared with 2·0–3·0 for SARS-CoV and the 1918 influenza pandemic, 0·9 for MERS-CoV, and 1·5 for the 2009 influenza pandemic. SARS-CoV-2 causes mild or asymptomatic disease in most cases; however, severe to critical illness occurs in a small proportion of infected individuals, with the highest rate seen in people older than 70 years. The measured case fatality rate varies between countries, probably because of differences in testing strategies. Population-based mortality estimates vary widely across Europe, ranging from zero to high. Numbers from the first affected region in Italy, Lombardy, show an all age mortality rate of 154 per 100 000 population. Differences are most likely due to varying demographic structures, among other factors. However, this new virus has a focal dissemination; therefore, some areas have a higher disease burden and are affected more than others for reasons that are still not understood. Nevertheless, early introduction of strict physical distancing and hygiene measures have proven effective in sharply reducing R_0 and associated mortality and could in part explain the geographical differences.

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Introduction

WHO declared the COVID-19 outbreak, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a pandemic on March 11, 2020.[1] Initially, superspreading events, a cruise ship in Japan, mass gathering of a religious group in South Korea, skiing resorts in Italy and Austria, and a popular pilgrimage city (Iran) contributed to the rapid dissemination globally. Since then, the rate of global spread has accelerated, and widespread epidemics have occurred in numerous countries.

The SARS-CoV-2 virus is genetically closely related to severe acute respiratory syndrome coronavirus (SARS-CoV), the first pandemic threat of a novel and deadly coronavirus that emerged in late 2002 and caused an outbreak of severe acute respiratory syndrome (SARS). SARS-CoV was highly lethal but faded out after intense public health mitigation measures.[2] By contrast, the novel SARS-CoV-2 that emerged in December, 2019, rapidly caused a global pandemic. The SARS 2003 outbreak ceased in June, 2003, with a global total of 8098 reported cases and 774 deaths, and a case fatality rate of 9·7%, with most cases being acquired nosocomially.[2] In comparison, the Middle East respiratory syndrome coronavirus (MERS-CoV)—another deadly coronavirus, but which is currently not presenting a pandemic threat—emerged in 2012, and has caused 2494 reported cases and 858 deaths in 27 countries and has a very high case fatality rate of 34%.[3] Because MERS-CoV is widespread in dromedary camels, zoonotic cases continue to occur, unlike SARS-CoV, which emerged from wildlife and was eliminated from the intermediate host reservoir.

The new coronavirus SARS-CoV-2 is less deadly but far more transmissible than MERS-CoV or SARS-CoV. The virus emerged in December, 2019, and as of June 29, 2020, 6 months into the first pandemic wave, the global count is rapidly approaching 10 million known cases and has passed 500 000 deaths.[4] Because of its broad clinical spectrum and high transmissibility, eradicating SARS-CoV-2, as was done with SARS-CoV in 2003, does not seem a realistic goal in the short term.

In this Personal View we summarise key epidemiological characteristics of SARS-CoV-2 in comparison with other epidemic coronaviruses and pandemic influenza. We explore what makes SARS-CoV-2 different from pandemic influenza virus and the other epidemic severe coronaviruses such as SARS-CoV and MERS-CoV. We study the various characteristics of each virus, including the transmission and severity characteristics, case fatality rates (mortality in individuals with the disease), and the

Key messages

- The basic reproductive rate (R_0) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is similar to, or higher than, the R_0 of SARS-CoV and pandemic influenza
- Mortality due to SARS-CoV-2 and SARS-CoV is strongly skewed towards people older than 70 years, dissimilar to the 1918 and 2009 influenza pandemics
- The proportion of symptomatic people requiring hospital admission is higher for SARS-CoV-2 infections than for the 2009 influenza pandemic
- The population risk of admission to the intensive care unit is five to six times higher in patients infected with SARS-CoV-2 than in those with the fairly mild 2009 influenza pandemic
- The case fatality rate is probably around 1% after adjusting for asymptomatic and mild illness; serological studies will aid in refining this estimate

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See Online for appendix

population-level mortality of the SARS-CoV-2 pandemic (table 1).

Transmissibility and the basic reproductive rate

Estimating the ability of a new pathogen to spread is a key measure in an emerging disease outbreak. A metric used to describe this spread is the basic reproductive rate (R_0). R_0 is defined as the average number of secondary transmissions from one infected person; when R_0 is greater than 1, the epidemic is growing. The R_0 estimates for SARS-CoV, SARS-CoV-2, MERS-CoV, and the influenza pandemics are summarised in the appendix (p 1).

The R_0 for the SARS outbreak in 2003 was estimated to be between 2·0 and 3·0 in the early months (until the end of April), before public health control measures were introduced.[2,5,6] Various control measures soon reduced the transmissibility to 1·1, with a wide IQR of 0·4–2·4.[6,7] For MERS-CoV, the R_0 (unmitigated) was estimated to be 0·69 (95% CI 0·50–0·92), consistent with MERS-CoV never having caused sustained epidemics.[8,37] For SARS-CoV-2, a recent China joint mission by WHO concluded that "transmission of SARS-CoV-2 is mostly driven by clusters in close contacts, particularly family clusters, and less so by community transmission".[9] Since the statement was released, this conclusion has been challenged, although superspreading events continue to occur in the pandemic. Studies have estimated the R_0 at 2·2 (95% CI 1·4–3·9)[10] and 2·7 (2·5–2·9);[11] therefore, an average R_0 of 2·5 seems a reasonable estimate (appendix p 1). By comparison, the initial R_0 estimate for the 2009 influenza A H1N1 pandemic was 1·7,[12] later estimated between 0·17 and 1·3 after mitigation was initiated.[13–15] R_0 for the 1918 influenza pandemic was estimated at around 2·0 in the first wave in July, 1918.[16]

The R_0 values have important implications for disease control. R_0 magnitude indicates the level of mitigation efforts needed to bring an epidemic under control.[6] Mitigation reduces the effective transmission coefficient, now called R_e. R_e needs to be reduced to less than 1 to ensure cessation of an epidemic, which can be done by rapid case identification, quarantine measures, and physical distancing to prevent secondary transmissions. For childhood diseases such as measles, the cessation of epidemic spread was achieved with an effective vaccine. However, a vaccine has never been a major tool for control of pandemics because they either occurred before the era of modern vaccines or, as in 2009, the vaccine became available only after the first waves had already occurred.

For SARS-CoV-2 with an R_0 value of approximately 2·5, transmission would need to be reduced by more than 60% to reach R_e of less than 1 ($1–1/R_0$). The transmissibility coefficient declines over time as control measures start having an effect, which was seen during the successful eradication of SARS-CoV in 2003.[8] By contrast with SARS-CoV and SARS-CoV-2, MERS-CoV has limited transmissibility even in the absence of mitigation, although the virus has caused several nosocomial outbreaks since 2012, mainly in hospitals in Saudi Arabia, Jordan, and South Korea.[17]

Incubation period of SARS-CoV-2 and viral excretion

All three coronaviruses have a longer incubation period (time from infection to symptom onset) than influenza viruses. One study estimated the mean incubation period of SARS-CoV-2 to be 5·8 days, ranging from 1·3 to 11·3 days.[18] Another study estimated the median incubation period to be 5·1 days and found that 97·5% of people showed symptoms within 11·5 days of infection.[19] A study from China estimated an incubation period of 5·2 days.[9]

A notable difference between SARS-CoV, SARS-CoV-2, and MERS-CoV are the kinetics of virus shedding. Whereas SARS-CoV and MERS-CoV have tropism for lower airways, with less virus present in the upper respiratory tract, this tropism is different in SARS-CoV-2. For SARS-CoV-2, the average viral load in a family cluster was $6·8\times10^5$ copies per upper respiratory tract swab during the first 5 days, and live virus isolates were

	SARS-CoV-2	SARS-CoV	Pandemic influenza 1918	Pandemic influenza 2009	Interpretation
Transmissibility, R_0	2·5	2·4	2·0	1·7	SARS-CoV-2 has the highest average R_0
Incubation period, days	4–12	2–7	Unknown	2	Longer incubation period; SARS-CoV epidemics form slower
Interval between symptom onset and maximum infectivity, days	0	5–7	2	2	SARS-CoV-2 is harder to contain than SARS-CoV
Proportion with mild illness	High	Low	High	High	Facilitates undetected transmission
Proportion of patients requiring hospitalisation	Few (20%)	Most (>70%)	Few	Few	Concern about capacity in the health sector
Proportion of patients requiring intensive care	1/16 000	Most (40%)	Unknown	1/104 000	Concern about capacity in the health sector
Proportion of deaths in people younger than 65 years out of all deaths	0·6–2·8%	Unknown	95%	80%	SARS-CoV-2 might cause as many deaths as the 1918 influenza pandemic, but fewer years of life lost and disability-adjusted life-years, as deaths are in the older population with underlying health conditions
Risk factors for severe illness	Age, comorbidity	Age, comorbidity	Age (<60 years)	Age (<60 years)	..

Data from the following references.[2,3,5–36] MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 1: **Characteristics of SARS-CoV-2, SARS-CoV, and pandemic influenza**

obtained from swabs during the first week of illness.[20] In a study from Hong Kong,[38] high viral loads were found in the first samples obtained after admission to hospital. This finding was confirmed in a study from China,[39] which found a high viral load at the onset of symptoms that declined in the following 5–6 days. This quick decline in the viral load makes isolation and quarantine of patients with SARS-CoV-2 and their contacts much more challenging and less effective, as it has to be done as soon as possible after illness onset in order to reduce transmission. By contrast, for SARS-CoV viral loads peaked at 6–11 days after symptom onset,[21,22] allowing a full extra week to identify and isolate cases before transmission occurred. This difference would in part explain why SARS could be eradicated in 2003 compared with the trajectory seen in the SARS-CoV-2 pandemic.

There is increasing evidence of transmission from asymptomatic people, although what proportion of these individuals are presymptomatic remains unknown. It is clear that COVID-19 has a broad clinical picture which includes asymptomatic and mild illness.[23,40] A study from Iceland[24] found that 43% of PCR-positive cases had no symptoms, although some individuals showed symptoms later on (number of days remains unknown). Unofficial data from China suggest that 78% of cases were asymptomatic.[25]

Viral shedding might be occurring for prolonged periods. A study of viral load[26] in respiratory tract samples, faeces, and blood from 96 patients with COVID-19 found a viral load of 10^5–10^6 copies per mL up to 3 weeks after symptom onset. Viral shedding tended to be longer in stool samples; however, as of June 9, 2020, there is no documented evidence of faecal–oral transmission. Viral load is higher and persists for longer in the lower respiratory tract of patients who are severely ill with COVID-19.[26] For SARS, lower respiratory tract infection occurred without upper respiratory tract infection. As a consequence, transmission of SARS-CoV was infrequent during the first 5 days of illness,[2] and unlike transmission of influenza, transmission in household settings was rare.[41]

Case fatality and risk of severe illness

A key difference between SARS-CoV-2 and pandemic influenza is the age distribution of patients who are severely ill. The mortality rate in people infected with SARS-CoV-2 increases steeply with age, and fatal outcomes are almost exclusively seen in people older than 50 years (table 2). This age-related increase in severe morbidity and mortality was also observed for SARS-CoV (although with a far greater case fatality). In Hong Kong, the case fatality due to SARS-CoV was 0% for age group 0–24 years, 6% for those aged 25–44 years, 15% for those aged 45–64 years, and 52% for people who were 65 years and older.[2,27] For both SARS and COVID-19, children rarely had severe illness (table 2). Recently, a rare hyperinflammatory syndrome has been reported in children with COVID-19.[45] In one study looking at close household contacts of people with COVID-19,[28] children and adults both had a secondary attack rate of 15%, but whether children transmit the virus as effectively as adults is still unknown.

Clinical case fatality, for which the case definition was fever and respiratory symptoms (including pneumonia), was around 5% in Hubei province and only around 1% in the rest of China and South Korea.[43] In the USA, case fatality rates among patients with COVID-19 were less than 1% for people aged 20–54 years, 1–5% in those aged 55–64 years, 3–11% in those aged 65–84 years, and 10–27% in people aged 85 years and older. Early in the outbreak there have been few deaths in children and young adults younger than 20 years.[46] Although most patients (90%) with COVID-19 have mild clinical illness, there is considerable demand for intensive care because of the subset of patients who develop acute respiratory distress syndrome. This requirement for respiratory support is higher for SARS-CoV-2 cases than for the influenza pandemic in 2009 (table 1). In a study[29] of patients who were admitted to hospital in New York, NY, USA, 14% required intensive care (median age 68 years).

A Danish study of the 2009 influenza A H1N1 pandemic[47] found that the proportion of patients with pandemic influenza never exceeded 4·5% of the total national intensive care unit (ICU) bed capacity, and the ICU admission rate was estimated to be approximately one patient per 5500 patients infected with influenza A H1N1.[48] Such figures are lacking for the COVID-19 pandemic, but it is evident that ICU capacity in this pandemic is a crucial element. In Lombardy, Italy, an estimated 2·3% of COVID-19 cases needed an ICU bed.[44] Comparing these rates is difficult because most people in the 2009 pandemic were younger than 60 years, whereas SARS-CoV-2 affects mainly older individuals. We compared key variables and features of the 1918 and 2009 influenza pandemics with SARS-CoV-2, SARS-CoV, and MERS-CoV in table 3.

	Morbidity, % of positive tests			Fatality rates, %		
	China	South Korea	Italy (Lombardy)	China	South Korea	Italy (all regions)
0–9 years	0·9	1·0	0·4	0·0	0·0	0·0
10–19 years	1·2	5·2	0·8	0·2	0·0	0·0
20–29 years	8·1	28·0	2·7	0·2	0·0	0·0
30–39 years	17	10·3	5·1	0·2	0·1	0·0
40–49 years	19·2	14·0	9·4	0·4	0·1	0·1
50–59 years	22·4	19·3	16·6	1·3	0·4	0·6
60–69 years	19·2	12·4	17·5	17·5	1·6	2·7
70–79 years	8·8	6·5	23·2	8·0	5·4	9·6
≥80 years	3·2	3·3	19·7	14·8	10·2	16·6

Data for China,[42] South Korea,[43] and Italy.[44] Average age of death in Italy is 81 years, and mortality in Italy in people older than 90 years was 19%.[44]

Table 2: **COVID-19 age-specific case morbidity and fatality rates**

	Number of deaths (adjusted to year 2000 population)	Mean age at death (years)	Years of life lost (adjusted to year 2000 population)
2009 influenza pandemic	7500–44 100*; 8500–17 600†	37·4	334 000–1 973 000; 328 900–680 300
1968 influenza pandemic	86 000‡	62·2	1 693 000
1957 influenza pandemic	150 600‡	64·6	2 698 000
1918 influenza pandemic	1 272 300‡	27·2	63 718 000
1979–2001 average influenza A H3N2 season	47 800	75·7	594 000
2003 SARS-CoV	774	Unknown	Unknown
2012 MERS-CoV	858	>65·0	Unknown
2019 SARS-CoV-2	302 059§	Unknown	Unknown

MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Range based on estimates of excess pneumonia and influenza deaths (lower range number) and all-cause deaths (upper range number); estimated from projections of mortality surveillance from 122 cities. †Probabilistic estimates from the Centers for Disease Control and Prevention using 2009 pandemic survey data.[35] ‡Estimates based on the excess mortality approach applied to final national vital statistics and adjusted to year 2000 population-age structure. §As per the May 17, 2020, WHO situation report.[4]

Table 3: **Mortality from influenza and coronaviruses[30,31]**

	Number of known cases	Known cases per 100 000 population	Deaths	Deaths per 100 000 population	Tests per 100 000 population
USA	1 382 362	421	83 819	26	3623
South Korea	11 037	21	262	0·5	1458
Spain	230 183	490	27 459	58	6498
Italy (Lombardy)	84 119	841	5374	54	9398
Germany	173 772	209	7881	9	3759
UK	236 715	353	33 998	51	3670
South Africa	13 524	23	247	0·4	742

Data taken from the WHO situation report on May 17, 2020.[4] Population data from Eurostat.

Table 4: **Cumulated prevalence, mortality, and diagnostic tests per country**

For the **COVID-19 Eurostat data** see https://www.worldometers.info/coronavirus/

Population-based mortality

The mortality impact of seasonal and pandemic influenza has long been estimated as the excess mortality above baseline. Excess mortality is ideally estimated from a mortality time series updated once per week, during, or at the end of a pandemic.[30,31] A study on excess mortality in the 2009 influenza pandemic used data from 33 countries,[31] and found that the global burden was approximately 300 000 deaths. The mean excess mortality for seasonal influenza was 0·1–6·4 per 100 000 people younger than 65 years, 2·9–44·0 per 100 000 people aged 65–74 years, and 17·9–223·5 per 100 000 people aged 75 years and older.[31] It is too early to study excess mortality for COVID-19 in South Korea and Italy, but such studies from China would be helpful. As of June 8, 2020, in Lombardy (Italy), the mortality rate for COVID-19 has reached 159 per 100 000 population.[32] Notably, these data are not from the end of the outbreak and numbers are expected to increase further, as some patients spent 4 weeks in intensive care and thus have not yet resolved the infection.

The timely European Morbidity and Mortality (EuroMOMO) surveillance system updated once per week is a great resource for accessing excess mortality studies relating to the COVID-19 pandemic in European countries.[49] The website shows *Z* score elevations in a time series of deaths due to any cause, allowing comparison with elevations caused by seasonal influenza. The EuroMOMO data show high COVID-19 associated excess mortality in a number of countries including Italy, Spain, the UK, and Sweden, whereas other countries such as Germany, Norway, and Greece have found no, or low, excess mortality (appendix p 2). Case fatality rates are shown in table 4.[49] In the USA, the Centers for Disease Control and Prevention also reports substantial elevation in national respiratory deaths.[50] For comparison, the influenza pandemic excess mortality has ranged from extreme (1918) to mild (2009) over the past 100 years (table 3). A study modelling global excess mortality for the moderate 1957 influenza A H2N2 pandemic[30] found a respiratory excess mortality rate of 0·02%. For the deadly 1918 influenza pandemic estimates show that about 1–2% of the global population died.[51] However, excess mortality for the 2009 pandemic was not much greater than that of a severe seasonal influenza, at about 0·04% deaths in the global population[30,31]

Because the mean age at death varied greatly in past pandemics, one excess mortality study also looked at excess years of life lost.[30] Using years of life lost as a metric, this study found that the three influenza pandemics in 1957, 1968, and 2009 had a similar size effect. Although it is too early to draw conclusions, the effect of COVID-19 might be higher in terms of excess mortality, possibly with numbers somewhere in between the 1957 and 1918 influenza pandemics. However, in terms of excess years of life lost, because of the mean age (~80 years) of COVID-19 fatalities, the COVID-19 pandemic would score lower, perhaps similarly to the 1957 and 1968 influenza pandemics. More time and data are needed before the COVID-19 pandemic can be accurately compared with past pandemics.

Incidence of SARS-CoV-2 infections

Because of the broad clinical spectrum, it has become evident that to find out the true attack rate of SARS-CoV-2 serological studies are needed. Meanwhile we can look at reported cases, deaths, and the number of tests per 100 000 population, understanding that more testing and a broader clinical case definition mean a higher rate of cases. Currently, each country is in a different phase of the pandemic, which will lead to a bias in early country comparisons.

Official figures are available for the USA, South Korea, the UK, Spain, Germany, and South Africa (table 4, appendix pp 3–4). As of Feb 16, 2020, Hubei, the earliest affected province in China, had 67 466 confirmed cases of COVID-19 and 2902 deaths reported.[9] These figures correspond to 0·11% of the population being affected and a mortality rate of 4·8 per 100 000 population, which

is low compared with certain countries in Europe,[52] possibly because people with mild symptoms were not tested.[23–25] Serological surveys will shed light on these discrepancies. For comparison, seasonal influenza attack rates are in the range of 10–20% every winter.[53]

SARS-CoV-2 spread compared with SARS-CoV

It is still unclear what characteristics the newly emerging coronavirus, SARS-CoV-2, possesses—which its relative SARS-CoV did not possess in 2003—allowing it to succeed in causing a global pandemic. Even at the height of the 2003 SARS-CoV epidemic, 140 new infections were reported per week,[2] compared with more than 100 000 infections with SARS-CoV-2. In 2003, SARS began to spread globally after a patient travelled from mainland China to Hong Kong. International flight traffic from China has increased at least ten times since 2003, and a massive high-speed train network connects a large part of eastern China and Wuhan where the COVID-19 outbreak began in 2019. Aside from this dissemination advantage, patients with COVID-19 begin viral shedding a few days before symptom onset, which is very different from SARS-CoV and makes quarantine measures much less efficient.

SARS-CoV-2 and warmer weather

A recent study[54] modelled possible scenarios for COVID-19 up to 2024, on the basis of epidemiology of the seasonal coronaviruses OC43 and HKU1. The study assumed a winter-time R_0 of 2·2 and a summertime R_0 of 1·3, and predicted winter cycles of COVID-19 after the pandemic phase. By comparison, the A H1N1 influenza pandemic started in Mexico in February, 2009, and by June a total of 73 countries had reported more than 26 000 laboratory-confirmed cases.[55] In July, 1918, there was a peak of H1N1 influenza infections seen in Copenhagen before the second wave hit in November.[16,56] These previous pandemics have shown that influenza transmission does occur over the summer and seasonality is difficult to predict.

Temperature and humidity makes a difference for viral survival in the environment. A study using enveloped virus Phi6 as a surrogate virus[57] found that infectivity was sensitive to temperature and decreased by two orders of magnitude between 19°C and 25°C. Some data on the effect of temperature are available for SARS-CoV only. A study of SARS-CoV found a two-log reduction in virus titre after 7 h at 38°C and 95% humidity.[58] At 4°C, SARS-CoV persisted for up to 28 days, and the lowest level of inactivation occurred at 20% relative humidity. Inactivation was faster at 20°C than at 4°C at all humidity levels. These experimental data suggest that SARS-CoV-2 might be less able to survive in the summer.

SARS-CoV-2 and the effect of containment measures

A mortality study[59] in 17 cities in the USA during the 1918 influenza pandemic found that the cities which implemented mitigation strategies early on had a delayed, flatter epidemic curve, with a 50% lower peak mortality, and a 20% lower overall mortality. Thus, mitigating policies are of paramount importance to ensure that the burden on the health-care system remains manageable. The examples of China and South Korea, and early signs of bending the curve seen in Europe, show that influencing the spread of SARS-CoV-2 is possible. However, the socioeconomical costs are enormous and will be long lasting.

Radical containment measures have been used to curb the pandemic in some affected countries. The approach taken in South Korea was especially effective, done by rapidly applying extensive testing, quarantine, and contact tracing of individuals from a large church group in the early stages of the outbreak. Also, schools were closed, and all international arrivals were quarantined for 2 weeks.[43] China, South Korea, and Singapore show that mitigation using a combination of contact tracing and rigorous social distancing measures is possible.[60] However, new outbreaks have started to occur in each of these countries and renewed control measures have been implemented

Countries such as Denmark, Italy, Spain, and Germany have relied mostly on social distancing and hygiene measures, in population lockdowns of various magnitudes of intensity. Such draconic measures were used when the epidemics were progressing too fast and capacity for effective case identification, contact tracing, and containment became impossible. The consensus is that rigorous mitigation measures are needed early to slow down SARS-CoV-2 transmission.[61] Drastic measures of quarantine and mobility restrictions put in place by China, Europe, and the USA are no different than those used for plague in the 14th century. The COVID-19 pandemic so far has shown that such measures could possibly halt the pandemic if individuals follow the specific country guidelines.

Conclusion

The first WHO "disease X" scenario has become a reality.[33] The SARS-CoV-2 pandemic has already caused severe morbidity and mortality in older adults, much higher than in the pandemic influenza. Although children are clearly less affected, their role in the transmission of the virus still needs to be studied.

At this early stage in the pandemic there are no effective treatments such as antivirals or passive immunisation schemes. Development of a safe and effective vaccine will take time. Thus, only supportive treatment in hospitals is currently available, and efforts to slow and limit the spread of the virus continue. The goal is to reduce the impact of the virus, prevent overwhelming the health-care system, and protect the people at highest risk of severe outcomes, while waiting for an effective vaccine and treatments.

Historical evidence from influenza pandemics which occurred in the past century shows us that pandemics

tend to come in waves over the first 2–5 years as the population immunity builds-up (naturally or through vaccination), and then the number of infected cases tends to decrease. This observation is the most likely trajectory for the SARS-CoV-2 virus. However, the near future will require a transition to a new normal, in which a combination of physical distancing, enhanced testing, quarantine, and contact tracing will be needed for a long time. While clinical research and testing of antivirals and vaccine candidates is ongoing, scientists will learn from regions and countries that were first affected. Also, epidemiological and phylogenetic studies can yield much information about risk factors (other than age) such as disease transmission, the role of children in transmission, and a better estimate of case fatality.

It is highly likely that after SARS-CoV-2 there will be another pandemic. It might be another coronavirus, an influenza virus, a paramyxovirus, or a completely new disease. We believe that learning from this experience is crucial so that we can meet a future pandemic threat with far better preparation in terms of testing, adequate stocks of personal protective equipment, and critical care capability. International pandemic planning is needed to ensure collaboration between countries, including better surveillance of emerging infections especially zoonoses. Controlling an outbreak has everything to do with mitigating casualties such as economic losses, joblessness, loneliness, and even loss of human dignity at the end of life.

Contributors

EP and SAK drafted the Personal View. MK contributed to the description of influenza virus, MERS-CoV, SARS-CoV, and SARS-CoV-2. UG, DHH, NP, FC, and MS helped with the data. UG provided expertise on South Korea, DHH provided expertise on the USA, and NP and FC provided expertise on Italy. MS contributed with data from Denmark and LS contributed with the historical analysis of previous influenza pandemics.

Declaration of interests

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REFERENCE 4

World Health Organization

Transmission of SARS-CoV-2: implications for infection prevention precautions

Scientific Brief

9 July 2020

This document is an update to the scientific brief published on 29 March 2020 entitled “Modes of transmission of virus causing COVID-19: implications for infection prevention and control (IPC) precaution recommendations” and includes new scientific evidence available on transmission of SARS-CoV-2, the virus that causes COVID-19.

Overview

This scientific brief provides an overview of the modes of transmission of SARS-CoV-2, what is known about when infected people transmit the virus, and the implications for infection prevention and control precautions within and outside health facilities. This scientific brief is not a systematic review. Rather, it reflects the consolidation of rapid reviews of publications in peer-reviewed journals and of non-peer-reviewed manuscripts on pre-print servers, undertaken by WHO and partners. Preprint findings should be interpreted with caution in the absence of peer review. This brief is also informed by several discussions via teleconferences with the WHO Health Emergencies Programme ad hoc Experts Advisory Panel for IPC Preparedness, Readiness and Response to COVID-19, the WHO ad hoc COVID-19 IPC Guidance Development Group (COVID-19 IPC GDG), and by review of external experts with relevant technical backgrounds.

The overarching aim of the global Strategic Preparedness and Response Plan for COVID-19*(1)* is to control COVID-19 by suppressing transmission of the virus and preventing associated illness and death. Current evidence suggests that SARS-CoV-2, the virus that causes COVID-19, is predominantly spread from person-to-person. Understanding how, when and in what types of settings SARS-CoV-2 spreads is critical to develop effective public health and infection prevention and control measures to break chains of transmission.

Modes of transmission

This section briefly describes possible modes of transmission for SARS-CoV-2, including contact, droplet, airborne, fomite, fecal-oral, bloodborne, mother-to-child, and animal-to-human transmission. Infection with SARS-CoV-2 primarily causes respiratory illness

ranging from mild disease to severe disease and death, and some people infected with the virus never develop symptoms.

Contact and droplet transmission

Transmission of SARS-CoV-2 can occur through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions or their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.(2-10) Respiratory droplets are >5-10 μm in diameter whereas droplets ≤5μm in diameter are referred to as droplet nuclei or aerosols.(11) Respiratory droplet transmission can occur when a person is in close contact (within 1 metre) with an infected person who has respiratory symptoms (e.g. coughing or sneezing) or who is talking or singing; in these circumstances, respiratory droplets that include virus can reach the mouth, nose or eyes of a susceptible person and can result in infection. Indirect contact transmission involving contact of a susceptible host with a contaminated object or surface (fomite transmission) may also be possible (see below).

Airborne transmission

Airborne transmission is defined as the spread of an infectious agent caused by the dissemination of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time.(11) Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols ("aerosol generating procedures").(12) WHO, together with the scientific community, has been actively discussing and evaluating whether SARS-CoV-2 may also spread through

aerosols in the absence of aerosol generating procedures, particularly in indoor settings with poor ventilation.

The physics of exhaled air and flow physics have generated hypotheses about possible mechanisms of SARS-CoV-2 transmission through aerosols.*(*13-16*)* These theories suggest that 1) a number of respiratory droplets generate microscopic aerosols (<5 μm) by evaporating, and 2) normal breathing and talking results in exhaled aerosols. Thus, a susceptible person could inhale aerosols, and could become infected if the aerosols contain the virus in sufficient quantity to cause infection within the recipient. However, the proportion of exhaled droplet nuclei or of respiratory droplets that evaporate to generate aerosols, and the infectious dose of viable SARS-CoV-2 required to cause infection in another person are not known, but it has been studied for other respiratory viruses.*(*17*)*

One experimental study quantified the amount of droplets of various sizes that remain airborne during normal speech. However, the authors acknowledge that this relies on the independent action hypothesis, which has not been validated for humans and SARS-CoV-2. *(*18*)* Another recent experimental model found that healthy individuals can produce aerosols through coughing and talking *(*19*)*, and another model suggested high variability between individuals in terms of particle emission rates during speech, with increased rates correlated with increased amplitude of vocalization.*(*20*)* To date, transmission of SARS-CoV-2 by this type of aerosol route has not been demonstrated; much more research is needed given the possible implications of such route of transmission.

Experimental studies have generated aerosols of infectious samples using high-powered jet nebulizers under controlled laboratory conditions. These studies

found SARS-CoV-2 virus RNA in air samples within aerosols for up to 3 hours in one study *(21)* and 16 hours in another, which also found viable replication-competent virus.*(22)* These findings were from experimentally induced aerosols that do not reflect normal human cough conditions.

Some studies conducted in health care settings where symptomatic COVID-19 patients were cared for, but where aerosol generating procedures were not performed, reported the presence of SARS-CoV-2 RNA in air samples *(23-28)*, while other similar investigations in both health care and non-health care settings found no presence of SARS-CoV-2 RNA; no studies have found viable virus in air samples.*(29-36)* Within samples where SARS-CoV-2 RNA was found, the quantity of RNA detected was in extremely low numbers in large volumes of air and one study that found SARS-CoV-2 RNA in air samples reported inability to identify viable virus. *(25)* The detection of RNA using reverse transcription polymerase chain reaction (RT-PCR)-based assays is not necessarily indicative of replication- and infection-competent (viable) virus that could be transmissible and capable of causing infection.*(37)*

Recent clinical reports of health workers exposed to COVID-19 index cases, not in the presence of aerosol-generating procedures, found no nosocomial transmission when contact and droplet precautions were appropriately used, including the wearing of medical masks as a component of the personal protective equipment (PPE). *(38, 39)* These observations suggest that aerosol transmission did not occur in this context. Further studies are needed to determine whether it is possible to detect viable SARS-CoV-2 in air samples from settings where no procedures that generate aerosols are performed and what role aerosols might play in transmission.

Outside of medical facilities, some outbreak reports related to indoor crowded spaces *(40)* have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice *(7)*, in restaurants *(41)* or in fitness classes.*(42)* In these events, short-range aerosol transmission, particularly in specific indoor locations, such as crowded and inadequately ventilated spaces over a prolonged period of time with infected persons cannot be ruled out. However, the detailed investigations of these clusters suggest that droplet and fomite transmission could also explain human-to-human transmission within these clusters. Further, the close contact environments of these clusters may have facilitated transmission from a small number of cases to many other people (e.g., superspreading event), especially if hand hygiene was not performed and masks were not used when physical distancing was not maintained.*(43)*

Fomite transmission

Respiratory secretions or droplets expelled by infected individuals can contaminate surfaces and objects, creating fomites (contaminated surfaces). Viable SARS-CoV-2 virus and/or RNA detected by RT-PCR can be found on those surfaces for periods ranging from hours to days, depending on the ambient environment (including temperature and humidity) and the type of surface, in particular at high concentration in health care facilities where COVID-19 patients were being treated. *(21, 23, 24, 26, 28, 31-33, 36, 44, 45)* Therefore, transmission may also occur indirectly through touching surfaces in the immediate environment or objects contaminated with virus from an infected person (e.g. stethoscope or thermometer), followed by touching the mouth, nose, or eyes.

Despite consistent evidence as to SARS-CoV-2 contamination of surfaces and the survival of the virus on certain surfaces, there are no specific reports which have directly demonstrated fomite transmission. People who come into contact with potentially infectious surfaces often also have close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern. However, fomite transmission is considered a likely mode of transmission for SARS-CoV-2, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way.

Other modes of transmission

SARS-CoV-2 RNA has also been detected in other biological samples, including the urine and feces of some patients.*(46-50)*One study found viable SARS-CoV-2 in the urine of one patient.*(51)*Three studies have cultured SARS-CoV-2 from stool specimens. *(48, 52, 53)* To date, however, there have been no published reports of transmission of SARS-CoV-2 through feces or urine.

Some studies have reported detection of SARS-CoV-2 RNA, in either plasma or serum, and the virus can replicate in blood cells. However, the role of bloodborne transmission remains uncertain; and low viral titers in plasma and serum suggest that the risk of transmission through this route may be low.*(48, 54)* Currently, there is no evidence for intrauterine transmission of SARS-CoV-2 from infected pregnant women to their fetuses, although data remain limited. WHO has recently published a scientific brief on breastfeeding and COVID-19.*(55)* This brief explains that viral RNA fragments have been found by RT-PCR testing in a few breast milk

samples of mothers infected with SARS-CoV-2, but studies investigating whether the virus could be isolated, have found no viable virus. Transmission of SARS-CoV-2 from mother to child would necessitate replicative and infectious virus in breast milk being able to reach target sites in the infant and also to overcome infant defense systems. WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed.*(55)*

Evidence to date shows that SARS-CoV-2 is most closely related to known betacoronaviruses in bats; the role of an intermediate host in facilitating transmission in the earliest known human cases remains unclear.*(56, 57)* In addition to investigations on the possible intermediate host(s) of SARS-CoV-2, there are also a number of studies underway to better understand susceptibility of SARS-CoV-2 in different animal species. Current evidence suggests that humans infected with SARS-CoV-2 can infect other mammals, including dogs*(58)*, cats*(59)*, and farmed mink.*(60)* However, it remains unclear if these infected mammals pose a significant risk for transmission to humans.

When do people infected with SARS-CoV-2 infect others?

Knowing when an infected person can spread SARS-CoV-2 is just as important as how the virus spreads (described above). WHO has recently published a scientific brief outlining what is known about when a person may be able to spread, based on the severity of their illness.*(61)*

In brief, evidence suggests that SARS-CoV-2 RNA can be detected in people 1-3 days before their symptom onset, with the highest viral loads, as measured by RT-PCR, observed around the day of symptom onset, followed by a gradual decline over time.*(47, 62-65)* The duration of RT-PCR positivity generally appears to be 1-2 weeks for asymptomatic persons, and up to 3 weeks or more for patients with mild to moderate disease.*(62, 65-68)* In patients with severe COVID-19 disease, it can be much longer.*(47)*

Detection of viral RNA does not necessarily mean that a person is infectious and able to transmit the virus to another person. Studies using viral culture of patient samples to assess the presence of infectious SARS-CoV-2 are currently limited. *(61)* Briefly, viable virus has been isolated from an asymptomatic case,*(69)* from patients with mild to moderate disease up to 8-9 days after symptom onset, and for longer from severely ill patients.*(61)* Full details about the duration of viral shedding can be found in the WHO guidance document on “Criteria for releasing COVID-19 patients from isolation”. *(61)* Additional studies are needed to determine the duration of viable virus shedding among infected patients.

SARS-CoV-2 infected persons who have symptoms can infect others primarily through droplets and close contact

SARS-CoV-2 transmission appears to mainly be spread via droplets and close contact with infected symptomatic cases. In an analysis of 75,465 COVID-19 cases in China, 78-85% of clusters occurred within household settings, suggesting that transmission occurs during close and prolonged contact.*(6)* A study of the first

patients in the Republic of Korea showed that 9 of 13 secondary cases occurred among household contacts. *(70)* Outside of the household setting, those who had close physical contact, shared meals, or were in enclosed spaces for approximately one hour or more with symptomatic cases, such as in places of worship, gyms, or the workplace, were also at increased risk of infection.*(7, 42, 71, 72)* Other reports have supported this with similar findings of secondary transmission within families in other countries.*(73, 74)*

SARS-CoV-2 infected persons without symptoms can also infect others

Early data from China suggested that people without symptoms could infect others.*(6)* To better understand the role of transmission from infected people without symptoms, it is important to distinguish between transmission from people who are infected who never develop symptoms*(75)* (asymptomatic transmission) and transmission from people who are infected but have not developed symptoms yet (pre-symptomatic transmission). This distinction is important when developing public health strategies to control transmission.

The extent of truly asymptomatic infection in the community remains unknown. The proportion of people whose infection is asymptomatic likely varies with age due to the increasing prevalence of underlying conditions in older age groups (and thus increasing risk of developing severe disease with increasing age), and studies that show that children are less likely to show clinical symptoms compared to adults.*(76)* Early studies from the United States *(77)* and China *(78)* reported that many cases were asymptomatic, based on the lack of

symptoms at the time of testing; however, 75-100% of these people later developed symptoms. A recent systematic review estimated that the proportion of truly asymptomatic cases ranges from 6% to 41%, with a pooled estimate of 16% (12%–20%).*(79)* However, all studies included in this systematic review have important limitations.*(79)* For example, some studies did not clearly describe how they followed up with persons who were asymptomatic at the time of testing to ascertain if they ever developed symptoms, and others defined “asymptomatic” very narrowly as persons who never developed fever or respiratory symptoms, rather than as those who did not develop any symptoms at all. *(76, 80)* A recent study from China that clearly and appropriately defined asymptomatic infections suggests that the proportion of infected people who never developed symptoms was 23%.*(81)*

Multiple studies have shown that people infect others before they themselves became ill, *(10, 42, 69, 82, 83)* which is supported by available viral shedding data (see above). One study of transmission in Singapore reported that 6.4% of secondary cases resulted from pre-symptomatic transmission.*(73)* One modelling study, that inferred the date of transmission based on the estimated serial interval and incubation period, estimated that up to 44% (25-69%) of transmission may have occurred just before symptoms appeared.*(62)* It remains unclear why the magnitude of estimates from modelling studies differs from available empirical data.

Transmission from infected people without symptoms is difficult to study. However, information can be gathered from detailed contact tracing efforts, as well as epidemiologic investigations among cases and contacts. Information from contact tracing efforts reported to WHO by Member States, available transmission studies and a recent pre-print systematic reviews suggests that

individuals without symptoms are less likely to transmit the virus than those who develop symptoms.*(*10*,* 81*,* 84*,* 85*)* Four individual studies from Brunei, Guangzhou China, Taiwan China and the Republic of Korea found that between 0% and 2.2% of people with asymptomatic infection infected anyone else, compared to 0.8%-15.4% of people with symptoms.*(*10*,* 72*,* 86*,* 87*)*

Remaining questions related to transmission

Many unanswered questions about transmission of SARS-CoV-2 remain, and research seeking to answer those questions is ongoing and is encouraged. Current evidence suggests that SARS-CoV-2 is primarily transmitted between people via respiratory droplets and contact routes – although aerosolization in medical settings where aerosol generating procedures are used is also another possible mode of transmission - and that transmission of COVID-19 is occurring from people who are pre-symptomatic or symptomatic to others in close contact (direct physical or face-to-face contact with a probable or confirmed case within one meter and for prolonged periods of time), when not wearing appropriate PPE. Transmission can also occur from people who are infected and remain asymptomatic, but the extent to which this occurs is not fully understood and requires further research as an urgent priority. The role and extent of airborne transmission outside of health care facilities, and in particular in close settings with poor ventilation, also requires further study.

As research continues, we expect to gain a better understanding about the relative importance of different transmission routes, including through droplets, physical contact and fomites; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required for transmission to occur, the

characteristics of people and situations that facilitate superspreading events such as those observed in various closed settings, the proportion of infected people who remain asymptomatic throughout the course of their infection; the proportion of truly asymptomatic persons who transmit the virus to others; the specific factors that drive asymptomatic and pre-symptomatic transmission; and the proportion of all infections that are transmitted from asymptomatic and pre-symptomatic individuals.

Implications for preventing transmission

Understanding how, when and in which settings infected people transmit the virus is important for developing and implementing control measures to break chains of transmission. While there is a great deal of scientific studies becoming available, all studies that investigate transmission should be interpreted bearing in mind the context and settings in which they took place, including the infection prevention interventions in place, the rigor of the methods used in the investigation and the limitations and biases of the study designs.

It is clear from available evidence and experience, that limiting close contact between infected people and others is central to breaking chains of transmission of the virus causing COVID-19. The prevention of transmission is best achieved by identifying suspect cases as quickly as possible, testing, and isolating infectious cases. *(*88*,* 89*)* In addition, it is critical to identify all close contacts of infected people *(*88*)* so that they can be quarantined *(*90*)* to limit onward spread and break chains of transmission. By quarantining close contacts, potential secondary cases will already be separated from others before they develop symptoms or

they start shedding virus if they are infected, thus preventing the opportunity for further onward spread. The incubation period of COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days. *(82, 91)* Thus, quarantine should be in place for 14 days from the last exposure to a confirmed case. If it is not possible for a contact to quarantine in a separate living space, self-quarantine for 14 days at home is required; those in self-quarantine may require support during the use of physical distancing measures to prevent the spread of the virus.

Given that infected people without symptoms can transmit the virus, it is also prudent to encourage the use of fabric face masks in public places where there is community transmission[1] and where other prevention measures, such as physical distancing, are not possible. *(12)* Fabric masks, if made and worn properly, can serve as a barrier to droplets expelled from the wearer into the air and environment.*(12)* However, masks must be used as part of a comprehensive package of preventive measures, which includes frequent hand hygiene, physical distancing when possible, respiratory etiquette, environmental cleaning and disinfection. Recommended precautions also include avoiding indoor crowded gatherings as much as possible, in particular when physical distancing is not feasible, and ensuring good environmental ventilation in any closed setting. *(92, 93)*

Within health care facilities, including long term care facilities, based on the evidence and the advice by the COVID-19 IPC GDG, WHO continues to recommend droplet and contact precautions when caring for COVID-19 patients and airborne precautions when and where aerosol generating procedures are performed. WHO also recommends standard or transmission-based precautions for other patients using an approach guided

by risk assessment.*(94)* These recommendations are consistent with other national and international guidelines, including those developed by the European Society of Intensive Care Medicine and Society of Critical Care Medicine *(95)* and by the Infectious Diseases Society of America. *(96)*

Furthermore, in areas with COVID-19 community transmission, WHO advises that health workers and caregivers working in clinical areas should continuously wear a medical mask during all routine activities throughout the entire shift.*(12)* In settings where aerosol-generating procedures are performed, they should wear an N95, FFP2 or FFP3 respirator. Other countries and organizations, including the United States Centers for Diseases Control and Prevention *(97)* and the European Centre for Disease Prevention and Control *(98)* recommend airborne precautions for any situation involving the care of COVID-19 patients. However, they also consider the use of medical masks as an acceptable option in case of shortages of respirators.

WHO guidance also emphasizes the importance of administrative and engineering controls in health care settings, as well as rational and appropriate use of all PPE *(99)* and training for staff on these recommendations (IPC for Novel Coronavirus [COVID-19] Course. Geneva; World Health Organization 2020, available at (https://openwho.org/courses/COVID-19-IPC-EN). WHO has also provided guidance on safe workplaces. *(92)*

Key points of the brief

Main findings

- **Understanding how, when and in what types of settings SARS-CoV-2 spreads between people is critical to develop effective public health and infection prevention measures to break chains of transmission.**
- **Current evidence suggests that transmission of SARS-CoV-2 occurs primarily between people through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings.**
- **Airborne transmission of the virus can occur in health care settings where specific medical procedures, called aerosol generating procedures, generate very small droplets called aerosols. Some outbreak reports related to indoor crowded spaces have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice, in restaurants or in fitness classes.**
- **Respiratory droplets from infected individuals can also land on objects, creating fomites (contaminated surfaces). As environmental contamination has been documented by many reports, it is likely that people can also be infected by touching these surfaces and touching their eyes, nose or mouth before cleaning their hands.**
- **Based on what we currently know, transmission of COVID-19 is primarily occurring from people when they have symptoms, and can also occur just before they develop symptoms, when they are in close proximity to others for prolonged periods of time. While someone who never develops symptoms can also pass the virus to others, it is still not clear to what extent this occurs and more research is needed in this area.**
- **Urgent high-quality research is needed to elucidate the relative importance of different transmission routes; the role of airborne transmission in the absence of aerosol generating procedures; the dose of virus required**

for transmission to occur; the settings and risk factors for superspreading events; and the extent of asymptomatic and pre-symptomatic transmission.

How to prevent transmission

The overarching aim of the Strategic Preparedness and Response Plan for COVID-19*(1)* is to control COVID-19 by suppressing transmission of the virus and preventing associated illness and death. To the best of our understanding, the virus is primarily spread through contact and respiratory droplets. Under some circumstances airborne transmission may occur (such as when aerosol generating procedures are conducted in health care settings or potentially, in indoor crowded poorly ventilated settings elsewhere). More studies are urgently needed to investigate such instances and assess their actual significance for transmission of COVID-19.

To prevent transmission, WHO recommends a comprehensive set of measures including:

- **Identify suspect cases as quickly as possible, test, and isolate all cases (infected people) in appropriate facilities;**
- **Identify and quarantine all close contacts of infected people and test those who develop symptoms so that they can be isolated if they are infected and require care;**
- **Use fabric masks in specific situations, for example, in public places where there is community transmission and where other prevention measures, such as physical distancing, are not possible;**
- **Use of contact and droplet precautions by health workers caring for suspected and confirmed COVID-19 patients, and use of airborne precautions when aerosol generating procedures**

are performed;
- **Continuous use of a medical mask by health workers and caregivers working in all clinical areas, during all routine activities throughout the entire shift;**
- **At all times, practice frequent hand hygiene, physical distancing from others when possible, and respiratory etiquette; avoid crowded places, close-contact settings and confined and enclosed spaces with poor ventilation; wear fabric masks when in closed, overcrowded spaces to protect others; and ensure good environmental ventilation in all closed settings and appropriate environmental cleaning and disinfection.**

WHO carefully monitors the emerging evidence about this critical topic and will update this scientific brief as more information becomes available.

[1]Defined by WHO as “experiencing larger outbreaks of local transmission defined through an assessment of factors including, but not limited to: large numbers of cases not linkable to transmission chains; large numbers of cases from sentinel surveillance; and/or multiple unrelated clusters in several areas of the country/territory/area” (https://www.who.int/publications-detail/global-surveillance-for-covid-19-caused-by-human-infection-with-covid-19-virus-interim-guidance)

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WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief document will expire 2 years after the date of publication.

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REFERENCE 5

CORRESPONDENCE

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1

TO THE EDITOR: A novel human coronavirus that is now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (formerly called HCoV-19) emerged in Wuhan, China, in late 2019 and is now causing a pandemic.[1] We analyzed the aerosol and surface stability of SARS-CoV-2 and compared it with SARS-CoV-1, the most closely related human coronavirus.[2]

We evaluated the stability of SARS-CoV-2 and SARS-CoV-1 in aerosols and on various surfaces and estimated their decay rates using a Bayesian regression model (see the Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org). SARS-CoV-2 nCoV-WA1-2020 (MN985325.1) and SARS-CoV-1 Tor2 (AY274119.3) were the strains used. Aerosols (<5 μm) containing SARS-CoV-2 ($10^{5.25}$ 50% tissue-culture infectious dose [$TCID_{50}$] per milliliter) or SARS-CoV-1 ($10^{6.75\text{-}7.00}$ $TCID_{50}$ per milliliter) were generated with the use of a three-jet Collison nebulizer and fed into a Goldberg drum to create an aerosolized environment. The inoculum resulted in cycle-threshold values between 20 and 22, similar to those observed in samples obtained from the upper and lower respiratory tract in humans.

Our data consisted of 10 experimental conditions involving two viruses (SARS-CoV-2 and SARS-CoV-1) in five environmental conditions (aerosols, plastic, stainless steel, copper, and cardboard). All experimental measurements are reported as means across three replicates.

SARS-CoV-2 remained viable in aerosols throughout the duration of our experiment (3 hours), with a reduction in infectious titer from $10^{3.5}$ to $10^{2.7}$ $TCID_{50}$ per liter of air. This reduction was similar to that observed with SARS-CoV-1, from $10^{4.3}$ to $10^{3.5}$ $TCID_{50}$ per milliliter (Fig. 1A).

SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected up to 72 hours after application to these surfaces (Fig. 1A), although the virus titer was greatly reduced (from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per milliliter of medium after 72 hours on plastic and from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per milliliter after 48 hours on stainless steel). The stability kinetics of SARS-CoV-1 were similar (from $10^{3.4}$ to $10^{0.7}$ $TCID_{50}$ per milliliter after 72 hours on plastic and from $10^{3.6}$ to $10^{0.6}$ $TCID_{50}$ per milliliter after 48 hours on stainless steel). On copper, no viable SARS-CoV-2 was measured after 4 hours and no viable SARS-CoV-1 was measured after 8 hours. On cardboard, no viable SARS-CoV-2 was measured after 24 hours and no viable SARS-CoV-1 was measured after 8 hours (Fig. 1A).

Both viruses had an exponential decay in virus titer across all experimental conditions, as indicated by a linear decrease in the $\log_{10}TCID_{50}$ per liter of air or milliliter of medium over time (Fig. 1B). The half-lives of SARS-CoV-2 and SARS-CoV-1 were similar in aerosols, with median estimates of approximately 1.1 to 1.2 hours and 95% credible intervals of 0.64 to 2.64 for SARS-CoV-2 and 0.78 to 2.43 for SARS-CoV-1 (Fig. 1C, and Table S1 in the Supplementary Appendix). The half-lives of the two viruses were also similar on copper. On cardboard, the half-life of SARS-CoV-2 was longer than that of SARS-CoV-1. The longest viability of both viruses was on stainless steel and plastic; the estimated median half-life of SARS-CoV-2 was approximately 5.6 hours on stainless steel and 6.8 hours on plastic (Fig. 1C). Estimated differences in the half-lives of the two viruses were small except for those on cardboard (Fig. 1C). Individual replicate data were noticeably "noisier" (i.e., there was more variation in the experiment, resulting in a larger standard error) for cardboard than for other surfaces (Fig. S1 through S5), so we advise caution in interpreting this result.

We found that the stability of SARS-CoV-2 was similar to that of SARS-CoV-1 under the experimental circumstances tested. This indicates that differences in the epidemiologic characteristics of these viruses probably arise from other factors, including high viral loads in the upper

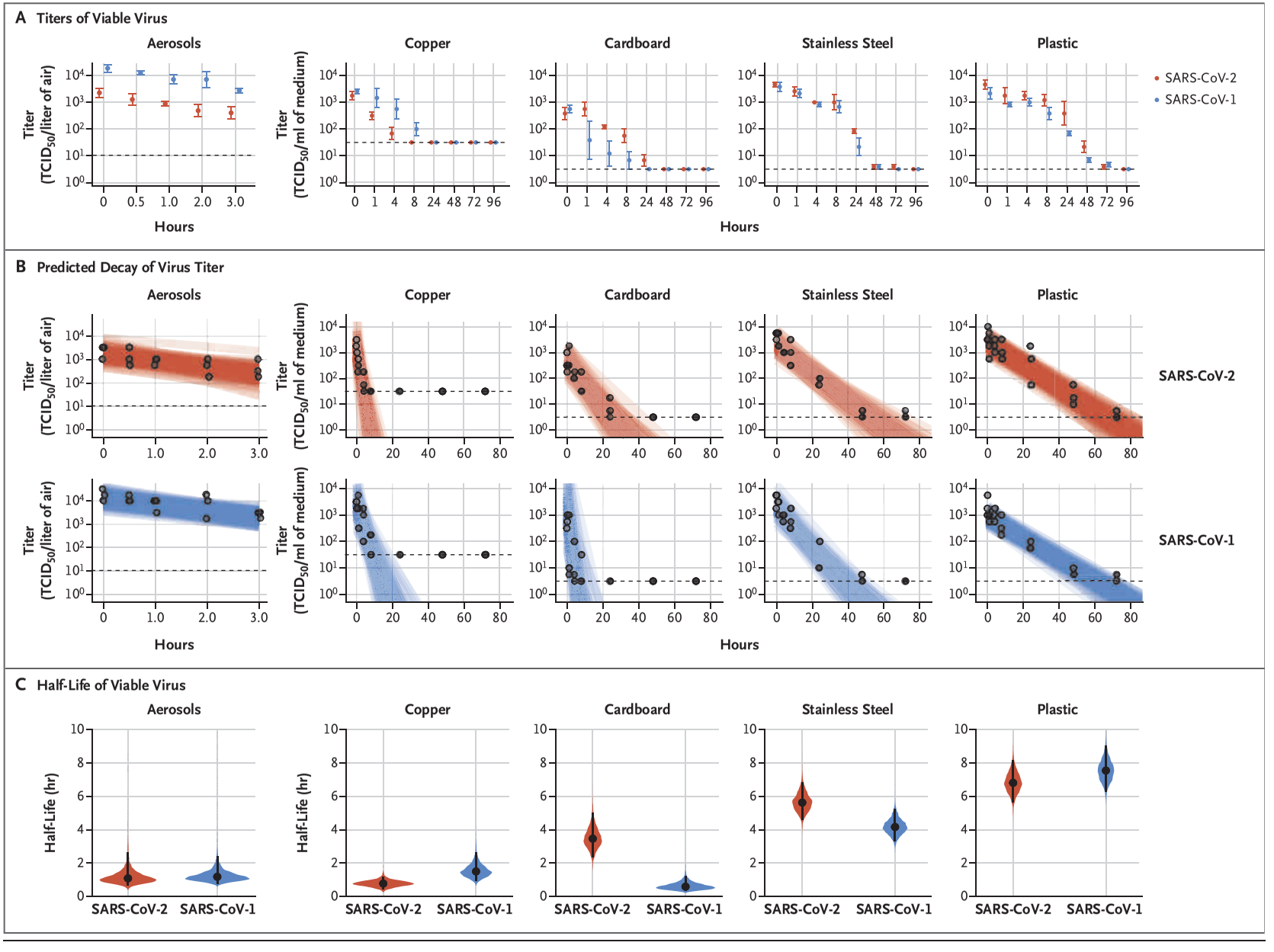
A Titers of Viable Virus
Aerosols
Copper
Cardboard
Stainless Steel
Plastic
Titer (TCID50/liter of air)
Titer (TCID50/ml of medium)
Hours
SARS-CoV-2
SARS-CoV-1
B Predicted Decay of Virus Titer
C Half-Life of Viable Virus
Half-Life (hr)

Figure 1 (facing page). Viability of SARS-CoV-1 and SARS-CoV-2 in Aerosols and on Various Surfaces.

As shown in Panel A, the titer of aerosolized viable virus is expressed in 50% tissue-culture infectious dose ($TCID_{50}$) per liter of air. Viruses were applied to copper, cardboard, stainless steel, and plastic maintained at 21 to 23°C and 40% relative humidity over 7 days. The titer of viable virus is expressed as $TCID_{50}$ per milliliter of collection medium. All samples were quantified by end-point titration on Vero E6 cells. Plots show the means and standard errors (I bars) across three replicates. As shown in Panel B, regression plots indicate the predicted decay of virus titer over time; the titer is plotted on a logarithmic scale. Points show measured titers and are slightly jittered (i.e., they show small rapid variations in the amplitude or timing of a waveform arising from fluctuations) along the time axis to avoid overplotting. Lines are random draws from the joint posterior distribution of the exponential decay rate (negative of the slope) and intercept (initial virus titer) to show the range of possible decay patterns for each experimental condition. There were 150 lines per panel, including 50 lines from each plotted replicate. As shown in Panel C, violin plots indicate posterior distribution for the half-life of viable virus based on the estimated exponential decay rates of the virus titer. The dots indicate the posterior median estimates, and the black lines indicate a 95% credible interval. Experimental conditions are ordered according to the posterior median half-life of SARS-CoV-2. The dashed lines indicate the limit of detection, which was $3.33\times10^{0.5}$ $TCID_{50}$ per liter of air for aerosols, $10^{0.5}$ $TCID_{50}$ per milliliter of medium for plastic, steel, and cardboard, and $10^{1.5}$ $TCID_{50}$ per milliliter of medium for copper.

respiratory tract and the potential for persons infected with SARS-CoV-2 to shed and transmit the virus while asymptomatic.[3,4] Our results indicate that aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed). These findings echo those with SARS-CoV-1, in which these forms of transmission were associated with nosocomial spread and super-spreading events,[5] and they provide information for pandemic mitigation efforts.

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The findings and conclusions in this letter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Names of specific vendors, manufacturers, or products are included for public health and informational purposes; inclusion does not imply endorsement of the vendors, manufacturers, or products by the CDC or the Department of Health and Human Services.

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REFERENCE 6

Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care

WHO Guidelines

PANDEMIC AND
EPIDEMIC DISEASES

World Health Organization

WHO Library Cataloguing-in-Publication Data

Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care.

1.Guideline I.World Health Organization.

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Contents

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Foreword

This document is an update to the World Health Organization (WHO) interim guidelines *Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care* (2007). These updated guidelines incorporate the emergency guidance given in the WHO publication *Infection prevention and control during health care for confirmed, probable, or suspected cases of pandemic (H1N1) 2009 virus infection and influenza-like illness* (2009). The revision was informed by both evidence that has emerged since the first edition was published and the practical lessons learnt during the influenza pandemic in 2009.

The WHO Guidelines *Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care* provide recommendations, best practices and principles for non-pharmacological aspects of infection prevention and control (IPC) for acute respiratory infections (ARI) in health care, with special emphasis on ARI that can present as epidemics or pandemics. The guidelines are intended to help policy-makers, administrators and health-care workers to prioritize effective IPC measures.

The document also provides guidance on the application of basic IPC precautions, such as Standard Precautions, and on the importance of maintaining appropriate IPC measures in routine circumstances to strengthen a healthcare facility's capacity to put them into practice during outbreaks. These measures should therefore be part of the hospital's permanent IPC strategy, and we hope that the guidelines will help in the implementation of IPC programmes both at national and health-care facility levels.

The development of the guidelines followed the process established in the WHO handbook for guideline development, which involved active participation of the Global Infection Prevention and Control Network (GIPCN). The resulting recommendations were peer reviewed by internal and external experts.

WHO remains committed to providing guidance for the prevention and control of health-care associated infections in all circumstances. We believe these guidelines will contribute to improving health-care practices worldwide.

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Abbreviations and acronyms

ACH	air changes per hour
ARI	acute respiratory infection
ASTM	American Society for Testing and Materials (now ASTM International)
BFE	bacterial filtration efficiency
BiPAP	bilevel positive airway pressure
CDC	Centers for Disease Control and Prevention, Atlanta, US
CoV	Coronavirus
EU	European Union
FDA	Food and Drug Administration (US)
FFP	filtering facepiece
GIPCN	WHO Global Infection Prevention and Control Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEPA	high-efficiency particulate air
IHR	International Health Regulations
ILI	influenza-like illness
IPC	infection prevention and control (in health care)
NIOSH	National Institute for Occupational Safety and Health (US)
L/s	litres per second
m	metre
OR	operating room
PPE	personal protective equipment
ppm	parts per million
RCT	randomized controlled trial
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAR	Special Administrative Region (Hong Kong)
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
TB	Tuberculosis
UVGI	ultraviolet germicidal irradiation
WHO	World Health Organization

Glossary

Acute respiratory diseases

Acute upper or lower respiratory tract diseases, frequently infectious in etiology, that can result in a spectrum of illnesses, ranging from asymptomatic or mild infection to severe or fatal disease. The severity depends on the causative pathogen, and on environmental and host factors.

Acute respiratory infection

An acute respiratory tract disease that is caused by an infectious agent. Although the spectrum of symptoms of acute respiratory infection (ARI) may vary, the onset of symptoms is typically rapid, ranging from hours to days after infection. Symptoms include fever, cough and, often, sore throat, coryza, shortness of breath, wheezing, or difficulty in breathing. The pathogens that cause this disease include influenza virus, parainfluenza virus, rhinovirus, respiratory syncytial virus (RSV) and severe acute respiratory syndrome coronavirus (SARS-CoV).

Acute respiratory infections of potential concern

Infections in which the pathogens can cause outbreaks on a large scale or with high morbidity and mortality. Examples include SARS-CoV (Section 1.3.1), new influenza viruses causing human infection (Section 1.3.2) and novel ARI pathogens with the potential for a high public health impact (Section 1.3.3).

Adequately ventilated patient room or area

A room or area that has an adequate ventilation rate without controlled direction of airflow. For a naturally ventilated general ward room, adequate ventilation is considered to be 60 litres/second (L/s) per patient (*1*). For a mechanically ventilated single room, adequate ventilation is considered to be at least two outdoor air changes (ACH) per hour and at least six total ACH per hour (*2*).

Aerosol-generating procedures associated with increased risk of pathogen transmission

Medical procedures that have been reported to be aerosol-generating and consistently associated with an increased risk of pathogen transmission (Annex A).

Air changes per hour

See Environmental ventilation rate.

Airborne Precaution room

A room with high ventilation rate and controlled direction of airflow that can be used to contain airborne infections (*1, 3-5*) and ARIs caused by a novel agent with the potential to pose a public health risk (*6, Article 1*). An Airborne Precaution room can be naturally or mechanically ventilated (Annex B):

- In a *naturally ventilated* Airborne Precaution room, the airflow should be directed to areas free of transit, or should permit the rapid dilution of contaminated air into the surrounding areas and the open air; the average ventilation rate should be 160 l/s per patient (*1*).
- In a *mechanically ventilated* Airborne Precaution room, negative pressure is created to control the direction of airflow; the ventilation rate should be at least 12 ACH (*3, 7*).

Such a room is equivalent to the "airborne infection isolation room" described by the CDC (*8*).

Airborne transmission

The spread of an infectious agent caused by the dissemination of droplet nuclei that remain infectious when suspended in air over long distances and time. Airborne transmission can be further categorized into obligate or preferential airborne transmission (*9*).

- *Obligate airborne transmission* refers to pathogens that are transmitted only by deposition of droplet nuclei under natural conditions (e.g. pulmonary tuberculosis).
- *Preferential airborne transmission* refers to pathogens that can initiate infection by multiple routes, but are predominantly transmitted by droplet nuclei (e.g. measles and chickenpox).

Alcohol-based hand rub

An alcohol-containing preparation designed for application to the hands for antisepsis.

Anteroom

A small room leading from a corridor into another room, often an isolation room.

Caregiver

A person who provides support and assistance (formal or informal) to elderly people or to people with disabilities or long-term ill health (*10*).

Cleaning

The removal of dirt from a device or surface, either by physically scrubbing with a surfactant or detergent and water, or through an energy-based process (e.g. ultrasonic cleaner).

Clinical triage

A system by which patients are screened for specific signs, symptoms and epidemiological clues upon initial contact with the health-care system, for the purpose of determining further diagnostic tests, isolation precautions, treatment and reporting.

Clinical waste

Hazardous waste (also known as infectious waste) capable of causing infections in humans. Such waste includes contaminated animal waste, human blood and blood products, waste from isolation areas, pathological waste (e.g. human tissues), and discarded sharps (needles, scalpels or broken medical instruments). The definition of clinical waste may vary depending on local legislation and regulations.

Cohorting

The placement of patients infected or colonized with the same laboratory-confirmed pathogens in the same designated unit, zone or ward (with or without the same staff). This term is also frequently applied to grouped patient placement based on clinical and epidemiological information without laboratory confirmation of the pathogen; however, such an arrangement is referred to as *special measure*s throughout this document (see Special measures).

Contact transmission

The spread of an infectious agent caused by physical contact of a susceptible host with people or objects.

- *Direct contact transmission* involves both a direct body-surface-to-body-surface contact and physical transfer of microorganisms between an infected or colonized person and a susceptible host.
- *Indirect contact transmission* involves contact of a susceptible host with a contaminated intermediate object (e.g. contaminated hands) that carries and transfers the microorganisms (*5*).

Disinfection

A process that eliminates all viable pathogenic microorganisms (other than bacterial spores) from inanimate objects.

Droplet transmission

The spread of an infectious agent caused by the dissemination of droplets. Droplets are primarily generated from an infected (source) person during coughing, sneezing and talking. Transmission occurs when these droplets that contain microorganisms are propelled (usually < 1 m) through the air and deposited on the conjunctivae, mouth, nasal, throat or pharynx mucosa of another person. Most of the volume (> 99%) comprises large droplets that travel short distances (< 1 m) and do not remain suspended in the air. Thus, special air handling and ventilation are not required to prevent droplet transmission (*5*).

Environmental ventilation

There are three types of environmental ventilation:

- *Mechanical environmental ventilation* uses mechanical fans to introduce or exhaust outdoor or properly treated recycled air into or out of a building or a room.
- *Natural environmental ventilation* uses natural forces to introduce and distribute outdoor air into a building (*1*). Such forces include wind pressure or pressure generated by the density difference between indoor and outdoor air.
- *Mixed-mode environmental ventilation* combines mechanical and natural ventilation.

Environmental ventilation rate

The ventilation flow rate can be measured by either an absolute ventilation flow rate in L/s or L/s per cubic metre (L/s/m^3), or by ACH, relative to the volume of the space. In these guidelines, we refer to the ventilation rate as the absolute amount of inflow air per unit time (L/s or L/s/m^3), and the air change rate as the relative amount of inflow air per unit time (ACH) (*1*).

Hand hygiene

A general term that applies to handwashing, antiseptic handwashing, antiseptic hand rubbing or surgical hand antisepsis.

Health-care facility

Any establishment that is engaged in direct care of patients on site (*10*).

Health-care setting

Context where health care is provided (e.g. hospital, outpatient clinic or home).

Health-care worker

One of a variety of professionals (e.g. medical practitioners, nurses, physical and occupational therapists, social workers, pharmacists and spiritual counsellors) involved in providing coordinated and comprehensive health care (*10*).

Health personnel

Anyone employed or contracted to provide health services (*10*).

Infection prevention and control

Infection prevention and control (IPC) is the practical discipline concerned with preventing healthcare-associated infection. IPC is an essential part of the health care infrastructure. Its purpose in health care is as follows:

- to prevent the occurrence of healthcare-associated infections in patients, health-care workers, visitors and other persons associated with health-care settings;
- to prepare health-care facilities for the early detection and management of epidemics and to organize a prompt and effective response;
- to contribute to a coordinated response to control community-acquired infectious diseases, endemic or epidemic, that may be "amplified" via health care;
- to contribute to preventing the emergence of antimicrobial resistance and/or dissemination of resistant strains of microorganisms; and
- to minimize the environmental impact of these infections or their management.

Infectious respiratory aerosols

Respiratory aerosols that contain infectious particles. Aerosol size is determined by the force and pressure involved in the generation of the particles. The final size depends on the nature of the fluid containing the organisms, the force and pressure at emission, the initial size of the aerosol, environmental conditions (e.g. temperature, relative humidity and airflow), the time spent airborne, and the size of the organisms within a droplet. The distance travelled and the length of time particles remain suspended in the air is determined by the types of organism, particle size, settling velocity, relative humidity and airflow. Large particles typically remain suspended in the air for a limited period of time and settle within 1 m (3 feet) of the source. Smaller particles evaporate quickly; the resulting dried residues settle from the air slowly, and remain suspended in the air for variable lengths of time. The definitions and classification of the different types of infectious respiratory aerosols are evolving, and the implications for IPC measures are not yet clear. However, for the purpose of this document, infectious respiratory aerosols are classified into:

- *droplets* – *r*espiratory aerosols > 5 μm in diameter; and
- *droplet nuclei* – the residue of dried respiratory aerosols (≤ 5 μm in diameter) that results from evaporation of droplets coughed or sneezed into the atmosphere or by aerosolization of infective material.

Isolation precautions

Measures designed to minimize the risk of transmission of infections. They are often referred to as IPC precautions. Isolation precautions are typically separated into:

- *Standard Precautions* – these should always be in place for all patient care; and
- *additional precautions* – these are required in particular circumstances and comprise Contact, Droplet and Airborne Precautions.

Litres per second per cubic metre

See Environmental ventilation rate.

Mechanical ventilation

See Environmental ventilation.

Medical mask

Also known as a surgical or procedure mask. As personal protective equipment, a facial mask is intended to protect caregivers and health-care workers against droplet-transmitted pathogens, or to serve as part of facial protection for patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions or excretions (Annex A provides details of usage and standards for medical masks). In this document, the term refers to disposable masks only.

Mixed-mode ventilation

See Environmental ventilation.

Natural ventilation

See Environmental ventilation.

Negative pressure room

A room in which the air pressure differential between the room and the adjacent indoor airspace directs the air into the room (i.e. room air is prevented from leaking out of the room and into adjacent areas such as a corridor).

New influenza virus

A new strain of influenza virus found in people that has not previously been circulating in humans. Current animal viruses that may have the potential to begin circulating among people include H5 and H7 strains of avian influenza, most notably A(H5N1). New influenza viruses are often of swine or avian origin.

Obligate airborne transmission

See Airborne transmission.

Pandemic

An epidemic occurring worldwide or over a wide area, crossing boundaries of several countries, and usually affecting a large number of people (*13*).

Particulate respirator

Also known as a filtering facepiece respirator. A type of facial mask that uses a filter as an integral part of the facepiece, or in which the entire facepiece is composed of the filtering medium and a means of sealing to the face.

Preferential airborne transmission

See Airborne transmission.

Procedure mask

See Medical mask.

Respiratory hygiene

The practice of covering the mouth and nose during coughing or sneezing (using a medical mask, cloth mask, tissues, a sleeve or flexed elbow), followed by hand hygiene, to reduce the dispersal of respiratory secretions that may contain infectious particles.

Spatial separation

Physical separation or distancing of at least 1 m between patients or between patients and health-care workers, which may be within a confined space such as a room, or between two separate bays, rooms or wards.

Special measures

The placement of patients with the same suspected diagnosis (similar epidemiological and clinical information) in the same designated unit, zone or ward (with or without the same staff) when the etiological agent has not been laboratory confirmed.

Surgical mask

See Medical mask.

Executive summary

Acute respiratory infections (ARIs) are the leading cause of morbidity and mortality from infectious disease worldwide, particularly affecting the youngest and oldest people in low- and middle-income nations. These infections, typically caused by viruses or mixed viral–bacterial infections, can be contagious and spread rapidly. Although knowledge of transmission modes is ever-evolving, current evidence indicates that the primary mode of transmission of most acute respiratory diseases is through droplets, but transmission through contact (including hand contamination followed by self-inoculation) or infectious respiratory aerosols at short range can also happen for some pathogens in particular circumstances.

In modern medicine, infection prevention and control (IPC) measures in health-care settings are of central importance to the safety of patients, health-care workers and the environment, and to the management of communicable disease threats to the global and local community. Application of basic IPC precautions, such as Standard Precautions, is a cornerstone for providing safe health care. In an era of emerging and re-emerging infectious diseases, IPC in health care is as important now as ever. The management of ARIs is no exception. Because many symptoms of ARIs are common and nonspecific, the application of IPC measures for ARIs in health care can be fraught with difficulty and confusion, especially in outbreaks where resources may be strained. Yet such measures, including early identification, prompt isolation precautions, proper patient placement and adequate ventilation, are essential to contain and mitigate the impact of pathogens that may constitute a major public health threat.

To address the need for clear advice on applying IPC measures for ARIs, these guidelines focus on recommendations for non-pharmacological[1] aspects of IPC for ARIs in health care. The document is intended for IPC professionals and members of IPC teams, health-care managers and policy-makers. The secondary audience is health-care workers, including doctors, nurses, allied health professionals, auxiliary and community health workers, and others involved in provision of health care. Given that etiological diagnosis is often not achievable, these guidelines prioritize a syndromic and epidemiological approach for assessing risks of infection and application of additional IPC measures. Special emphasis is placed on ARIs that can present as epidemics or pandemics. Committed and engaged leadership in health-care facilities is essential to ensure an institutional safety climate and continuous and consistent application of IPC measures, both during outbreak events and at all other times.

These guidelines represent an update to the World Health Organization (WHO) interim guidelines *Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care*, 2007 (*16*). They also incorporate the emergency guidance given in the WHO publication *Infection prevention and control during health care for confirmed, probable, or suspected cases of pandemic (H1N1) 2009 virus infection and influenza-like illness,* 2009 (*17*). It was considered imperative to review and incorporate

[1] Documents from WHO that specifically address the use of vaccines and antivirals for influenza are the *WHO guidelines for the use of seasonal influenza vaccine in humans*, 2004 (*14*) and the *WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses, 2010* (*15*). Recommendations in the current guidelines that refer to the use of vaccines and antivirals are based on these documents.

relevant research data that have become available since publication of the interim guidelines in 2007. The revision was a multistage process that included a field evaluation and an extensive literature review, conducted in accordance with the WHO standard for guideline development (*18*), as well as a review of practical experience and lessons learnt from pandemic influenza A (H1N1) 2009.

A WHO Steering Group engaged in defining the scope of the revision, establishing guideline development and external review groups, and ensuring the necessary declarations of conflict of interest. It also formulated specific questions for systematic review in several areas of relevance to these guidelines. Systematic reviews were commissioned and critical reviews of the literature conducted, as needed, to address these questions. The quality of evidence and other important considerations (e.g. balance of benefits versus disadvantages, costs, values and feasibility) were assessed and summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process (Annex K). Recommendations were formulated on that basis and then submitted for broad internal and external peer review.

There has been no change to most of the recommendations contained in the previous version of these guidelines; however, additional reference information has been added in many areas. The important changes that were made to these guidelines as a result of the revision process relate to the duration of additional isolation precautions, vaccination of health-care workers against influenza, antiviral prophylaxis for health-care workers exposed to ARIs, and environmental ventilation. The guidelines now recommend:

- that additional precautions for patients with all ARIs should be maintained for the duration of symptomatic illness (rather than various durations depending on the pathogen and patient information, as was previously recommended);
- vaccination of health-care workers for those caring for patients at high risk of complicated influenza illness (rather than for all health-care workers, as was previously recommended); and
- that antiviral prophylaxis should not routinely be given to health-care workers exposed to ARIs (providing more clarity to this issue than was given previously).

Information on the technical details of environmental ventilation is no longer in this document, because this information is now available in a separate WHO publication, *Natural ventilation for infection control in health-care settings*, 2009 (*1*). These guidelines retain reference to natural ventilation as an effective method for IPC.

The main document comprises:

- an introduction to the concepts discussed in the guidelines (Chapter 1);
- a detailed description of the IPC recommendations, best practices, and principles (Chapter 2);
- an outline of the main components of preparedness plans for health-care facilities to prevent and control ARI outbreaks that may constitute an international public health concern (Chapter 3);
- a description of the research gaps that were identified in relation to these recommendations (Chapter 4); and
- annexes that provide background information for the recommendations in Chapter 2, including evaluations of the evidence for key recommendations.

This guidance will be reviewed in 2016. A guideline review group will be convened to evaluate the new evidence and revise the recommendation if needed. The Department of Pandemic and Epidemic Diseases at the WHO headquarters in Geneva, along with its internal

partners, will be responsible for coordinating the guideline update, following the *WHO handbook for guideline development* (*18*) procedures. If new evidence that may require changing current recommendations is published, the guideline will be updated before the review date indicated above. In addition and as companions to this document, updated summary guidance document and training materials targeted specifically to health care workers are currently being prepared.

The recommendations are summarized in the box below. The decision tables for these recommendations are provided in Annex K

Recommendations in guidelines

Recommendations	Quality of evidence	Strength of recommendation
Use clinical triage for the early identification of patients with ARIs in order to prevent the transmission of ARI pathogens to health-care workers and other patients.	Very low to low	Strong
Respiratory hygiene (i.e. covering the mouth and nose during coughing or sneezing with a medical mask, tissue, or a sleeve or flexed elbow, followed by hand hygiene) should be practised by people with ARIs to reduce the dispersal of respiratory secretions containing potentially infectious particles.	Very low	Strong
Maintain spatial separation (distance of at least 1 m) between each ARI patient and others, including health-care workers (without the use of personal protective equipment [PPE]), to reduce the transmission of ARI.	Very low to low	Strong
Consider the use of patient cohorting (i.e. the placement of patients infected or colonized with the same laboratory-identified pathogens in the same designated unit, zone or ward). If cohorting is not possible, apply special measures (i.e. the placement of patients with the same suspected diagnosis – similar epidemiological and clinical information – in the same designated unit, zone or ward) to reduce transmission of ARI pathogens to health-care workers and other patients.	Low to moderate	Conditional
Use appropriate PPE as determined by risk assessment (according to the procedure and suspected pathogen). Appropriate PPE when providing care to patients presenting with ARI syndromes may include a combination of: medical mask (surgical or procedure mask); gloves; long-sleeved gowns; and eye protection (goggles or face shields).	Low to moderate	Strong
Use PPE, including gloves, long-sleeved gowns, eye protection (goggles or face shields), and facial mask (surgical or procedure mask, or particulate respirators) during aerosol-generating procedures that have been consistently associated with an increased risk of transmission of ARI pathogens. The available evidence suggests that performing or being exposed to endotracheal intubation either by itself or in combination with other procedures (e.g. cardiopulmonary resuscitation or bronchoscopy) is consistently associated with increased risk of transmission.	Very low to low	Conditional
Use adequately ventilated single rooms when performing aerosol-generating procedures that have been consistently associated with increased risk of ARI transmission.	Very low to low	Conditional
Vaccinate health-care workers caring for patients at high risk of severe or complicated influenza disease, to reduce illness and mortality among these patients.	Very low to low	Strong
Ultraviolet Germicidal Irradiation (UVGI) for disinfection of air – no recommendation possible	-	-
Implement additional IPC precautions at the time of admission and continue for the duration of symptomatic illness, and modify according to the pathogen and patient information. Always use Standard Precautions. There is no evidence to support the routine application of laboratory tests to determine the duration of IPC precautions.	Very low	Conditional

1 Introduction and scope of the guidelines

1.1 Acute respiratory infections in health care

Acute respiratory infections (ARIs) are the leading cause of morbidity and mortality from infectious disease in the world. Almost four million people die from ARIs each year, with 98% of these deaths due to lower respiratory tract infections. Mortality rates are particularly high in infants, children, and the elderly, particularly in low-income and middle-income countries (*19, 20*). ARIs are one of the most frequent causes of consultation or admission to health-care facilities, particularly in paediatric services (*21*).

Bacteria are a major cause of lower respiratory tract infection, with *Streptococcus pneumoniae* being the most common cause of bacterial community-acquired pneumonia in many countries. However, the pathogens that most often cause ARIs are viruses or mixed viral–bacterial infections. ARIs that have epidemic or pandemic potential, and may pose a public-health risk, warrant special precautions and preparedness (*22*).

The incidence of specific ARIs, their distribution and the outcome of disease varies according to several factors, including (*23-25*):

- environmental conditions (e.g. air pollutants, household crowding, humidity, hygiene, season and temperature);
- availability and effectiveness of medical care and infection prevention and control (IPC) measures to contain spread such as vaccines, access to health-care facilities, and isolation capacity;
- host factors such as age, cigarette-smoking, host ability to transmit infection, immune status, nutritional status, prior or concurrent infection with other pathogens, and underlying medical conditions; and
- pathogenic characteristics, including modes of transmission, transmissibility, virulence factors (e.g. genes encoding toxins) and microbial load (inoculum size).

1.2 Scope of the current guidelines

This document provides recommendations and other information relating to IPC measures for ARIs in health-care settings, with specific emphasis on ARIs that have the potential for rapid spread and may cause epidemics or pandemics (or both). Some of the epidemic-prone ARIs may constitute a global public-health emergency. According to the *International Health Regulations* (IHR), 2005 (*6*) the respiratory disease events that may constitute a public-health emergency of international concern include:

- severe acute respiratory syndrome (SARS);
- human influenza caused by a new subtype, including human episodes of avian influenza;
- pneumonic plague; and
- novel ARIs that can cause large-scale outbreaks, or outbreaks with high morbidity and mortality.

Recommendations for prevention and control of pneumonic plague have been addressed in a previous World Health Organization (WHO) publication *Operational guidelines on plague surveillance, diagnosis, prevention and control*, 2009 (*26*), and a summary of IPC precautions is provided in Table 2.1 in these guidelines.

Tuberculosis (TB) seldom presents as an ARI. However, its spread has been associated with health care and is a major global health concern. Recommendations for prevention and control of TB in health-care facilities have been addressed in a previous WHO publication – *WHO policy on TB infection control in health-care facilities, congregate settings and households,* 2009 (*27*) – and a summary of IPC precautions is provided in the Table 2.1.

This document focuses on the most common ARIs, and highlights ARIs of potential concern. In particular, these guidelines address IPC precautions for ARIs that:

- cause acute respiratory tract infection, including pneumonia and acute respiratory distress syndrome;
- cause severe disease in susceptible people with apparently normal immune systems; and
- may constitute a public health emergency of international concern as defined by IHR (*6*), except in the case of pneumonic plague.

1.3 ARIs that may constitute a public health emergency of international concern covered in the current document

1.3.1 Severe acute respiratory syndrome

SARS is caused by the SARS coronavirus (SARS-CoV) (*28*) that can infect animals and humans. The disease was first reported in Asia in February 2003, and spread to people in over 24 countries in Asia, Europe, North America and South America before the outbreak was contained (*29*). SARS is currently not known to be circulating among people, but it could still be circulating in animal hosts and may thus re-emerge in humans (*30*). Human-to-human transmission of SARS occurs mainly through droplets or direct contact, although transmission through infectious respiratory aerosols of various sizes may occur at short range (*31*).

1.3.2 New influenza virus causing human infection

Influenza viruses can infect many species, including humans, birds, pigs, horses and seals. Birds, in particular, are the main reservoir for influenza A viruses. Influenza viruses tend to infect people sporadically or in seasonal epidemics; occasionally, when a new human influenza virus emerges, it can cause a worldwide pandemic. Seasonal epidemics are caused by influenza viruses that are well adapted to the human hosts they circulate in. When an influenza virus with the capacity to infect humans first emerges in another species, it is not yet adapted to humans and may circulate in animal hosts, generating sporadic human infections. Because it may subsequently evolve the ability for sustained human-to-human transmission, any new influenza virus that generates sporadic cases of human infection may present a pandemic risk. Thus, early detection, isolation and warning of sporadic infections are crucial to minimize the risk of serious public health impacts from new influenza viruses (*32*).

Direct transmission of avian influenza viruses – including H5N1, H7N9, H7N2 and H9N2 – to humans has been described on numerous occasions (*33-36*), and often results in a high fatality rate (*37*). The most important avian virus infecting humans in recent years has been

avian influenza A(H5N1), which can be highly pathogenic. Human cases of H5N1 were reported in Hong Kong Special Administrative Region (SAR), China, in 1997, and have been found in other countries since 2003. Because A(H5N1) is believed to be circulating widely among wild birds, more cases in people are expected. Most instances of avian influenza infection in people have resulted from contact with infected poultry (e.g. domesticated chickens, ducks or turkeys) or surfaces contaminated with secretions or excretions from infected birds (*33-40*). So far, however, no efficient or sustained human-to-human transmission of avian influenza A(H5N1) has been demonstrated. In the potential cases of human-to-human transmission, infection was associated with close, extensive unprotected contact, suggesting that the virus might have spread through respiratory droplets or contact (*37, 41*).

Pandemic influenza A (H1N1) 2009 virus resulted from genetic re-assortment of swine, avian and human viruses, and it is efficiently spread through human-to-human transmission (*42*). First recognized in North America in April 2009, A(H1N1)pdm09 subsequently spread around the globe, causing a pandemic between June 2009 until August 2010 (*43, 44*).

1.3.3 Novel acute respiratory infections with potential for a high public health impact

Infectious diseases have spread across populations and regions throughout history, and it is likely that newly emerging infectious diseases will continue to be identified. Many infectious diseases with animal reservoirs can sometimes infect humans. Two examples that occurred after the 2009 influenza pandemic are human cases of influenza A(H7N9) which first occurred in 2013, and of Middle East Respiratory Syndrome (MERS) coronavirus from 2012[1].

The following factors have been associated with the emergence and spread of infectious diseases (*22, 45*):

- changes in human demographics and behaviour;
- impact of new technologies and industries;
- economic development and changes in land use;
- increased international travel and commerce;
- microbial adaptation and change;
- poor implementation of public-health measures; and
- sharing an environment with domestic or wild animals, including birds.

When a new infectious disease is identified, the modes of transmission are not well understood. The epidemiological and microbiological studies needed to determine the modes of transmission and identify possible IPC measures may be protracted. Due to the lack of information on modes of spread, Airborne and Contact Precautions, as well as eye protection, should be added to the routine Standard Precautions whenever possible, to reduce the risk of transmission of a newly emerging agent (Annex B describes Standard and other precautions). These precautions should be implemented until further studies reveal the mode of transmission. Epidemiological and clinical clues can indicate when additional precautions are needed (Section 2.1).

It is essential to maintain close surveillance of health-care workers from the very beginning of an outbreak with a novel pathogen, and during the outbreak, since this could offer

[1] Information on current infectious disease outbreaks can be found at http://www.who.int/csr/disease/en/.

important information about means of transmission, both for community and health-care associated transmission.

1.4 Infection prevention and control guiding principles

The conditions and levels of complexity in health-care facilities vary within and between countries. Policy-makers and health administrators should identify strategies with optimal cost-effectiveness ratios based on the facilities' potential for sustainable and continuous quality improvement.

The principles of IPC for ARI patient care include:

- early and rapid recognition of patients;
- application of routine IPC precautions (Standard Precautions) for all patients;
- additional precautions in selected patients (e.g. based on the presumptive diagnosis);
- establishment of an IPC infrastructure for the health-care facility, to support IPC activities.

IPC strategies in health-care facilities are commonly based on early recognition and source control, administrative controls, environmental and engineering controls, and personal protective equipment (PPE).

1.4.1 Early recognition and source control

Infected patients are the main source of pathogens in health-care settings, and reducing or preventing the dissemination of the infectious agent from the source is critical. These methods of reduction and prevention include promotion of respiratory hygiene (Annex B, Section B.1.3), early recognition and investigation, prompt implementation of IPC precautions, reporting and surveillance, and treatment to make patients non-infectious.

1.4.2 Administrative controls

The health-care facility management team needs to ensure that the necessary resources are available for implementation of IPC measures. These resources include the establishment of sustainable IPC infrastructures and activities; clear policies on early recognition of ARIs of potential concern; access to prompt laboratory testing for identification of the etiologic agent; implementation of appropriate IPC measures (e.g. Standard Precautions for all patients), and appropriate clinical triage and placement of patients; provision of regular supplies; and organization of services. The management team should also undertake staff planning to promote an adequate patient-to-staff ratio, provide staff training, and establish appropriate programmes for staff vaccination and prophylaxis.

1.4.3 Environmental and engineering controls

Environmental and engineering controls aim to reduce the concentration of infectious respiratory aerosols (e.g. droplet nuclei) in the air and to reduce the contamination of surfaces and inanimate objects. Examples of primary engineering controls for infectious respiratory aerosols include adequate environmental ventilation and spatial separation, with a distance of at least 1 m between patients. Adequate environmental ventilation is especially important to reduce the transmission of pathogens that are transmitted through the airborne route (e.g. pulmonary TB, measles and chickenpox). For infectious agents that spread by contact, important environmental control methods include cleaning and disinfection of contaminated surfaces and inanimate objects.

1.4.4 Personal protective equipment

These strategies all serve to reduce, but do not eliminate, the possibility of exposure to respiratory pathogens. The appropriate use of PPE serves to further reduce the risks of transmission of respiratory pathogens to health-care workers and other people interacting with the patients in the health-care facility. The use of PPE should be defined by policies and procedures addressing isolation precautions. Their effectiveness depends on adequate and regular supplies, adequate staff training, proper hand hygiene and, in particular, appropriate human behaviour.

All these controls are connected and should be harmonized to promote an institutional culture of safety.

1.5 Guideline development process

These guidelines were developed according to the *WHO handbook for guideline development,* 2012 (*18*). WHO commissioned systematic reviews and critical reviews of the literature as applicable. Every attempt was made to develop recommendations that focused on priority or controversial areas, using systematic reviews and evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (*18, 46-50*) (Annex K). The GRADE approach provides a structured and transparent assessment of the quality of evidence and its application to the guidelines process. A hierarchical approach was used to review the evidence when formulating the recommendations in these guidelines, with the highest ranking given to systematic reviews of human studies. Quality of evidence was ranked from randomized trials (deemed to be of highest quality), followed by prospective cohort studies, retrospective cohort studies, and finally controlled before-and-after studies (lowest quality). Similarly, priority of studies was ranked from in vivo animal studies relevant to the topic (deemed to be of highest priority) to in vitro laboratory studies relevant to the topic and theoretical considerations (lowest priority). The scientific evidence was also assessed for inconsistency, indirectness, imprecision, reporting bias, and other potential sources of bias. The summaries of each systematic review are provided in the Annex L, and the evidence profiles are available in published systematic reviews and referenced in the decision tables (Annex K) and in the Annex L.

Quality of evidence was considered of major importance in developing the guidelines. In addition, we considered the balance of the benefits or desired effects versus the disadvantages or undesired effects; values and preferences from a global perspective, including those of front-line health-care workers; cost and resource implications; and the feasibility of adopting a recommendation (*18, 46-50*). The recommendations were discussed internally with a Working Group within WHO, and then submitted to members of the Global Infection Prevention and Control Network (GIPCN) for review and feedback. Following the technical consultation meeting with the GIPCN, additional changes were made. The draft of these guidelines was also submitted for broad internal and external review.

2 Infection prevention and control recommendations

2.1 Recommendations for early recognition and source control

Early recognition of ARIs and application of source control, including respiratory hygiene, are administrative control measures aimed at reducing or preventing the dissemination of infectious agents from the source. The early identification, isolation and reporting of ARIs of potential concern are therefore central to effective containment and treatment.

2.1.1 Recommendations for health-care facilities and public health authorities

Health-care facilities

- Use clinical triage for early identification of patients with ARIs to prevent the transmission of ARI pathogens to health-care workers and other patients (Strong recommendation, very low to low quality of evidence) (*27, 51*) (Annex K, Table K.1). Regularly monitor and evaluate the clinical triage system to ensure effectiveness (*52-55*).
- Place ARI patients in an area separate from other patients, and evaluate clinical and epidemiological aspects of the case as soon as possible (*51, 52, 56*). Complement investigation with laboratory evaluation if applicable (*57, 58*).
- In people with ARIs, encourage the use of respiratory hygiene (i.e. covering the mouth and nose during coughing or sneezing with a medical mask [surgical or procedure mask], cloth mask, tissue, sleeve or flexed elbow), followed by hand hygiene, to reduce the dispersal of respiratory secretions containing potentially infectious particles (Strong recommendation, very low quality of evidence) (*27, 51, 59-63*) (Annex K, Table K.2).
- Implement additional IPC precautions promptly according to the suspected pathogen (Table 2.1) (*64*).
- Report all available essential information regarding episodes of ARIs of potential concern to public health authorities via the local surveillance system. This is in line with the requirements of the IHR (2005) (*6*), which have been in force since June 2007. The IHR (2005) require the international notification to WHO by States Parties of events that may constitute a public health emergency of international concern.

Public health authorities

- Establish channels to inform health-care facilities and the community about ongoing epidemic ARIs, so that the facilities will be aware of the extent and types of problems likely to be encountered.

Early recognition of ARIs of potential public health concern may be difficult, given the large number of etiological agents, and the similarities of presentation of patients with acute respiratory disease. Although the case definition may vary according to the specific disease, there are some general epidemiological and clinical clues to prompt suspicion, as outlined below:

- *Epidemiological clues* – A patient's history of travel to areas where there are patients known to be infected with an ARI of potential concern within the known or suspected

incubation period; possible occupational exposure to pathogens or novel agents causing ARIs of potential concern; unprotected contact with patients with ARIs of potential concern within the known or suspected incubation period; or being part of a rapidly spreading cluster of patients with ARI of unknown cause (*52, 65-69*), including exposure to household members with ARIs. Family members who live with patients with ARIs of potential concern can be assumed to have been exposed to the same ARI, and could be evaluated for both epidemiological clues and active infection (*52, 53, 69-75*). For novel agents, the epidemiological clues may change as additional information becomes available.

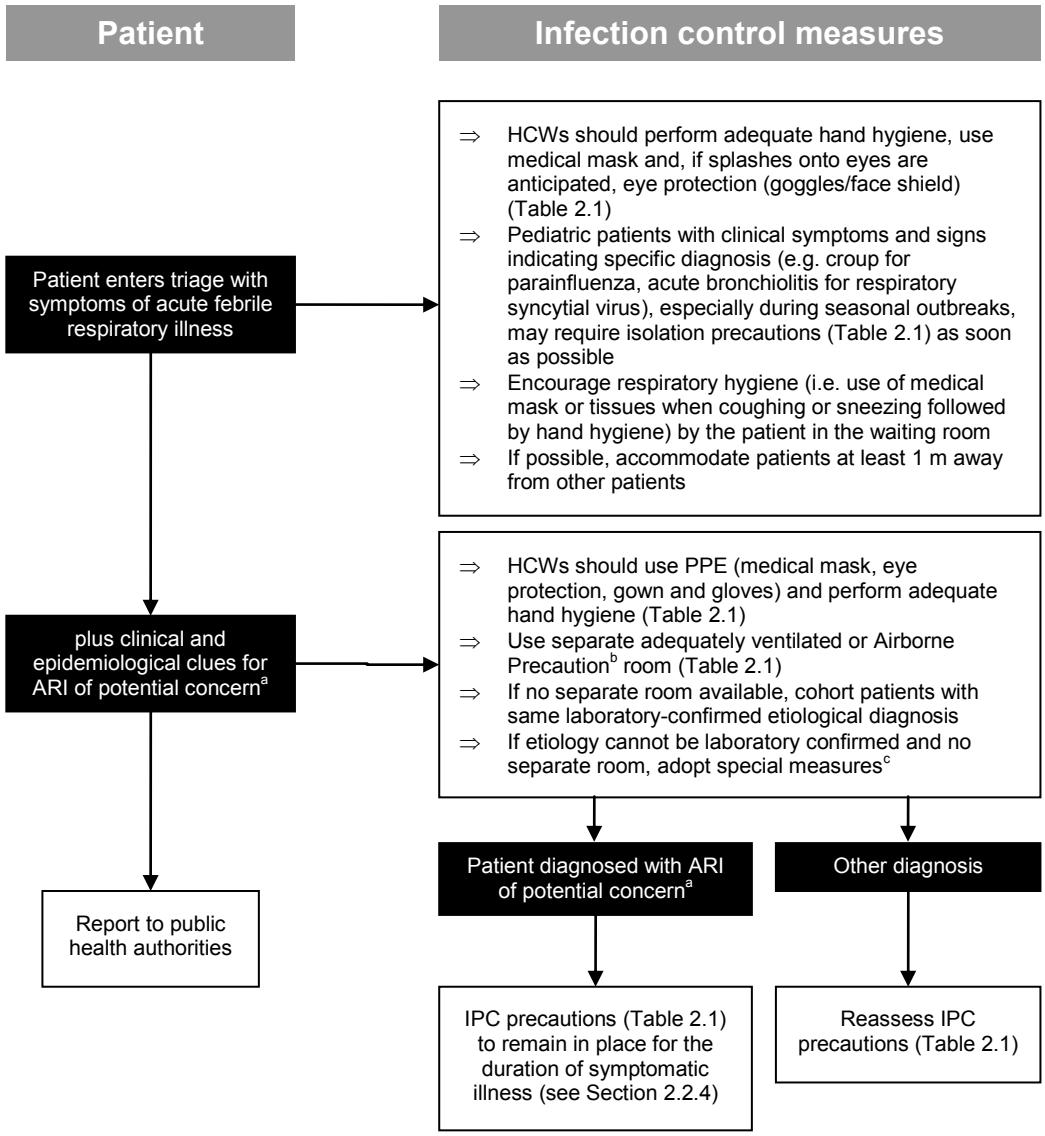
- *Clinical clues* – All patients who present with, or who have died of, unexplained severe acute febrile respiratory illness (e.g. fever > 38 °C, cough or shortness of breath) in the presence or absence of other severe unexplained illness (e.g. encephalopathy or diarrhoea) (*52, 53, 69-73*), with an exposure history consistent with the ARI of potential concern mentioned above, within the known or suspected incubation period.

Rationale

Prompt identification of ARI patients will enable the immediate implementation of IPC measures, reduce transmission to others in the health-care facility, and thus prevent outbreaks of epidemic-prone infections.

Since patients with severe ARIs tend to seek care at health-care facilities, such facilities are critical in identifying early signals of emerging ARIs that could constitute a public health emergency, either locally or internationally. Early identification and reporting offers an opportunity for successful containment. Prompt identification and management of patients, health-care workers or visitors who may be infected with an ARI of potential concern with pandemic and epidemic potential are key administrative control measures. Thus, they are critical to minimize the risk of health-care associated transmission and to enable an efficient public health response. The response includes implementation of adequate IPC measures, patient treatment and immediate reporting. The recognition of possible episodes depends on the case definition, which may evolve as additional epidemiological and clinical information becomes available.

Figure 2.1 Decision-tree for infection prevention and control measures for patients known or suspected to have an acute respiratory infection



[a]For the purpose of this document, ARIs of potential concern include SARS, new influenza virus causing human infection (e.g. human cases of avian influenza), and novel organism-causing ARIs that can cause outbreaks with high morbidity and mortality. Clinical and epidemiological clues (Section 2.1) include severe disease in a previously healthy host, exposure to household member or close contact with severe ARI, cluster of cases, travel, exposure to ill animals or laboratory.

[b]Airborne Precaution rooms include both mechanically and naturally ventilated rooms with ≥ 12 ACH and controlled direction of airflow (see Glossary).

[c]The term "special measures" means allowing patients with epidemiological and clinical information suggestive of a similar diagnosis to share a room, but with a spatial separation of at least 1 m.

Table 2.1 Infection prevention and control precautions for health-care workers and caregivers providing care for patients with acute respiratory infection and tuberculosis

Precaution		No pathogen identified, no risk factor for TB or ARI of potential concern (e.g. influenza-like illness without risk factor for ARI of potential concern)	Pathogen						
			Bacterial ARI[a], including plague	TB	Other ARI viruses (e.g. parainfluenza RSV, adenovirus)	Influenza virus with sustained human-to-human transmission (e.g. seasonal influenza, pandemic influenza)	New influenza virus with no sustained human-to-human transmission (e.g. avian influenza)	SARS	Novel ARI[b]
Hand hygiene[c]		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gloves		Risk assessment[d]	Risk assessment[d]	Risk assessment[d]	Yes	Risk assessment[d]	Yes	Yes	Yes
Gown[e]		Risk assessment[d]	Risk assessment[d]	Risk assessment[d]	Yes	Risk assessment[d]	Yes	Yes	Yes
Eye protection		Risk assessment[f]	Risk assessment[f]	Risk assessment[f]	Risk assessment[f]	Risk assessment[f]	Yes	Yes	Yes
Medical mask for health-care workers and caregivers		Yes	Risk assessment[f]	No	Risk assessment[f] /Yes[g]	Yes	Yes[h]	Yes[i]	Not routinely[b]
Particulate respirator for Health-care workers and caregivers	for room entry	No	No	Yes	No	No	Not routinely[h]	Not routinely[i]	Yes
	within 1 m of patient	No	No	Yes	No	No	Not routinely[h]	Not routinely[i]	Yes
	for aerosol-generating procedures[j]	Yes[k]	Yes[k]	Yes	Yes[k]	Yes[k]	Yes[k]	Yes	Yes[b,k]
Medical mask for patient when outside isolation areas[l]		Yes	Yes	Yes	Yes[m]	Yes	Yes	Yes	Yes
Adequately ventilated separate room		Yes, if available[n]	No	No	Yes, if available[n]	Yes, if available[n]	Yes	Yes	Not routinely[b]

Precaution	No pathogen identified, no risk factor for TB or ARI of potential concern (e.g. influenza-like illness without risk factor for ARI of potential concern)	Pathogen						
		Bacterial ARI[a], including plague	TB	Other ARI viruses (e.g. parainfluenza RSV, adenovirus)	Influenza virus with sustained human-to-human transmission (e.g. seasonal influenza, pandemic influenza)	New influenza virus with no sustained human-to-human transmission (e.g. avian influenza)	SARS	Novel ARI[b]
Airborne Precaution room[o]	No	No	Yes[p]	No	No	Not routinely[p]	Not routinely[p]	Yes[p]
Summary of isolation precautions for routine patient care, excluding aerosol-generating procedures[j] (Annex B)	Standard	Standard	Standard	Standard	Standard	Standard	Standard	Standard
	Droplet	--	--	Droplet	Droplet	Droplet	Droplet	--
	--	--	--	Contact	--	Contact	Contact	Contact
	--	--	Airborne	--	--	--	--	Airborne

ARI, acute respiratory infection; IPC, infection prevention and control; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; TB, tuberculosis

a Bacterial ARI refers to common bacterial respiratory infections caused by organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydophila* spp. and *Mycoplasma pneumoniae*.

b When a novel ARI is newly identified, the mode of transmission is usually unknown. Implement the highest available level of IPC precautions, until the situation and mode of transmission is clarified.

c Perform hand hygiene in accordance with Standard Precautions (Annex B).

d Gloves and gowns should be worn in accordance with Standard Precautions (Annex B). If glove demand is likely to exceed supply, glove use should always be prioritized for contact with blood and body fluids (nonsterile gloves), and contact with sterile sites (sterile gloves).

e If splashing with blood or other body fluids is anticipated and gowns are not fluid resistant, a waterproof apron should be worn over the gown.

f Facial protection, i.e. a medical mask and eye protection (eye visor, goggles) or a face shield, should be used in accordance with Standard Precautions by health-care workers if activities are likely to generate splashes or sprays of blood, body fluids, secretions and excretions onto mucosa of eyes, nose or mouth; or if in close contact with a patient with respiratory symptoms (e.g. coughing/sneezing) and sprays of secretions may reach the mucosa of eyes, nose or mouth.

g Adenovirus ARI may require use of medical mask

h As of the publication of this document, no sustained efficient human-to-human transmission of avian influenza A(H5N1) is known to have occurred, and the available evidence does not suggest airborne transmission from humans to humans. Therefore a medical mask is adequate for routine care.

i The current evidence suggests that SARS transmission in health-care settings occurs mainly by droplet and contact routes; therefore, a medical mask is adequate for routine care

j See Table K4, Annex K.

k Some aerosol-generating procedures have been associated with increased risk of transmission of SARS (Annex A; Annex L, Table L.1). The available evidence suggests performing or being exposed to endotracheal intubation either by itself or combined with other procedures (e.g. cardiopulmonary resuscitation, bronchoscopy) was consistently associated with increased risk of transmission of SARS. The risk of transmission of other ARI when performing the aerosol-generating procedures is currently unknown.

l If medical masks are not available, use other methods for respiratory hygiene (e.g. covering the mouth and nose with tissues or flexed elbow followed by hand hygiene).

m These are common pathogens in children, who may not be able to comply with this recommendation.

n Cohort patients with the same diagnosis. If this is not possible, place patient beds at least 1 m (3 feet) apart.

o Airborne Precaution rooms can be naturally or mechanically ventilated, with adequate ventilation rate of 160 l/s/patient or at least 12 air changes per hour and controlled direction of airflow.

p Airborne Precaution rooms, if available, should be prioritized for patients with airborne infections (e.g. pulmonary TB, chickenpox and measles) and for those with novel organisms causing ARI.

2.2 Recommendations for administrative control strategies for health-care facilities

Effective IPC programmes can reduce the frequency and financial burden of health-care associated infections (*76-78*). The 10-year long SENIC (Study on the Efficacy of Nosocomial Infection Control) study in the United States of America showed that organized IPC programmes are both effective and cost effective (*77*). Currently, IPC programmes are considered an integral part of the delivery of patient care[1] (*79, 80*). In addition to the recommendations for early recognition and source control described in Section 2.1, the following administrative control strategies for IPC programmes in health-care facilities outlined below are recommended.

For all ARIs

- Strengthen or establish an IPC committee and IPC programmes with trained personnel to keep policies current (*52, 53, 69-75, 79, 81, 82*).
- Monitor and increase compliance with IPC precautions using evidence-based methods, including multimodal strategies (e.g. change in infrastructure, education, posters, reminders, senior management engagement and performance feedback) (*83-85*).
- Educate health-care workers about ARIs, including the IPC precautions to be used for patients who present with a febrile ARI (*55, 86, 87*).
- Ensure that adequate IPC supplies are provided (*55, 87-89*), for example:
  - hand-hygiene facilities (e.g. soap and clean running water, alcohol-based hand rub, and paper or single-use towels);
  - PPE for patient care (e.g. masks, respirators, gowns, gloves and eye protection);
  - PPE for heavy duties (e.g. closed protective footwear, waterproof aprons and rubber gloves); and
  - an adequate supply of appropriate materials for cleaning and disinfection.

For ARIs of potential concern

- Reinforce the health-care facility's system that triggers patients and visitors to immediately alert health-care workers to symptoms of severe febrile ARI (e.g. signposting all entrances and clinical evaluation areas, such as emergency departments), in areas with reported ARIs of potential concern (*90*).
- Increase surveillance to detect evidence of transmission to other patients and health-care workers when a patient with a confirmed ARI of potential concern has been admitted to the facility (*91-93*).

Rationale

Hospital administrators and governments play a key role in preventing the spread of health-care associated pathogens by creating the necessary conditions at an institutional level. Targets for improvement include written guidelines, availability of necessary resources (staff and supplies), promotion of a culture or tradition of adherence to IPC practices, and administrative leadership or support. Important opportunities for improvement include

[1] For more details consult the WHO document *Core components for infection prevention and control programmes* (*79*).

enhancing individual and institutional attitudes to the feasibility of making changes, obtaining active participation, and promoting a safety climate.

In the SARS outbreak, important factors associated with compliance were the perception of health-care workers that their facilities had clear policies and protocols, the perceived attitudes and actions of management about the importance of occupational health and safety, adequate training in IPC procedures, and fast access to specialists. Education, regular supplies, adequate staffing, institutional climate and leadership are the cornerstones for promotion of good IPC practices (*88*). It is essential that health-care facilities develop preparedness plans addressing these elements (Chapter 4).

2.2.1 Isolation precautions

IPC precautions are measures designed to minimize the risk of transmission of infections. Such precautions are typically separated into Standard Precautions and additional precautions, such as Contact, Droplet and Airborne Precautions. Annex B summarizes the application and principles of Standard and additional precautions in health care.

Additional precautions may be needed depending on:

- the suspected or confirmed causative agents of the ARIs (*53, 65, 67-69, 94*);
- the presence of epidemiological and clinical clues suggesting that patients have ARIs of potential concern; and
- the types of contact and procedures that are undertaken with patients with ARIs.

IPC precautions to be applied when a patient with a suspected acute respiratory infection presents to a health-care facility

- Apply Standard Precautions routinely to ALL patients in ALL health-care settings (*95*) (Annex B).
- Apply Standard and Droplet Precautions (Annex B) at the initial evaluation of a patient with a suspected ARI. Modify isolation precautions according to the specific diagnosis, as it becomes available (Table 2.1).
- Apply Standard, Contact and Droplet Precautions (Annex B) at initial evaluation of a paediatric patient presenting with a suspected ARI during the peak season of certain viruses (e.g. croup and parainfluenza, acute bronchiolitis, and respiratory syncytial virus). Modify isolation precautions according to the specific diagnosis (Table 2.1).
- Evaluate the risk to determine whether additional protective measures may be necessary; for example, when providing care for patients infected with some specific pathogens (Table 2.1). If the patient has indications suggestive of a novel ARI with epidemic or pandemic potential (Section 1.3.3) and the route of transmission has not been established, add Airborne and Contact Precautions, plus eye protection, to Standard Precautions (Annex B).

Rationale

Because droplets are the major mode of transmission for most ARIs, Droplet Precautions should be applied in addition to Standard Precautions when an ARI is suspected. This is of particular importance in clinical areas that receive new patients who do not yet have a diagnosis (e.g. outpatient department and emergency room). The prompt application of

appropriate isolation precautions in these clinical areas, in particular, can help to mitigate spread of infections within the facility. However, since other modes of transmission are sometimes involved in ARI transmission, the type of precautions used should be reviewed once diagnosis has been confirmed (Table 2.1). In addition, enhanced isolation precautions are warranted for medical procedures with consistently documented increased risk of infection transmission (Annex A, Section A.1; Annex L, Table L.1).

Details of different types of isolation precautions are described in Annex B.

2.2.2 Cohorting and special measures

For all ARIs

- Consider the use of patient cohorting – that is, place patients infected or colonized with the same laboratory-confirmed pathogens in the same designated unit, zone or ward (with or without the same staff) – to reduce transmission of ARI pathogens to health-care workers and other patients (Conditional recommendation, low to moderate quality of evidence) (*51*) (Annex K, Table K.4).

- When there is no laboratory confirmation, apply special measures – that is, place patients with the same suspected diagnosis (similar epidemiological and clinical information) in the same designated unit, zone or ward (with or without the same staff) – to reduce transmission of ARI pathogens to health-care workers and other patients (Conditional recommendation, low to moderate quality of evidence) (*51*) (Annex K, Table K.4).

- Avoid sharing of equipment. If sharing is unavoidable, ensure that reusable equipment is appropriately disinfected between patients (*95*).

For ARIs of potential concern

- If single rooms used for the isolation of ARIs of potential concern are insufficient for the number of individuals, apply either cohorting of patients or special measures.

- For patient-care units that house patients with ARIs of potential concern, wherever possible, assign health-care workers who are experienced with IPC for ARIs and outbreak settings. Also, if possible, these workers should not "float" or be assigned to other patient-care areas.

- Limit the number of people entering the assigned unit or area for isolation, cohorting or special measures, to the minimum number required for patient care and support (*86, 96*).

2.2.3 Transport of patients inside and outside health-care facilities

Patient transport within health-care facilities

For all ARIs

- Encourage the use of medical masks by patients with ARI during transport or when care is necessary outside of the isolation room or area (*51, 95*) (Annex K, Table K.2). If medical masks are not available or not tolerated by the patient, other methods to reduce the dispersal of respiratory secretions, including covering the mouth and nose with a tissue or flexed elbow during coughing or sneezing (*90*), can be used, and should be followed by hand hygiene (*97, 98*). For more information on respiratory hygiene, see Annex B.

For ARIs of potential concern

Implement the measures described above for all ARIs, plus the following measures:

- Avoid the movement and transport of patients out of the isolation room or area unless medically necessary (*95*). The use of designated portable X-ray equipment and other important diagnostic equipment may make this easier. If transport is necessary, use routes of transport that minimize the exposures of staff, other patients and visitors to potential infection.

- As soon as possible, notify the receiving area of the patient's diagnosis and precautions that will be required before the patient's arrival.

- Clean and disinfect surfaces that the patient comes into contact with (e.g. bed) after use (99).

- Ensure that health-care workers who are transporting patients with an ARI of potential concern wear appropriate PPE and perform hand hygiene afterwards (*51*).

Pre-hospital care and transport outside health-care facilities

For all ARIs

- Screen patients with severe acute febrile respiratory illness for risk factors associated with ARIs of potential concern (*52, 66, 100*).

- After pre-hospital care or transport has been provided, follow recommended procedures for waste disposal, and for cleaning and disinfecting emergency vehicles and reusable patient-care equipment, as described for Standard Precautions (Annex B) (*95*).

- Avoid crowding of patients during examination and in outpatient treatment areas (*51*).

For ARIs of potential concern

Implement the measures described above for all ARIs, plus the following measures:

- Avoid aerosol-generating procedures associated with risk of pathogen transmission (e.g. intubation) during pre-hospital care and transport, unless required for life-support (*101, 102*). (Annex A, Section A.1)

- Ensure that transport vehicles have as high a volume of air exchange as possible (e.g. by opening the windows) (*1*). Separate the driver's and patients' compartments whenever possible.

- Notify the receiving facility as soon as possible before arrival that a patient with a suspected ARI of potential concern is due to arrive, and indicate whether additional precautions are required.

2.2.4 Duration of infection prevention and control precautions and patient discharge

Duration of IPC precautions

For all ARIs

Always implement Standard Precautions. Implement additional IPC precautions (Section 2.2.1) at the time of admission, and continue for the duration of symptomatic illness, modifying according to the pathogen and patient information (Table 2.1 and Table K.10).[1] Do not routinely use laboratory tests to determine the duration of IPC precautions, as there is no evidence that this is effective (*103, 104*).

For ARIs of potential concern

Avian and human influenza

The latest evidence indicates that at least 80% of pandemic H1N1 influenza transmission events occur within 2 days of symptom-onset (*104*). Although earlier research had suggested that influenza virus shedding may be protracted in infants (*105*) and young children (*106*), evidence from household settings now suggests that this shedding may not translate into an increased risk of influenza transmission (*104*). Therefore, the recommended duration of additional IPC precautions for influenza is the same as for ARIs in general (see above).

Severe acute respiratory syndrome

The duration of infectivity for SARS is not well defined. Although it has been reported that conversion to a negative reverse transcriptase-polymerase chain reaction (RT-PCR) may take a long time (median 30 days, longest 81 days), the clinical and epidemiological significance of this conversion is not known. In studies in Hong Kong SAR, China, no SARS-CoV could be cultured from clinical samples once the infected patients became asymptomatic (*107*).

Newly emerging ARIs

Implement additional IPC precautions at the time of admission, and continue for the duration of symptomatic illness, modifying according to the pathogen and patient information. Base the precautions used and their duration on information about transmission risk as it becomes available, and on local health authority recommendations. It may be prudent to implement the highest level of IPC precautions possible, including the use of particulate respirators, until the mode of transmission is clarified.

Discharge of patients infected with an ARI of potential concern

These are the recommendations suggested for discharging patients who are still symptomatic:

- Determine whether or not to discharge the patient on the basis of their clinical condition. If a patient with an ARI of potential concern no longer requires hospital care, assess the infection risk before discharge by assessing the patient's home environment. A sample checklist is provided in Annex C. To reduce the risk of transmission in the home setting, avoid discharging patients if IPC measures cannot be implemented, (*74, 75*).

[1] Patient information (e.g. age, immune status and medication) should be considered in situations where there is concern that a patient may be infectious for a prolonged period.

- Educate patients and their family members about personal hygiene and basic IPC measures (e.g. respiratory hygiene, hand hygiene, use of PPE if necessary, and adequate ventilation of rooms) (*51, 108, 109*).
- Enquire about household members who may be at higher risk of ARIs or their complications. Such people include those who are immunocompromised, pregnant women, people with chronic illness (e.g. heart, lung or kidney disease, and sickle cell disease), young children (< 2 years of age), and the elderly (> 65 years of age). These individuals should not have contact with the patient until the patient is asymptomatic. If this is not possible, alternative housing during the patient's isolation period could be considered (*110, 111*).
- Provide the patient or caregiver with instructions for follow-up clinic visits and a means to contact a health-care provider, if necessary (*112, 113*).

2.2.5 Family member and visitors

For all ARIs

- Advise visitors about the possible risk of ARI transmission, and ask them about whether they have any symptoms before they enter the facility or ward (*96, 114-116*).
- In the case of a paediatric patient, encourage and support parents, relatives or legal guardians to accompany the child throughout the hospitalization (*117, 118*). Parents, relatives or legal guardians could also assist in providing care to ARI patients in some situations (e.g. where there is a lack of resources), provided that it is possible to ensure hand hygiene and an adequate supply of PPE (with training and supervision of PPE use) (*117, 119*).

For ARIs of potential concern

Implement the recommendations given above for all ARIs, plus the following measures:

- Instruct visitors about the appropriate use of PPE and hand-hygiene before entry into an isolation room or area (*115, 120*).
- Evaluate family members and visitors with respiratory symptoms as possible cases of ARI of potential concern (*74, 96, 115, 116, 121*).

Rationale

Care of a patient in isolation can become a challenge when:

- resources are inadequate;
- the patient has poor hygiene habits or cannot assist in maintaining IPC precautions;
- the patient receives visitors;
- family members are frequently involved in the care of the patient.

Nevertheless, it is essential that the patient's right to receive visits and the child's right to be accompanied by a parent, relative or legal guardian is guaranteed. Therefore, the risk of ARI transmission should be mitigated by providing IPC instructions to visitors and accompanying guardians.

2.2.6 Specimen collection, transport and handling within health-care facilities

For all ARIs

- Ensure that health-care workers who collect specimens from patients with ARIs wear appropriate PPE (Table 2.1).
- Place specimens for transport in leak-proof specimen bags that have a separate sealable pocket for the specimen (i.e. a plastic biohazard specimen bag), with the patient's label on the specimen container, and a clearly written request form (*122*).
- Ensure that personnel who transport specimens are trained in safe handling practices and spill decontamination procedures (*123*).
- Ensure that laboratories in health-care facilities adhere to best biosafety practices according to the type of organism being handled (*124*).

For ARIs of potential concern

Implement the recommendations given above for all ARIs, plus the following measures:

- Deliver all specimens by hand whenever possible. Do not use pneumatic-tube systems to transport specimens (*125*).
- State the name of the suspected ARI of potential concern clearly on the accompanying request form. Notify the laboratory as soon as possible that the specimen is being transported.

Rationale

All specimens should be regarded as potentially infectious, and health-care workers who collect or transport clinical specimens should adhere rigorously to Standard Precautions, to minimize the possibility of exposure to pathogens. For further information on specimen handling and collection guidelines, see:

- *WHO laboratory biosafety guidelines for handling specimens suspected of containing avian influenza A virus*, 2005 (*126*);
- *WHO guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection*, 2005 (*127*).

For further information on laboratory biosafety guidelines, see the WHO *laboratory biosafety manual*, 2004 (*128*).

2.2.7 Health-care worker vaccination and occupational health

Health-care facility administrators

- Vaccinate health-care workers caring for patients who are at higher risk of severe or complicated influenza disease, to reduce illness and mortality among these patients (Strong recommendation, very low to low quality of evidence) (*129-131*) (Annex K, Table K.8).[1]
- Inform health-care workers who are at high risk of severe or complicated illness from influenza and ARIs of potential concern about the medical risks of providing care to ARI patients and offer alternative work assignments (*111, 132, 133*).
- Develop a surveillance system for health-care workers for influenza-like illness (ILI).

[1] Refer to the WHO *Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection*, 2004 (*14*).

- Exclude health-care workers with ILI from units, zones or wards that house patient populations that are at high risk of severe disease from ARIs (e.g. neonatal intensive care unit, and haematopoietic stem cell transplantation unit) (*134-137*).

Special recommendations for health-care facilities managing patients with ARIs of potential concern are as follows:

- Keep a register of health-care workers who have provided care for patients with ARIs of potential concern, for contact tracing (*138*).
- Develop a system to monitor health-care workers' health, especially that of workers providing care for patients with ARIs of potential concern, that uses self-reporting by symptomatic workers (Annex D) (*139, 140*). Provide prompt access to diagnosis, counselling and treatment if these are available.
- Antiviral prophylaxis is not routinely recommended. If local policy recommends antiviral prophylaxis, health-care facility administrators should contact public health officials for assistance in obtaining adequate supplies for prophylaxis of health-care workers providing care for patients with ARIs of potential concern, in line with local guidance. Details of appropriate use of antiviral prophylaxis for influenza are provided in *WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses*, 2010 (*15*).
- Consider developing methods to provide additional support to health-care workers taking care of patients with ARIs of potential concern (e.g. emotional and family support), as necessary (*141, 142*).

Health-care workers who provide care for patients known or suspected to be infected with an ARI of potential concern

- Organize health-care workers into groups designated for caring for patients. Check temperature regularly (e.g. before each work shift), and monitor for symptoms of ILI (cough, sore throat and difficulty in breathing) for 7–10 days after last possible exposure to a patient with an ARI of potential concern (Annex D) (*93, 143*).
- Advise workers to take the following actions if they develop a fever > 38 °C or symptoms of ILI (*93, 144*):
  - stop work immediately or do not report to work;
  - limit interactions with others;
  - exclude themselves from public areas; and
  - notify management or the team dealing with IPC and occupational health that they are symptomatic and have had contact with patients with an ARI of potential concern.

Rationale

During ARI outbreaks, health-care workers can become infected either through exposure in the community or in the health-care facility (i.e. not necessarily as a result of patient exposure) (*145*). Once infected, these workers can serve as sources of transmission to other staff and to their patients, who may be at higher risk of severe or complicated illness from ARIs. Therefore, influenza vaccination of workers caring for patients at high risk for severe disease could reduce the risk of infection among these patients. (For more information on the evaluation of vaccination of health-care workers, see Annex K.) While seasonal influenza vaccine does not provide protection against new influenza viruses, such as avian influenza, it

will help to prevent concurrent infection with seasonal human influenza (*146*), and thus reduce confusion in diagnosis and unnecessary work furlough in areas with frequent reported cases of avian influenza. Antibody responses are usually developed within 2 weeks of influenza vaccination in adults. Vaccination should not preclude the full application of IPC precautions.

2.3 Recommendations for engineering and environmental control for acute respiratory infection

2.3.1 Placement of patients and spatial separation

For all ARIs

- Place patients infected with ARIs in adequately ventilated rooms.
- Maintain spatial separation (distance of at least 1 m) between each ARI patient and other individuals not wearing PPE, to reduce the transmission of ARI pathogens (Strong recommendation, very low to low quality of evidence) (*12, 51, 143, 147*) (Annex K, Table K.3).

ARIs of potential concern

- Place patients infected with an ARI of potential concern in adequately ventilated single rooms or Airborne Precaution rooms (*51*).
- If possible, situate rooms used for isolation of ARIs of potential concern (i.e. single rooms) in an area that is clearly segregated from other patient-care areas (*31, 51, 86, 99, 148*).

Rationale

Patient placement should be planned according to:

- the presence of epidemiological and clinical clues of ARIs of potential concern;
- the precautions undertaken, in addition to Standard Precautions, for the suspected or confirmed causative agents; and
- the availability of facilities.

Airborne Precaution rooms should be prioritized for patients with obligate (pulmonary TB) or preferential airborne infections (e.g., measles and chickenpox) and for patients infected with novel agents causing ARIs of potential concern for which there is no information on possible routes of transmission.

Transmission of ARIs through droplet nuclei at short range can occur during aerosol-generating procedures associated with increased risk of pathogen transmission (Annex A) under special situations (e.g. inadequate use of PPE or poor environmental ventilation). Rooms should be kept adequately ventilated.

Section 2.2.2 discusses cohorting and special measures; Annex B gives details of isolation precautions; and Annex E gives details of isolation rooms.

2.3.2 Design of triage and waiting areas

- Ensure that triage and waiting areas are adequately ventilated (*1-3*).
- Organize the space and the processes to allow for spatial separation (at least 1 m) between patients waiting to be seen (*51*), and undertake rapid triage of patients with

acute febrile respiratory diseases. Screen patients for risk factors associated with ARIs of potential concern (*52, 54, 86*).

2.3.3 Environmental controls for aerosol-generating procedures

- Use adequately ventilated single rooms when performing aerosol-generating procedures that have been consistently associated with increased risk of ARI transmission (Conditional recommendation, very low to low quality of evidence) (*1, 149*) (Annex K, Table K.7; Annex A).

2.3.4 Corridors

- Maintain a ventilation rate of 2.5 L/s/m3 in corridors and other transient spaces. When patient care is regularly undertaken in corridors during emergency or other situations, apply the same ventilation rate requirements as for regular patient-care areas (60 l/s/patient) (*1*).

2.3.5 Ultraviolet germicidal irradiation in health-care settings

At this time, it is not possible to make a recommendation about the use of ultraviolet germicidal irradiation (UVGI) to reduce the risk of transmission of ARI pathogens in health-care facilities (Annex K.2, Table K.9).

Rationale

There is very limited evidence to suggest that the transmission of ARI pathogens from patients to health-care workers or other patients can be prevented by the use of UVGI in health-care settings (*150*). Additional research is needed to understand whether the use of UVGI for disinfection of air reduces transmission of specific ARI pathogens from patients to health-care workers during care delivery in health-care settings, with or without the use of other precautions. In addition, more research is required to assess the potential harms and cost effectiveness of using UVGI in these settings. Therefore, no recommendation about the use of UVGI to reduce the risk of transmission of ARI pathogens in health-care facilities is possible at this time.

2.4 Recommendations for use of personal protective equipment

- Use PPE in the context of other prevention and control strategies (*151*), and in accordance with IPC recommendations (e.g. Standard, Contact, Droplet or Airborne Precautions) (*95*).
- Use appropriate PPE as determined by risk assessment (according to the procedure and suspected pathogen, see Table 2.1). Appropriate PPE that may be required when providing care to patients presenting with ARI syndromes includes one or more of the following: medical mask (surgical or procedure mask), gloves, long-sleeved gowns and eye protection (goggles or face shields) (Strong recommendation, low to moderate quality of evidence) (*51*) (Annex K, Table K.5).
- Use PPE – including gloves, long-sleeved gowns, eye protection (goggles or face shields) and facial mask (surgical or procedure mask, or particulate respirators)[1] – during aerosol-generating procedures that have been consistently associated with an increased

[1] There is no evidence to suggest a difference in the effectiveness of particulate respirators over medical masks as a component in the use of PPE for routine care. However, it is not known whether there is any difference in the setting of care involving aerosol-generating procedures. When performing such procedures associated with an increased risk of transmission of ARI pathogens, it may be preferable to use particulate respirators (Annex A).

risk of transmission of ARI pathogens (*27, 51*).[1] The evidence suggests that performing or being exposed to endotracheal intubation, either by itself or combined with other procedures (e.g. cardiopulmonary resuscitation or bronchoscopy), is consistently associated with increased risk of transmission (Conditional recommendation, very low to low quality of evidence) (*149*) (Annex K, Table K.6).

- Monitor health-care workers' compliance with proper use of PPE. This is particularly important when caring for patients with ARIs of potential concern.
- Ensure that staff receive appropriate training on the use of PPE (*87, 151-155*).

Annex E gives details of preparation of an isolation room or area, and of wearing and removing PPE.

2.4.1 Rational use of personal protective equipment

- Ensure sufficient supplies of appropriate PPE (*87, 152, 154, 155*). If resources are limited and disposable PPE items are not available, use reusable items (e.g. disinfectable cotton gowns) and disinfect properly after each use (*99*). To avoid wastage, critically evaluate situations in which PPE is indicated (using Table 2.1), and maximize the provision of clinical care during each entry to the patient's room (*95*).
- Avoid reuse of disposable PPE items. It is not known whether reusing disposable PPE is as safe and effective as using new PPE, and reuse may increase the risk of infection for health-care workers (*156 , 157*).

Respiratory protection

- Ensure that users receive training on how to put on a particulate respirator, and that they understand the need to perform the seal check every time the respirator is worn, to avoid contamination during use, and to remove and dispose of the respirator (*158*). If patients with known or suspected airborne infections (e.g. pulmonary TB) are cohorted in a common area or in several rooms on a nursing unit, and if multiple patients will be visited sequentially, it may be practical for a health-care worker to wear a single particulate respirator for the duration of the activity. This type of use requires that the respirator not be removed at any time during the activity, and that the user does not touch the respirator. If the respirator gets wet or dirty with secretions, it must be changed immediately.
- If supplies are limited, prioritize the use of particulate respirators for workers who provide care to patients with obligate and preferentially airborne-transmitted diseases, and who are performing aerosol-generating procedures that have been consistently associated with increased risk of pathogen transmission (Annex A, Section A.1). If a particulate respirator is not available, whenever possible, avoid performance of aerosol-generating procedures associated with an increased risk of pathogen transmission in patients with ARIs of potential concern (*101, 102, 116, 159, 160*).

Medical masks

- Wear medical masks fitted tightly to the face, and discard immediately after use (*161, 162*). If the mask gets wet or dirty with secretions, it must be changed immediately.

[1] When a novel ARI is identified and the mode of transmission is unknown, it may be prudent to implement the highest level of IPC precautions whenever possible (including the use of particulate respirators), until the mode of transmission has been clarified.

Gloves

- If supplies of gloves are limited, reserve gloves for situations where there is a likelihood of contact with blood, respiratory secretions, or body fluids, including during aerosol-generating procedures that have been consistently associated with increased risk of pathogen transmission (Annex A) (*155, 163, 164*). Apply standard IPC practices for glove use (e.g. changing gloves between patients). The use of gloves does not eliminate the need to perform hand hygiene (Annex B).

Gowns

- If supplies of gowns for health-care workers are limited, prioritize the use of gowns for aerosol-generating procedures that have been consistently associated with increased risk of pathogen transmission (Annex A, Section A.1) and for activities that involve close contact with the patient (e.g. in paediatric settings) (*155, 163*). Gowns may also be worn during the care of more than one patient in a single cohort area only, provided that the gown does not come into direct contact with any patient.

Eye protection

- Reusable eye protective equipment can be used (e.g. goggles or face shield), but may pose a risk of cross-infection if not cleaned and decontaminated properly according to the manufacturer's instructions after each use (*87*). Ensure that equipment is thoroughly cleaned before disinfection (*165-170*). Perform hand hygiene after disposal or cleaning of eye protection equipment that may be contaminated with splash or spray (*97, 98*).
- Do not use conventional eye glasses as eye protection, because they are not designed to protect against splashes to the eye mucosa.

Rationale

PPE is meant to provide additional protection for the user but should not result in increased risk for other individuals or the environment. PPE supplies may be limited, and reuse of PPE items unavoidable; however, items should be reused under safe conditions. Avoid use of unnecessary PPE.

2.5 Recommendations for care of the deceased

2.5.1 Removal of the body from the isolation room or area

- Ensure proper use of PPE, according to Standard Precautions, to avoid direct contact with body fluids (*51, 95*).
- Apply principles of cultural sensitivity. If the family of the patient wishes to view the body after removal from the isolation room or area, they may be allowed to do so with the application of Standard Precautions (*95*). Annex F provides details of recommended PPE and procedures for body packing and transport for ARI of potential concern.

2.5.2 Mortuary care

- Ensure that mortuary staff and the burial team apply Standard Precautions (i.e. perform proper hand hygiene and use appropriate PPE, including long sleeved gown, gloves and facial protection if there is a risk of splashes from the patient's body fluids or secretions onto the body or face of the staff member) (*51, 95, 97, 98, 171, 172*).
- Apply Standard Precautions if hygienic preparation of the deceased (e.g. cleaning of body, tidying of hair, trimming of nails and shaving) is desired (*95*).

Rationale

Transmission of lethal infectious diseases associated with mortuary care has been reported (*173*), however, the cultural context of the local community should also be respected (*174*). Assess the risk during the mortuary care process, and provide adequate explanation to the family. If indicated, provide PPE to the family, with instruction in its use. Manage each situation on a case-by-case basis, balancing the rights of the family with the risks of exposure to infection.

2.5.3 Postmortem examination

- Ensure that safety measures are in place when performing postmortem examinations and collection of samples for microbiologic analyses (Annex F).
- Apply appropriate safety measures to protect those performing the examination (*175-177*) (Annex F).
- Engage a minimum number of staff in the procedure, and perform only if (*178, 179*):
  - an adequately ventilated room suitable for the procedure is available; and
  - appropriate PPE is available; for details of PPE suggested, and how to put on and take off PPE, refer to Annex F.

2.5.4 Engineering and environmental controls for autopsy

- Perform autopsies in an adequately ventilated room (*180*).
- Minimize aerosols in the autopsy room (e.g. during lung excision) by:
  - avoiding the use of power saws whenever possible (*181, 182*);
  - avoiding splashes when removing, handling or washing organs, especially lung tissue and the intestines (*181, 182*); and
  - using exhaust ventilation to contain aerosols and reduce the volume of aerosols released into the ambient air environment; exhaust systems around the autopsy table should direct air and aerosols away from health-care workers performing the procedure (e.g. exhaust downward) (*182-184*).

For details of how to reduce aerosol generation during autopsy, refer to Annex F.

- Clean surfaces that have become contaminated with tissues or body fluids and decontaminate by (*179*):
  - removing most of the tissue or body substance with absorbent materials;
  - cleaning surfaces with water and detergent;
  - applying the disinfectant standardized by the health-care facility – if sodium hypochlorite solution is used (Annex G, Table G.1), wet the surface with the solution and allow at least 10 minutes contact time;
  - rinsing thoroughly.

Rationale

Safety procedures for deceased individuals infected with an ARI should be consistent with those used for any autopsy procedure. In general, the known hazards of work in the autopsy room seem to arise from contact with infectious materials and, particularly, with splashes onto body surfaces of health-care workers rather than from inhalation of infectious material. However, if a patient with an ARI of potential concern died during the infectious period, the

lungs and other organs may still contain live virus, and additional respiratory protection is needed during procedures that generate small-particle aerosols (e.g. use of power saws and washing of intestines). Therefore, postmortem examinations of patients with ARIs of potential concern deserve special caution.

3 Health-care facility preparedness planning for acute respiratory infection epidemics

The SARS outbreak of the early 2000s, and the influenza pandemic (H1N1) 2009, highlighted the importance of preparedness to reduce the spread of potentially epidemic or pandemic ARIs. Health-care facilities should prepare for communicable disease emergencies by (*185-188*):

- organizing permanent IPC activities, surveillance and training of dedicated personnel and clinical staff;
- creating a multidisciplinary group within the health-care facility to develop a preparedness plan;
- developing a preparedness plan in the health-care facility;
- performing a plan evaluation and monitoring exercise, and updating the plan as necessary; and
- strengthening liaison with other levels of the health-care system and public health authorities.

Rationale

Most of the population will have no immunity against a new respiratory virus that could potentially cause an epidemic or pandemic. Thus, if the initial containment fails, a substantial proportion of the population, including health-care workers, may fall ill and require health-care services. There may be a need to manage large numbers of ill patients requiring various levels of health care, and to contain the spread of ARIs of potential concern associated with heath care. Preparedness of health-care facilities is considered an essential part of general emergency preparedness plans (*189, 190*). The main goals are to:

- identify, isolate and report early cases of a putative epidemic or pandemic ARI virus;
- keep the health-care system functioning for pandemic and non-pandemic patients; and
- reduce the risk of pandemic ARI transmission associated with health care.

The capacity of the health-care facility to respond efficiently to epidemic or pandemic threats at any given moment is highly dependent on existing standards of practice. The implementation of additional measures during an outbreak is challenging, and the lack of good baseline standards may hamper efforts to respond to the epidemic or pandemic. Thus, ARI epidemic or pandemic preparedness requires continuous strengthening of early detection systems and safe care practices in the health-care facility. Promotion of routine Standard Precautions in health care is the cornerstone of reducing the spread of pathogens. Such promotion should be increased worldwide, to support the preparedness of health-care facilities for epidemics and a potential pandemic.

3.1 Components of health-care facility pandemic acute respiratory infection preparedness plans

These plans should take into account the geographical location of the facility and the progress of the ongoing pandemic, if any. The strategy should include actions to be taken

before, during, and after the epidemic or pandemic event and be part of the overall Emergency Response Plan, based on the health-care facility's risk assessment. They should address the issues outlined below: surveillance, triage, surge capacity, access, risk communication, IPC, occupational health, patient flow and discharge planning, mortuary and promotion of outpatient care.

3.1.1 Surveillance

- As a priority, establish within the health-care facility processes for the early recognition and investigation of possible pandemic ARI patients (*57, 58*).
- Connect the hospital and public-health infectious diseases surveillance systems, and immediately report any essential information about possible pandemic ARI cases to public health authorities. The reporting should occur through the local surveillance system, as per Annex 1 of the IHR (2005) (*6*).
- Public-health authorities should keep health-care facilities informed about ongoing epidemics.
- In the case of pandemic influenza:
  - enhance ILI surveillance (Annex D) (*185, 191*);
  - define criteria that would shift surveillance of episodes of influenza of potential concern (e.g. human cases of avian influenza) from passive to active (*185, 188, 192*).

3.1.2 Triage

- Define IPC measures for triage, flow, and placement of patients, and early reporting and treatment.
- Organize front-line services (e.g. emergency department) for triage of patients with respiratory symptoms (*52, 192*).
- Promptly initiate IPC precautions when a possible epidemic or pandemic ARI episode is suspected (*64, 189, 193*).

3.1.3 Surge capacity

- Plan for surge capacity according to the estimated impact of a potential pandemic on health care (*194-198*). (Annex H provides information on how to do this.)
- Identify the supplies and infrastructures needed to implement IPC measures.
- Outline the limits of the health-care facility's surge capacity to provide care, and suggest thresholds at which alternative sites for provision of health care (i.e. off-site care facilities) should be implemented (*194-198*).

Outline surge capacity in relation to (*194-198*):

- supplies (e.g. pharmaceuticals and PPE);
- ventilators and supplemental oxygen;
- staff – develop plans to maintain sufficient personnel to carry out activities (e.g. by planning alternative shifts or staffing assignments, and having a supplemental staffing plan);
- infrastructure;
- space;

- laboratory and diagnostic capacity; and
- security policies to handle an unexpected increase in demand for services.

3.1.4 Access

Establish policies for access to the health-care facility for (*114*):

- the public;
- visitors (those who are allowed to enter should be educated on respiratory hygiene and risk of disease transmission, and screened or surveyed for ARIs);
- health-care workers (i.e. flow of workers through the facility); and
- patients (i.e. patient flow).

3.1.5 Risk communication policy

Develop a risk communication policy to cover communication (*199*):

- within the health-care facility;
- with other health-care facilities;
- with other public health bodies, government agencies and ministries;
- with other societal bodies (e.g. media, professional societies and nongovernmental organizations).

3.1.6 Infection prevention and control

Undertake IPC measures, as follows:

- Engage health-care workers in prioritization of resources and training (e.g. use of PPE).
- Engage health-care workers in the process of implementing the IPC measures to decrease the infection risk.
- For all staff members involved in IPC prepare Job Action Sheets describing their roles and tasks in an emergency situation; ensure they participate in regular exercises in order to enhance their ability to fulfil their roles.
- Reinforce Standard Precautions (Annex B), to promote a culture of safe practices (*154*).
- Educate health-care workers about pandemic ARIs, with information about the main pathogens, epidemiology, morbidity, routes of transmission, breaking the chain of transmission and PPE use (e.g. risk assessment, proper ways to put on and take off, and safe disposal) (*55, 86, 144, 158*).
- Plan which areas in health-care facilities will be used for pandemic ARI patients.
- Apply IPC precautions according to the pandemic pathogen (Table 2.1) (*95, 200*).
- For specimen collection, transport and handling within the health-care facility (*201*):
  - when collecting specimens, use IPC precautions according to the pandemic pathogen (Table 2.1);
  - when transporting specimens to the laboratory, use Standard Precautions;
  - when handling specimens, follow appropriate biosafety practices.
- Define procedures for safe transport of patients both within the health-care facility and between facilities.

- Establish environmental and engineering controls, such as ensuring effective environmental ventilation and cleaning.

3.1.7 Occupational health programme

- Monitor and support the health of health-care workers.
- Consider appropriate vaccination (e.g. seasonal influenza vaccine) (*190, 202, 203*).
- Consider vaccination against a new ARI of potential concern, if a vaccine is available.
- Emphasize ILI surveillance among health-care workers; this may help to provide early signals of human-to-human transmission of a new ARI agent (*202*).
- Treat and follow up health-care workers infected with epidemic or pandemic ARI (*15, 204*).
- Plan staff reassignment according to risk assessment (*111, 132, 133, 205*).
- Provide psychosocial support.

3.1.8 Patient flow and discharge planning

- Heighten awareness of the clinical presentation of the ARI during an outbreak period, to increase early recognition of possible cases (*52*).
- Plan a safe flow of patients, to help prevent transmission of ARI-causing pathogens (*52*). For example, provide health services targeting uninfected populations (e.g. prenatal care, injury care, well-child visits and treatment of non-infectious diseases), particularly those who are at high risk of a complicated ARI (e.g. the immunocompromised and the elderly), in an area separate from patients known or suspected to have the ARI.
- Plan the discharge of a patient based on the patient's clinical conditions, assessment of the patient's home conditions and the capability of home caregivers to comply with instructions. (See Section 2.2.4 for details.)

3.1.9 Mortuary

- Plan strategies to cope with mass fatalities, including how to conduct burials for a large number of people.
- Take cultural and religious aspects into consideration (*174*).

3.1.10 Promotion of outpatient care of ARI patients in the event of pandemic

- Liaise with other stakeholders within the health-care system (e.g. community health centres) to help support outpatient care when the patient needs higher levels of care than usual. For example, acute-care health-care facilities may refer patients to ambulatory-care facilities for diagnosis, treatment and follow-up, according to the patient's clinical status (*188*). For additional information about IPC across the continuum of health care, see Annex J.
- Apply strategies to limit unnecessary office visits by ill patients; for example, divert patients to designated pandemic influenza triage and evaluation sites, and use triage before arrival at the health-care facility to determine which patients need on-site medical evaluation.

4 Research gaps

The recommendations in this document are based on the scientific evidence available at the time of publication. However, there are research gaps in many areas pertinent to IPC practices for ARIs. For example, there is a lack of high-quality research on (*206, 207*):

- several facets of the transmission of ARIs, and the effectiveness of interventions to reduce transmission of ARIs, particularly with respect to epidemiologically relevant outcomes; and
- the cost and resource implications of interventions to reduce transmission of ARIs, and the social and cultural factors that might compromise compliance with the application of interventions.

The identification of these research gaps will be useful in planning and conducting future studies in areas relevant to ARIs and in using IPC approaches to reduce the transmission of ARI pathogens.

4.1 Aerosol-generating procedures

There is a significant research gap regarding the epidemiology of ARI transmission from patients to health-care workers during aerosol-generating procedures, particularly with respect to pathogens other than SARS-CoV. This gap is compounded by a lack of precision in the literature with regard to the definition for aerosol-generating procedures. In addition, little information exists on the minimum ventilation requirements to reduce pathogen transmission during such procedures. There is no evidence to suggest a difference in the effectiveness of particulate respirators over medical masks as a component of PPE for routine care; however, research is needed to determine whether there is a difference between the effectiveness of particulate respirators and medical masks in the context of aerosol-generating procedures that have been consistently associated with increased risk of pathogen transmission.

4.2 Epidemiology of transmission

Additional research is required to fully elucidate the epidemiology of transmission of specific ARIs from patients to health-care workers, and to other patients, during care delivery in health-care settings:

- with and without the use of specific precautions;
- with the use of triage and early identification alone versus its use in combination of other selected precautions; and
- with the use of spatial separation alone versus spatial separation with the use of other selected precautions. In relation to spatial separation, high-quality epidemiological studies are needed to examine the effect of discrete parameters (e.g. 1 m, 2 m) of spatial separation on the reduction of transmission and infection by ARIs.

4.3 Duration of IPC precautions

The specific duration of infectious period for ARI pathogens is unknown. In particular, research is needed to undertand whether extending the duration of additional IPC precautions after the resolution of symptoms for patients with ARIs in health-care settings

reduces the risk of transmission to other patients and to health-care workers. There is also a need for research into:

- using routine laboratory tests as a guide to define the duration of IPC precautions for individuals with ARI in health-care settings; and
- the harms and cost implications of using laboratory tests to define the duration of IPC precautions.

4.4 Cohorting and special measures

In relation to cohorting (placement of patients infected with the same known pathogen in a common designated unit, zone or ward) and special measures (placement of patients with the same suspected but not laboratory-confirmed diagnosis in a common designated unit, zone or ward), additional research is required to:

- fully validate the equivalence of special measures and cohorting with respect to the reduction of transmission of ARI pathogens;
- fully elucidate the epidemiology of ARI transmission from patients to health-care workers with the use of cohorting alone compared to cohorting with other selected precautions, such as PPE; and
- study the cost and resource implications for cohorting in different settings around the world.

4.5 Other interventions

The effectiveness of respiratory hygiene in people with ARI as a means to reduce droplet dispersion and clinical illness among contacts needs to be determined.

Research is also needed:

- into whether the use of UVGI for disinfection of air in health-care settings further reduces the risk of transmission of and infection with specific ARI pathogens in such settings, with and without the use of other precautions; and
- to assess the potential harms and cost effectiveness of the use of UVGI in health-care settings.

Studies suggest that influenza vaccination of health-care workers provides a protective effect to patients in long-term residential care facilities (where patient turn-over is very low compared to standard health-care settings and where most patients are at high risk of complications from influenza infection); however, the relevance of these findings to acute health-care facilities requires further study. The benefits of other vaccinations, as well as the safety and cost effectiveness of implementing a vaccination programme for workers are yet to be determined.

Annex A Respiratory protection

A.1 High-risk aerosol-generating procedures

Aerosols are produced when an air current moves across the surface of a film of liquid, generating small particles at the air–liquid interface. The particle size is inversely related to the velocity of air. Therefore, if a procedure causes air to travel at high speed over the respiratory mucosa and epithelium, the production of aerosols containing infectious agents is a potential risk. An aerosol-generating procedure is defined as any medical procedure that can induce the production of aerosols of various sizes, including droplet nuclei. Previously, the association between medical procedures that are known to produce aerosols and an increased risk of pathogen transmission had not been rigorously evaluated. However, a systematic review on aerosol-generating procedures and the risk of ARI transmission has now made it easier to determine which procedures are associated with a high risk of transmission and provides a basis for recommendations (*149*). The review also highlighted the following research gaps:

- a lack of information about the risk of ARI transmission from patients to health-care workers during aerosol-generating procedures, particularly with respect to pathogens other than SARS-CoV;
- a lack of precision in the definition of aerosol-generating procedures;
- the need to determine the minimum environmental ventilation requirements in terms of variable ventilation rate;
- the need for control of airflow direction for aerosol-generating procedures.

Our understanding of the aerobiology of aerosol-generating procedures will continue to evolve. Annex L (Table L.1 and Figs L.2A & B) describes the results of studies evaluating the infection risk associated with aerosol-generating procedures. All included studies were found to be very low quality by the GRADE evaluation framework (*149*).

The evidence, the best of which comes from studies of SARS-CoV, suggests a consistent association between pathogen transmission and tracheal intubation (*149*). In addition, a few studies reported an increased risk of SARS-CoV infection associated with tracheotomy, non-invasive ventilation, and manual ventilation before intubation. However, because these findings were identified from only a few studies of very low quality, interpretation and practical application is difficult. No other procedures were found to be significantly associated with any increased risk of ARI transmission.

Recommendations for environmental controls and PPE use for health-care workers performing aerosol-generating procedures on ARI patients have been addressed in Chapter 2 (Sections 2.3.3 and 2.4).

A.2 Selection of respiratory protection equipment

A.2.1 Particulate respirators

Considerations for health-care workers:

- If caring for patients with an airborne infection (e.g. pulmonary TB), or undertaking aerosol-generating procedures associated with an increased risk of transmission of ARI

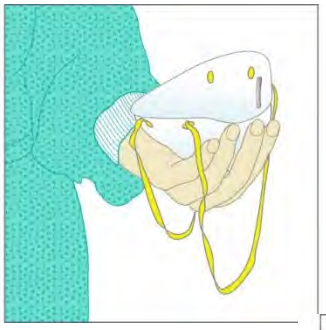
pathogens, select the highest level of respiratory protection equipment available, preferably a particulate respirator.

- When putting on a disposable particulate respirator, always check the seal (Fig. A.1, below).

Considerations for health-care facilities:

- The fit and seal of disposable particulate respirators are important for effective function. If the fit and seal are poor, airborne particles may be inhaled from leaks, and the particulate respirator may not be effective. Consider undertaking respirator fit-testing with users, to determine which model or models will achieve an acceptable fit, before procuring large stocks of respirators.
- Train those who may need to wear a particulate respirator in how to use the device (e.g. putting on of respirator, avoiding self-contamination during use and on removal, and achieving the best seal) (*158*). The inclusion of fit-testing in respirator user-training has not been shown to be an effective means to improve compliance with proper use of respirators (*158*). Follow local regulations regarding the regular performance of the fit test.

Figure A.1 Sequence of steps in a particulate respirator seal check



1 Cup the respirator in your hand with the nosepiece at your fingertips allowing the headbands to hang freely below your hand.

2 Position the respirator under your chin with the nosepiece up.

3 Pull the top strap over your head resting it high at the back of your head. Pull the bottom strap over your head and position it around the neck below the ears.

4 Place fingertips of both hands at the top of the metal nosepiece. Mould the nosepiece (USING TWO FINGERS OF EACH HAND) to the shape of your nose. Pinching the nosepiece using one hand may result in less effective respirator performance.

5 Cover the front of the respirator with both hands, being careful not to disturb the position of the respirator.

5A Positive seal check
- Exhale sharply. A positive pressure inside the respirator = no leakage. If leakage, adjust position and/or tension straps. Retest the seal.
- Repeat the steps until respirator is sealed properly.

5B Negative seal check
- Inhale deeply. If no leakage, negative pressure will make respirator cling to your face.
- Leakage will result in loss of negative pressure in the respirator due to air entering through gaps in the seal.

- Facial hair impedes good fit, and a seal may not be achieved, decreasing the efficiency of the particulate respirator. Health-care workers with facial structure abnormalities also may be unable to obtain a good seal and need alternative approaches for respiratory protection.
- Examples of acceptable disposable particulate respirators in use in various parts of the world include[1]:
  - Australia/New Zealand: P2 (94%), P3 (99.95%)
  - China: II (95%), I (99%)
  - European Union: Conformité Européenne-certified filtering facepiece class 2 (FFP2) (95%), or class 3 (FFP3) (99.7%)
  - Japan: 2nd class (95%), 3rd class (99.9%)
  - Republic of Korea: 1st class (94%), special (99.95%)
  - US: National Institute for Occupational Safety and Health (NIOSH)-certified N95 (95%), N99 (99%), N100 (99.7%).
- Some factors to consider when choosing particulate respirators in health-care settings are affordability, availability, impact on mobility, impact on patient care, potential for exposure to high levels of aerosolized respiratory secretions, and potential for transmission via contact with contaminated respiratory surfaces.
- Particulate respirators should be changed after each use or if they become wet or dirty (Annex H).

A.2.2 Medical masks

- Medical masks[2] are surgical or procedure masks that are flat or pleated (some are like cups); they are affixed to the head with straps. Such masks should be used when caring for patients infected by droplet-transmitted pathogens or as part of facial protection during patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions or excretions.
- However, medical masks may not offer adequate respiratory protection against small-particle aerosols (droplet nuclei). Therefore, particulate respirators are preferable when caring for patients with diseases caused by airborne pathogens (e.g. TB) or a novel ARI pathogen for which the route of transmission is not known (*208-210*). Medical masks are not designed to provide a face seal, and thus do not prevent leakage around the edge of the mask when the user inhales; this is a potential major limitation for protection against droplet nuclei (*211*).
- Medical masks should be changed after each use or if they become wet or dirty (Annex H). Medical masks are considered clinical waste and should be placed in an appropriate clinical waste container.

[1] The percentages in parentheses refer to respirator filter efficiency

[2] In this document, the term "medical mask" refers to **disposable** surgical or procedure masks. Although some alternative barriers to standard medical masks are used in certain settings (e.g. cloth masks, paper masks, etc.), there is insufficient information available on their effectiveness.

A.2.3 Medical mask standards

Medical masks protect the wearer's nose and mouth from inadvertent exposures (e.g. through splashes) to blood and other body fluids. However, there are no minimum standards or standardized testing methods for mask filter efficiency, and available masks vary widely in the efficiency of their filters. As an example of standards, the Association of Perioperative Registered Nurses recommends that surgical masks filter particles of at least 0.3 μm for regular use and 0.1 μm for laser use (i.e. to protect the wearer against laser smoke), or have 90–95% bacterial filtration efficiency. Furthermore, surgical masks are classified as medical devices in Europe and the US and are regulated appropriately. For example, the US Food and Drug Administration (FDA) standards for surgical masks are as follows: [1]

- Fluid resistance:
  - American Society for Testing and Materials (ASTM) F 1862–00a: standard test method for resistance of surgical mask to penetration by synthetic blood.
- Filtration efficiency:
  - particulate filtration efficiency (PFE) – 0.1 μ polystyrene latex sphere;
  - bacterial filtration efficiency (BFE) – ASTM F 2101–01: standard test method for evaluating the BFE of surgical masks using a biological aerosol of *Staphylococcus aureus*.
- Air exchange (differential pressure, delta-P):
  - measure of breathability and comfort of surgical masks.
- Flammability:
  - Class 1 and Class 2 flammability rating material for use in the operating room (OR);
  - Class 4 flammability rating is not appropriate for use in the OR (would be labelled as “not for OR use”).
- Biocompatibility.

[1] For more information, see http://www.fda.gov/cdrh/ode/guidance/094.html

Annex B Isolation precautions

B.1 Standard Precautions

Standard Precautions (*95*) are routine IPC precautions that should apply to ALL patients, in ALL health-care settings. The precautions, described in detail below in Sections B.1.1 to B.1.7, are:

- hand hygiene;
- use of PPE;
- respiratory hygiene;
- environmental controls (cleaning and disinfection);
- waste management;
- packing and transporting of patient-care equipment, linen and laundry, and waste from isolation areas;
- prevention of needle-stick or sharps injuries.

Rationale

Standard Precautions are the basic IPC precautions in health care. They are intended to minimize spread of infection associated with health care, and to avoid direct contact with patients' blood, body fluids, secretions and, non-intact skin. The SARS outbreak illustrated the critical importance of basic IPC precautions in health-care facilities. Transmission of SARS within health-care facilities was often associated with lack of compliance with Standard Precautions. The threat of emerging respiratory infectious diseases makes the promotion of Standard Precautions more important than ever and it should be a priority in all health-care facilities.

For additional information on Standard Precautions, see:

- *Practical guidelines for infection control in health care facilities*, 2004 (*212*);
- *Prevention of hospital-acquired infections: A practical guide*, 2002 (*213*);
- *Aide-memoire: Infection control Standard Precautions in health care*, 2006 (*214*).

B.1.1 Hand hygiene

Hand hygiene is one of the most important measures to prevent and control spread of disease in health-care facilities, and is a major component of Standard Precautions (*215*). Although hand hygiene is a simple procedure, numerous studies have shown that compliance is low. Its implementation is complex, requiring continued reinforcement and multidisciplinary team coordination. The use of alcohol-based hand rubs in health-care facilities has been implemented in recent years, in an attempt to increase compliance with hand hygiene. The main points are as follows:

- If hands are not visibly soiled, hand hygiene should be done using an alcohol-based hand rub, or by washing hands with soap and water, and drying them using a single-use towel.
- If hands are visibly dirty or soiled with blood or other body fluids, or if broken skin might have been exposed to potentially infectious material, hands should be washed thoroughly with soap and water.

Perform hand hygiene:

- before and after any direct contact with patients;
- immediately after removal of gloves;
- before handling an invasive device not requiring a surgical procedure, including central intravascular catheters, urinary catheters or peripheral vascular catheters;
- after touching blood, body fluids, secretions, excretions, non-intact skin or contaminated items, even if gloves are worn;
- when moving from a contaminated to a clean body site on the same patient;
- after contact with inanimate objects in the immediate vicinity of the patient; and
- after using the lavatory.

For additional information on hand hygiene, see:

- *WHO guidelines on hand hygiene in health care*, 2009 (*215*).

B.1.2 Selection of personal protective equipment based on risk assessment

- Routinely assess the risk of exposure to body substances or contaminated surfaces before any anticipated health-care activity.
- Select PPE based on the assessment of risk.
- Ensure that appropriate PPE is available at all times, so that it can be used in the event of an unexpected emergency.

Gloves

- Wear gloves whenever contact with blood, body fluids, secretions, excretions, mucous membranes or non-intact skin is anticipated.
- Change gloves between tasks and procedures on the same patient after contact with potentially infectious material.
- Remove gloves after use, before touching non-contaminated items and surfaces, and before going to another patient.
- Perform hand hygiene immediately after removing gloves.

Facial protection

Wear facial protection, including a medical mask and eye protection (face shield or goggles), to protect the conjunctivae and the mucous membranes of the nose, eyes and mouth during activities that are likely to generate splashes or sprays of blood, body fluids, secretions or excretions. When providing care in close contact with a patient with respiratory symptoms (e.g. coughing or sneezing), use eye protection, because sprays of secretions may occur.

Gowns

- Wear gowns to protect skin and prevent soiling of clothing during activities that are likely to generate splashes or sprays of blood, body fluids, secretions or excretions.
- Select a gown that is appropriate for the activity and the amount of fluid likely to be encountered. If the gown in use is not fluid-resistant, wear a waterproof apron over the gown if splashing or spraying of potentially infectious material is anticipated.
- Remove a soiled gown as soon as possible, place it in a waste or laundry receptacle (as appropriate), and perform hand hygiene.

B.1.3 Respiratory hygiene

Controlling the spread of pathogens from infected patients (source control) is key to avoiding transmission to unprotected contacts. For diseases transmitted through large droplets or droplet nuclei, respiratory hygiene should be applied by all individuals with respiratory symptoms (*90*). Respiratory hygiene refers to covering the mouth and nose during coughing or sneezing using medical masks (Annex A, Section A.2.2), cloth masks, tissues or flexed elbow, followed by hand hygiene to reduce the dispersal of respiratory secretions containing potentially infectious particles.

Health-care facility management should promote respiratory hygiene as follows:

- Promote the use of respiratory hygiene by all health-care workers, patients and family members with ARIs.
- Educate health-care workers, patients, family members and visitors on the importance of containing respiratory aerosols and secretions to help prevent the transmission of ARI pathogens.
- Consider providing resources for hand hygiene (e.g. dispensers of alcohol-based hand rubs and handwashing supplies) and respiratory hygiene (e.g. tissues); prioritize areas of gathering, such as waiting rooms.

B.1.4 Environmental controls: cleaning and disinfection

The viruses and bacteria that cause ARIs can survive in the environment for variable periods of time (hours to days). The bioburden of such microorganisms can be reduced by cleaning, and infectious agents can be inactivated by the use of standard hospital disinfectants. Environmental cleaning and disinfection is intended to remove pathogens or significantly reduce their numbers on contaminated surfaces and items, thus breaking the chain of transmission. Disinfection is a physical or chemical means of killing microorganisms (but not spores), and should be used for non-critical medical equipment used or shared by patients.

- No disinfection is required for surfaces and equipment that do not come into direct contact with patients. These surfaces or equipment should be thoroughly cleaned between patients.

- Clean equipment or surfaces in a way that avoids possible generation of aerosols; this process alone significantly reduces the bioburden of microorganisms.
- When disinfection is required, ensure that cleaning is done before disinfection. Items and surfaces cannot be disinfected if they are not first cleaned of organic matter (e.g. patient excretions, secretions, dirt and soil).
- Follow the manufacturer's recommendations for use or dilution, contact time and handling of disinfectants.
- The viruses and bacteria that cause ARIs are inactivated by a range of disinfectants (*99, 216-220*). However, in some countries, regulatory agencies will control the types of disinfectant available for hospital use. Common hospital disinfectants include:
  - sodium hypochlorite (household bleach);
  - alcohol;
  - phenolic compounds;
  - quaternary ammonium compounds; and
  - peroxygen compounds.
- Sodium hypochlorite and alcohol are available in most countries. The use of these two disinfectants is detailed in Annex G.

Cleaning the patient-care environment

- Clean horizontal surfaces in isolation rooms or areas – focusing particularly on surfaces where the patient has been lying or has frequently touched, and immediately around the patient's bed – regularly and on discharge (*221*).
- To avoid the possible generation of aerosols of ARI pathogens, use damp cleaning (moistened cloth) rather than dry dusting or sweeping.
- During wet cleaning, cleaning solutions and equipment soon become contaminated; change cleaning solutions, cleaning cloths and mop heads frequently, according to health-care facility's policies.
- Ensure that equipment used for cleaning and disinfection is cleaned and dried after each use.
- Launder mop heads daily and dry them thoroughly before storage or reuse (*222*).
- To facilitate daily cleaning, keep areas around the patient free of unnecessary supplies and equipment.
- Use disinfectant to wipe down surfaces used by patients who are known or suspected to be infected with an ARI of potential concern (*52*).
- Do not spray (i.e. fog) occupied or unoccupied rooms with disinfectant; this is a potentially dangerous practice that has no proven disease-control benefit (*223*).
- To facilitate cleaning, and to reduce the potential for generation of aerosols caused by use of a vacuum cleaner, accommodate patients in uncarpeted rooms or areas where possible. If vacuuming is necessary, use a vacuum cleaner that is equipped with a high-efficiency particulate air (HEPA) filter, if available.

Patient-care equipment

- If equipment is reused, follow general protocols for disinfection and sterilization (*224, 225*).
- If not visibly soiled, wipe external surfaces of large portable equipment (e.g. X-ray machines and ultrasound machines) that has been used in the isolation room or area with an approved hospital disinfectant upon removal from the patient's room or area.
- Proper cleaning and disinfection of reusable respiratory equipment is essential in ARI patient care (*226-230*). See Annex G for further details on use of disinfectants.

Dishes and eating utensils

- When possible, wash reusable items in a dishwasher (*231, 232*). If no dishwasher is available, wash the items by hand with detergents. Use nonsterile rubber gloves if washing items by hand.
- Wash dishes and eating utensils for the patient after each meal or use.
- Discard disposable items as waste, classified as directed by the relevant state, territory or national legislation and regulations (*8*).

Linen and laundry

- Remove large amounts of solid material (e.g. faeces) from heavily soiled linen (while wearing appropriate PPE), and dispose of the solid waste in a toilet before placing the linen in the laundry bag (*233-235*).
- Avoid sorting linen in patient-care areas. Place contaminated linen directly into a laundry bag in the isolation room or area with minimal manipulation or agitation, to avoid contamination of air, surfaces and people (*8*).
- Wash and dry linen according to routine standards and procedures of the health-care facility. For hot-water laundry cycles, wash with detergent or disinfectant in water at 70 °C (160 °F) for at least 25 minutes. If low-temperature (i.e. < 70 °C; < 160 °F) laundry cycles are used, choose a chemical that is suitable for low-temperature washing when used at the proper concentration (*236-238*).

B.1.5 Waste management

Waste disposal should be safe for those handling the waste and for the environment. Definitions of clinical (infectious) waste may differ according to local regulations and legislation.

- Classify waste as directed by relevant state, territory or national legislation and regulations. If waste from ARI-infected patients is classified as infectious, then consider all waste from the patient-care area as clinical waste, and treat and dispose of it according to the health-care facility's policy, and in accordance with national regulations pertaining to such waste (*8*).
- Handle faeces with caution to avoid possible generation of aerosols (e.g. during removal of faeces from bedpan, commode or clothing, or when spraying reusable incontinence pads with water) (*233*).
- Flush liquid waste (e.g. urine) or solid faecal waste into the sewerage system, if there is an adequate system in place (*239, 240*).
- Ensure that health-care workers use appropriate PPE whenever there is risk of splash or spray during handling of waste (*95*).

B.1.6 Packing and transporting patient-care equipment, linen and laundry, and waste from isolation areas

- Place used equipment and soiled linen and waste directly into containers or bags in the isolation room or area.
- Contain the used equipment and soiled linen and waste in a manner that prevents the containers or bags from opening or bursting during transport.
- One layer of packing is adequate, provided that the used equipment and soiled linen and waste can be placed in the bag without contaminating the outside of the bag. Double-bagging is unnecessary.
- Ensure that all personnel handling the used equipment and soiled linen and waste use Standard Precautions, and perform hand hygiene after removing PPE. Heavy-duty tasks (e.g. cleaning of the environment) require more resistant PPE (e.g. rubber gloves and apron, and resistant closed shoes).

B.1.7 Prevention of needle-stick or sharps injuries

Although it may not be crucial for prevention and control of ARIs, prevention of needle-stick or sharp injuries is a component of Standard Precautions. It targets the reduction and elimination of transmission of bloodborne pathogens to health-care workers, other patients and people with any possible contact with the related waste.[1]

- Take care to prevent injuries when using needles, scalpels and other sharp instruments or devices when handling sharp instruments after procedures, when cleaning used instruments and when disposing of used needles.
- Never recap used needles.
- Never direct the point of a needle towards any part of the body except before injection.
- Do not remove used needles from disposable syringes by hand, and do not bend, break or otherwise manipulate used needles by hand.
- Dispose of syringes, needles, scalpel blades and other sharp items in appropriate puncture-resistant containers. Such containers should be located as close as practicable to the area in which the items were used.
- Avoid the use of reusable syringes.

B.2 Droplet Precautions

Respiratory pathogens that are transmitted through large droplets include adenovirus, avian influenza A(H5N1), human influenza and SARS-CoV. Adenovirus infections are more common among children, and influenza and SARS-CoV can affect both adults and children. During an influenza pandemic, the circulating human virus is expected to be transmitted in the same manner as seasonal influenza viruses; hence, Droplet Precautions should be applied in addition to Standard Precautions.

[1] Detailed recommendations from the Safe Injection Global Network (SIGN) Alliance (*241*).

Droplet Precautions include (*95*):

- *PPE* – Use a medical mask if working within 1 m of the patient (*154, 242-244*). For practical purposes, it is advisable to use a medical mask when entering the patient's room.
- *Patient placement* – Place patients in single rooms, or cohort those with the same etiological diagnosis. If an etiological diagnosis is not possible, group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation of at least 1 m.
- *Patient transport* – Limit patient movement and ensure that patients wear medical masks when outside their rooms.

B.3 Contact Precautions

In addition to transmission by large droplets, some common respiratory pathogens (e.g. parainfluenza and respiratory syncytial virus) can be transmitted through contact – particularly by hand contamination and self-inoculation into conjunctival or nasal mucosa. Contact transmission may also play a role in avian influenza A(H5N1) and SARS infections. Contact Precautions include PPE, use of equipment and environment, and patient placement and transport, as outlined below (*95*).

PPE

Put on PPE when entering the room and remove it when leaving. PPE includes:

- *Gloves* – wear clean, nonsterile latex gloves, disposing of the gloves after each patient contact;
- *Gowns*:
  - use either a disposable gown made of synthetic fibre, or a washable cloth gown; ensure that the gown is the appropriate size to fully cover the areas to be protected;
  - if possible, wear a gown once only, then place it in a waste or laundry receptacle, as appropriate, and perform hand hygiene; and
  - if the gown is permeable, wear an apron to reduce fluid penetration (do not use an apron alone to prevent contact contamination).

Equipment and environment

- If possible, use either disposable equipment or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers) when dealing with patients under Contact Precautions. If equipment needs to be shared among patients, clean and disinfect it between each patient use.
- Ensure that health-care workers refrain from touching their eyes, nose or mouth with potentially contaminated gloved or ungloved hands (*245*).
- Avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches).

Patient placement

Use single rooms, or cohort patients with the same etiological diagnosis, to facilitate the application of IPC measures.

Patient transport

Limit patient movement and minimize patient contact with those who are not infected.

B.4 Airborne Precautions

Airborne pathogens are transmitted through inhalation of droplet nuclei that remain infectious over a long distance (e.g. > 1 m), and require special air handling (*4, 5*). Their transmission is further classified as obligate or preferential (*9*):

- obligate airborne transmission applies to agents naturally transmitted exclusively through droplet nuclei deposited in the distal part of the lung (e.g. *Mycobacterium tuberculosis* causing pulmonary TB); and
- preferential airborne transmission applies to pathogens (e.g. measles) that are transmitted by droplet nuclei deposited in the airways but can also be transmitted by other routes.

Transmission of droplet nuclei at short range may also occur with SARS-CoV, human influenza, and perhaps with other viral respiratory infections, during special circumstances; for example:

- performance of aerosol-generating procedures associated with pathogen transmission (Annex A, Section A.1), in rooms that are inadequately ventilated; and
- lack of adequate use of PPE (e.g. as happened with SARS).

This type of transmission has been referred to as opportunistic airborne transmission (*9*), and does not involve transmission over long distances as obligate and preferential airborne transmission do (*4*).

B.4.1 Infection prevention and control precautions for airborne diseases

For airborne pathogens (*4, 5, 7, 246*), supplement Standard Precautions with additional precautions, as outlined below.

Personal protective equipment

When entering the isolation room or area, or when providing care to a patient with an obligate or preferential airborne infectious disease in other settings, use a particulate respirator that is at least as protective as a NIOSH-certified N95 or equivalent (Annex A).

Patient placement

- Place the patient in an Airborne Precaution room (*3*).
- If a ventilated isolation room is not available, place patients in separate well-ventilated rooms.
- If single rooms are not available, cohort patients according to the same etiological diagnosis in well-ventilated places.
- To perform any aerosol-generating procedures associated with pathogen transmission, use appropriate PPE in an Airborne Precaution room.

Patient transport

- Limit patient movement and ensure that patients wear medical masks when outside their room or area.

B.4.2 Infection prevention and control precautions for diseases that can be opportunistically transmitted through droplet nuclei

For most diseases that can be opportunistically transmitted through droplet nuclei, Droplet Precautions should be added to Standard Precautions during routine patient care. Take additional measures during aerosol-generating procedures associated with increased risk of pathogen transmission.

Personal protective equipment

- At a minimum, use a medical mask (surgical or procedure mask) if working at a distance of less than 1 m from the patient (*247-249*).
- When performing aerosol-generating procedures associated with pathogen transmission, use a particulate respirator that is at least as protective as a NIOSH-certified N95, EU FFP2 or equivalent, and wear gloves, gowns and eye protection (e.g. goggles) (*86, 120, 250*).

Patient placement

- Use adequately ventilated rooms. Group patients according to the laboratory-confirmed etiological diagnosis (cohorting) or suspected diagnosis (special measures) (*31, 148*). If more than one patient is housed in a room, place patients so that they are at least 1 m apart.
- Airborne Precaution rooms are not obligatory. If they are available, prioritize them for patients with airborne-transmitted diseases (*31, 148*).
- To perform aerosol-generating procedures associated with increased risk of pathogen transmission, use adequately ventilated single rooms (*101, 102, 153, 251*).

Patient transport

- Limit the movement of patients and ensure that they wear medical masks when outside their room or area.

Annex C Sample checklist assessment of environmental conditions for home care of patients with ARIs of potential concern

The sample checklists below can be used to assess environmental conditions for home care of patients with ARIs of potential concern. Circle "Y" (yes) or "N" (no) for each option.

Infrastructure

Functioning telephone	Y	N
Any other means to rapidly communicate with the health system	Y	N
Potable water	Y	N
Sewerage system	Y	N
Cooking source (and fuel)	Y	N
Operable electricity	Y	N
Operable heat source when required	Y	N
Adequate environmental ventilation	Y	N

Accommodation

Separate room or bedroom for the patient	Y	N
Accessible bathroom	Y	N

Resources

Food	Y	N
Necessary medications	Y	N
Medical masks[a] (patient)	Y	N
Medical masks[a] (care providers, household contacts)	Y	N
Gloves[a]	Y	N
Hand-hygiene items (soap, alcohol-based hand rub)	Y	N
Household cleaning products	Y	N

a Check feasibility of training patient and household contacts on use of PPE

Primary care and support

Person to provide care and support	Y	N
Access to medical advice and care	Y	N
Any at-risk people at home (e.g. children < 2 years of age, elderly > 65 years of age, immunocompromised people)	Y	N

Annex D Sample health-care worker influenza-like illness monitoring form for workers exposed to patients with ARIs of potential concern

The sample form given below can be used to monitor ILI in workers exposed to patients with ARIs of potential concern.

Name: _____
Home telephone number: _____
Job title: _____
Work location:_____
Date/s of exposure (list all, use back of page if necessary): ____/____/_____ ____/____/_____
Type of contact with patient with ARI of potential concern, with patient's environment, or with virus:
_____
Was the following personal protective equipment (PPE) used:

	Yes	No	Don't know
Gown	☐	☐	☐
Gloves	☐	☐	☐
Particulate respirator	☐	☐	☐
Medical mask	☐	☐	☐
Eye protection	☐	☐	☐
Other (Please specify)	☐	☐	☐

List any non-occupational exposures (e.g. exposure to anyone with severe acute febrile respiratory illness):
_____
Please check your temperature twice a day, in the morning (AM) and evening (PM), for 10 days after providing care for a patient infected with an acute respiratory disease of potential concern (including 10 days after your last exposure), and also monitor yourself for any of the following influenza-like illness (ILI) symptoms including:

- fever > 38 °C
- cough
- acute onset of respiratory illness
- sore throat
- arthralgia
- myalgia or prostration
- gastrointestinal symptoms (e.g. diarrhoea, vomiting, abdominal pain)

If any symptoms of ILI occur, **immediately** limit your interactions with others, exclude yourself from public areas, and notify _____at _____

Sample health-care worker influenza-like illness monitoring form for workers exposed to patients with ARIs of potential concern

Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Date ____/____/_____	Date ____/____/_____	Date ____/____/_____	Date ____/____/_____	Date ____/____/_____
AM temperature: _____	AM temperature: _____	AM temperature: _____	AM temperature: _____	AM temperature: _____
PM temperature: _____	PM temperature: _____	PM temperature: _____	PM temperature: _____	PM temperature: _____
ILI symptoms: No ____ Yes ___	ILI symptoms: No ___ Yes ___	ILI symptoms: No ___ Yes ____	ILI symptoms: No ___ Yes ____	ILI symptoms: No ___ Yes ____

Day 6	**Day 7**	**Day 8**	**Day 9**	**Day 10**
Date ____/____/_____	Date ____/____/_____	Date ____/____/_____	Date ____/____/_____	Date ____/____/_____
AM temperature: _____	AM temperature: _____	AM temperature: _____	AM temperature: _____	AM temperature: _____
PM temperature: _____	PM temperature: _____	PM temperature: _____	PM temperature: _____	PM temperature: _____
ILI symptoms: No ___ Yes ___	ILI symptoms: No ___ Yes ____	ILI symptoms: No ___ Yes ____	ILI symptoms: No ___ Yes ____	ILI symptoms: No ___ Yes ____

Annex E Isolation rooms or areas

E.1 Preparation of the isolation room or area

- Ensure that appropriate handwashing facilities and hand-hygiene supplies are available.
- Stock the sink area with suitable supplies for handwashing, and with alcohol-based hand rub, near the point of care and the room door.
- Ensure adequate room ventilation.
- Post signs on the door indicating that the space is an isolation area.
- Ensure that visitors consult the health-care worker in charge (who is also responsible for keeping a visitor record) before being allowed into the isolation areas. Keep a roster of all staff working in the isolation areas, for possible outbreak investigation and contact tracing.
- Remove all non-essential furniture and ensure that the remaining furniture is easy to clean, and does not conceal or retain dirt or moisture within or around it.
- Stock the PPE supply and linen outside the isolation room or area (e.g. in the change room). Set up a trolley outside the door to hold PPE. A checklist may be useful to ensure that all equipment is available (see sample checklist in Section E.3, below).
- Place appropriate waste bags in a bin. If possible, use a touch-free bin. Ensure that used (i.e. dirty) bins remain inside the isolation rooms.
- Place a puncture-proof container for sharps disposal inside the isolation room or area.
- Keep the patient's personal belongings to a minimum. Keep water pitchers and cups, tissue wipes, and all items necessary for attending to personal hygiene, within the patient's reach.
- Dedicate non-critical patient-care equipment (e.g. stethoscope, thermometer, blood pressure cuff and sphygmomanometer) to the patient, if possible. Thoroughly clean and disinfect patient-care equipment that is required for use by other patients before use.
- Place an appropriate container with a lid outside the door for equipment that requires disinfection or sterilization.
- Keep adequate equipment required for cleaning or disinfection inside the isolation room or area, and ensure scrupulous daily cleaning of the isolation room or area.
- Set up a telephone or other method of communication in the isolation room or area to enable patients, family members or visitors to communicate with health-care workers. This may reduce the number of times the workers need to don PPE to enter the room or area.

E.2 Wearing and removing personal protective equipment

Before entering the isolation room or area:

- collect all equipment needed;
- perform hand hygiene with an alcohol-based hand rub (preferably when hands are not visibly soiled) or soap and water;

- put on PPE in the order that ensures adequate placement of PPE items and prevents self-contamination and self-inoculation while using and taking off PPE; an example of the order in which to don PPE when all PPE items are needed is hand hygiene, gown, mask or respirator, eye protection and gloves, as illustrated in Fig. E.1A, below.

E.2.1 Leaving the isolation room or area

- Either remove PPE in the anteroom or, if there is no anteroom, make sure that the PPE will not contaminate either the environment outside the isolation room or area, or other people.
- Remove PPE in a manner that prevents self-contamination or self-inoculation with contaminated PPE or hands. General principles are:
  - remove the most contaminated PPE items first;
  - perform hand hygiene immediately after removing gloves;
  - remove the mask or particulate respirator last (by grasping the ties and discarding in a rubbish bin);
  - discard disposable items in a closed rubbish bin;
  - put reusable items in a dry (e.g. without any disinfectant solution) closed container; an example of the order in which to take off PPE when all PPE items are needed is gloves (if the gown is disposable, gloves can be peeled off together with gown upon removal), hand hygiene, gown, eye protection, mask or respirator, and hand hygiene (Fig. E.1B, below).

Perform hand hygiene with an alcohol-based hand rub (preferably) or soap and water whenever ungloved hands touch contaminated PPE items.

Figure E.1 Putting on and removing personal protective equipment

A. Putting on PPE (when all PPE items are needed)

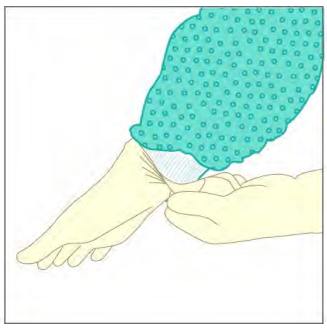
1

- Identify hazards and manage risk.
- Gather the necessary PPE.
- Plan where to put on and take off PPE.
- Do you have a buddy? Mirror?
- Do you know how you will deal with waste?

2 Put on a gown.

3 Put on particulate respirator or medical mask; perform user seal check if using a respirator.

4 Put on eye protection, e.g. face shield/goggles (consider anti-fog drops or fog-resistant goggles). Caps are optional: if worn, put on after eye protection.



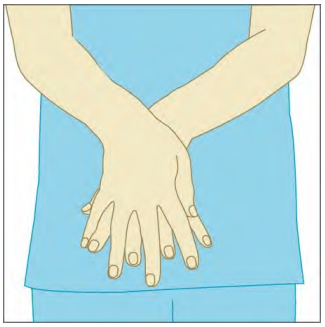
5 Put on gloves (over cuff).

B. Taking off PPE

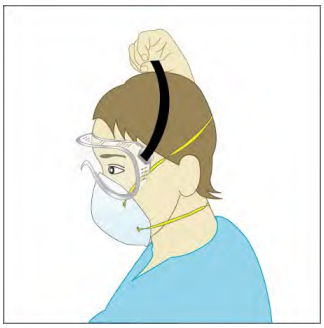
1

- Avoid contamination of self, others and the environment.
- Remove the most heavily contaminated items first.

Remove gloves and gown:
- peel off gown and gloves and roll inside, out;
- dispose of gloves and gown safely.



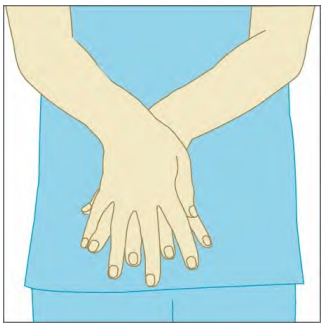
2 Perform hand hygiene.



3

- Remove cap (if worn).
- Remove goggles from behind.
- Put goggles in a separate container for reprocessing.

4 Remove respirator from behind.



5 Perform hand hygiene.

E.3 Checklist for isolation room or area trolley or table

The following items should be kept on the trolley at all times so that PPE is always available for health-care workers.

Equipment	Stock present
Eye protection (visor or goggles)	
Face shield (provides eye, nose and mouth protection)	
Gloves • reusable vinyl or rubber gloves for environmental cleaning • latex single-use gloves for clinical care	
Hair covers (optional)	
Particulate respirators (N95, FFP2, or equivalent)	
Medical (surgical or procedure) masks	
Gowns and aprons • single-use long-sleeved fluid-resistant or reusable non-fluid-resistant gowns • plastic aprons (for use over non-fluid-resistant gowns if splashing is anticipated and if fluid-resistant gowns are not available)	
Alcohol-based hand rub	
Plain soap (liquid if possible, for washing hands in clean water)	
Clean single-use towels (e.g. paper towels)	
Sharps containers	
Appropriate detergent for environmental cleaning and disinfectant for disinfection of surfaces, instruments or equipment	
Large plastic bags	
Appropriate clinical waste bags	
Linen bags	
Collection container for used equipment	

For more information on isolation precautions, see:

- *Practical guidelines for infection control in health care facilities*, 2004 (*212*)
- *Prevention of hospital-acquired infections: A practical guide*, 2002 (*213*).

For additional information on hand hygiene, see:

- *WHO guidelines on hand hygiene in health care*, 2009 (*215*).

Annex F Mortuary care and postmortem examination

F.1 Packing and transport of the dead body of patients with ARI of potential concern, to a mortuary, crematorium or burial

- Ensure that the body is fully sealed in an impermeable body bag before being removed from the isolation room or area, and before being transferred to the pathology department or the mortuary, to avoid leakage of body fluid.
- Transfer the body to the mortuary as soon as possible after death.
- When properly packed in the body bag, the body can be safely removed for storage in the mortuary, sent to the crematorium, or placed in a coffin for burial.
- If an autopsy is being considered, the body may be kept in refrigeration in the mortuary and the autopsy conducted only when a safe environment can be provided (Section 2.5).

F.2 Personal protective equipment for handling dead bodies

- Wear a disposable, long-sleeved, cuffed gown; if the outside of the body is visibly contaminated with body fluids, excretions, or secretions, ensure that this gown is waterproof. If no waterproof gown is available, wear a waterproof apron in addition to the gown.
- Wear nonsterile gloves (single layer) that cover the cuffs of the gown.
- If splashing of body fluids is anticipated, use facial protection: preferably a face shield, or if not, goggles and a medical mask.
- Perform hand hygiene after taking off the PPE.
- Use PPE for heavy-duty tasks (e.g. rubber gloves, rubber apron and resistant closed shoes) in addition to regular PPE.

F.3 Personal protective equipment during autopsy

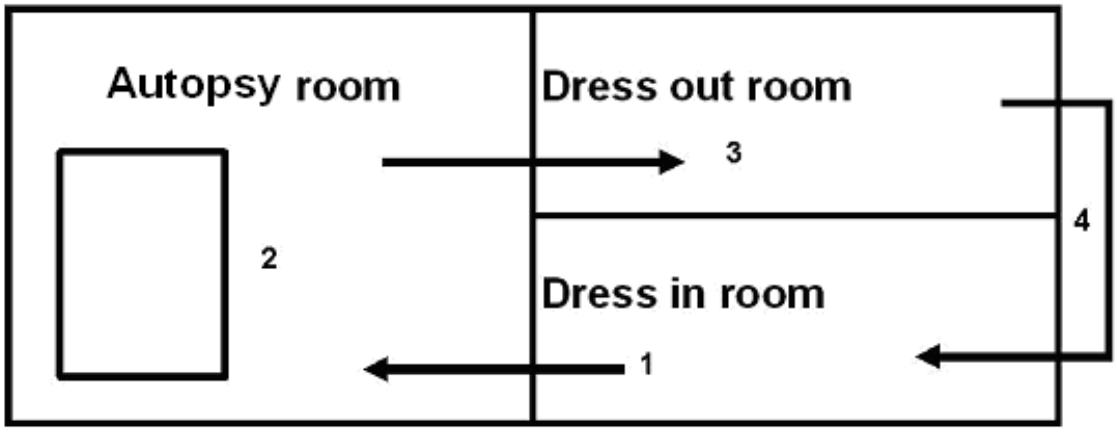
PPE to be provided during autopsy includes:

- scrub suit – tops and trousers, or equivalent garments;
- single-use, fluid-resistant, long-sleeved gown;
- surgical mask or, if small-particle aerosols might be generated during autopsy procedures, a particulate respirator at least as protective as a NIOSH-certified N95, EU FFP2 or equivalent;
- face shield (preferably) or goggles;
- either autopsy gloves (cut-proof synthetic mesh gloves) or two pairs of nonsterile gloves;
- knee-high boots.

Placement of PPE:

- put on PPE in the dress in room (Fig. F.1) before entering the autopsy room where the body is located;
- in the dress in room, replace outer street clothes and shoes with scrub suits, or equivalent coverall garments, plus boots;
- proceed to the autopsy room where the body is located.

Figure F.1 Suggested movement of the autopsy team undertaking a postmortem examination in a health-care facility



To remove PPE:

- exit the autopsy room to the dress out room as suggested in Fig. F.1;
- remove PPE in the designated dress out room, dispose of the PPE in accordance with recommendations, and perform hand hygiene.

F.4 Suggested methods to reduce aerosol generation during autopsy

To reduce aerosol generation during autopsy:

- use containment devices whenever possible (e.g. biosafety cabinets for the handling and examination of smaller specimens);
- use vacuum shrouds for oscillating saws;
- do not use high-pressure water sprays;
- if opening intestines, do so under water.

Annex G Use of disinfectants: alcohol and bleach

Different countries have different disinfection protocols. Health-care facilities with limited resources may not have access to a variety of hospital disinfectants, however, alcohol and bleach are acceptable chemical disinfectants if used appropriately. As with any other disinfectants, soiled surfaces need to be cleaned with water and detergent first.

G.1 Alcohol

Alcohol is effective against influenza virus (*252*). Ethyl alcohol (70%) is a powerful broad-spectrum germicide and is considered generally superior to isopropyl alcohol. Alcohol is often used to disinfect small surfaces (e.g. rubber stoppers of multiple-dose medication vials, and thermometers) and occasionally external surfaces of equipment (e.g. stethoscopes and ventilators). Since alcohol is flammable, limit its use as a surface disinfectant to small surface-areas and use it in well-ventilated spaces only. Prolonged and repeated use of alcohol as a disinfectant can also cause discoloration, swelling, hardening and cracking of rubber and certain plastics.

G.2 Bleach

Bleach is a strong and effective disinfectant – its active ingredient sodium hypochlorite is effective in killing bacteria, fungi and viruses, including influenza virus – but it is easily inactivated by organic material. Diluted household bleach disinfects within 10–60 minutes contact time (see Table G.1 below for concentrations and contact times), is widely available at a low cost, and is recommended for surface disinfection in health-care facilities. However, bleach irritates mucous membranes, the skin and the airways; decomposes under heat and light; and reacts easily with other chemicals. Therefore, bleach should be used with caution; ventilation should be adequate and consistent with relevant occupational health and safety guidance. Improper use of bleach, including deviation from recommended dilutions (either stronger or weaker), may reduce its effectiveness for disinfection and can injure health-care workers.

Procedures for preparing and using diluted bleach

To prepare and use diluted bleach:

- use a mask, rubber gloves and waterproof apron; goggles also are recommended to protect the eyes from splashes;
- mix and use bleach solutions in well-ventilated areas;
- mix bleach with cold water (hot water decomposes the sodium hypochlorite and renders it ineffective);
- if using bleach containing 5% sodium hypochlorite, dilute it to 0.05%, as shown in Table G.1 below.

Table G.1 Sodium hypochlorite: concentration and use

Starting solution Most household bleach solutions contain 5% sodium hypochlorite (50 000 ppm available chlorine).
Recommended dilution 1:100 dilution of 5% sodium hypochlorite is the usual recommendation. Use 1 part bleach to 99 parts cold tap water (1:100 dilution) for disinfection of surfaces. *Adjust ratio of bleach to water as needed to achieve appropriate concentration of sodium hypochlorite. For example, for bleach preparations containing 2.5% sodium hypochlorite, use twice as much bleach (i.e. 2 parts bleach to 98 parts water).*
Available chlorine after dilution For bleach preparations containing 5% sodium hypochlorite, a 1:100 dilution will yield 0.05% or 500 ppm available chlorine. *Bleach solutions containing other concentrations of sodium hypochlorite will contain different amounts of available chlorine when diluted.*
Contact times for different uses Disinfection by wiping of nonporous surfaces: a contact time of ≥ 10 minutes is recommended. Disinfection by immersion of items: a contact time of 30 minutes is recommended. *N.B. Surfaces must be cleaned of organic materials, such as secretions, mucus, vomit, faeces, blood or other body fluids before disinfection or immersion.*

ppm: parts per million

Precautions for the use of bleach

- Bleach can corrode metals and damage painted surfaces.
- Avoid touching the eyes. If bleach gets into the eyes, immediately rinse with water for at least 15 minutes, and consult a physician.
- Do not use bleach together with other household detergents, because this reduces its effectiveness and can cause dangerous chemical reactions. For example, a toxic gas is produced when bleach is mixed with acidic detergents, such as those used for toilet cleaning, and this gas can cause death or injury. If necessary, use detergents first, and rinse thoroughly with water before using bleach for disinfection.
- Undiluted bleach emits a toxic gas when exposed to sunlight; thus, store bleach in a cool, shaded place, out of the reach of children.
- Sodium hypochlorite decomposes with time. To ensure its effectiveness, purchase recently produced bleach, and avoid over-stocking.
- If using diluted bleach, prepare the diluted solution fresh daily. Label and date it, and discard unused mixtures 24 hours after preparation.
- Organic materials inactivate bleach; clean surfaces so that they are clear of organic materials before disinfection with bleach.
- Keep diluted bleach covered and protected from sunlight, and if possible in a dark container, and out of the reach of children.

Annex H Surge capacity: personal protective equipment needs of health-care facilities during epidemics or pandemics

It is difficult to provide guidance for hospitals wishing to stockpile PPE for epidemic or pandemic ARIs. This annex is intended to provide a step-by-step approach for estimating additional PPE needs for health-care facilities. Some key steps include:

- defining assumptions;
- producing estimates; and
- defining a purchasing strategy to meet the planned needs, replenishment and monitoring of stock expiration and use.

A recent systematic review explored resource use as well as the economic implications (e.g. total cost and cost–effectiveness ratios) associated with physical barriers (e.g. masks, gowns and gloves) to interrupt or reduce the spread of respiratory viruses (*207*). The researchers concluded that, while the use of physical interventions to interrupt or reduce the spread of respiratory viruses increases during epidemics and pandemics, PPEs appear to be an economically attractive option in reducing the burden of illness associated with respiratory viruses, due to the relatively low costs of these interventions. The economic benefits rise when transmission rates and fatality rates are high. However, few studies were available for review, and the overall quality of data was low.

Each health-care facility should follow the national assumptions, and adapt to its local policies and rationale.

Assumptions to be taken into consideration include those concerning the use of PPE, expected impact of an epidemic (e.g. proportion of the population diseased, seeking care or being hospitalized), organization of health services (e.g. frequency of encounters between health-care workers and patients), recommended IPC precautions and duration of the epidemic. The rest of this annex discusses considerations that health-care facilities can use in making assumptions about supplies of PPE for surge capacity.

Medical masks

Medical masks should be changed between uses, and also whenever they become wet, damaged or visibly soiled. In conditions of increased air temperature and humidity, assume that masks will become wet with perspiration more quickly (surgical mask standards are described in Annex A). Wearing additional PPE, such as gowns and gloves will also increase perspiration.

Respirators

There are no data on how long particulate respirators remain effective. Respirators are disposable, but can be reused repeatedly by the same heath-care worker when working with TB patients, because TB has not been documented to spread by contact, and contamination of the respirator is not a concern in TB transmission. Humidity, dirt, and crushing, reduce the efficiency of the respirator; thus, respirators should be stored in a clean, dry location. When

used in the care of TB patients, respirators can be reused until they are wet, soiled, damaged or difficult to breathe through (i.e. when the filter becomes "clogged" with trapped particles). Filtration efficiency actually increases as more particles are trapped in the filter. However, because many ARI pathogens (e.g. SARS, and avian or pandemic influenza) can be spread by contact as well as by respiratory aerosols, contaminated respirators could contribute to disease transmission. The concern about the reuse of respirators and other equipment relates to surface contamination and the possible risks of self-contamination and self-inoculation that may result when heath-care workers handle potentially contaminated equipment. It is essential to educate workers on how to safely remove, store, handle and re-apply potentially contaminated equipment.

At this time, there are no recommendations on the reuse of respirators when caring for patients with ARIs, and medical masks and respirators should be discarded after each use in these circumstances.

Entry of health-care workers into the isolation room or area

Other issues that must be considered when making assumptions about PPE are:

- the number of times that health-care workers are expected to enter the isolation room or area;
- whether any PPE will be reused by the same worker during a shift; and
- how many different workers will enter the isolation room or area.

These factors directly influence how much PPE will be used. The number of different health-care workers entering the isolation room or area, and the number of times that each worker goes in an out of the room, should be limited to the minimum necessary. Ways to minimize the number of different workers who enter the isolation area include:

- ensuring that tasks are carried out by as few workers as possible, without hampering the quality of health-care;
- having a means of communication (such as a telephone) between the patient or family in the room and health-care workers outside the room.

Cohorting patients could decrease the need for masks or respirators and eye protection, since several patients could be attended in one visit to the room or area, without the health-care worker needing to change these items of PPE. Other PPE – including gloves and gowns – must be changed between patients, even when providing care in a cohort or isolation room or area. Health-care workers providing care to patients with ARIs of potential concern will also need "PPE breaks”, because wearing PPE is hot and tiring, and these factors may contribute to inadvertent IPC breaches.

Assumptions about factors such as these must be built into any mathematical model used for estimating the amounts of PPE needed, such as:

- number of epidemic or pandemic ARI patients per day for an average of X number of days;
- number of times that a health-care worker enters the isolation room or area per shift, and length of shifts;
- number of different workers who have direct contact with epidemic or pandemic patients per day;
- IPC precautions recommended;

- duration of the epidemic or pandemic wave;
- estimated numbers of cohorted patients (e.g. X patients per cohort unit versus X patients in single rooms);
- number of times items can be reused (e.g. cloth gowns, goggles and face shields); fewer masks may be needed in patient cohort units because the same respiratory protection equipment could be worn during the care of multiple patients (as mentioned above);
- whether medical masks would be provided for patients and visitors.

Several countries have developed planning assumptions. (Examples of national pandemic preparedness plans are available at http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/influenza/country-work/national-plans)

Annex I Cleaning and disinfection of respiratory equipment

Equipment used for respiratory therapy (e.g. items that come into contact with mucous membranes) is considered semicritical[1]; such items should be cleaned and then receive at least high-level disinfection between patients (*225*). High-level disinfection of respiratory equipment takes place after cleaning, and is typically accomplished by chemical germicides or physical methods, as outlined below (*253*).

Chemical germicides

Chemical germicides used for high-level disinfection include (*225*):

- glutaraldehyde-based formulations (2%);
- stabilized hydrogen peroxide (6%);
- peracetic acid (variable concentrations, but ≤ 1% is sporicidal);
- sodium hypochlorite (5.25%, diluted to 1000 ppm available chlorine – 1:50 dilution).

The most appropriate chemical germicide for a particular situation should be selected on the basis of the object to be disinfected, its composition and intended use; the level of disinfection needed; and the scope of the services, physical facilities, resources and personnel available.

Physical methods

Physical methods for high-level disinfection include hot-water disinfection (pasteurization) or steam (e.g. autoclaving at lower temperature). Pasteurization is a non-toxic, cost-effective alternative to high-level disinfection with chemical germicides. Equipment should be submerged for at least 30 minutes in water at a temperature of about 70 °C (less than the temperature that typically damages plastic). Pasteurization can be accomplished using a commercial washer or pasteurizer (*254*). After pasteurization, wet equipment is typically dried in a hot-air drying cabinet before storage. Steam sterilization is an inexpensive and effective method for sterilization or high-level disinfection. Steam sterilization is, however, unsuitable for processing plastics with low melting points, powders or anhydrous oils. Bacterial spores may survive after high-level disinfection. Microbiological sampling can verify that high-level disinfection has resulted in the destruction of vegetative bacteria; however, such sampling is not routinely recommended.

I.1 Steps for cleaning and disinfection of plastic pieces of respiratory equipment

PPE is required when cleaning or processing equipment and instruments, to protect against splashing, spraying or aerosols.

1. Wash the equipment with soap (e.g. liquid dish soap) and clean water.
2. Rinse the equipment completely with clean water.
3. Disinfect the equipment to inactivate any remaining pathogens.

[1] According to Spaulding's classification (*224*), semicritical items are devices that come into contact with mucous membranes or nonintact skin

There are several ways to disinfect equipment, and the products available at the health-care facility should be used. Safe methods of disinfection include:

- heat for heat-resistant equipment that can withstand high temperature (e.g. 80 °C); such equipment can be disinfected using a washer–disinfector;
- if a washer or pasteurizer is not available, use a high-end or commercial dishwasher with a "sanitize" feature that can reach 70 °C ;
- for plastic equipment that may not tolerate 80 °C and for equipment that may be damaged by boiling, or in the absence of the equipment described above, use chemical disinfection (e.g. soak in 1:100 sodium hypochlorite solution for 30 minutes, as described in Annex G).

4. If using chemical disinfection, rinse with sterile or clean water (i.e. water boiled for 5 minutes and cooled). Sterile water is preferred for rinsing off residual liquid chemical disinfectant from a respiratory device that has been chemically disinfected for reuse, because tap or distilled water may harbour microorganisms that can cause pneumonia. However, when rinsing with sterile water is not feasible, instead, rinse with tap water or filtered water (i.e. water passed through a 0.2 µ filter), followed by an alcohol rinse and forced-air drying.

5. Dry equipment.

- Physical equipment (e.g. a washer, pasteurizer or autoclave) often has a drying feature within the machine.
- For chemical methods, let equipment parts air dry on a clean towel or cloth.

6. Store equipment dry in closed packages.

Summary: Wash with soap and clean water, rinse, disinfect, rinse (if chemical method), dry and store.

I.2 Cleaning and disinfection of mechanical ventilators

To clean and disinfect a mechanical ventilator, wipe down the controls and entire outside of the equipment with a compatible disinfectant (e.g. sodium hypochlorite solution of 0.05% or 500 ppm for non-metal surfaces).

Disinfect tubing using sodium hypochlorite solution of 0.1% or 1000 ppm, ensuring that the entire lumen of the tubing is flushed (Section I.1, above).

It is not necessary to routinely clean respiratory and pressure lines within a ventilator between patients, because the lines are not exposed to the patient or the patient's respiratory secretions.

Usually, the entire expiratory side tubing is removable (the expiratory end has a valve to control the escape of gas from the circuit and may also have a flow measurement device or a water trap, or both). This tubing should be disassembled and cleaned first with a detergent, rinsed clean, and then subjected to either high-level disinfection or sterilization. High-level disinfection is the minimum required procedure for these items, but due to the practicability of some sterilization methods and health-care facility protocols (e.g. steam), these items can, if suitably designed, be submitted to sterilization.

When mechanical ventilators are used in the care of a patient with an ARI of potential concern, bacterial and viral filters are recommended on exhalation valves.

Annex J Infection prevention and control across the continuum of health care

The principles of IPC are the same across the continuum of health care. Areas that require particular attention such as emergency and outpatient care, paediatric acute care and home care for ARI patients, are discussed in this section.

J.1 Emergency and outpatient care

Measures for countries with no reported ARIs of potential concern

In countries with no reported ARIs of potential concern, implement the following measures:

- Post signage that alerts people with severe acute febrile respiratory illness to notify staff immediately, and to use respiratory hygiene (*255*).
- Assess patients with acute febrile respiratory illness as promptly as possible.
- Consider designating separate areas for patients with acute febrile respiratory illness, and whenever possible keep a distance of 1 m between each patient in the waiting area.
- Provide tissues in the waiting area so that patients can contain respiratory secretions when coughing or sneezing whenever possible. Provide receptacles for disposal of used tissues (if possible, these should be no-touch receptacles).
- Give people with acute febrile respiratory illness medical masks on entry, if possible.
- Encourage hand hygiene after contact with respiratory secretions, and provide hand-hygiene facilities (e.g. sinks equipped with water, soap and single-use towel, alcohol-based hand rub) in waiting areas whenever possible.
- Clean environmental surfaces in waiting and patient-care areas at least daily and when visibly soiled.
- Ensure that patient-care equipment is appropriately cleaned and disinfected between patients.
- Use Standard and Droplet Precautions when providing close contact care to patients with acute febrile respiratory illness.
- Undertake any aerosol-generating procedures associated with an increased risk of ARI transmission in a well-ventilated separate room, and ensure that health-care workers use appropriate PPE (Chapter 2, Section 2.4).
- If a patient known or suspected to be infected with an ARI of potential concern is referred to another facility, notify receiving staff of the necessary IPC precautions.

Additional measures for countries with reported ARIs of potential concern

In countries with reported ARIs of potential concern, implement the following additional measures:

- During pandemics, apply strategies to limit unnecessary office visits by ill patients; for example, divert patients to designated pandemic influenza triage and evaluation sites, and use pre-facility triage to determine which patients need on-site medical evaluation.

- Educate the public about the clues (i.e. signs or symptoms) of ARIs of potential concern, and ask them to seek medical care promptly for assessment and admission.
- Establish triage criteria to promptly identify people at risk of infection with an ARI of potential concern.
- If an ARI of potential concern is suspected, ensure that health-care workers use appropriate PPE (Chapter 2, Table 2.1), as available.
- After a patient known or suspected to be infected with an ARI of potential concern has left the ambulatory-care setting, clean surfaces in the examination room or other areas where the patient was located, and clean and disinfect any patient-care equipment used for the patient.

J.2 Acute paediatric care

Implementing IPC measures for paediatric patients requires special consideration:

- Family members are essential for the emotional support of children admitted to hospital (*56, 256*). The child's right to be accompanied by a parent, relative or legal guardian at all times should be guaranteed (*257*).
- Family members can be critical in assisting in the care of hospitalized children, particularly if there is a shortage of health-care workers (*117*).
- Children are likely to be infectious with ARIs for longer than adults; this may affect the duration of IPC precautions (*105*).
- Paediatric patients may not be able to comply with respiratory hygiene.
- Some pathogens are more prevalent among children and require additional precautions; for example, Contact Precautions for respiratory syncytial virus or parainfluenza virus; and Contact plus Droplet Precautions for adenovirus or metapneumovirus (*244*).
- Contamination of the environment may be more prominent with children than with adult or continent patients.
- Clean and disinfect toys between different children, and take precautions when gathering patients in the playroom (follow the same principles as for cohorting) (*258-261*).

J.3 Home care for patients with acute respiratory infection

During a public-health emergency, such as a pandemic, it may not be possible to provide acute or ambulatory-care services for all who might need them. Also, ambulatory-care facilities may be unable to meet the demand for health-care services, and may only be able to provide care for the most severely ill patients (*262*). In this situation, patients infected with ARIs of potential concern may require care at home, and they may still be infectious to household contacts (*263, 264*).

Infection prevention and control for the home setting

ARIs can spread easily within a household. Anyone who has not already been infected is at risk of infection if they come into contact with an ARI patient. Thus, household members should observe the following recommendations:

- If a household member develops symptoms of ARI, including fever, cough, sore throat and difficulty breathing, they should follow public-health recommendations.

- Limit contact with the ill person as much as possible. Stay in a different room or, if that is not possible, stay as far away from the ill person as possible (e.g. sleep in a separate bed).
- Ensure that shared spaces (e.g. restrooms, kitchen and bathroom) are well ventilated (e.g. keep windows open).
- If close contact care must be provided to the ill person, ensure that the ill person covers his or her mouth or nose with hands or other materials (e.g. tissues, handkerchiefs or, if available, a mask);
- Discard materials used to cover the mouth or nose, or clean them appropriately.
- Avoid direct contact with body fluids. If contact occurs, perform hand hygiene immediately afterwards.
- Perform hand hygiene, either by washing with soap and water or using an alcohol-based hand rub. Address safety concerns (e.g. accidental ingestion and fire hazards) before recommending alcohol-based hand rubs for household use.
- Ensure that anyone who is at increased risk of severe disease does not care for the ill person or come into close contact with the ill person. For seasonal influenza, people at increased risk include those with heart, lung or kidney disease; diabetes; immunosuppression; blood disease (e.g. sickle cell anaemia); pregnancy; and aged over 65 years or under 2 years.
- Avoid other types of possible exposure to the ill person or contaminated items; for example, avoid sharing toothbrushes, cigarettes, eating utensils, drinks, towels, washcloths or bed linen.
  - Ensure that people caring for a family member suffering from an ARI of potential concern limit their contact with each other, and follow national or local policies regarding home quarantine recommendations. where possible, the caregiver also wears a medical mask or the best available protection against respiratory droplets when in close contact with the ill person, and performs hand hygiene (*265*).

Actions to take if a contact of a patient with an ARI of potential concern becomes ill

- Notify the health-care provider of the diagnosis and receive instructions on where to seek care, when and where to enter the health-care facility, and the IPC precautions that are to be followed.
- Avoid public transportation if possible; call an ambulance or transport the ill person with own vehicle and open the windows of the vehicle.
- Always perform respiratory hygiene.
- Stand or sit as far away from others as possible (at least 1 m), when in transit and when in the health-care facility.
- Use hand hygiene whenever appropriate.

Annex K Strength of infection prevention and control recommendations based on GRADE

These guidelines were updated in accordance with the *WHO handbook for guideline development*, 2012 (*18*). The process comprised multiple steps, including setting up a guideline development group, scoping the revision of the document, and setting up an external expert review group to guide the systematic reviews using the PICOT framework (which clearly defined the IPC intervention in terms of question, population, comparator and outcome), and the conduct of the systematic reviews, including evidence retrieval and synthesis. Where systematic reviews could not be undertaken, evidence-based reviews or critical appraisals of the literature were done instead. Evidence was synthesized and recommendations formulated using the GRADE framework (*18, 46-50*).

Major systematic reviews of relevance to these guidelines are summarized in Annex L, and the evidence profiles of individual studies are available in the published papers (51, 130, 149, 207).

The tables that make up the remainder of this annex summarize the assessment of evidence and other important factors that support the content and strength of key recommendations according to the GRADE framework (*18, 46-50*). These tables were drafted after careful review of existing evidence, and were extensively reviewed by expert members of the Global Infection Prevention and Control Network. The topics covered by the tables are:

- Table K.1 – Clinical triage and early identification;
- Table K.2 – Respiratory hygiene;
- Table K.3 – Spatial separation;
- Table K.4 – Cohorting and special measures;
- Table K.5 – Personal protective equipment;
- Table K.6 – Personal protective equipment for aerosol-generating procedures;
- Table K.7 – Environmental ventilation for aerosol-generating procedures;
- Table K.8 – Vaccination of health-care workers;
- Table K.9 – Ultraviolet germicidal irradiation;
- Table K.10 – Duration of additional infection prevention and control precautions.

Where consensus was reached that benefits clearly outweighed harms, there was no major variability of values and preferences, and the feasibility of recommendations was high, the factors were labelled as favourable, providing rationale for making a strong recommendation. The same label was assigned where the recommendations were considered not too resource-intensive. Where there was uncertainty about the balance of benefits versus harms, values and preferences, resource implications, and feasibility, the factors were labelled as conditional.

Recommendations were considered strong when the guideline development group was confident that the desirable effects of adherence outweigh the undesirable effects. Recommendations were labelled as conditional when the desirable effects of adherence were deemed to probably outweigh any undesirable effects, but the group was not confident about the trade-off.

Table K.1 Considerations for clinical triage and early identification

Recommendation: Use clinical triage for the early identification of patients with ARIs in order to prevent the transmission of ARI pathogens to health-care workers and other patients. (Chapter 2, Section 2.1)		
Population: People with ARI in health-care settings		
Intervention: Clinical triage and early identification		
Factor	**Assessment**	**Explanation**
Quality of evidence	Very low to low (*27, 51*) (Annex L.2)	There is limited evidence available to suggest that the spread of respiratory virus, particularly RSV, can be prevented by the use of triage and early identification, when combined with other hygienic measures, especially for younger children (*51*). In addition, a systematic review of the use of triage of individuals with symptoms suggestive of TB with and without separation of infectious cases supports the use of triage as an administrative process (*27*).
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Early identification will benefit proper management of patients. Reduction of ARI exposure and infection of health-care workers and other patients by respiratory pathogens during care delivery to patients with ARI in health-care settings. Triage may also help in early identification of events or pathogens of potential public health concern as per the IHR, 2005 (*6*).
Values and preferences	Favourable	Reduction of ARI exposure and infection of health-care workers and other patients by respiratory pathogens while delivering care to patients with ARI in health-care settings.
Costs	Conditional	There is a cost implication for health-care facilities for the use of triage and early identification.
Feasibility	Conditional	The use of triage and early identification during care delivery for patients with ARIs depends on reorganization of services with possible resource implications.
Overall ranking	**STRONG RECOMMENDATION** Although the quality of evidence was considered very low to low, there was consensus that the advantages of early identification of patients with ARIs and an assessment of values and preferences provided sufficient basis for the strong recommendation.	
Research gap	Additional research is required to fully elucidate the epidemiology of the risk of transmission of specific pathogens causing acute respiratory diseases from infected patients to health-care workers and other patients with the use of triage and early identification alone versus its use in combination with other selected precautions.	

ARI, acute respiratory infection; IHR, International Health Regulations; RSV, respiratory syncytial virus; TB, tuberculosis

Table K.2 Considerations for respiratory hygiene

Recommendation: Encourage the use of respiratory hygiene (i.e. covering the mouth and nose during coughing or sneezing with a medical mask, tissue, or a sleeve or flexed elbow, followed by hand hygiene), in all people with ARIs to reduce the dispersal of respiratory secretions containing potentially infectious particles. (Chapter 2, Section 2.1)

Population: People with ARI in health-care settings

Intervention: Respiratory hygiene

Factor	Assessment	Explanation
Quality of evidence	Very low (*51*) (Annex L.2)	The evidence suggests that: • behavioural changes that probably included the principles of respiratory hygiene, when applied within households, were associated with a reduced frequency of influenza illness during an outbreak of influenza (*59*); • coughing and sneezing in those with symptomatic ARIs are associated with the production of droplets and aerosols that contain viable viral particles (*60*); • maximal symptoms for influenza correlate with the peak viral shedding demonstrated by both viral culture and RT-PCR assay (*61*); • the use of medical masks in those with ARI serves as a barrier against RT-PCR detectable influenza virus (*62*); • the use of medical masks in patients with active smear-positive TB with cough is associated with a significant reduction in transmission of TB in an in vivo animal model setting (*63*); and • respiratory virus spread and infection can be reduced by hygienic measures, including hand hygiene and PPE use (*51*).
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Potential reduction of the exposure of non-infected individuals to respiratory pathogens in health-care settings. Use of medical or cloth masks by those with ARI symptoms may be uncomfortable and not well-tolerated, and thus few infected patients may actually adhere to wearing a face mask.
Values and preferences	Favourable	Potential reduction of the exposure of individuals to respiratory pathogens in health-care settings. A similar approach was used for reduction in exposure and infection for TB (*27*).
Costs	Conditional	The reduction of dispersal of respiratory secretions may reduce the exposure to ARI pathogens and thus reduce new cases of ARI and related costs. There is a cost implication for the health-care facility in the use of medical masks, tissues and hand-hygiene supplies.
Feasibility	Conditional	Infants and young children may not be capable of adequate respiratory hygiene. While adults may be capable of following respiratory hygiene, ensuring compliance can be complex since it is affected by the availability of supplies but also by other factors (e.g. attitude, knowledge, peer pressure, motivation and organizational climate), which may widely vary according to the setting.
Overall ranking	**STRONG RECOMMENDATION** Although the quality of evidence was considered very low, there was consensus that the advantages of the use of respiratory hygiene and an assessment of values and preferences provided sufficient basis for the strong recommendation.	
Research gap	A significant research gap exists regarding the maximal effectiveness of respiratory hygiene in those with ARI as a means to reduce droplet dispersion and clinical illness among contacts.	

ARI, acute respiratory infection; PPE, personal protective equipment; RT-PCR, reverse transcriptase-polymerase chain reaction; TB, tuberculosis

Table K.3 Considerations for spatial separation

Recommendation: Maintain spatial separation (distance of at least 1 m) between each ARI patient and others, including health-care workers (without the use of PPE), to reduce the transmission of ARI. (Chapter 2, Section 2.3.1)		
Population: People with ARI in health-care settings		
Intervention: Spatial separation		
Factor	**Assessment**	**Explanation**
Quality of evidence	Very low to low (*51*) (Annex L.2)	Limited evidence suggests that: • spread of respiratory virus, particularly RSV and SARS, can be reduced by the use of spatial separation or distancing between those infected and those not infected, when combined with other hygienic measures (*12, 51*); and • a distance of less than 1 m is associated with increase in risk of ARI pathogen transmission (*143, 147*).
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Reduction of ARI exposure and infection of health-care workers and patients by respiratory pathogens during delivery of care to patients with ARI in health-care settings. There are cost and resource implications for health-care facilities for the use of spatial separation combined with other measures.
Values and preferences	Favourable	Reduction of ARI exposure and infection to health-care workers and other patients by respiratory pathogens during delivery of care to patients with ARI in health-care settings.
Costs	Conditional	There are cost and resource implications to health-care facilities for the use of spatial separation.
Feasibility	Conditional	The use of spatial separation for patients with ARIs depends on availability of space and surge capacity (beds), and may not be readily implementable in all health-care settings.
Overall ranking	**STRONG RECOMMENDATION**	Although the quality of evidence was considered very low to low, there was consensus that the advantages of the spatial separation between each ARI patient and others and an assessment of values and preferences provided sufficient basis for the strong recommendation.
Research gap	Additional research is required to fully elucidate the epidemiology of the risk of transmission of specific pathogens causing acute respiratory diseases from infected patients to health-care workers and other patients with the use of spatial separation alone compared to spatial separation with the use of other selected precautions. A significant research gap exists for studies that examine discrete parameters (e.g. 1 m, 2 m) of spatial separation with respect to the impact on the reduction of transmission and infection by ARIs.	

ARI, acute respiratory infection; PPE, personal protective equipment; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome

Table K.4 Considerations for cohorting and special measures

Recommendation: Consider the use of patient cohorting (i.e. the placement of patients infected or colonized with the same laboratory-identified pathogens in the same designated unit, zone or ward). If cohorting is not possible apply special measures (i.e. the placement of patients with the same suspected diagnosis – similar epidemiological and clinical information – in the same designated unit, zone or ward) to reduce transmission of ARI pathogens to health-care workers and other patients. (Chapter 2, Section 2.2.2)		
Population: People with ARI in health-care settings		
Intervention: Cohorting		
Factor	**Assessment**	**Explanation**
Quality of evidence	Low to moderate – cohorting combined with other measures (*51*) (Annex L.2)	Evidence suggests that nosocomial respiratory virus spread and infection, particularly RSV, can be reduced by the use of cohorting when combined with other hygienic measures, especially for younger children (*51*).
Balance of benefits or desired effects versus disadvantages or undesired effects	Conditional	Reduction of ARI exposure and infection of health-care workers and other patients during delivery of care to patients with ARI in health-care settings. The benefits clearly outweigh the disadvantages for ARIs associated with high morbidity or mortality (e.g. SARS), but are less clear for ARIs associated with lesser morbidity or mortality. There are cost and human resource implications for health-care facilities for the use of cohorting.
Values and preferences	Favourable	Reduction of ARI exposure and infection of health-care workers and other patients during care delivery to patients with ARIs in health-care settings.
Costs	Conditional	There are cost implications for health-care facilities for the use of cohorting.
Feasibility	Conditional	The use of cohorting for patients with ARIs depends on the availability of beds and staff that can be allocated for cohorting.
Overall ranking	**CONDITIONAL RECOMMENDATION**	
Research gap	Additional research is required to: • elucidate the epidemiology of the risk of transmission of specific pathogens causing acute respiratory diseases from patients to health-care workers with the use of cohorting alone versus cohorting with the use of other selected precautions; • elucidate the cost and resource implications for cohorting in different settings around the world; • validate that the use of special measures, when the pathogen is suspected but not known, is equivalent to the use of cohorting with respect to the reduction of transmission and infection of ARI pathogens.	

ARI, acute respiratory infection; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome

Table K.5 Considerations for personal protective equipment

Recommendation: Use appropriate PPE as determined by risk assessment (according to the procedure and suspected pathogen). Appropriate PPE when providing care to patients presenting with ARI syndromes may include a combination of the following: medical mask (surgical or procedure mask), gloves, long-sleeved gowns and eye protection (goggles or face shields).[1] (Chapter 2, Section 2.4)		
Population: People with ARI in health-care settings		
Intervention: PPE		
Factor	**Assessment**	**Explanation**
Quality of evidence	Low to moderate – PPE measures combined with hand hygiene (*51*) (Annex L.2)	Evidence suggests that respiratory virus spread and infection can be reduced by hygienic measures, including hand hygiene and PPE use (*51*). Most of this evidence comes from studies on RSV, SARS and influenza virus. Case–control studies that focused on SARS suggest that barriers to transmission (e.g. isolation and PPE) are effective at containing epidemic spread of this virus (*51*). The use of masks (medical or N95 particulate respirators) was the measure with the most consistent and comprehensive supportive evidence across all studies. There is moderate evidence that medical masks are non-inferior to particulate respirators (e.g. N95, facial filtering protection 2), and that the latter are more expensive and uncomfortable, and cause skin irritation.
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Reduction of ARI exposure and infection of health-care workers and patients by respiratory pathogens associated with delivery of care to patients with ARI in health-care settings. The benefits clearly outweigh the disadvantages for ARIs associated with high morbidity or mortality (e.g. SARS), but are less clear for ARIs associated with lesser morbidity or mortality. There are unintended effects (e.g. skin reactions) related to the use of PPE in health-care facilities. Use of PPE may be uncomfortable and may create difficulties in interacting with patients.
Values and preferences	Conditional	Although the use of PPE based on risk assessment appears to reduce ARI infection of health-care workers and other patients by respiratory pathogens during care delivery to patients with ARI in health-care settings, PPE may be uncomfortable and may limit interactions with the patient.
Costs	Conditional	There are cost implications for the use of PPE in health-care faciilties, depending on the jurisdiction; other health priorities may hamper acquisition of PPE.
Feasibility	Conditional	The use of PPE during care delivery for patients with ARIs depends on availability of supplies and compliance with recommendations. In turn, compliance is complex and affected by many factors (e.g. attitude, knowledge, peer pressure, motivation and organizational climate), which may widely vary across facilities.
Overall ranking	**STRONG RECOMMENDATION** Although the quality of evidence was considered low to moderate, there was consensus that the advantages of the use of appropriate PPE provided sufficient basis for the strong recommendation.	
Research gap	Additional research is required to elucidate the epidemiology of transmission of specific ARI pathogens from patients to health-care workers and other patients during care delivery in health-care settings, with and without the use of specific precautions.	

ARI, acute respiratory infection; PPE, personal protective equipment; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome

[1] When a novel ARI is identified and the mode of transmission is unknown, it may be prudent to implement the highest level of IPC precautions whenever possible, including the use of particulate respirators, until the mode of transmission is clarified.

Table K.6 Considerations for personal protective equipment for aerosol-generating procedures

Recommendation: Use PPE, including gloves, long-sleeved gowns, eye protection (goggles or face shields) and facial mask (surgical or procedure mask, or particulate respirators) during aerosol-generating procedures that have been consistently associated with an increased risk of transmission of ARI pathogens.[1] The available evidence suggests that performing or being exposed to endotracheal intubation either by itself or combined with other procedures (e.g. cardiopulmonary resuscitation or bronchoscopy) is consistently associated with increased risk of transmission. (Chapter 2, Section 2.4)

Population: People with ARI in health-care settings

Intervention: PPE

Factor	Assessment	Explanation
Quality of evidence	Very low to low (*51, 149*) (Annexes L.1-L.2)	Evidence suggests that: • some procedures potentially capable of generating aerosols are associated with increased risk of SARS transmission to health-care workers, with the most consistent association across multiple studies being identified with tracheal intubation (*149*); • an increased risk of SARS infection is associated with tracheotomy, non-invasive ventilation and manual ventilation before intubation, but these findings were identified from a limited number of very low quality studies, which makes the interpretation difficult;[1] no other procedures were found to be significantly associated with any increased risk of transmission; these studies also assessed whether health-care workers had proper IPC training;
	Low to moderate	• respiratory virus spread can be prevented by hygienic measures, including hand hygiene and the use of PPE with gloves, gowns, eye protection (goggles or face shields) and facial mask (medical masks or particulate respirators) (*51*), with medical masks or particulate respirators being the most consistent and comprehensive protective measures.
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Reducing the exposure of health-care workers to respiratory pathogens during aerosol-generating procedures associated with increased risk of infection transmission. Use of PPE may be uncomfortable and may create difficulties for the interaction with patients.
Values and preferences	Favourable	Reducing the exposure of health-care workers to respiratory pathogens during aerosol-generating procedures that are associated with increased risk of infection transmission. A similar approach for this factor was used for reduction in exposure and infection for TB (*27*).
Costs	Conditional	The use of PPE carries cost and resource implications for health-care faciliies.
Feasibility	Conditional	The use of barrier precautions during aerosol-generating procedures associated with increased risk of infection transmission may be feasible but compliance is complex and affected by many factors (e.g. attitude, knowledge, peer pressure, motivation and organizational climate), which may vary according to the setting.
Overall ranking	**STRONG RECOMMENDATION** Although the quality of evidence was considered very low to moderate, there was consensus that the advantages of the use of appropriate personal protective equipment for aerosol-generating procedures and an assessment of values and preferences provided sufficient basis for the strong recommendation.	

[1] When a novel ARI is identified and the mode of transmission is unknown, it may be prudent to implement the highest level of IPC precautions whenever possible, including the use of particulate respirators, until the mode of transmission is clarified.

Research gap	A significant research gap exists regarding the epidemiology of ARI transmission from patients to health-care workers during aerosol-generating procedures. This gap is compounded by a lack of precision in the literature with regard to the definition for aerosol-generating procedures. There is a need to determine the minimum ventilation requirements to reduce pathogen transmission during these procedures. While there is no evidence to suggest a difference in the effectiveness of particulate respirators over medical masks as a component in the use of PPE for routine care, it is not known whether a difference exists in the context of aerosol-generating procedures that have been consistently associated with increased risk of pathogen transmission.

ARI, acute respiratory infection; IPC, infection prevention and control; PPE, personal protective equipment; SARS, severe acute respiratory syndrome; TB, tuberculosis

Table K.7 Considerations for environmental ventilation for aerosol-generating procedures

Recommendation: Use adequately ventilated single rooms when performing aerosol-generating procedures that have been consistently associated with increased risk of ARI transmission. (Chapter 2, Section 2.3.3)		
Population: People with ARI in health-care settings		
Intervention: Environmental ventilation		
Factor	**Assessment**	**Explanation**
Quality of evidence	Very low to low (*149*) (Annex L.1)	Evidence suggests that some procedures potentially capable of generating aerosols are associated with increased risk of SARS transmission to health-care workers, with the most consistent association across multiple studies identified with tracheal intubation.(*149*) An increased risk of SARS infection was associated with tracheotomy, non-invasive ventilation and manual ventilation before intubation, but these findings were identified from a limited number of very low quality studies, which makes the interpretation difficult (*149*). No other procedures were found to be significantly associated with any increased risk of transmission. Some of these studies also assessed whether health-care workers had proper IPC training. A mathematical modelling study suggests that the environmental ventilation rate could be associated with a decrease in risk (*1*).
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Reduction of infection with respiratory pathogens to health-care workers during the performance of aerosol-generating procedures that are conducted on patients with ARI in health-care settings.
Values and preferences	Favourable	Reduction of infection with respiratory pathogens to health-care workers during the performance of aerosol-generating procedures that are conducted on patients with ARI in health-care settings. Good ventilation provides a comfortable sensation.
Costs	No strength	There are cost, space and timing implications for health-care facilities for the use of environmental controls during the performance of aerosol-generating procedures. Low cost is possible if simple natural ventilation is used and is properly designed according to local climate. Higher costs are likely if full mechanical or hybrid ventilation or high-tech natural ventilation is used (*1*).
Feasibility	Conditional	The use of environmental controls during the performance of aerosol-generating procedures is not always feasible and depends on the setting. Natural ventilation is less feasible in extreme climates.
Overall ranking	**CONDITIONAL RECOMMENDATION**	
Research gap	There are significant research gaps: • in the epidemiology of the risk of transmission of acute respiratory diseases from patients undergoing aerosol-generating procedures to health-care workers, and a lack of precision in the definition for aerosol-generating procedures; • regarding the effectiveness of measures to reduce the risk of infection associated with the procedure; and • regarding the minimum ventilation requirements for natural ventilation in terms of variable ventilation rate and airflow direction control for aerosol-generating procedures.	

ARI, acute respiratory infection; IPC, infection prevention and control; SARS, severe acute respiratory syndrome

Table K.8 Considerations for vaccination of health-care workers

Recommendation: Vaccinate health-care workers caring for patients at high risk of severe or complicated influenza disease, to reduce illness and mortality among these patients. (Chapter 2, Section 2.2.7)		
Population: Health-care workers caring for patients with ARI in health-care settings		
Intervention: Vaccination		
Factor	**Assessment**	**Explanation**
Quality of evidence	Very low to low (*130*) (Annex L.4)	Evidence suggests a reduction in ILI, all-cause mortality and, to some extent, laboratory-confirmed influenza among patients at high risk of severe or complicated illness from influenza using a strategy of influenza vaccination of health-care workers providing care for these patients. The protective effects were predominantly demonstrated in residents of long-term residential care facilities (*130*).
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Reduction of illness and mortality among patients at high risk of severe or complicated illness from influenza. There are cost and resource implications to health-care facilities for the use and implementation of influenza vaccination among health-care workers; these will vary among different settings. Influenza vaccination may be associated with side effects.
Values and preferences	Favourable	Reduction of illness and mortality among patients at high risk of severe or complicated illness from influenza.
Costs	Conditional	Influenza vaccination for health-care workers carries cost and resource implications for health-care facilities.
Feasibility	Conditional	The use of an influenza vaccination programme for health-care workers depends on availability of vaccine, administrative capacity and willingness to receive vaccine, and it may not be readily implementable in all settings.
Overall ranking	**STRONG RECOMMENDATION** Although the quality of evidence was considered very low to low, there was consensus that the advantages of the vaccination of health-care workers and an assessment of values and preferences provided sufficient basis for the strong recommendation.	
Research gap	Additional research is required to elucidate the protective effect of influenza vaccination in populations beyond residents of long-term residential care facilities, the benefits of other vaccinations, and the safety and the cost effectiveness of the implementation of a vaccination programme for health-care workers.	

ARI, acute respiratory infection; ILI, influenza-like illness

Table K.9 Considerations for ultraviolet germicidal irradiation

Recommendation: No recommendation possible. (Chapter 2, Section 2.3.5)		
Population: People with ARI in health-care settings		
Intervention: UVGI		
Factor	**Assessment**	**Explanation**
Quality of evidence	Very low	There is very limited evidence available to suggest that respiratory pathogen spread from patients to health-care workers or other patients can be prevented by the use of UVGI for disinfection of air in health-care settings (*150*).
Balance of benefits or desired effects versus disadvantages or undesired effects	No strength	Reduction of the exposure to and infection of health-care workers by respiratory pathogens during care delivery to patients with ARI in health-care settings. Use of UVGI is associated with cost and resource implications for health-care facilities and harms to health-care workers due to excessive exposure. Effective use of UVGI requires expertise in design, installation and testing, maintenance and cleaning, electricity and air mixing (*27*). Direct exposure or overexposure to UVGI results in temporary adverse effects (photokeratitis and erythema).
Values and preferences	No strength	Reduction of exposure and infection to health-care workers by respiratory pathogens during care delivery to patients with ARI in health-care settings.
Costs	No strength	The use and maintenance of UVGI carries cost and resource implications for health-care facilities.
Feasibility	Conditional	The use of UVGI during care delivery for patients with ARIs depends on appropriate safeguards and expertise to install and maintain them.
Overall ranking	**No recommendation possible**	
Research gap	Additional research is required to elucidate whether the use of UVGI for disinfection of air in health-care settings reduces the risk of transmission and infection of specific pathogens causing ARIs from patients to health-care workers during the delivery of care, with and without the use of other precautions. Additional research is also required to assess the potential harms and cost effectiveness of the use of UVGI in these settings.	

ARI, acute respiratory infection; UVGI, ultraviolet germicidal irradiation

Table K.10 Considerations for duration of additional infection prevention and control (IPC) precautions

Recommendation: Implement additional IPC precautions at the time of admission and continue for the duration of symptomatic illness, and modify according to the pathogen and patient information.[1] Always use Standard Precautions. There is no evidence to support the routine application of laboratory tests to determine the duration of IPC precautions. (Chapter 2, Section 2.2.4)

Population: People with ARI in health-care settings

Intervention: Duration of additional IPC precautions

Factor	Assessment	Explanation
Quality of evidence	Very low	The scant evidence on the precise duration of additional precautions for patients with ARI is based on the duration of symptomatic illness and virological and epidemiological data on the infectivity period (*103, 104*). There is no evidence available to suggest that respiratory pathogen spread from patients to health-care workers or other patients is reduced by the use of additional IPC precautions for a longer duration.
Balance of benefits or desired effects versus disadvantages or undesired effects	Favourable	Reduction of exposure and infection to health-care workers and other patients by respiratory pathogens during care delivery to patients with ARI in health-care settings. Avoidance of unnecessary costs and better use of resources. Laboratory tests, using molecular techniques, are a highly sensitive diagnostic measure and may detect traces of viral nucleic acids. A positive result does not necessarily indicate ongoing virus replication and infectious risk.
Values and preferences	Favourable	Reduction of exposure and infection of health-care workers and other patients by respiratory pathogens during care delivery to patients with ARI in health-care settings.
Costs	No strength	The use of IPC precautions for a longer duration, or the use of laboratory tests, carry implications of cost and the use of beds in health-care facilities
Feasibility	Conditional	Increasing the duration of IPC precautions may be feasible in some settings, but it depends on availability of space and surge capacity (beds) and may not be easily implementable in all health-care settings.
Overall ranking	**CONDITIONAL**	
Research gap	Additional research is required: • to fully elucidate whether a longer (e.g. beyond resolution of symptoms) duration of additional IPC precautions for patients with ARIs in health-care settings reduces the risk of transmission and infection of specific pathogens causing ARIs from patients to health-care workers and other patients; • regarding the application of routine laboratory tests as a guide to define the duration of IPC precautions needed to reduce the spread of infection from infected patients to health-care workers or other patients; • to assess the harms and cost implications of using laboratory tests to define the duration of IPC precautions for individuals with ARI in health-care settings.	

ARI, acute respiratory infection; IPC, infection prevention and control

[1] Patient information (e.g. age, immune status and medication) should be considered in situations where there is concern that a patient may be infectious for a prolonged period.

Annex L Summaries of relevant systematic reviews of the literature

L.1 Summary of *Aerosol-generating procedures and risk of transmission of acute respiratory diseases: A systematic review*

Systematic review objective

The 2011 review *Aerosol-generating procedures and risk of transmission of acute respiratory diseases: A systematic review* (*149*) assessed the clinical evidence on the risk of transmission of ARIs to health-care workers exposed to aerosol-generating clinical procedures compared with the risk to workers not exposed to the same procedures.

Methods

The authors used a predefined strategy to search electronic health-care databases including PubMed, MEDLINE, EMBASE, CINAHL, The Cochrane Library (Issue 10, 2010), University of York Centre for Reviews and Dissemination databases, EuroScan, LILACS, Indian Medlars, Index Medicus for South East Asia and international health technology agencies; they also conducted a focused Internet search. Information sources were limited to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized controlled studies and guidelines published between 1 January 1990 and 22 October 2010. The search strategy contained no language limitation. Studies included in the review were those that examined the relevant study population (health-care workers caring for patients with ARIs), intervention (provision of care for patients undergoing aerosol-generating procedures), comparator (provision of care for patients not undergoing aerosol-generating procedures) and outcome (transmission of ARI from patient to health-care worker).

Of the 1862 abstracts identified by electronic search and screened against inclusion criteria, 86 citations were retrieved. Of these, 10 relevant non-randomized studies (5 case–control and 5 retrospective cohort studies) met the criteria for inclusion in the systematic review (Fig. L.1). The quality of evidence was rated using the GRADE framework (*47*).

Results and conclusions

All studies included in the review assessed the transmission of SARS-CoV to health-care workers associated with the performance of potentially aerosol-generating procedures while caring for ill patients in hospital or intensive care unit settings during the SARS outbreaks of 2002–2003.

The most consistent statistically significant association of an increased risk of SARS transmission to workers was found in tracheal intubation (eight studies) (Table L.1 and Fig. L.2). Increased risk of SARS transmission was also reported in non-invasive ventilation (two studies), tracheotomy (one study), and manual ventilation before intubation (one study); however, these findings were identified from a limited number of very low quality studies, which makes interpretation difficult. There was no significant difference in the risk of SARS transmission between exposed and unexposed health-care

workers for all other procedures evaluated – suction before intubation, suction after intubation, manual ventilation after intubation, bronchoscopy, nebulizer treatment, manipulation of oxygen mask, manipulation of bilevel positive airway pressure (BiPAP) mask, defibrillation, chest compressions, insertion of nasogastric tube, collection of sputum sample, high-frequency oscillatory ventilation, high-flow oxygen, endotracheal aspiration, suction of body fluid, administration of oxygen, chest physiotherapy and mechanical ventilation (Table L.1). All studies were rated very low quality according to GRADE criteria (*47*).

The findings suggest that some procedures potentially capable of generating aerosols are associated with increased risk of SARS transmission to health-care workers, with the most consistent association being across multiple studies identified with tracheal intubation. Other associations included non-invasive ventilation from two studies, and manual ventilation before intubation and tracheotomy, each from single studies. The authors note that these results must be interpreted in the context of the very low quality of the studies. A significant research gap was identified in this area: studies of higher methodological quality are required to provide more precise information about the risk of aerosol generation and the risk of transmission of microbes causing specific acute respiratory diseases, including influenza, from patients undergoing aerosol-generating procedures to health-care workers.

Figure L.1 Selection of publications for *Aerosol-generating procedures and risk of transmission of acute respiratory diseases: A systematic review*

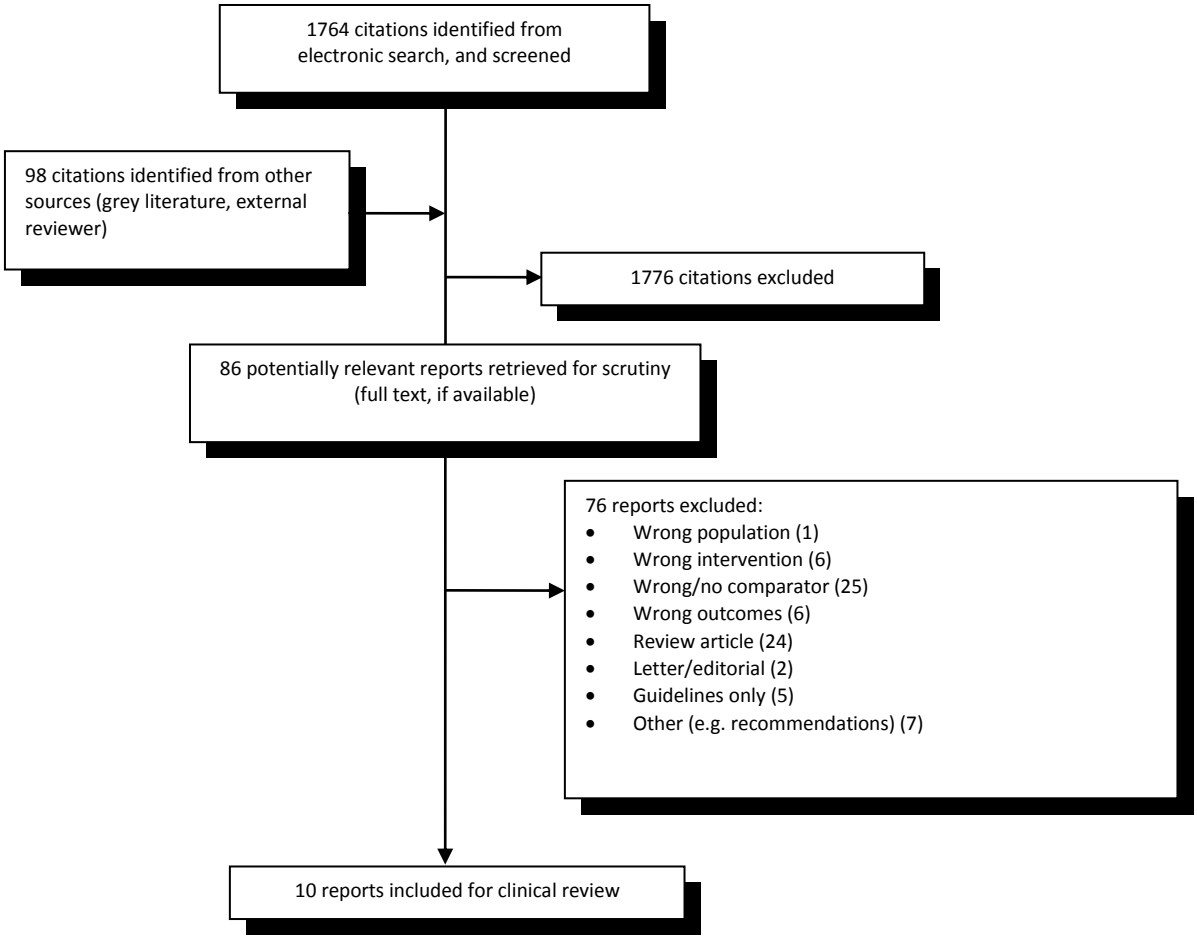


Table L.1 Summary of results from studies selected in the systematic review *Aerosol-generating procedures and risk of transmission of acute respiratory diseases: A systematic review*

Aerosol-generating procedures	Odds ratio[a] (95% CI)
Tracheal intubation (4 cohort studies)	3.0 (1.4, 6.7)
	22.8 (3.9, 131.1)
	13.8 (1.2, 161.7)
	5.5 (0.6, 49.5)
Pooled estimate (I^2 = 39.6%)	6.6 (2.3, 18.9)
Tracheal intubation (4 case–control studies)	0.7 (0.1, 3.9)
	9.2 (4.2, 20.2)
	8.0 (3.9, 16.6)
	9.3 (2.9, 30.2)
Pooled estimate (I^2 = 61.4%)	6.6 (4.1, 10.6)
Suction before intubation (2 cohort studies)	13.8 (1.2, 161.7)
	1.7 (0.7, 4.2)
Pooled estimate (I^2 = 59.2%)	3.5 (0.5, 24.6)
Suction after intubation (2 cohort studies)	0.6 (0.1, 3.0)
	1.8 (0.8, 4.0)
Pooled estimate (I^2 = 28.8%)	1.3 (0.5, 3.4)
Nebulizer treatment (3 cohort studies)	6.6 (0.9, 50.5)
	0.1 (0.0*, 1.0)
	1.2 (0.1, 20.7)
Pooled estimate (I^2 = 73.1%)	0.9 (0.1, 13.6)
Manipulation of oxygen mask (2 cohort studies)	17.0 (1.8, 165.0)
	2.2 (0.9, 4.9)
Pooled estimate (I^2 = 64.8%)	4.6 (0.6, 32.5)
Bronchoscopy (2 cohort studies)	3.3 (0.2, 59.6)
	1.1 (0.1, 18.5)
Pooled estimate (I^2 = 0%)	1.9 (0.2, 14.2)
Non-invasive ventilation (2 cohort studies)	2.6 (0.2, 34.5)
	3.2 (1.4, 7.2)
Pooled estimate (I^2 = 0%)	3.1 (1.4, 6.8)
Insertion of nasogastric tube (2 cohort studies)	1.7 (0.2, 11.5)
	1.0 (0.2, 4.5)
Pooled estimate (I^2 = 0%)	1.2 (0.4, 4.0)

Aerosol-generating procedures	Odds ratio[a] (95% CI)
Chest compressions (1 case–control study)	4.5 (1.5, 13.8)
Chest compressions (2 cohort studies)	3.0 (0.4, 24.5)
	0.4 (0.0**, 7.8)
Pooled estimate (I^2 = 27.3%)	1.4 (0.2, 11.2)
Defibrillation (2 cohort studies)	0.5 (0.0**, 12.2)
	7.9 (0.8, 79.0)
Pooled estimate (I^2 = 55.3%)	2.5 (0.1, 43.9)
Chest physiotherapy (2 cohort studies)	1.3 (0.2, 8.3)
	0.5 (0.1, 3.5)
Pooled estimate (I^2 = 0%)	0.8 (0.2, 3.2)
High-frequency oscillatory ventilation (1 cohort study)	0.7 (0.1, 5.5)
High-flow oxygen (1 cohort study)	0.4 (0.1, 1.7)
Tracheotomy (1 case–control study)	4.2 (1.5, 11.5)
Intubation, tracheotomy, airway care, and cardiac resuscitation (1 case–control study)	6.2 (2.2, 18.1)
Manipulation of BiPAP mask (1 cohort study)	4.2 (0.6, 27.4)
Endotracheal aspiration (1 cohort study)	1.0 (0.2, 5.2)
Suction of body fluid (1 case–control study)	1.0 (0.4, 2.8)
Administration of oxygen (1 case–control study)	1.0 (0.3, 2.8)
Mechanical ventilation (1 cohort study)	0.9 (0.4, 2.0)
Manual ventilation before intubation (1 cohort study)	2.8 (1.3, 6.4)
Manual ventilation after intubation (1 cohort study)	1.3 (0.5, 3.2)
Manual ventilation (1 cohort study)	1.3 (0.2, 8.3)
Collection of sputum sample (1 cohort study)	2.7 (0.9, 8.2)

BiPAP: bilevel positive airway pressure; CI: confidence interval

* actual value is 0.01; ** actual value is 0.02

[a] Studies included in this table met the criteria for inclusion in a systematic review of the evidence (i.e. they measured the risk of SARS transmission to health-care workers who were exposed to the listed procedures compared to workers who were not exposed the same procedures). Inclusion in this table is not a validation of study quality.

Figure L.2A Risk of SARS transmission to health-care workers exposed to tracheal intubation

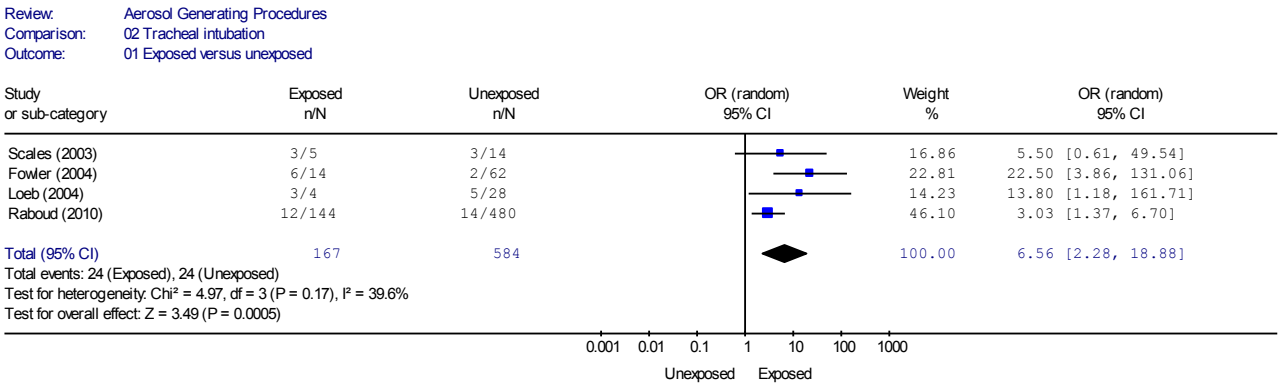
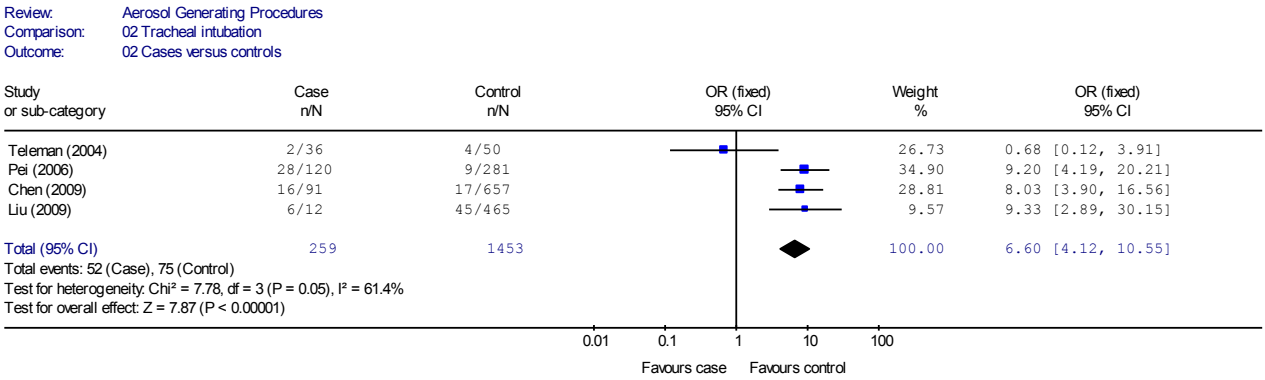


Figure L.2B Tracheal intubation as risk factor for SARS transmission



CI, confidence interval; n, number of events; N, sample size; OR, odds ratio; SARS, severe acute respiratory syndrome

L.2 Summary of *Physical interventions to interrupt or reduce the spread of respiratory viruses*

Systematic review objective

This 2011 review – *Physical interventions to interrupt or reduce the spread of respiratory viruses* (*51*) – examined evidence for the effectiveness of physical barriers (e.g. screening at entry ports, isolation, quarantine, social distancing, barriers, personal protection and hand hygiene) in reducing the spread of respiratory viruses. It represents an update of a previously conducted systematic review of the same topic in 2010 (*266*), with some adaptations designed to inform the review of the WHO interim guidelines *Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care*, 2007 (*16*).

Methods

The authors used predefined criteria to search the relevant databases, including The Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL 2010, Issue 3), which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to October 2010), OLDMEDLINE (1950 to 1965), EMBASE (1990 to October 2010), CINAHL (1982 to October 2010), LILACS (2008 to October 2010), Indian MEDLARS (2008 to October 2010) and IMSEAR (2008 to October 2010). Of 3775 titles identified, 3560 were scanned and excluded, 215 were retrieved in full text and 67 were selected for inclusion. Included studies were those that investigated any intervention intended to prevent transmission of respiratory viruses compared with no intervention or with another intervention and that measured several negative outcomes associated with respiratory virus transmission (i.e. death, number of cases of viral illness, severity of viral illness and proxies for the preceding outcomes).

Results and conclusions

After screening potential publications for inclusion criteria, a total of 67 studies were included in the review, comprising RCTs, cluster-RCTs and observational studies, with a mixed risk of bias. The review identified seven studies – four RCTs and three observational studies – that were not in the previous review (*266*).

The risk of bias for most of the RCTs and cluster-RCTs was high, with the exception of one cluster-RCT that was considered of medium risk of bias and one RCT that was considered of low risk of bias. Data from observational studies were of mixed quality. The results of the case–control studies were considered sufficiently homogeneous to allow pooling and meta-analysis. Most of the information sources studied SARS; therefore, applying the review findings to other diseases will require additional research.

The results of the best quality cluster-RCTs suggest that respiratory virus spread can be prevented by hygiene measures, such as handwashing, especially when interventions are aimed at young children or households with young children. The conclusion that hygiene measures reduce transmission from children to other members of the household was broadly supported by other studies, although these conclusions came from studies that have a greater potential for confounding. No conclusion could be drawn regarding the benefit of adding virucidals or antiseptics to standard handwashing. The pooled case-control studies suggested that implementing transmission barriers, isolation and hygiene measures are effective at reducing respiratory virus transmission. Facial masks (surgical masks or N95 respirators) were the intervention that was found to perform most consistently, and the evidence did not indicate superiority of N95 respirators over simple surgical masks in

decreasing transmission of acute respiratory disease. One study found that screening at entry ports was associated with a marginal delay in spread; however, this association was not significant. The review found limited evidence that social distancing or spatial separation (i.e. keeping a distance of at least 1 m between infected patients and others) was effective. The results are summarized in Table L.2, below.

Table L.2 Summary of main results from the systematic review *Physical interventions to interrupt or reduce the spread of respiratory viruses*

Intervention	RCT (*N* = 6)	Cluster-RCT (*N* = 17)	Case–control (*N* = 9)	Prospective cohort (*N* = 16)	Retrospective cohort (*N* = 6)	Before–after (*N* = 13)
Handwashing	–	2 trials in children, effective (*267, 268*)	7 studies OR 0.54 (95% CI 0.44–0.67)(*154, 269-274*)	2 studies found effect (*275, 276*) 2 found no effect on ARIs (*277, 278*)	–	1 study in military recruits: handwashing more than 5 times per day effective (*279*)
Handwashing with antiseptic	–	2 trials in children, effective: antiseptic more effective (*280, 281*) 1 trial in children: antiseptic ≡ soap (*98*)	–	2 studies found added effect of antiseptic (*282, 283*) 1 study found no difference (*284*)	–	–
Handwashing and surface disinfection	–	1 study in day-care centre, effective (*285*) 1 study in school, no effect of adding disinfection to handwashing and cleaning on ARI (*286*) 1 study in families, no effect of adding disinfection to handwashing and cleaning on ARI (*287*) 1 study, no effect of handwashing with disinfection of surfaces in child day care (*288*)	–	–	–	1 study in special school with children with Down syndrome < 5 yrs effective (*289*)
Hand disinfection	3 trials effective (*290, 291*)	–	–	–	–	–
Gargling with iodine	1 trial effective (*292*)	–	–	–	–	–

Intervention	RCT (*N* = 6)	Cluster-RCT (*N* = 17)	Case–control (*N* = 9)	Prospective cohort (*N* = 16)	Retrospective cohort (*N* = 6)	Before–after (*N* = 13)
Nose wash	–	–	2 studies OR 0.30 (95% CI 0.16 to 0.57) (*269, 293*)	–	–	–
Virucidal tissues	–	1 trial small effect (*294*) 2 trials non-significant difference (*294, 295*)	–	1 study effective (*296*)	–	–
Disinfection of living quarters	–	–	1 study OR 0.30 (95% CI 0.23 to 0.39) (*270*)	–	–	–
Use of eye protection	–	–	3 studies OR 0.10 (95% CI 0.05–0.17) (*269, 274, 293*)	–	–	–
Barriers (masks, gloves, gowns combined)	–	–	2 studies OR 0.09 (95% CI 0.02 to 0.35) (*154, 271*)	1 study: masks + gowns no added effect to handwashing (*297*)	–	3 studies: combined with isolation effective 1 study: barriers combined with isolation effective (*298*) 1 study: masks and gowns added to isolation not effective (*299*) 1 study: gowns and gloves effective in paediatric ward (*300*)

Intervention	**RCT (*N* = 6)**	**Cluster-RCT (*N* = 17)**	**Case–control (*N* = 9)**	**Prospective cohort (*N* = 16)**	**Retrospective cohort (*N* = 6)**	**Before–after (*N* = 13)**
Mask	1 trial: surgical masks no effect (*301*)	1 trial: no effect if mask added to handwashing (*302*) 1 trial: no effect of P2 mask (*303*) 1 trial: mask added to handwashing effective if implemented < 36 hours after onset of illness (*265*) 1 trial: if mask added to handwashing effective during weeks 4 to 6 (*304*) 1 trial: no effect added to handwashing (*305*)	7 studies OR 0.32 (95% CI 0.26 to 0.39) (*154, 269-271, 273, 274, 293*)	3 studies: masks effective (*58, 306, 307*), with air filter safer (*210*)	1 study: harm related to mask wearing (*308*)	1 study in children's hospital effective (*309*)
N95 respirator	1 trial: surgical masks non-inferior to N95 respirators (*310*)	–	3 studies OR 0.17 (95% CI 0.07 to 0.43) (*154, 272, 293*)	–	1 study: harm related to N95 respirator wearing (*308*)	–
Gloves	–	–	6 studies OR 0.32 (95% CI 0.23 to 0.45) (*154, 269, 271, 272, 274, 293*)	–	1 study: harm related to glove wearing (*308*)	–
Gowns	–	–	5 studies OR 0.33 (95% CI 0.24 to 0.45) (*154, 269, 271, 272, 274*)	–	1 study: harm related to gown wearing (*308*)	1 study: no added effect in neonatal intensive care unit (*311*)

Intervention	RCT (*N* = 6)	Cluster-RCT (*N* = 17)	Case–control (*N* = 9)	Prospective cohort (*N* = 16)	Retrospective cohort (*N* = 6)	Before–after (*N* = 13)
Distancing	–	–	–	1 study: no effect in military recruits (*312*) 2 studies: cohorting in hospitals effective (*56, 58*)	1 study: cohorting in paediatric wards effective (*313*) 1 study: cohorting and handwashing in paediatric wards effective (*314*) 1 study: cohorting with handwashing and gowns effective in military hospital (*315*)	2 studies: early identification of cases and isolation effective (*298, 316*) 1 study: cohorting in combination with barriers effective in children's hospital (*317*) 1 study: cohorting of RSV cases and education effective in paediatric hospital (*318*) 1 study: isolation of close contacts in paediatric ward effective (*147*)
Quarantine	–	–	–	1 study: quarantine of anyone with known or suspected exposure effective during SARS epidemic (*319*)	1 study: isolation of close contacts effective (*320, 321*) 1 study: marginal non-significant benefit of border entry screening (*322*)	1 study: closure of primary school effective (*323, 324*) 1 ecological study: quarantine may be effective in SARS epidemic (*55*)

ARI: acute respiratory infection; CI: confidence interval; OR: odds ratio; RCT, randomized controlled trial; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome

L.3 Summary of *Physical interventions to interrupt or reduce the transmission of respiratory viruses – resource use implications: A systematic review*

Systematic review objective

This 2011 review – *Physical interventions to interrupt or reduce the transmission of respiratory viruses – resource use implications: A systematic review* (*207*) – examined the economic literature related to resource implications and costs and cost effectiveness of physical barriers used to interrupt or reduce the spread of respiratory viruses. It was intended to supplement information provided in the Cochrane Review, *Physical interventions to interrupt or reduce the spread of respiratory viruses* (*51*) (Section L.2), and represents an important source of information for decision-makers considering the resource use implications of these interventions.

Methods

The authors used a peer-reviewed search strategy to search the following electronic bibliographic databases: EMBASE 1980 to 2010 Week 43, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to 2010, The Cochrane Library (2010, Issue 10), including the NHS Economic Evaluation Database (NHS EED), Health Economic Evaluations Database (HEED), CINAHL and PubMed. The initial search was completed in November 2010, with regular alerts established on EMBASE, MEDLINE and PubMed through April 2011. The publications identified were limited to economic studies published between 1995 and 2010. The search was not limited by language. Additional relevant information sources were sought through searches of the web sites of health technology assessment and related agencies, professional associations and other specialised databases, and of Google, Google Scholar and other Internet search engines, plus review of bibliographies and abstracts of key papers and consultation with experts.

The literature search yielded 1146 citations, the abstracts of which were screened for inclusion criteria. A total of 158 were retrieved for more detailed evaluation, of which 39 studies were subjected to full review. Seven studies reported information on resource use of physical interventions or assessed the cost effectiveness of physical interventions and were, therefore, selected for inclusion in the systematic review (Fig. L.3).

Results and conclusions

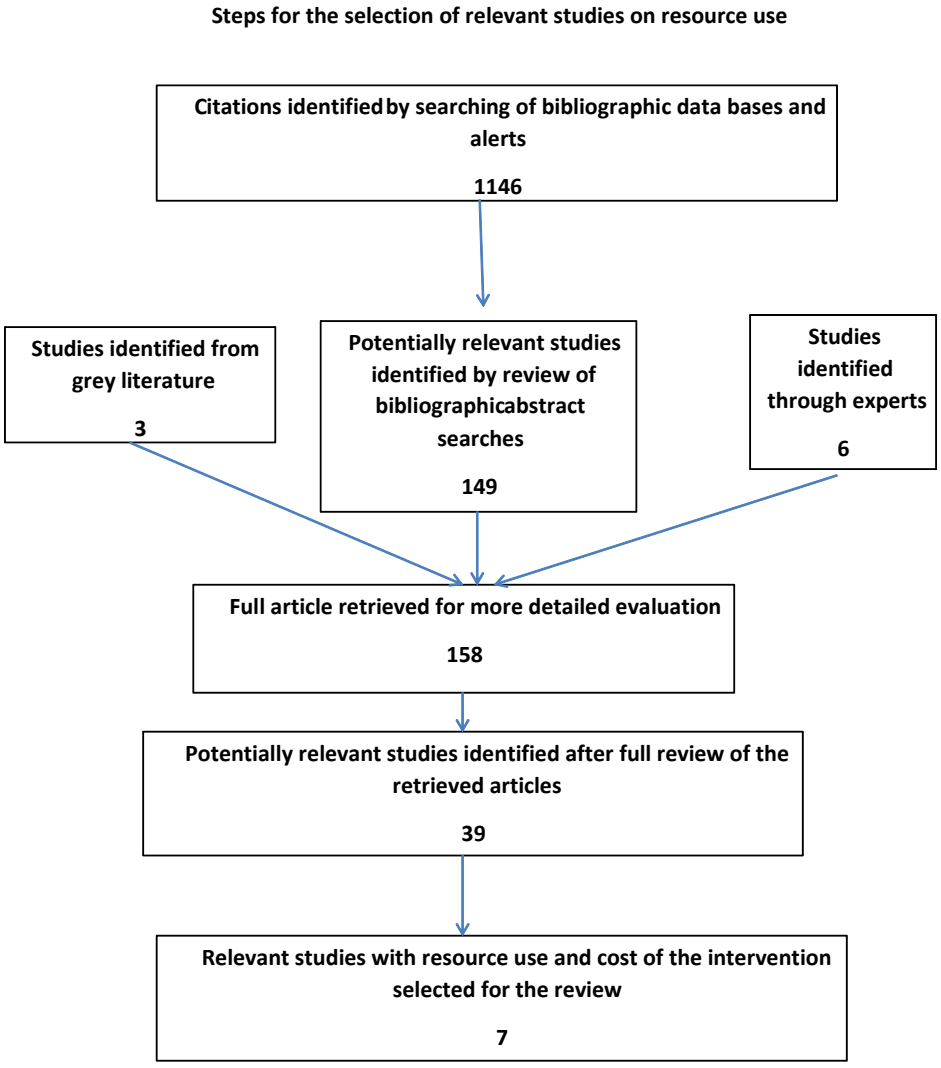
Using the GRADE appraisal methodology, the evidence provided by all seven studies was of very low quality, largely due to issues of study design, indirectness, and precision or sample size. The authors noted that, in some cases, the reliability of modelling results was questionable due to sensitivity to input assumptions. In addition, all economic studies included in the review were designed to address specific study questions and were conducted in settings subject to local recommendations and policies that differed from place to place. As a result, direct comparison of the findings and formulation of general conclusions was difficult.

A major finding of this review was the serious lack of high-quality research examining resource use and economic implications associated with PPE and other physical barriers for the interruption or reduction of respiratory virus transmission. In general, the current evidence

suggests that the use of PPE (e.g. medical masks, respirators, eye protection, gloves and gowns) to reduce the burden of respiratory viruses may be economically attractive, particularly in situations of rapid or prolific transmission and high fatality rate. The authors noted that these results depend on multiple assumptions, including transmission rate, facility infection rate and compliance with the interventions. In addition, the results suggested that there is an increase in the use of physical interventions to interrupt or reduce the spread of respiratory viruses during epidemics and pandemics, with two studies indicating that PPE may actually be overused during pandemics. The authors concluded that, while appropriate use of PPE is likely to be cost effective in certain situations, overuse could eliminate the overall cost effectiveness.

The authors noted that generalizability of the results to different respiratory virus types and settings other than hospitals still needs to be evaluated.

Figure L.3 Selection of publications for *Physical interventions to interrupt or reduce the transmission of respiratory viruses – resource use implications: A systematic review*



L.4 Summary of *The effectiveness of vaccination of healthcare workers for the protection of patients at higher risk of acute respiratory disease: A systematic review*

Systematic review objective

This review – *The effectiveness of vaccination of healthcare workers for the protection of patients at higher risk of acute respiratory disease: A systematic* review (*130*) – examined evidence for the effectiveness of influenza and pneumococcal vaccination of health-care workers in protecting patients at higher risk of severe or complicated disease from ARI.

Methods

The authors used a predefined strategy to search electronic health-care databases including EMBASE, CINAHL, MEDLINE, PubMed, The Cochrane Library, J-Stage, BDSP, EASTVIEW, Index-F, eLIBRARY, WHO regional indexes, and the WHO portal of clinical trials; they also accessed relevant evidence-based reviews, guidelines and grey literature. Publications were reviewed against eligibility criteria in a three-stage process to ensure appropriate study types (experimental or observational study or systematic review), subject population (patients of all ages who were at higher risk of severe or complicated illness as a result of ARI), intervention (vaccination of any person providing health care to high-risk patients with influenza or pneumococcal vaccines in any dose, preparation or schedule), comparator (no vaccination, placebo or use of long-term prophylaxis) and outcome (cases of or consultations for ARI; cases of, consultations for or laboratory evidence of ILI where relevant; mortality from respiratory infection, ILI, acute respiratory disease or associated complications; or measurements of health-care usage due to respiratory infection, ILI or acute respiratory disease). Reference and citation tracking was undertaken for all citations meeting eligibility criteria at the full-text stage.

Of the 12 352 total citations identified, 11 234 were excluded following a review of the titles, 941 following a review of the abstracts, and 160 following review of the full text (Fig. L.4). A total of 20 papers were included, 17 from the original search and an additional 3 records identified from citation or reference tracking. Of these, 14 were primary research papers and 6 were reports of two systematic reviews.

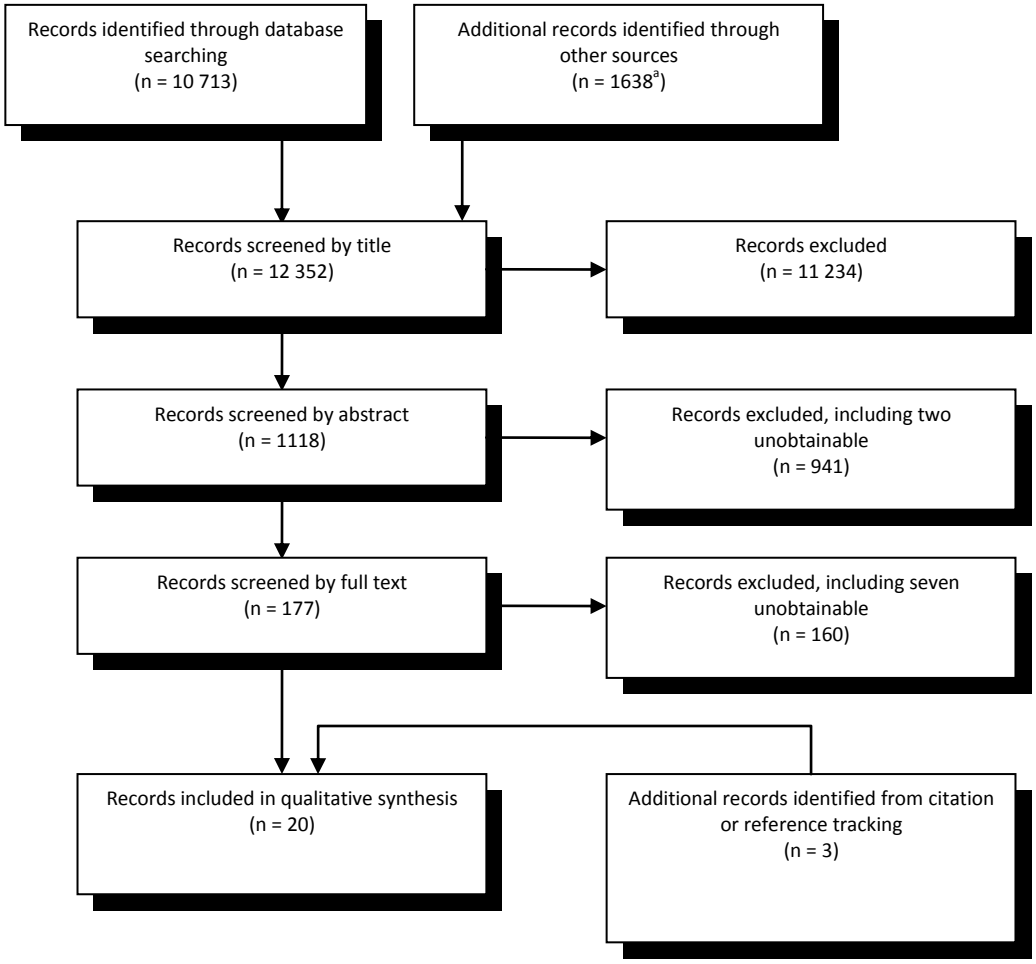
Results and conclusions

There was marked heterogeneity in the populations, interventions or exposures and outcomes considered, limiting the comparability of the included papers. Of the 14 primary research papers, 11 were in long-term residential care settings, and all were judged to be at risk of bias. Four were RCTs, and data from these had been pooled in a previous systematic review. This demonstrated a statistically significant protective effect with regard to measures of ILI and all-cause mortality among elderly residents. Additional observational data identified in this review suggested a uniform direction of effect across several measures of ILI, with a similar pattern for laboratory-confirmed influenza. The authors concluded that, although limited, a true underlying protective effect for patients at higher risk of severe or complicated ARI disease due to vaccination of health-care workers in long-term residential settings is likely (Table L.3).

The authors identified a major research gap in the topic area, noting that existing evidence provides little information about groups other than those in long-term residential settings. More

research is required to determine the effectiveness of vaccination of health-care workers in protecting other higher-risk patient populations.

Figure L.4 Selection of publications for *The effectiveness of vaccination of healthcare workers for the protection of patients at higher risk of acute respiratory disease: A systematic review*



[a] Includes one paper not identified with the original search strategy but transferred from a parallel review conducted in the same department.

Table L.3 Summary of findings from *The effectiveness of vaccination of healthcare workers for the protection of patients at higher risk of acute respiratory disease: A systematic review*

Outcome	Evidence available	Narrative synthesis
Acute respiratory disease	Statistical estimates from one RCT (*325*) providing two different measures of effect (clinical episodes of viral illness / lower respiratory tract infection).	Inconsistent effect but uniform in direction, suggesting possible protection. Difficult to ascertain whether this may be attributable to influenza infection due to the nonspecific nature of the measures used.
Clinically defined cases of ILI / influenza	Statistical estimates of clinically defined ILI measured from three RCTs (*325-327*) and two prospective cohort studies (*328, 329*), although different definitions employed. Further observational data from one cross-sectional study with no supporting statistical analysis. Additional (*330*) statistical estimate of cases of influenza from one cross-sectional study (*331*).	Pooled data (*332*) from the three RCTs suggest a statistically significant protective effect when adjusted for clustering. This is supported by additional observational data; two of the three studies providing statistical analyses (*328, 329*) demonstrating effects that were consistent in direction, although at higher risk of bias.
GP consultations for ILI	Statistical estimate from one RCT (*327*).	Small, statistically significant reduction in the rate of consultations for one season only, although overall statistically significant protective effect when converted to an adjusted odds ratio (*331*).
Outbreaks / cluster of ILI	Statistical estimates from three observational studies (*329, 333, 334*), although different definitions employed.	All three studies demonstrate statistically significant protective effects although imprecise estimates and a high risk of bias.
Laboratory-diagnosed influenza	Statistical estimates from one RCT (*335*) and two observational studies (*336, 337*). Observational data from a further RCT (*325*).	Pooled data from two RCTs (*331*) suggest a non-significant protective effect. Direction of effect supported by data from two additional observation studies (*336, 337*) which demonstrated statistically significant protective effects. Notable risk of bias and imprecision due to very small sample sizes.
Laboratory-confirmed outbreaks of influenza	Statistical estimate from one observational study (*338*).	No statistically significant difference, although vaccination coverage appeared higher in homes experiencing outbreaks. Analyses were, however, unadjusted and imprecise due to small numbers.
Respiratory mortality	Statistical estimates from four RCTs (*325-327, 335*) although each provided a different measure (respiratory deaths, deaths associated with pneumonia, deaths with ILI and laboratory-diagnosed influenza at death).	Pooled estimate (*331*) using data for respiratory deaths (*326*) and deaths associated with pneumonia (*325*) suggest a small, non-significant protective effect. Small, non-significant protective effects for mortality following ILI (*327*), and mortality due to laboratory-confirmed influenza (*335*), were also demonstrated in individual studies Generalisability was limited because of the different measures employed.
All-cause mortality	Statistical estimate from four RCTs (*325-327, 335*).	Inconsistent effect, but uniform in direction. Pooled data (*331*) suggest a statistically significant protective effect when adjusted for clustering.
Hospitalization	Statistical estimates from two RCTs (*326, 327*) providing three different	No clear effect demonstrated.

Outcome	Evidence available	Narrative synthesis
	measures of effect (hospitalization, hospitalization for respiratory causes and admission with ILI).	

GP, general practitioner; ILI: influenza-like illness; RCT, randomized controlled trial

Annex M Management of conflict of interest

All guideline group members, external peer reviewers and representatives of the Global Infection Prevention and Control Network member institutions participating in the GRADE process for the development of these guidelines submitted a declaration of interests form, together with their curriculum vitae. The potential interests declared by members of the guideline development group and external expert and resource persons are summarized below.

Professor Barry Cookson declared that he had once served on a panel and provided one-to-one expert advice (on three occasions) on effectiveness and strategy for products in the previous three years. The companies were Wyeth, Rubbermaid, 3M and Vernacare/Baxter. The products were a vaccine for Staphylococcus, microfiber cleaning wipes, and disinfectants. All consultancies had ceased by the time of his involvement in the review of these guidelines. These interests were deemed not to conflict with his ability to review the guidelines, since the financial compensation received during that time were not significant and the work had already ceased.

Professor Babacar Ndoye declared that he received support from bioMérieux Clinical Diagnostics, the Pasteur Institute, and local companies for participating or organizing meetings, workshops or conferences, none of which exceeded US$1,000. Professor Wing Hong Seto declared that he received travel support for speaking at a scientific conference organized by Pfizer. These were not deemed to be conflicts, since the amounts received were not significant.

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REFERENCE 7

High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice — Skagit County, Washington, March 2020

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On May 12, 2020, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

On March 17, 2020, a member of a Skagit County, Washington, choir informed Skagit County Public Health (SCPH) that several members of the 122-member choir had become ill. Three persons, two from Skagit County and one from another area, had test results positive for SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19). Another 25 persons had compatible symptoms. SCPH obtained the choir's member list and began an investigation on March 18. Among 61 persons who attended a March 10 choir practice at which one person was known to be symptomatic, 53 cases were identified, including 33 confirmed and 20 probable cases (secondary attack rates of 53.3% among confirmed cases and 86.7% among all cases). Three of the 53 persons who became ill were hospitalized (5.7%), and two died (3.7%). The 2.5-hour singing practice provided several opportunities for droplet and fomite transmission, including members sitting close to one another, sharing snacks, and stacking chairs at the end of the practice. The act of singing, itself, might have contributed to transmission through emission of aerosols, which is affected by loudness of vocalization (*1*). Certain persons, known as superemitters, who release more aerosol particles during speech than do their peers, might have contributed to this and previously reported COVID-19 superspreading events (*2*–*5*). These data demonstrate the high transmissibility of SARS-CoV-2 and the possibility of superemitters contributing to broad transmission in certain unique activities and circumstances. It is recommended that persons avoid face-to-face contact with others, not gather in groups, avoid crowded places, maintain physical distancing of at least 6 feet to reduce transmission, and wear cloth face coverings in public settings where other social distancing measures are difficult to maintain.

Investigation and Findings

The choir, which included 122 members, met for a 2.5-hour practice every Tuesday evening through March 10. On March 15, the choir director e-mailed the group members to inform them that on March 11 or 12 at least six members had developed fever and that two members had been tested for SARS-CoV-2 and were awaiting results. On March 16, test results for three members were positive for SARS-CoV-2 and were reported to two respective local health jurisdictions, without indication of a common source of exposure. On March 17, the choir director sent a second e-mail stating that 24 members reported that they had developed influenza-like symptoms since March 11, and at least one had received test results positive for SARS-CoV-2. The email emphasized the importance of social distancing and awareness of symptoms suggestive of COVID-19. These two emails led many members to self-isolate or quarantine before a delegated member of the choir notified SCPH on March 17.

All 122 members were interviewed by telephone either during initial investigation of the cluster (March 18–20; 115 members) or a follow-up interview (April 7–10; 117); most persons participated in both interviews. Interviews focused on attendance at practices on March 3 and March 10, as well as attendance at any other events with members during March, other potential exposures, and symptoms of COVID-19. SCPH used Council of State and Territorial Epidemiologists case definitions to classify confirmed and probable cases of COVID-19 (*6*). Persons who did not have symptoms at the initial interview were instructed to quarantine for 14 days from the last practice they had attended. The odds of becoming ill after attending each practice were computed to ascertain the likelihood of a point-source exposure event.

No choir member reported having had symptoms at the March 3 practice. One person at the March 10 practice had cold-like symptoms beginning March 7. This person, who had also attended the March 3 practice, had a positive laboratory result for SARS-CoV-2 by reverse transcription–polymerase chain reaction (RT-PCR) testing.

In total, 78 members attended the March 3 practice, and 61 attended the March 10 practice (Table 1). Overall, 51 (65.4%) of the March 3 practice attendees became ill; all but one of these persons also attended the March 10 practice. Among 60 attendees at the March 10 practice (excluding the patient who became ill March 7, who also attended), 52 (86.7%) choir members subsequently became ill. Some members exclusively attended one practice; among 21 members who only attended March 3, one became ill and was not tested (4.8%), and among three members who only attended March 10, two became ill (66.7%), with one COVID-19 case being laboratory-confirmed.

Summary

What is already known about this topic?

Superspreading events involving SARS-CoV-2, the virus that causes COVID-19, have been reported.

What is added by this report?

Following a 2.5-hour choir practice attended by 61 persons, including a symptomatic index patient, 32 confirmed and 20 probable secondary COVID-19 cases occurred (attack rate = 53.3% to 86.7%); three patients were hospitalized, and two died. Transmission was likely facilitated by close proximity (within 6 feet) during practice and augmented by the act of singing.

What are the implications for public health practice?

The potential for superspreader events underscores the importance of physical distancing, including avoiding gathering in large groups, to control spread of COVID-19. Enhancing community awareness can encourage symptomatic persons and contacts of ill persons to isolate or self-quarantine to prevent ongoing transmission.

Because illness onset for 49 (92.5%) patients began during March 11–15 (Figure), a point-source exposure event seemed likely. The median interval from the March 3 practice to symptom onset was 10 days (range = 4–19 days), and from the March 10 practice to symptom onset was 3 days (range = 1–12 days). The odds of becoming ill after the March 3 practice were 17.0 times higher for practice attendees than for those who did not attend (95% confidence interval [CI] = 5.5–52.8), and after the March 10 practice, the odds were 125.7 times greater (95% CI = 31.7–498.9). The clustering of symptom onsets, odds of becoming ill according to practice attendance, and known presence of a symptomatic contagious case at the March 10 practice strongly suggest that date as the more likely point-source exposure event. Therefore, that practice was the focus of the rest of the investigation. Probable cases were defined as persons who attended the March 10 practice and developed clinically compatible COVID-19 symptoms, as defined by Council of State and Territorial Epidemiologists (*6*). The choir member who was ill beginning March 7 was considered the index patient.

The March 10 choir rehearsal lasted from 6:30 to 9:00 p.m. Several members arrived early to set up chairs in a large multipurpose room. Chairs were arranged in six rows of 20 chairs each, spaced 6–10 inches apart with a center aisle dividing left and right stages. Most choir members sat in their usual rehearsal seats. Sixty-one of the 122 members attended that evening, leaving some members sitting next to empty seats. Attendees practiced together for 40 minutes, then split into two smaller groups for an additional 50-minute practice, with one of the groups moving to a smaller room. At that time, members in the larger room moved to seats next to one another, and members in the smaller room sat next to one another on benches. Attendees then had a 15-minute break, during which cookies and oranges were available at the back of the large room, although many members reported not eating the snacks. The group then reconvened for a final 45-minute session in their original seats. At the end of practice, each member returned their own chair, and in the process congregated around the chair racks. Most attendees left the practice immediately after it concluded. No one reported physical contact between attendees. SCPH assembled a seating chart of the all-choir portion of the March 10 practice (not reported here because of concerns about patient privacy).

Among the 61 choir members who attended the March 10 practice, the median age was 69 years (range = 31–83 years); 84% were women. Median age of those who became ill was 69 years, and 85% of cases occurred in women. Excluding the laboratory-confirmed index patient, 52 (86.7%) of 60 attendees became ill; 32 (61.5%) of these cases were confirmed by RT-PCR testing and 20 (38.5%) persons were considered to have probable infections. These figures correspond to secondary attack rates of 53.3% and 86.7% among confirmed and all cases, respectively. Attendees developed symptoms 1 to 12 days after the practice (median = 3 days). The first SARS-CoV-2 test was performed on March 13. The last person was tested on March 26.

Three of the 53 patients were hospitalized (5.7%), including two who died (3.8%). The mean interval from illness onset to hospitalization was 12 days. The intervals from onset to death were 14 and 15 days for the two patients who died.

SCPH collected information about patient signs and symptoms from patient interviews and hospital records (Table 2). Among persons with confirmed infections, the most common signs and symptoms reported at illness onset and at any time during the course of illness were cough (54.5% and 90.9%, respectively), fever (45.5%, 75.8%), myalgia (27.3%, 75.0%), and headache (21.2%, 60.6%). Several patients later developed gastrointestinal symptoms, including diarrhea (18.8%), nausea (9.4%), and abdominal cramps or pain (6.3%). One person experienced only loss of smell and taste. The most severe complications reported were viral pneumonia (18.2%) and severe hypoxemic respiratory failure (9.1%).

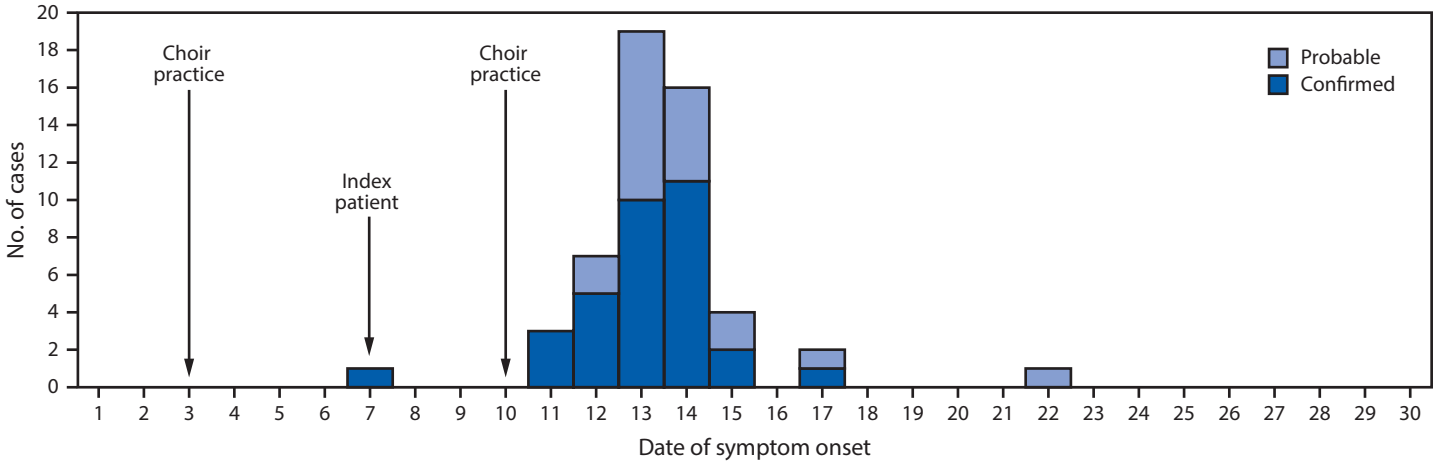
Among the recognized risk factors for severe illness, the most common was age, with 75.5% of patients aged ≥65 years. Most patients (67.9%) did not report any underlying medical conditions, 9.4% had one underlying medical condition, and 22.6% had two or more underlying medical conditions. All three hospitalized patients had two or more underlying medical conditions.

TABLE 1. Number of choir members with and without COVID-19–compatible symptoms (N = 122)* and members' choir practice attendance† — Skagit County, Washington, March 3 and 10, 2020

	No. (row %)					
	March 3 practice			March 10 practice		
Attendance	Total	Symptomatic	Asymptomatic	Total	Symptomatic	Asymptomatic
Attended	78	51 (65.4)	27 (34.6)	61	53§ (86.9)	8 (13.1)
Did not attend	40	4 (10.0)	36 (90.0)	61	3 (4.9)	58 (95.1)
Attendance information missing	4	1 (25.0)	3 (75.0)	0	0 (—)	0 (—)
Attended only one practice	21	1 (4.8)	20 (95.2)	3	2 (66.7)	1 (33.3)

Abbreviation: COVID-19 = coronavirus disease 2019.
* No choir members were symptomatic at the March 3 practice.
† Thirty-seven choir members attended neither practice; two developed symptoms, and 35 remained asymptomatic.
§ Includes index patient; if the index patient excluded, 52 secondary cases occurred among the other 60 attendees (attack rate = 86.7%).

FIGURE. Confirmed* and probable† cases of COVID-19 associated with two choir practices, by date of symptom onset (N = 53) — Skagit County, Washington, March 2020



Abbreviation: COVID-19 = coronavirus disease 2019.
* Positive reverse transcription–polymerase chain reaction test result.
† Attendance at the March 10 practice and clinically compatible symptoms as defined by the Council of State and Territorial Epidemiologists, Interim-20-ID-01: Standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19). https://cdn.ymaws.com/www.cste.org/resource/resmgr/2020ps/interim-20-id-01_covid-19.pdf.

Public Health Response

SCPH provided March 10 practice attendees with isolation and quarantine instructions by telephone, email, and postal mail. Contacts of patients were traced and notified of isolation and quarantine guidelines. At initial contact, 15 attendees were quarantined, five of whom developed symptoms during quarantine and notified SCPH.

Before detection of this cluster on March 17, Skagit County had reported seven confirmed COVID-19 cases (5.4 cases per 100,000 population). At the time, SCPH informed residents that likely more community transmission had occurred than indicated by the low case counts.* On March 21, SCPH issued a press release to describe the outbreak and raise awareness about community transmission.† The press release emphasized the highly contagious nature of COVID-19 and the importance of following social distancing guidelines to control the spread of the virus.

Discussion

Multiple reports have documented events involving superspreading of COVID-19 (*2*–*5*); however, few have documented a community-based point-source exposure (*5*). This cluster of 52 secondary cases of COVID-19 presents a unique opportunity for understanding SARS-CoV-2 transmission following a likely point-source exposure event. Persons infected with SARS-CoV-2 are most infectious from 2 days before through 7 days after symptom onset (*7*). The index patient developed symptoms on March 7, which could have placed the patient within this infectious period during the March 10 practice. Choir members who developed symptoms on March 11 (three) and March 12 (seven) attended both the March 3

* Skagit County, updated social distancing information. https://skagitcounty.net/departments/home/press/031620.htm.
† Skagit County, public health investigating cluster of related COVID-19 cases. https://skagitcounty.net/departments/home/press/032120.htm.

TABLE 2. Signs and symptoms reported at the onset of COVID-19 illness and during the course of illness among persons infected at a choir practice (N = 53)* — Skagit County, Washington, March 2020

Sign or symptom	No. (%)		no./No. (%)	
	Reported at onset of illness		Reported during course of illness	
	All cases (N = 53)	Confirmed cases (N = 33)	All cases (N = 53)	Confirmed cases (N = 33)
Cough	27 (50.9)	18 (54.5)	47/53 (88.7)	30/33 (90.9)
Fever	28 (52.8)	15 (45.5)	36/53 (67.9)	25/33 (75.8)
Myalgia	13 (24.5)	9 (27.3)	34/52 (65.4)	24/32 (75.0)
Headache	10 (18.9)	7 (21.2)	32/53 (60.4)	20/33 (60.6)
Chills or rigors	7 (13.2)	6 (18.2)	23/51 (45.1)	16/31 (51.6)
Congestion	4 (7.5)	2 (6.1)	25/52 (48.1)	15/32 (46.9)
Pharyngitis	2 (3.8)	2 (6.1)	12/52 (23.1)	8/32 (25.0)
Lethargy	4 (7.5)	2 (6.1)	5/52 (9.6)	3/32 (9.4)
Fatigue	3 (5.7)	1 (3.0)	24/52 (46.2)	15/32 (46.9)
Aguesia (loss of taste)	1 (1.9)	1 (3.0)	11/48 (22.9)	5/28 (17.9)
Anosmia (loss of smell)	1 (1.9)	1 (3.0)	10/48 (20.8)	5/28 (17.9)
Chest congestion or tightness	1 (1.9)	1 (3.0)	5/52 (9.6)	4/32 (12.5)
Weakness	1 (1.9)	1 (3.0)	3/52 (5.8)	2/32 (6.3)
Eye ache	1 (1.9)	1 (3.0)	1/52 (1.9)	1/32 (3.1)
Dyspnea	0 (—)	0 (—)	8/51 (15.7)	8/31 (25.8)
Diarrhea	0 (—)	0 (—)	8/52 (15.4)	6/32 (18.8)
Pneumonia	0 (—)	0 (—)	6/53 (11.3)	6/33 (18.2)
Nausea	0 (—)	0 (—)	3/52 (5.8)	3/32 (9.4)
Acute hypoxemic respiratory failure	0 (—)	0 (—)	3/53 (5.7)	3/33 (9.1)
Abdominal pain or cramps	0 (—)	0 (—)	2/52 (3.8)	2/32 (6.3)
Malaise	1 (1.9)	0 (—)	1/52 (1.9)	0/32 (—)
Anorexia	0 (—)	0 (—)	1/52 (1.9)	0/32 (—)
Vomiting	0 (—)	0 (—)	0/52 (—)	0/32 (—)

Abbreviation: COVID-19 = coronavirus disease 19.
* Including the index patient.

and March 10 practices and thus could have been infected earlier and might have been infectious in the 2 days preceding symptom onset (i.e., as early as March 9). The attack rate in this group (53.3% and 86.7% among confirmed cases and all cases, respectively) was higher than that seen in other clusters, and the March 10 practice could be considered a superspreading event (*3*,*4*). The median incubation period of COVID-19 is estimated to be 5.1 days (*8*). The median interval from exposure during the March 10 practice to onset of illness was 3 days, indicating a more rapid onset.

Choir practice attendees had multiple opportunities for droplet transmission from close contact or fomite transmission (*9*), and the act of singing itself might have contributed to SARS-CoV-2 transmission. Aerosol emission during speech has been correlated with loudness of vocalization, and certain persons, who release an order of magnitude more particles than their peers, have been referred to as superemitters and have been hypothesized to contribute to superspeading events (*1*). Members had an intense and prolonged exposure, singing while sitting 6–10 inches from one another, possibly emitting aerosols.

The findings in this report are subject to at least two limitations. First, the seating chart was not reported because of concerns about patient privacy. However, with attack rates of 53.3% and 86.7% among confirmed and all cases, respectively, and one hour of the practice occurring outside of the seating arrangement, the seating chart does not add substantive additional information. Second, the 19 choir members classified as having probable cases did not seek testing to confirm their illness. One person classified as having probable COVID-19 did seek testing 10 days after symptom onset and received a negative test result. It is possible that persons designated as having probable cases had another illness.

This outbreak of COVID-19 with a high secondary attack rate indicates that SARS-CoV-2 might be highly transmissible in certain settings, including group singing events. This underscores the importance of physical distancing, including maintaining at least 6 feet between persons, avoiding group gatherings and crowded places, and wearing cloth face coverings in public settings where other social distancing measures are difficult to maintain during this pandemic. The choir mitigated further spread by quickly communicating to its members and notifying SCPH of a cluster of cases on March 18. When first contacted by SCPH during March 18–20, nearly all persons who attended the practice reported they were already self-isolating or quarantining. Current CDC recommendations, including maintaining physical distancing of at least 6 feet and wearing cloth face coverings if this is not feasible, washing hands often, covering coughs and sneezes, staying home when ill, and frequently cleaning and disinfecting

high-touch surfaces, remain critical to reducing transmission. Additional information is available at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html.

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during January 28–February 6, 2020, and intravenous immunoglobulin therapy (20 g/d) during January 28–February 1. In addition, we administered glucocorticoid therapy with methylprednisolon (20–60 mg 2×/d by intravenous drip) during January 29–February 1. The patient's fever abated on January 29. He tested negative for SARS-CoV-2 on February 4 and again on February 6. During the progression of his recovery, we observed gradual reduction of the white patches in the lung caused by SARS-CoV-2 infection (Appendix Figure 2). On January 28 and January 31, we observed multiple ground-glass–like high-density shadows on both lungs with blurred edges and interstitial changes. On February 3, high-density shadows were slightly absorbed in the upper lobe of the bilateral lungs. On February 6, some lesions in the lower lobe of both lungs were slightly absorbed, and we observed the same situation on February 8. The index patient was discharged to home on February 9.

In summary, our epidemiologic study demonstrates asymptomatic and human-to-human transmission of SARS-CoV-2 infection through close contacts in both familial and hospital settings. In addition, the laboratory test results, together with course of medical therapies described, can provide a practical reference for COVID-19 diagnosis and treatment.

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COVID-19 Outbreak Associated with Air Conditioning in Restaurant, Guangzhou, China, 2020

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During January 26–February 10, 2020, an outbreak of 2019 novel coronavirus disease in an air-conditioned restaurant in Guangzhou, China, involved 3 family clusters. The airflow direction was consistent with droplet transmission. To prevent the spread of the virus in restaurants, we recommend increasing the distance between tables and improving ventilation.

From January 26 through February 10, 2020, an outbreak of 2019 novel coronavirus disease (COVD-19) affected 10 persons from 3 families (families A–C)

[1]These authors contributed equally to this article.

who had eaten at the same air-conditioned restaurant in Guangzhou, China. One of the families had just traveled from Wuhan, Hubei Province, China. We performed a detailed investigation that linked these 10 cases together. Our study was approved by the Ethics Committee of the Guangzhou Center for Disease Control and Prevention.

On January 23, 2020, family A traveled from Wuhan and arrived in Guangzhou. On January 24, the index case-patient (patient A1) ate lunch with 3 other family members (A2–A4) at restaurant X. Two other families, B and C, sat at neighboring tables at the same restaurant. Later that day, patient A1 experienced onset of fever and cough and went to the hospital. By February 5, a total of 9 others (4 members of family A, 3 members of family B, and 2 members of family C) had become ill with COVID-19.

The only known source of exposure for the affected persons in families B and C was patient A1 at the restaurant. We determined that virus had been transmitted to ≥1 member of family B and ≥1 member of family C at the restaurant and that further infections in families B and C resulted from within-family transmission.

Restaurant X is an air-conditioned, 5-floor building without windows. The third floor dining area occupies 145 m^2; each floor has its own air conditioner (Figure). The distance between each table is about 1 m. Families A and B were each seated for an overlapping period of 53 minutes and families A and C for an overlapping period of 73 minutes. The air outlet and the return air inlet for the central air conditioner were located above table C (Figure, panel B).

On January 24, a total of 91 persons (83 customers, 8 staff members) were in the restaurant. Of these, a total of 83 had eaten lunch at 15 tables on the third floor. Among the 83 customers, 10 became ill with COVID-19; the other 73 were identified as close contacts and quarantined for 14 days. During that period, no symptoms developed, and throat swab samples from the contacts and 6 smear samples from the air conditioner (3 from the air outlet and 3 from the air inlet) were negative for severe acute respiratory syndrome coronavirus 2 by reverse transcription PCR.

From our examination of the potential routes of transmission, we concluded that the most likely cause of this outbreak was droplet transmission. Although the index patient (patient A1) was asymptomatic during the lunch, presymptomatic transmission has been reported (*1*). Given the incubation periods for family B (Appendix Figure, https://wwwnc.cdc.gov/EID/article/26/7/20-0764-App1.pdf), the most likely scenario is that all 3 family B members were directly infected by patient A1. However, we cannot not exclude the possibility that patients B2 and B3 were infected by patient B1, the first family B member to become ill. For family C, a possible scenario is that both patients C1 and C2 were infected by patient A1; another scenario is that the patient C1 acquired the infection while caring for patient C2, beginning on January 27.

Virus transmission in this outbreak cannot be explained by droplet transmission alone. Larger respiratory droplets (>5 μm) remain in the air for only a short time and travel only short distances, generally <1 m (*2*,*3*). The distances between patient A1 and persons at other tables, especially those at table C, were all >1 m. However, strong airflow from the air conditioner could have propagated droplets from table C to table A, then to table B, and then back to table C (Figure).

Virus-laden small (<5 μm) aerosolized droplets can remain in the air and travel long distances, >1 m (*4*). Potential aerosol transmission of severe acute respiratory syndrome and Middle East respiratory syndrome viruses has been reported (*5*,*6*). However, none of the staff or other diners in restaurant X were infected. Moreover, the smear samples from the air conditioner were all nucleotide negative. This finding is less consistent with aerosol transmission. However, aerosols would tend to follow the airflow, and the lower concentrations of aerosols at greater distances might have been insufficient to cause infection in other parts of the restaurant.

Our study has limitations. We did not conduct an experimental study simulating the airborne transmission route. We also did not perform serologic studies of swab sample–negative asymptomatic family members and other diners to estimate risk for infection.

We conclude that in this outbreak, droplet transmission was prompted by air-conditioned ventilation. The key factor for infection was the direction of the airflow. Of note, patient B3 was afebrile and 1% of the patients in this outbreak were asymptomatic, providing a potential source of outbreaks among the public (*7*,*8*). To prevent spread of COVID-19 in restaurants, we recommend strengthening temperature-monitoring surveillance, increasing the distance between tables, and improving ventilation.

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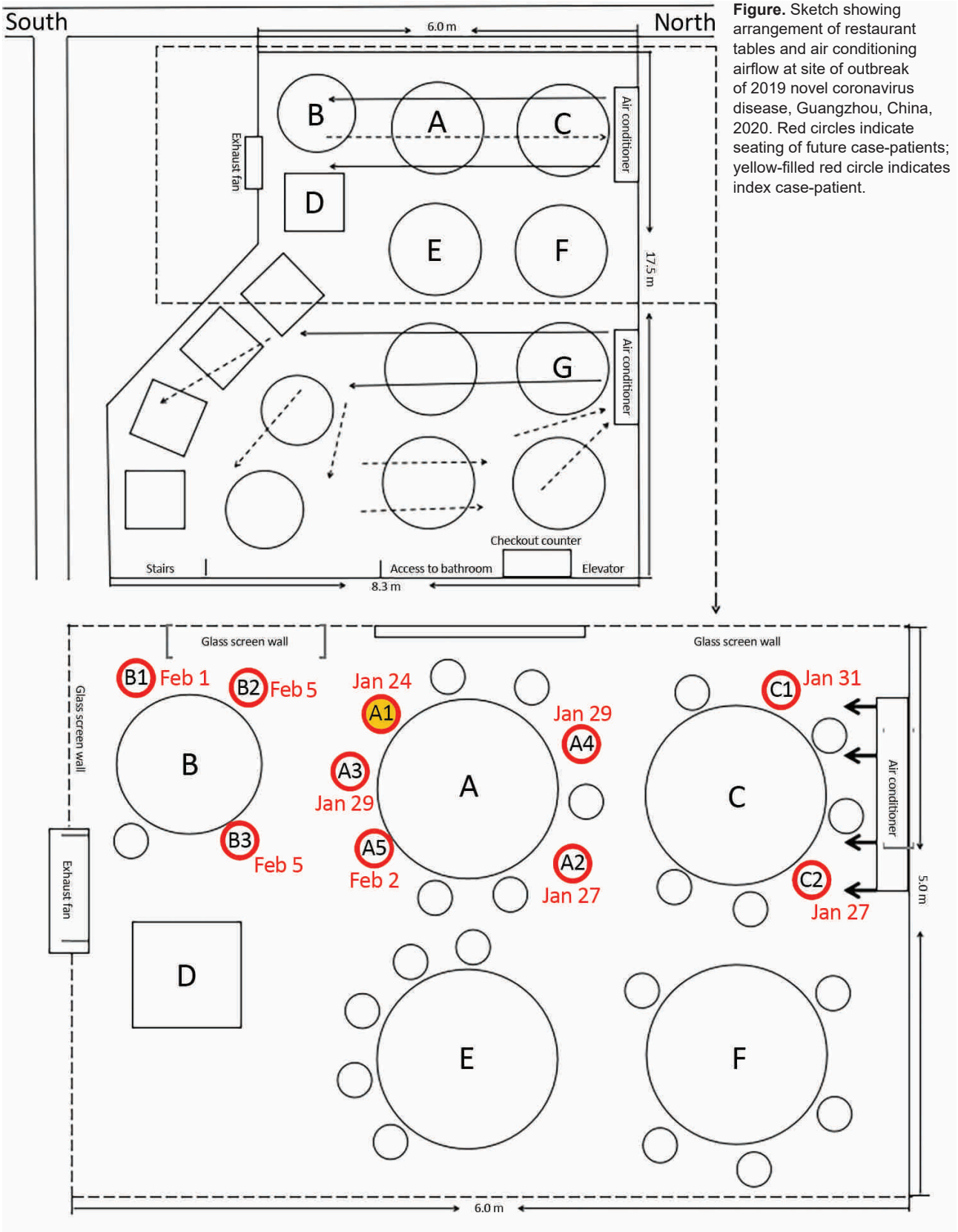

Figure. Sketch showing arrangement of restaurant tables and air conditioning airflow at site of outbreak of 2019 novel coronavirus disease, Guangzhou, China, 2020. Red circles indicate seating of future case-patients; yellow-filled red circle indicates index case-patient.

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Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations

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Because of high rates of 2019 novel coronavirus disease in Wuhan, China, Wuhan Blood Center began screening for severe acute respiratory syndrome coronavirus 2 RNA on January 25, 2020. We screened donations in real-time and retrospectively and found plasma samples positive for viral RNA from 4 asymptomatic donors.

Because of the rapid increase of cases of 2019 novel coronavirus disease (COVID-19; *1*) and detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in plasma (*2*,*3*), the safety of China's blood supply became a major concern (*4*). Most blood centers and blood banks in China began taking measures to ensure blood safety (*5*); on January 25, 2020, we began screening all donations collected at the Wuhan Blood Center.

We performed real-time reverse transcription PCR (RT-PCR) for SARS-CoV-2 RNA by using MultiScreen Pro RT-PCR assay (SYM-BIO LifeScience, https://www.sym-bio.com.cn). We performed pool testing by mixing plasma from 6–8 samples or individual testing by using 1.6 mL of plasma. We eluted 100 μL of nucleic acid template and added 40 μL of it to the RT-PCR mix.

By March 4, we had screened 2,430 donations in real-time, including 1,656 platelet and 774 whole blood donations. We identified the first positive donor in our center in a positive pool with a weak amplification of the open reading frame 1ab gene. The donor gave 2 units of platelets on January 28, which were included in the pool. However, the donor's prior donations collected on December 12 and 26 and January 13 were negative for viral RNA. Hubei Province Center for Disease Control and Prevention performed follow-up

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Cluster of Coronavirus Disease Associated with Fitness Dance Classes, South Korea

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During 24 days in Cheonan, South Korea, 112 persons were infected with severe acute respiratory syndrome coronavirus 2 associated with fitness dance classes at 12 sports facilities. Intense physical exercise in densely populated sports facilities could increase risk for infection. Vigorous exercise in confined spaces should be minimized during outbreaks.

By April 30, 2020, South Korea had reported 10,765 cases of coronavirus disease (COVID-19) (*1*); ≈76.2% of cases were from Daegu and North Gyeongsang provinces. On February 25, a COVID-19 case was detected in Cheonan, a city ≈200 km from Daegu. In response, public health and government officials from Cheonan and South Chungcheong Province activated the emergency response system. We began active surveillance and focused on identifying possible COVID-19 cases and contacts. We interviewed consecutive confirmed cases and found all had participated in a fitness dance class. We traced contacts back to a nationwide fitness dance instructor workshop that was held on February 15 in Cheonan.

Fitness dance classes set to Latin rhythms have gained popularity in South Korea because of the high aerobic intensity (*2*). At the February 15 workshop, instructors trained intensely for 4 hours. Among 27 instructors who participated in the workshop, 8 had positive real-time reverse transcription PCR (RT-PCR) results for severe acute respiratory syndrome coronavirus 2, which causes COVID-19; 6 were from Cheonan and 1 was from Daegu, which had the most reported COVID-19 cases in South Korea. All were asymptomatic on the day of the workshop.

By March 9, we identified 112 COVID-19 cases associated with fitness dance classes in 12 different sports facilities in Cheonan (Figure). All cases were confirmed by RT-PCR; 82 (73.2%) were symptomatic and 30 (26.8%) were asymptomatic at the time of laboratory confirmation. Instructors with very mild symptoms, such as coughs, taught classes for ≈1 week after attending the workshop

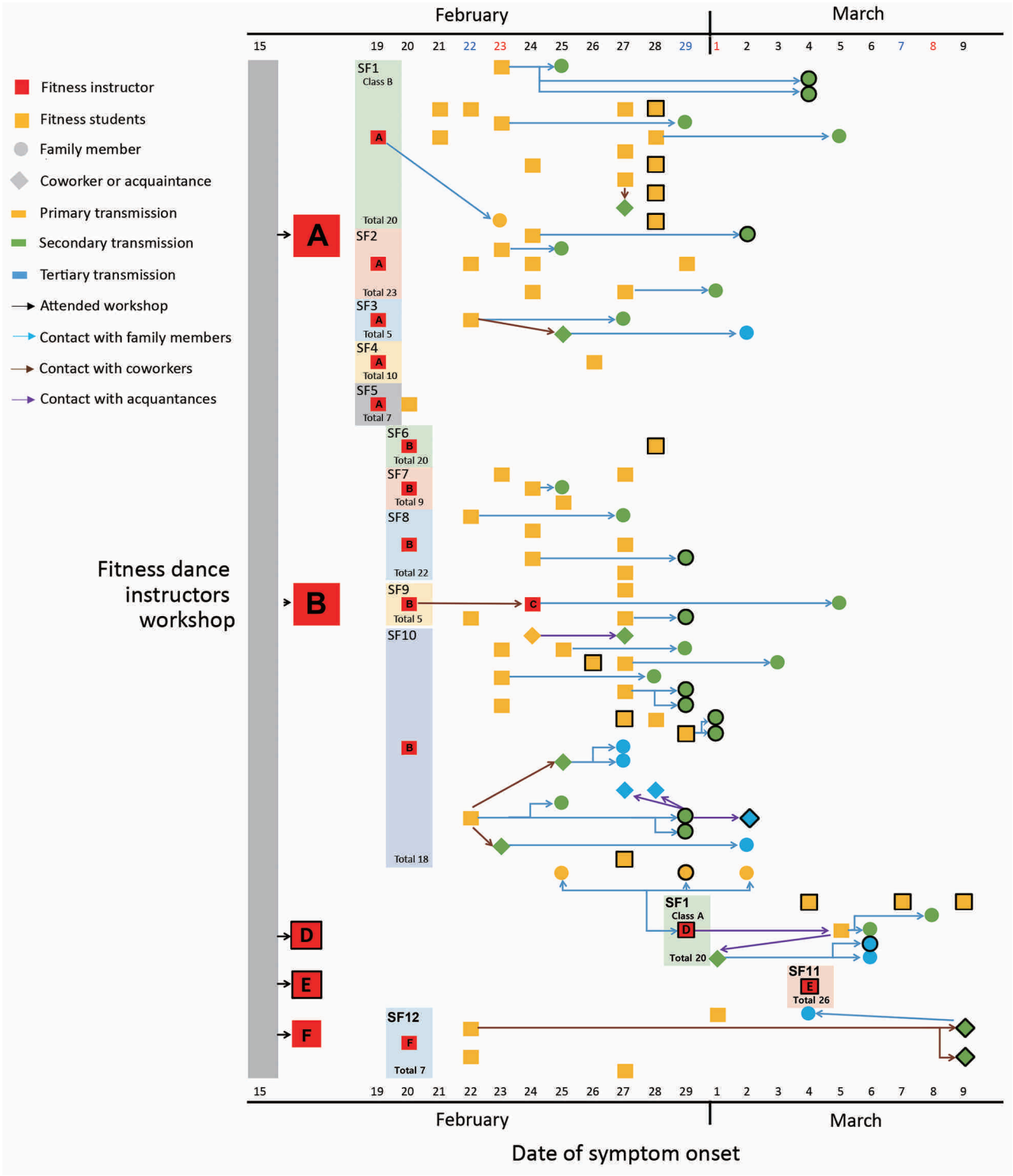

Figure. Case map of confirmed coronavirus disease (COVID-19) cases associated with fitness dance classes in Cheonan, South Korea, by date of symptom onset and relationship. Instructors outside of Cheonan are excluded. In 7 cases, transmission was suspected in the presymptomatic phase and the longest period before symptom onset was 5 days. None of the instructors had COVID-19 symptoms on the day of the workshop, but instructors from Daegu, which recently had a large outbreak, developed symptoms 3 days after the workshop. Sports facilities are represented by bars on the left with the number of students per class included. Bold outlines indicate a positive test for COVID-19 in a person in the presymptomatic phase.

(Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/26/8/20-0633.App1.pdf). The instructors and students met only during classes, which lasted for 50 minutes 2 times per week, and did not have contact outside of class. On average, students developed symptoms 3.5 days after participating in a fitness dance class (*3*). Most (50.9%) cases were the result of transmission from instructors to fitness class participants; 38 cases (33.9%) were in-family transmission from instructors and students; and 17 cases (15.2%) were from transmission during meetings with coworkers or acquaintances.

Among 54 fitness class students with confirmed COVID-19, the median age was 42, all were women, and 10 (18.5%) had preexisting medical conditions (Appendix Table 1). The most common symptom at the time of admission for isolation was cough in 44.4% (24/54) of cases; 17 (31.5%) case-patients had pneumonia. The median time to discharge or end of isolation was 27.6 (range 13–66) days after symptom onset.

Before sports facilities were closed, a total of 217 students were exposed in 12 facilities, an attack rate of 26.3% (95% CI 20.9%–32.5%) (Appendix Table 2). Including family and coworkers, transmissions from the instructors accounted for 63 cases (Appendix Figure 2). We followed up on 830 close contacts of fitness instructors and students and identified 34 cases of COVID-19, translating to a secondary attack rate of 4.10% (95% CI 2.95%–5.67%). We identified 418 close contacts of 34 tertiary transmissions before the quarantine and confirmed 10 quaternary cases from the tertiary cases, translating to a tertiary attack rate of 2.39% (95% CI 1.30%–4.35%).

The instructor from Daegu who attended the February 15 workshop had symptoms develop on February 18 and might have been presymptomatic during the workshop. Evidence of transmission from presymptomatic persons has been shown in epidemiologic investigations of COVID-19 (*4*,*5*).

Characteristics that might have led to transmission from the instructors in Cheonan include large class sizes, small spaces, and intensity of the workouts. The moist, warm atmosphere in a sports facility coupled with turbulent air flow generated by intense physical exercise can cause more dense transmission of isolated droplets (*6*,*7*). Classes from which secondary COVID-19 cases were identified included 5–22 students in a room ≈60 m^2 during 50 minutes of intense exercise. We did not identify cases among classes with <5 participants in the same space. Of note, instructor C taught Pilates and yoga for classes of 7–8 students in the same facility at the same time as instructor B (Figure; Appendix Table 2), but none of her students tested positive for the virus. We hypothesize that the lower intensity of Pilates and yoga did not cause the same transmission effects as those of the more intense fitness dance classes.

A limitation of our study is the unavailability of a complete roster of visitors to the sports facilities, which might have meant we missed infections among students during surveillance and investigation efforts. Discovery of outbreak cases centered on exercise facilities led to a survey of instructors who participated in a fitness dance workshop and provided clues to identifying additional cases among students. Early identification of asymptomatic persons with RT-PCR–confirmed infections helped block further transmissions. Because of the increased possibility of infection through droplets, vigorous exercise in closely confined spaces should be avoided (*8*) during the current outbreak, as should public gatherings, even in small groups (*9*,*10*).

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Infectious SARS-CoV-2 in Feces of Patient with Severe COVID-19

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Severe acute respiratory syndrome coronavirus 2 was isolated from feces of a patient in China with coronavirus disease who died. Confirmation of infectious virus in feces affirms the potential for fecal–oral or fecal–respiratory transmission and warrants further study.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recently emerged in China, causing a major outbreak of severe pneumonia and spreading to >200 other countries (*1*). As of May 5, 2020, a total of 3,517,345 cases of coronavirus disease (COVID-2019) and 243,401 deaths had been reported to the World Health Organization (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200505covid-19-sitrep-106.pdf?sfvrsn=47090f63_2). The virus is believed to be spread by direct contact, fomites, respiratory droplets, and possibly aerosols (*2*). Viral RNA has been detected in feces and urine of some patients (*3*–*7*). Infectious virus was also isolated from urine of a patient with severe COVID-19 (*8*). However, it is unclear whether the virus in feces is infectious and might be an additional source for transmission.

This study was approved by the Health Commission of Guangdong Province and the Ethics Committees of Guangzhou Medical University to use patient and healthy donor sample specimens. On January 17, 2020, a 78-year-old man who had a history of recent travel to Wuhan, China, was admitted to the Fifth Affiliated Hospital of Sun Yat-Sen University because of a cough for 7 days and intermittent fever (Appendix Figure 1, panel A, https://wwwnc.cdc.gov/EID/article/26/8/20-0681-App1.pdf). Computed tomography of his chest showed multiple, ground-glass opacities (Appendix Figure 2). Nasopharyngeal and oropharyngeal swab specimens were positive for SARS-CoV-2 RNA by quantitative reverse transcription PCR (qRT-PCR).

On January 22, the patient's condition deteriorated and he was intubated. Ventilator-assisted breathing was instituted. The first feces specimen was collected on January 27 and was positive for viral RNA by qRT-PCR. Serial feces samples were collected on January 29, February 1, and February 7. All samples were positive for viral RNA (Appendix Figure 1, panel A). Viral antigen was also detected in gastrointestinal epithelial cells of a biopsy sample, as reported (*9*). The patient died on February 20.

We collected fecal specimens on January 29 to inoculate Vero E6 cells. Cycle threshold values for the fecal sample were 23.34 for the open reading frame 1lab gene and 20.82 for the nucleoprotein gene. A

REFERENCE 10

It is Time to Address Airborne Transmission of COVID-19

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Commentary

We appeal to the medical community and to the relevant national and international bodies to recognize the potential for airborne spread of COVID-19. There is significant potential for inhalation exposure to viruses in microscopic respiratory droplets (microdroplets) at short to medium distances (up to several meters, or room scale), and we are advocating for the use of preventive measures to mitigate this route of airborne transmission.

Studies by the signatories and other scientists have demonstrated beyond any reasonable doubt that viruses are released during exhalation, talking, and coughing in microdroplets small enough to remain aloft in air and pose a risk of exposure at distances beyond 1 to 2 m from an infected individual (see e.g. [1-4]). For example, at typical indoor air velocities [5], a 5 µm droplet will travel tens of meters, much greater than the scale of a typical room, while settling from a height of 1.5 m to the floor. Several retrospective studies conducted after the SARS-CoV-1 epidemic demonstrated that airborne transmission was the most likely mechanism explaining the spatial pattern of infections e.g. [6]. Retrospective analysis has shown the same for SARS-CoV-2 [7-10]. In particular, a study in their review of records from a Chinese restaurant, observed no evidence of direct or indirect contact between the three parties [10]. In their review of video records from the restaurant, they observed no evidence of direct or indirect contact between the three parties. Many studies conducted on the spread of other viruses, including respiratory syncytial virus (RSV) [11], Middle East Respiratory Syndrome coronavirus (MERS-CoV) [8], and influenza [2,4], show that *viable* airborne viruses can be exhaled [2] and/or detected in the indoor environment of infected patients [11-12]. This poses the risk that people sharing such environments can potentially inhale these viruses, resulting in infection and disease. There is every reason to expect that SARS-CoV-2 behaves similarly, and that transmission via airborne microdroplets [10,13] is an important pathway. Viral RNA associated with droplets smaller than 5 µm has been detected in air [14], and the virus has

been shown to maintain infectivity in droplets of this size [9]. Other viruses have been shown to survive equally well, if not better, in aerosols compared to droplets on a surface [15].

The current guidance from numerous international and national bodies focuses on hand washing, maintaining social distancing, and droplet precautions. Most public health organizations, including the World Health Organization (WHO) [16], do not recognize airborne transmission except for aerosol-generating procedures performed in healthcare settings. Hand washing and social distancing are appropriate, but in our view, insufficient to provide protection from virus-carrying respiratory microdroplets released into the air by infected people. This problem is especially acute in indoor or enclosed environments, particularly those that are crowded and have inadequate ventilation [17] relative to the number of occupants and extended exposure periods (as graphically depicted in Figure 1). For example, airborne transmission appears to be the only plausible explanation for several superspreading events investigated which occurred under such conditions e.g. [10], and others where recommended precautions related to direct droplet transmissions were followed.

The evidence is admittedly incomplete for all the steps in COVID-19 microdroplet transmission, but it is similarly incomplete for the large droplet and fomite modes of transmission. The airborne transmission mechanism operates in parallel with the large droplet and fomite routes, e.g. [16] that are now the basis of guidance. Following the precautionary principle, we must address every potentially important pathway to slow the spread of COVID-19. The measures that should be taken to mitigate airborne transmission risk include:

- Provide sufficient and effective ventilation (supply clean outdoor air, minimize recirculating air) particularly in public buildings, workplace environments, schools, hospitals, and aged care homes.
- Supplement general ventilation with airborne infection controls such as local exhaust, high efficiency air filtration, and germicidal ultraviolet lights.
- Avoid overcrowding, particularly in public transport and public buildings.

Such measures are practical and often can be easily implemented; many are not costly. For example, simple steps such as opening both doors and windows can dramatically increase air flow rates in many buildings. For mechanical systems, organizations such as ASHRAE (the American Society of Heating, Ventilating, and Air-Conditioning Engineers) and REHVA (the Federation of European Heating, Ventilation and Air Conditioning Associations) have already provided guidelines based on the existing evidence of airborne transmission. The measures we propose offer more benefits than potential downsides, even if they can only be partially implemented.

Figure 1. Distribution of respiratory microdroplets in an indoor environment with (a) inadequate ventilation and (b) adequate ventilation.

It is understood that there is not as yet universal acceptance of airborne transmission of SARS-CoV2; but in our collective assessment there is more than enough supporting evidence so that the precautionary principle should apply. In order to control the pandemic, pending the availability of a vaccine, all routes of transmission must be interrupted.

We are concerned that the lack of recognition of the risk of airborne transmission of COVID-19 and the lack of clear recommendations on the control measures against the airborne virus will have significant consequences: people may think that they are fully protected by adhering to the current recommendations, but in fact, additional airborne interventions are needed for further reduction of infection risk.

This matter is of heightened significance now, when countries are re-opening following lockdowns - bringing people back to workplaces and students back to schools, colleges, and universities. We hope that our statement will raise awareness that airborne transmission of COVID-19 is a real risk and that control measures, as outlined above, must be added to the other precautions taken, to reduce the severity of the pandemic and save lives.

Disclaimer: The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any agency/institution.

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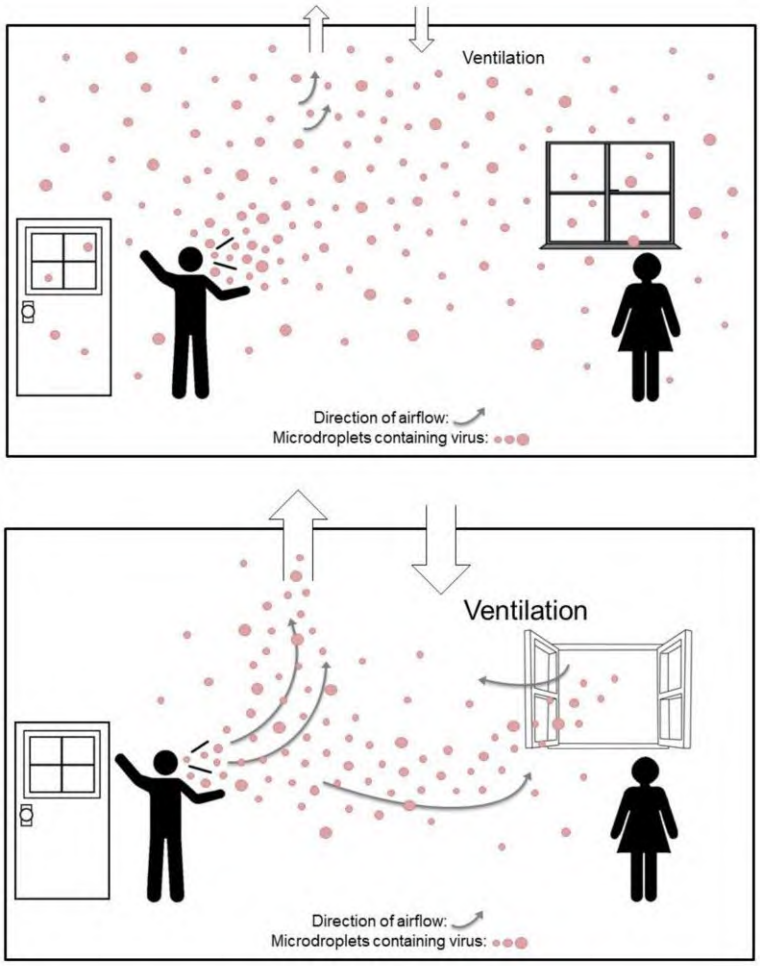
Figure 1



REFERENCE 11

Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study

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ABSTRACT

OBJECTIVE

To evaluate viral loads at different stages of disease progression in patients infected with the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the first four months of the epidemic in Zhejiang province, China.

DESIGN

Retrospective cohort study.

SETTING

A designated hospital for patients with covid-19 in Zhejiang province, China.

PARTICIPANTS

96 consecutively admitted patients with laboratory confirmed SARS-CoV-2 infection: 22 with mild disease and 74 with severe disease. Data were collected from 19 January 2020 to 20 March 2020.

MAIN OUTCOME MEASURES

Ribonucleic acid (RNA) viral load measured in respiratory, stool, serum, and urine samples. Cycle threshold values, a measure of nucleic acid concentration, were plotted onto the standard curve constructed on the basis of the standard product. Epidemiological, clinical, and laboratory characteristics and treatment and outcomes data were obtained through data collection forms from electronic medical records, and the relation between clinical data and disease severity was analysed.

RESULTS

3497 respiratory, stool, serum, and urine samples were collected from patients after admission and evaluated for SARS-CoV-2 RNA viral load. Infection was confirmed in all patients by testing sputum and saliva samples. RNA was detected in the stool of 55 (59%) patients and in the serum of 39 (41%) patients. The urine sample from one patient was positive for SARS-CoV-2. The median duration of virus in stool (22 days, interquartile range 17-31 days) was significantly longer than in respiratory (18 days, 13-29 days; P=0.02) and serum samples (16 days, 11-21 days; P<0.001). The median duration of virus in the respiratory samples of patients with severe disease (21 days, 14-30 days) was significantly longer than in patients with mild disease (14 days, 10-21 days; P=0.04). In the mild group, the viral loads peaked in respiratory samples in the second week from disease onset, whereas viral load continued to be high during the third week in the severe group. Virus duration was longer in patients older than 60 years and in male patients.

CONCLUSION

The duration of SARS-CoV-2 is significantly longer in stool samples than in respiratory and serum samples, highlighting the need to strengthen the management of stool samples in the prevention and control of the epidemic, and the virus persists longer with higher load and peaks later in the respiratory tissue of patients with severe disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

As of 9 April 2020, more than 1.5 million people globally have been affected by covid-19, and the numbers continue to increase rapidly

SARS-CoV-2 viral loads have been reported from respiratory, stool, serum, and urine samples in a small number of patients; however, changes in viral load during disease progression of different severities is not known

WHAT THIS STUDY ADDS

The duration of SARS-CoV-2 is significantly longer in stool samples than in respiratory and serum samples, highlighting the need to strengthen the management of stool samples in the prevention and control of the epidemic

The virus persists longer with higher load and peaks later in the respiratory tissue of patients with severe disease

To prevent transmission of SARS-CoV-2 it is therefore necessary to carry out strict management during each stage of severe disease

Introduction

A novel human coronavirus first detected during an unexplained cluster of pneumonia cases in Wuhan, China in December 2019 has spread globally.[1 2] As of 22 March 2020, the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (genus *Betacoronavirus*, family Coronaviridae) has been reported in 190 countries with more than 300 000 confirmed cases and 14 510 deaths.[3] A predominant number of cases has occurred in China,[4] with early clinical characterisation showing that 13.8% of those infected developed severe disease, and death occurred in 2.3% of the cases.

Viral load measurements from tissue samples are indicative of active virus replication and are routinely used to monitor severe viral respiratory tract infections,

including clinical progression, response to treatment, cure, and relapse.[5-7] One study described changes in viral loads in samples from the upper respiratory tract of 18 patients with coronavirus disease 2019 (covid-19, an infectious disease caused by SARS-CoV-2), showing that the viral loads were equally high among asymptomatic patients and those with symptoms.[8] However, the viral load dynamics in lower respiratory tract and other tissue samples and the relation between viral load and disease severity is unknown—information that are important for the formulation of disease control strategies and clinical treatment.

We systematically estimated the viral loads in more than 3000 samples collected from 96 patients after admission who were infected with SARS-CoV-2, and analysed the temporal change in viral loads and the correlation between viral loads in different sample types and disease severity.

Methods

Study design

This was a retrospective cohort study of patients with laboratory confirmed covid-19 admitted consecutively to the First Affiliated Hospital, College of Medicine, Zhejiang University from 19 January 2020 to 15 February 2020. This major general hospital has 3000 beds and serves as a designated hospital for patients with covid-19 in Zhejiang province.

Sample collection and laboratory confirmation

After admission, respiratory, serum, stool, and urine samples were collected daily whenever possible to determine the amount of SARS-CoV-2 ribonucleic acid (RNA) by polymerase chain reaction (PCR) analysis. Sputum samples were collected from the respiratory tract of patients with sputum, and saliva after deep cough was collected from patients without sputum.[9] Blood samples were collected in a special whole blood collection tube, and urine and stool samples were collected in a special sterile container. All medical staff were equipped with personal protection equipment for biosafety level 3 during sampling, including solid front wraparound gowns, goggles, and N95 respirators.

Viral RNA was extracted using the MagNA Pure 96 (Roche, Basel, Switzerland), and quantitative reverse transcription PCR (qRT-PCR) was performed using a China Food and Drug Administration approved commercial kit specific for SARS-CoV-2 detection (BoJie, Shanghai, China). The detection limit of the ORFab1 qRT-PCR assays was about 1000 copies per millilitre. Samples with cycle threshold (Ct) values of ≤38.0 were considered positive for SARS-CoV-2 RNA. Samples with Ct values >38.0 were repeated, and samples with repeated Ct values of >38.0 and samples with undetectable Ct values were considered negative. Viral load was calculated by plotting Ct values onto the standard curve constructed based on the standard product.

Data collection

The research team of the First Affiliated Hospital, College of Medicine, Zhejiang University analysed the medical records of patients. Epidemiological, clinical, and laboratory characteristics and treatment and outcomes data were obtained through data collection forms from hospital electronic medical records. A trained team of doctors reviewed the data. The clinical data included personal characteristics, comorbidities, date of symptom onset, symptoms and signs, timing of antiviral treatment, and progression and resolution of clinical illness. Comorbidities documented included diabetes mellitus, heart disease, chronic lung disease, renal failure, liver disease, HIV infection, cancer, and receipt of immunosuppressive treatment, including corticosteroids. We considered that the symptoms started when any of fever, cough, chills, dizziness, headache, and fatigue appeared.

The severity of illness was evaluated according to the sixth edition of the Guideline for Diagnosis and Treatment of SARS-CoV-2 issued by the National Health Commission of the People's Republic of China.[10] Mild cases include non-pneumonia or mild pneumonia. Severe disease refers to dyspnoea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, or lung infiltrates >50% within 24 to 48 hours. Patients who test negative for SARS-CoV-2 for two consecutive days in respiratory samples are considered to be clear of infection.

Statistical analysis

For most variables, we calculated descriptive statistics, such as medians with interquartile ranges (for data with skewed distribution) and proportions (percentages). Statistical comparisons between the mild and severe groups were evaluated by *t* test, analysis of variance, Mann-Whitney U tests, and Kruskal-Wallis tests when appropriate. To explore the variation of viral load across the days since symptom onset, we calculated the median of viral load each day, followed by fitting smooth lines using a loess method.[11] For this analysis, we only included patients with viral loads monitored for more than five days in respiratory and stool samples. Statistical analyses were performed using the R software package, v3.6.2. A P value of <0.05 was considered significant.

Patient and public involvement

This was a retrospective case series study and no patients were directly involved in the study design, setting the research questions, or the outcome measures. No patients were asked to advise on interpretation or writing up of results.

Results

Table 1 shows the clinical characteristics of 96 patients with confirmed covid-19: 22 with mild disease and 74 with severe disease. The median age was 55 years (interquartile range 44.3-64.8). Of the patients infected in Wuhan, a significantly higher proportion were in the severe group (35%) than in the mild group (9%). Hypertension (36%) and diabetes mellitus (11%) were the most common underlying disease. Most of

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the patients developed fever (89%) and cough (56%). Overall, 78 (81%) patients received glucocorticoids and 33 (34%) antibiotic treatment. All patients received antiviral treatment comprising interferon α inhalation, lopinavir-ritonavir combination, arbidol, favipiravir, and darunavir-cobicistat combination. Among them, 63 (66%) started antiviral treatment within five days from illness onset and 29 (30%) more than five days after illness onset. Thirty (41%) patients with severe disease were admitted to the intensive care unit. By 20 March, all patients tested negative for SARS-CoV-2, nine (9% of all patients) patients with severe disease were still in hospital, and no deaths had occurred. Supplementary figure S1 shows the outcome among patients infected with SARS-CoV-2, and supplementary table S1 the laboratory findings.

SARS-CoV-2 detection rates during disease progression and between sample types

A total of 1846 respiratory samples (668 sputum and 1178 saliva) were collected (average 18 samples per patient (range 3-40 samples)); 842 stool samples (7 samples per patient (1-32 samples)); 629 serum samples (7 samples per patient (1-20 samples)), and 180 urine samples (1 sample for each patient (1-6 samples)). Supplementary figure S2 shows the daily collection of different sample types.

SARS-CoV-2 infection was confirmed in all 96 patients by testing respiratory samples. Of these patients, viral nucleic acid was detected in the stool samples of 59% and serum samples of 41%. Rates of SARS-CoV-2 detection in the respiratory samples gradually decreased from 95% in the first week of symptom onset to 54% in the fourth week, with subsequent respiratory samples showing negative results, whereas the positive rate in stool samples and serum samples gradually increased from the first week and then decreased from the third week. In addition, the rate of detection in serum samples was higher in patients with severe disease than in patients with mild disease (45% *v* 27%), but the difference was not significant. The detection rate in stool did not differ between patients with mild disease and patients with severe disease. Only one urine sample collected from a critically ill patient on day 10 was positive for SARS-CoV-2 (table 2).

Table 1 | Personal and clinical characteristics of patients with severe acute respiratory syndrome coronavirus 2 infection by severity of disease

Characteristics	Total (n=96)	Disease severity		P value
		Mild (n=22)	Severe (n=74)	
Median (interquartile range) age (years)	55 (44.3-64.8)	47.5 (36.8-56.3)	57 (47.5-66)	0.01
Men	58 (60)	9 (41)	49 (66)	0.03
Infected in Wuhan	28 (29)	2 (9)	26 (35)	0.01
Underlying diseases:				
Hypertension	35 (36)	4 (18)	31 (42)	0.04
Diabetes mellitus	11 (11)	1 (5)	10 (14)	0.44
Heart disease	7 (7)	0 (0)	7 (9)	0.30
Lung disease	4 (4)	0 (0)	4 (5)	0.57
Liver disease	3 (3)	1 (5)	2 (3)	0.55
Renal disease	1 (1)	0 (0)	1 (1)	1.00
Malignancy	1 (1)	0 (0)	1 (1)	1.00
Immune compromise	1 (1)	0 (0)	1 (1)	1.00
Symptoms:				
Fever	85 (89)	17 (77)	68 (92)	0.13
Cough	54 (56)	12 (55)	42 (57)	0.85
Sputum	26 (27)	7 (32)	19 (26)	0.59
Chest distress	12 (13)	2 (9)	10 (14)	0.85
Dizziness	7 (7)	0 (0)	7 (9)	0.30
Headache	4 (4)	0 (0)	4 (5)	0.57
Nausea	5 (5)	2 (9)	3 (4)	0.32
Vomiting	2 (2)	0 (0)	2 (3)	1.00
Diarrhoea	10 (10)	0 (0)	10 (14)	0.15
Myalgia	19 (20)	6 (27)	13 (18)	0.49
Fatigue	9 (9)	1 (5)	8 (11)	0.64
Treatment:				
Gammaglobulin	53 (55)	4 (18)	49 (66)	<0.001
Glucocorticoids	78 (81)	9 (41)	69 (93)	<0.001
Antibiotics	33 (34)	1 (5)	32 (43)	0.001
Antivirals	96 (100)	22 (100)	74 (100)	NC
Time from illness onset to antiviral treatment (days):				
≤5	63 (66)	14 (64)	49 (66)	0.82
>5	29 (30)	8 (36)	21 (28)	0.58
Disease severity/support:				
Bilateral pulmonary infiltrates	80 (83)	12 (55)	68 (92)	<0.001
Invasive mechanical ventilation	10 (10)	0 (0)	10 (14)	0.15
ECMO	5 (5)	0 (0)	5 (7)	0.59
Intensive care unit admission	30 (31)	0 (0)	30 (41)	<0.001

ECMO=extracorporeal membrane oxygenation; NC=not calculable.

Correlation between viral duration in different sample types and disease severity

The median duration of virus in stool samples (22 days, interquartile range 17-31 days) was significantly longer than in respiratory (18 days, 13-29 days; P=0.02) and serum samples (16 days, 11-21 days; P<0.001) (fig 1). In the respiratory samples, the median duration of virus in patients with severe disease (21 days, 14-30 days) was significantly longer than in patients with mild disease (14 days, 10-21 days; P=0.04) (fig 1), whereas no significant difference was observed in the duration of virus between stool and serum samples among patients with different disease severities (fig 1). Supplementary figures S3-S5 show the duration of virus in different sample types in each patient.

Correlation between viral load in different sample types and disease severity

Viral load differed significantly by sample type, with respiratory samples showing the highest, followed by stool samples, and serum samples showing the lowest (fig 2). In respiratory samples, patients with severe disease had significantly higher viral loads than patients with mild disease (fig 2). Viral loads in stool and serum samples showed no significant difference between patients with mild disease and patients with severe disease (fig 2).

Using a loess regression analysis, we found that in the mild group, the viral load in respiratory samples was greater during the initial stages of the disease, reached a peak in the second week from disease onset, and was followed by lower loads (fig 3). In the severe group, however, the viral load in respiratory samples continued to be high during the third and fourth weeks after disease onset (fig 3). The viral load of stool samples was highest during the third and fourth weeks after disease onset (fig 3).

Factors associated with duration of virus and viral load

We found that types and timeliness of antiviral treatments had no overall effect on the duration of the virus and viral load. In the severe group, the duration of the virus was significantly higher in patients treated with glucocorticoids continuously for more than 10 days than in patients treated with glucocorticoids continuously for less than 10 days, whereas different treatments had no effect on viral load (supplementary table S2). When patients with severe disease were stratified, the duration of the virus was significantly longer in men than in women, and significantly longer in patients older than 60 years than younger (fig 4).

Discussion

We have systematically described the clinical characteristics of 96 patients with covid-19 and described the dynamic changes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) loads and disease progression in 3497 samples of multiple types, revealing the interaction between SARS-CoV-2 replication and clearance by host defence mechanisms. The median duration of virus in respiratory samples was 18 days, which was consistent with the median duration of 20 days for Middle East respiratory syndrome (MERS).[12] Peak viral shedding in respiratory specimens of patients with severe acute respiratory syndrome (SARS) occurred after about 10 to 12 days from symptom onset,[13 14] which is similar to the peak observed for SARS-CoV-2 in our study. Consistent with earlier reports of SARS-CoV-2,[15] we found differences in the viral load in patients with different disease severities, those with severe disease showing a significantly higher viral load than those with mild disease, which suggests that viral load can be used to assess prognosis.

Studies have found that the peak load of SARS-CoV-2 in upper respiratory tract specimens was during the early stages of the disease[8 16]; however, we found that the duration of virus shedding in lower respiratory tract samples was longer, and peak viral shedding occurred after about two weeks from symptom onset. These findings are important for effective control and prevention of the epidemic as it suggests strict

Table 2 | Detection of severe acute respiratory syndrome coronavirus 2 in patients with mild or severe disease at different stages after symptom onset in different sample types. Values are numbers affected/number tested (%) unless stated otherwise

Sample types	After admission	Weeks since onset of symptoms				P values
		1	2	3	4	
All patients:						
Respiratory	96/96 (100)	42/44 (95)	74/90 (82)	64/89 (72)	31/57 (54)	<0.001
Stool	55/93 (59)	9/23 (39)	28/59 (47)	32/71 (45)	20/57 (35)	0.54
Serum	39/95 (41)	5/36 (14)	20/85 (23)	19/85 (22)	5/55 (9)	0.12
Urine	1/67 (1)	0/15 (0)	1/53 (2)	0/21 (0)	0/19 (0)	NC
Mild disease:						
Respiratory	22/22 (100)	11/12 (92)	15/21 (71)	9/19 (47)	4/9 (44)	0.04
Stool	13/22 (59)	2/7 (29)	8/16 (50)	10/17 (59)	5/9 (56)	0.62
Serum	6/22 (27)	0/9 (0)	3/19 (16)	2/17 (12)	0/8 (0)	0.67
Urine	0/19 (0)	0/3 (0)	0/15 (0)	0/7 (0)	0/3 (0)	NC
Severe disease:						
Respiratory	74/74 (100)	31/32 (97)	59/69 (86)	55/70 (79)	27/48 (56)	<0.001
Stool	42/71 (59)	7/16 (44)	20/43 (47)	22/54 (41)	15/48 (31)	0.49
Serum	33/73 (45)	5/27 (19)	17/66 (26)	17/68 (25)	5/47 (11)	0.20
Urine	1/48 (2)	0/12 (0)	1/38 (3)	0/14 (0)	0/16 (0)	NC

NC=not calculable.

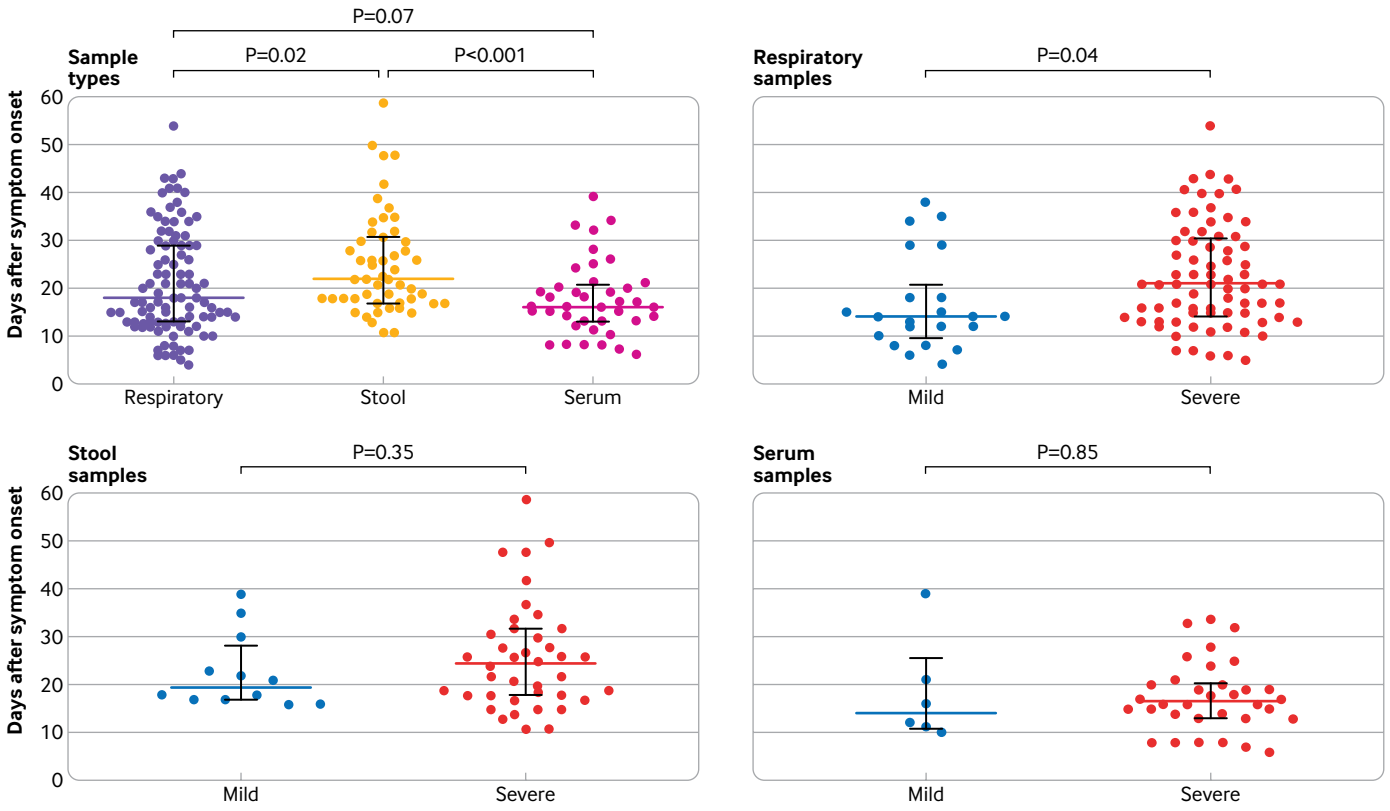

Fig 1 | Duration of detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by sample types and disease severity. Coloured bars represent medians and black bars represent interquartile ranges

management of the whole disease process in patients with SARS-CoV-2. In this study, we also found that the viral load in patients with severe disease was significantly higher than in patients with mild disease, suggesting that high viral load might be a risk factor for severe disease.

Active replication of SARS in the gut has been shown through live virus isolation.[17] During 2003, the prevalence of SARS RNA in stool samples was so high that testing of stool was proposed as a reliable and sensitive way to routinely diagnose the disease,[18 19] whereas MERS RNA was found in only 15% of stool samples, with a low RNA concentration.[20] In this study, we detected SARS-CoV-2 in the stool samples from 59% of patients and found that the duration of virus was longer and viral load peaked later in stool samples compared with respiratory samples. Based on this study, we think the role of faecal excretion in the spread of SARS-CoV-2 cannot be ignored; however, the importance of high detection in stool samples in the prevention and control of the SARS-CoV-2 epidemic requires comprehensive and careful evaluation. We rarely found SARS-CoV-2 RNA in urine samples in this study, although viral RNA detection rates of up to 50% have been found in the urine of patients with SARS.[18 19]

A clear difference between SARS and SARS-CoV-2 was in the detection of viral RNA in serum. Evidence has been found of SARS virus replicating in circulating lymphocytes, monocytes, macrophages, and dendritic cells, albeit at low levels.[21-23] In some studies, up to 79% of serum samples were found to contain SARS RNA during the first week of illness, and around 50% during the second week.[24-26] The rates were similar in MERS.[20] In this study, we found that the detection rate of SARS-CoV-2 in serum was only 41%.

At present, the therapeutic effect of glucocorticoids and antiviral drugs in patients with SARS-CoV-2 is unclear.[27 28] We found that the duration of treatment with glucocorticoids was positively correlated with viral duration in patients with severe disease. As we did not analysis the type and dose of antiviral drugs and glucocorticoids, however, we cannot evaluate the effect of antiviral drugs and glucocorticoids. Monitoring the effectiveness of antiviral drugs and glucocorticoids needs to be validated by multicentre randomised studies.

A sex dependent increase in disease severity after infection with pathogenic coronavirus was reported for both SARS and MERS,[29 30] and this was also found for SARS-CoV-2.[31] In this study, we found that the duration of virus was significantly longer in men than in women. Our results shed light on the causes of disease severity in men in terms of the duration of the virus. In addition to differences in immune status between men and women, it has also been reported to be related to differences in hormone levels.[32] In this study, we also found a correlation between age and duration of virus, which partly explains the high rate of severe illness in patients older than 60 years. This is partly because of immunosenescence.[33] Another reason is that older

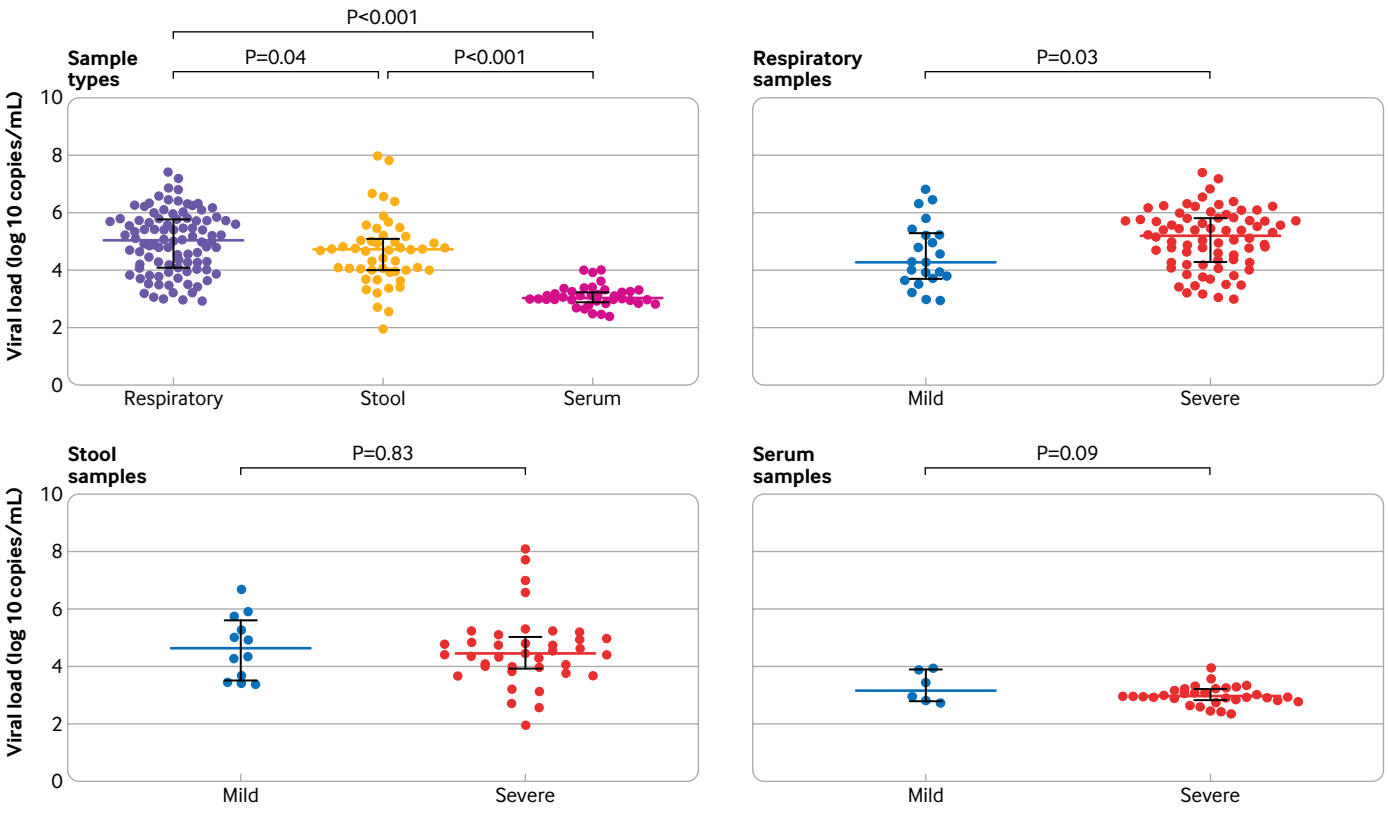

Fig 2 | Comparison of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load by sample types and disease severity. Coloured bars represent medians and black bars represent interquartile ranges

people have higher levels of angiotensin converting enzyme 2 in their alveoli,[34] which is thought to be a receptor for novel coronaviruses.

Limitations of this study

Our study has several limitations. Firstly, this study is a single centre cohort study, and the sample size was insufficient to compare treatment effects in different subgroups, which could lead to an unbalanced distribution of confounders when evaluating viral shedding and viral load. Secondly, viral load is influenced by many factors. The quality of collected samples directly affects the viral load, so the study of viral load only partly reflects the amount of virus in the body. Thirdly, polymerase chain reaction (PCR) cannot distinguish between viable and non-viable virus and does not reflect the replication level of the virus in different tissue. However, PCR has higher sensitivity, is easy to perform, and is widely used in the detection of viral load.[35] In addition, only collecting samples from patients who remain in hospital could overinflate estimates of viral load and duration at a later time point. Finally, since accurate diagnosis was not available during the early stages of the epidemic, stool and urine samples of the earliest infected patients were not collected until early February, hence we recruited patients with positive respiratory samples and could not evaluate patients with negative respiratory samples against other sample types.

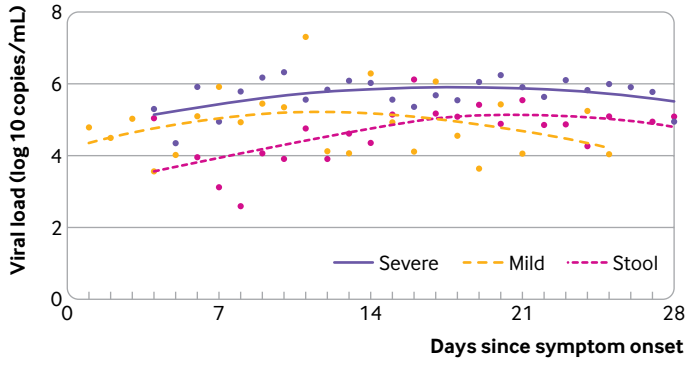

Fig 3 | Smooth lines were fitted using loess method to explore the variation of viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the days since symptoms onset in respiratory samples from patients with mild and severe disease and in stool samples

Conclusion

The duration of SARS-CoV-2 is significantly longer in stool samples than in respiratory and serum samples, highlighting the need to strengthen the management of stool samples in the prevention and control of the epidemic, especially for patients in the later stages of the disease. Compared with patients with mild disease, those with severe disease showed longer duration of SARS-CoV-2 in respiratory samples, higher viral load, and a later shedding peak. These findings suggest that reducing viral loads through clinical means and strengthening management during each stage of severe disease should help to prevent the spread of the virus.

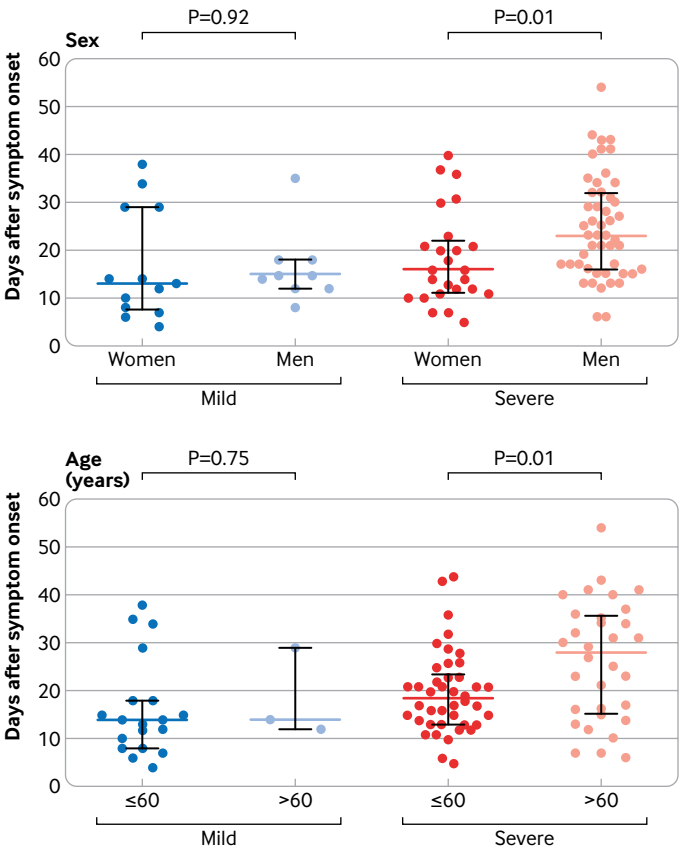

Fig 4 | Association between sex and age and duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Coloured bars represent medians and black bars represent interquartile ranges

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Contributors: TL and YC contributed equally to this paper and are joint corresponding authors. SZ, JF, FY, and BF are joint first authors. The corresponding and first authors conceived and designed the study. All authors selected the articles and extracted data. TL and YC were co-principal investigators. They designed and supervised the study and wrote the grant application (assisted by SZ). KX, XL, GW, JZ, QF, HC, YQ, and JS had roles in recruitment, data collection, and clinical management. SZ, JF, FY, BF, BL, QZ, GX, SL, RW, XY, WC, QW, DZ, YL, RG, ZM, SL, YX, YG, JZ, and HY did clinical laboratory testing and analysis. SZ, FY, BF, YC, and TL drafted the manuscript. All authors reviewed and revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. TL and YC are the guarantors.

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The lead authors and manuscript's guarantors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary information: tables S1 and S2 and figures S1-S5

REFERENCE 12

ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

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ABSTRACT

BACKGROUND

Since December 2019, when coronavirus disease 2019 (Covid-19) emerged in Wuhan city and rapidly spread throughout China, data have been needed on the clinical characteristics of the affected patients.

METHODS

We extracted data regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020. The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

RESULTS

The median age of the patients was 47 years; 41.9% of the patients were female. The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Only 1.9% of the patients had a history of direct contact with wildlife. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). Diarrhea was uncommon (3.8%). The median incubation period was 4 days (interquartile range, 2 to 7). On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission.

CONCLUSIONS

During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others.)

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*A list of investigators in the China Medical Treatment Expert Group for Covid-19 study is provided in the Supplementary Appendix, available at NEJM.org.

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In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province.[1] The pathogen has been identified as a novel enveloped RNA betacoronavirus[2] that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV.[3] Patients with the infection have been documented both in hospitals and in family settings.[4-8]

The World Health Organization (WHO) has recently declared coronavirus disease 2019 (Covid-19) a public health emergency of international concern.[9] As of February 25, 2020, a total of 81,109 laboratory-confirmed cases had been documented globally.[5,6,9-11] In recent studies, the severity of some cases of Covid-19 mimicked that of SARS-CoV.[1,12,13] Given the rapid spread of Covid-19, we determined that an updated analysis of cases throughout mainland China might help identify the defining clinical characteristics and severity of the disease. Here, we describe the results of our analysis of the clinical characteristics of Covid-19 in a selected cohort of patients throughout China.

Methods

Study Oversight

The study was supported by National Health Commission of China and designed by the investigators. The study was approved by the institutional review board of the National Health Commission. Written informed consent was waived in light of the urgent need to collect data. Data were analyzed and interpreted by the authors. All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data and for the adherence of the study to the protocol, available with the full text of this article at NEJM.org.

Data Sources

We obtained the medical records and compiled data for hospitalized patients and outpatients with laboratory-confirmed Covid-19, as reported to the National Health Commission between December 11, 2019, and January 29, 2020; the data cutoff for the study was January 31, 2020. Covid-19 was diagnosed on the basis of the WHO interim guidance.[14] A confirmed case of Covid-19 was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.[1] Only laboratory-confirmed cases were included in the analysis.

A Quick Take is available at NEJM.org

We obtained data regarding cases outside Hubei province from the National Health Commission. Because of the high workload of clinicians, three outside experts from Guangzhou performed raw data extraction at Wuhan Jinyintan Hospital, where many of the patients with Covid-19 in Wuhan were being treated.

We extracted the recent exposure history, clinical symptoms or signs, and laboratory findings on admission from electronic medical records. Radiologic assessments included chest radiography or computed tomography (CT), and all laboratory testing was performed according to the clinical care needs of the patient. We determined the presence of a radiologic abnormality on the basis of the documentation or description in medical charts; if imaging scans were available, they were reviewed by attending physicians in respiratory medicine who extracted the data. Major disagreement between two reviewers was resolved by consultation with a third reviewer. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, and measures of electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, and creatine kinase. We defined the degree of severity of Covid-19 (severe vs. nonsevere) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia.[15]

All medical records were copied and sent to the data-processing center in Guangzhou, under the coordination of the National Health Commission. A team of experienced respiratory clinicians reviewed and abstracted the data. Data were entered into a computerized database and cross-checked. If the core data were missing, requests for clarification were sent to the coordinators, who subsequently contacted the attending clinicians.

Study Outcomes

The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death. These outcomes

were used in a previous study to assess the severity of other serious infectious diseases, such as H7N9 infection.[16] Secondary end points were the rate of death and the time from symptom onset until the composite end point and until each component of the composite end point.

STUDY DEFINITIONS

The incubation period was defined as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e., cough, fever, fatigue, or myalgia). We excluded incubation periods of less than 1 day because some patients had continuous exposure to contamination sources; in these cases, the latest date of exposure was recorded. The summary statistics of incubation periods were calculated on the basis of 291 patients who had clear information regarding the specific date of exposure.

Fever was defined as an axillary temperature of 37.5°C or higher. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. Additional definitions — including exposure to wildlife, acute respiratory distress syndrome (ARDS), pneumonia, acute kidney failure, acute heart failure, and rhabdomyolysis — are provided in the Supplementary Appendix, available at NEJM.org.

LABORATORY CONFIRMATION

Laboratory confirmation of SARS-CoV-2 was performed at the Chinese Center for Disease Prevention and Control before January 23, 2020, and subsequently in certified tertiary care hospitals. RT-PCR assays were performed in accordance with the protocol established by the WHO.[17] Details regarding laboratory confirmation processes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. No imputation was made for missing data. Because the cohort of patients in our study was not derived from random selection, all statistics are deemed to be descriptive only. We used ArcGIS, version 10.2.2, to plot the numbers of patients with reportedly confirmed cases on a map. All the analyses were performed with the use of R software, version 3.6.2 (R Foundation for Statistical Computing).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Of the 7736 patients with Covid-19 who had been hospitalized at 552 sites as of January 29, 2020, we obtained data regarding clinical symptoms and outcomes for 1099 patients (14.2%). The largest number of patients (132) had been admitted to Wuhan Jinyintan Hospital. The hospitals that were included in this study accounted for 29.7% of the 1856 designated hospitals where patients with Covid-19 could be admitted in 30 provinces, autonomous regions, or municipalities across China (Fig. 1).

The demographic and clinical characteristics of the patients are shown in Table 1. A total of 3.5% were health care workers, and a history of contact with wildlife was documented in 1.9%; 483 patients (43.9%) were residents of Wuhan. Among the patients who lived outside Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city; 25.9% of nonresidents had neither visited the city nor had contact with Wuhan residents.

The median incubation period was 4 days (interquartile range, 2 to 7). The median age of the patients was 47 years (interquartile range, 35 to 58); 0.9% of the patients were younger than 15 years of age. A total of 41.9% were female. Fever was present in 43.8% of the patients on admission but developed in 88.7% during hospitalization. The second most common symptom was cough (67.8%); nausea or vomiting (5.0%) and diarrhea (3.8%) were uncommon. Among the overall population, 23.7% had at least one coexisting illness (e.g., hypertension and chronic obstructive pulmonary disease).

On admission, the degree of severity of Covid-19 was categorized as nonsevere in 926 patients and severe in 173 patients. Patients with severe disease were older than those with nonsevere disease by a median of 7 years. Moreover, the presence of any coexisting illness was more common among patients with severe disease than among those with nonsevere disease (38.7% vs. 21.0%). However, the exposure history between the two groups of disease severity was similar.

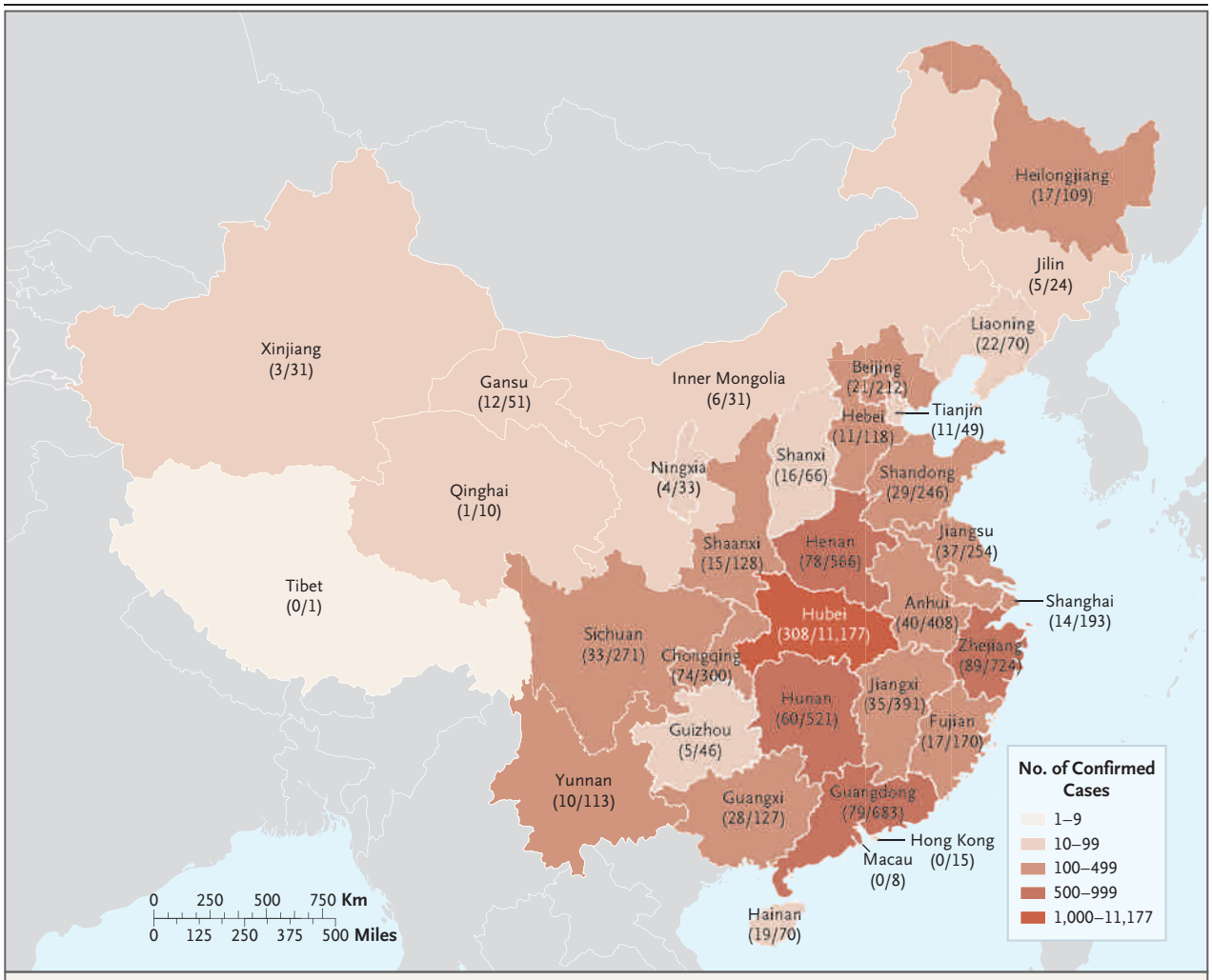

Figure 1. Distribution of Patients with Covid-19 across Mainland China.

Shown are the official statistics of all documented, laboratory-confirmed cases of coronavirus disease 2019 (Covid-19) throughout China, according to the National Health Commission as of February 4, 2020. The numerator denotes the number of patients who were included in the study cohort and the denominator denotes the number of laboratory-confirmed cases for each province, autonomous region, or provincial municipality, as reported by the National Health Commission.

RADIOLOGIC AND LABORATORY FINDINGS

Table 2 shows the radiologic and laboratory findings on admission. Of 975 CT scans that were performed at the time of admission, 86.2% revealed abnormal results. The most common patterns on chest CT were ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%). Representative radiologic findings in two patients with nonsevere Covid-19 and in another two patients with severe Covid-19 are provided in Figure S1 in the Supplementary Appendix. No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease.

On admission, lymphocytopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and D-dimer. Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with nonsevere disease.

Table 1. Clinical Characteristics of the Study Patients, According to Disease Severity and the Presence or Absence of the Primary Composite End Point.*

Characteristic	All Patients (N=1099)	Disease Severity		Presence of Primary Composite End Point†	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Age					
Median (IQR) — yr	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	63.0 (53.0–71.0)	46.0 (35.0–57.0)
Distribution — no./total no. (%)					
0–14 yr	9/1011 (0.9)	8/848 (0.9)	1/163 (0.6)	0	9/946 (1.0)
15–49 yr	557/1011 (55.1)	490/848 (57.8)	67/163 (41.1)	12/65 (18.5)	545/946 (57.6)
50–64 yr	292/1011 (28.9)	241/848 (28.4)	51/163 (31.3)	21/65 (32.3)	271/946 (28.6)
≥65 yr	153/1011 (15.1)	109/848 (12.9)	44/163 (27.0)	32/65 (49.2)	121/946 (12.8)
Female sex — no./total no. (%)	459/1096 (41.9)	386/923 (41.8)	73/173 (42.2)	22/67 (32.8)	437/1029 (42.5)
Smoking history — no./total no. (%)					
Never smoked	927/1085 (85.4)	793/913 (86.9)	134/172 (77.9)	44/66 (66.7)	883/1019 (86.7)
Former smoker	21/1085 (1.9)	12/913 (1.3)	9/172 (5.2)	5/66 (7.6)	16/1019 (1.6)
Current smoker	137/1085 (12.6)	108/913 (11.8)	29/172 (16.9)	17/66 (25.8)	120/1019 (11.8)
Exposure to source of transmission within past 14 days — no./total no.					
Living in Wuhan	483/1099 (43.9)	400/926 (43.2)	83/173 (48.0)	39/67 (58.2)	444/1032 (43.0)
Contact with wildlife	13/687 (1.9)	10/559 (1.8)	3/128 (2.3)	1/41 (2.4)	12/646 (1.9)
Recently visited Wuhan‡	193/616 (31.3)	166/526 (31.6)	27/90 (30.0)	10/28 (35.7)	183/588 (31.1)
Had contact with Wuhan residents‡	442/611 (72.3)	376/522 (72.0)	66/89 (74.2)	19/28 (67.9)	423/583 (72.6)
Median incubation period (IQR) — days§	4.0 (2.0–7.0)	4.0 (2.8–7.0)	4.0 (2.0–7.0)	4.0 (1.0–7.5)	4.0 (2.0–7.0)
Fever on admission					
Patients — no./total no. (%)	473/1081 (43.8)	391/910 (43.0)	82/171 (48.0)	24/66 (36.4)	449/1015 (44.2)
Median temperature (IQR) — °C	37.3 (36.7–38.0)	37.3 (36.7–38.0)	37.4 (36.7–38.1)	36.8 (36.3–37.8)	37.3 (36.7–38.0)
Distribution of temperature — no./total no. (%)					
<37.5°C	608/1081 (56.2)	519/910 (57.0)	89/171 (52.0)	42/66 (63.6)	566/1015 (55.8)
37.5–38.0°C	238/1081 (22.0)	201/910 (22.1)	37/171 (21.6)	10/66 (15.2)	228/1015 (22.5)
38.1–39.0°C	197/1081 (18.2)	160/910 (17.6)	37/171 (21.6)	11/66 (16.7)	186/1015 (18.3)
>39.0°C	38/1081 (3.5)	30/910 (3.3)	8/171 (4.7)	3/66 (4.5)	35/1015 (3.4)
Fever during hospitalization					
Patients — no./total no. (%)	975/1099 (88.7)	816/926 (88.1)	159/173 (91.9)	59/67 (88.1)	916/1032 (88.8)
Median highest temperature (IQR) — °C	38.3 (37.8–38.9)	38.3 (37.8–38.9)	38.5 (38.0–39.0)	38.5 (38.0–39.0)	38.3 (37.8–38.9)
<37.5°C	92/926 (9.9)	79/774 (10.2)	13/152 (8.6)	3/54 (5.6)	89/872 (10.2)
37.5–38.0°C	286/926 (30.9)	251/774 (32.4)	35/152 (23.0)	20/54 (37.0)	266/872 (30.5)
38.1–39.0°C	434/926 (46.9)	356/774 (46.0)	78/152 (51.3)	21/54 (38.9)	413/872 (47.4)
>39.0°C	114/926 (12.3)	88/774 (11.4)	26/152 (17.1)	10/54 (18.5)	104/872 (11.9)

Symptoms — no. (%)					
Conjunctival congestion	9 (0.8)	5 (0.5)	4 (2.3)	0	9 (0.9)
Nasal congestion	53 (4.8)	47 (5.1)	6 (3.5)	2 (3.0)	51 (4.9)
Headache	150 (13.6)	124 (13.4)	26 (15.0)	8 (11.9)	142 (13.8)
Cough	745 (67.8)	623 (67.3)	122 (70.5)	46 (68.7)	699 (67.7)
Sore throat	153 (13.9)	130 (14.0)	23 (13.3)	6 (9.0)	147 (14.2)
Sputum production	370 (33.7)	309 (33.4)	61 (35.3)	20 (29.9)	350 (33.9)
Fatigue	419 (38.1)	350 (37.8)	69 (39.9)	22 (32.8)	397 (38.5)
Hemoptysis	10 (0.9)	6 (0.6)	4 (2.3)	2 (3.0)	8 (0.8)
Shortness of breath	205 (18.7)	140 (15.1)	65 (37.6)	36 (53.7)	169 (16.4)
Nausea or vomiting	55 (5.0)	43 (4.6)	12 (6.9)	3 (4.5)	52 (5.0)
Diarrhea	42 (3.8)	32 (3.5)	10 (5.8)	4 (6.0)	38 (3.7)
Myalgia or arthralgia	164 (14.9)	134 (14.5)	30 (17.3)	6 (9.0)	158 (15.3)
Chills	126 (11.5)	100 (10.8)	26 (15.0)	8 (11.9)	118 (11.4)
Signs of infection — no. (%)					
Throat congestion	19 (1.7)	17 (1.8)	2 (1.2)	0	19 (1.8)
Tonsil swelling	23 (2.1)	17 (1.8)	6 (3.5)	1 (1.5)	22 (2.1)
Enlargement of lymph nodes	2 (0.2)	1 (0.1)	1 (0.6)	1 (1.5)	1 (0.1)
Rash	2 (0.2)	0	2 (1.2)	0	2 (0.2)
Coexisting disorder — no. (%)					
Any	261 (23.7)	194 (21.0)	67 (38.7)	39 (58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B infection¶	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer‖	10 (0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.
† The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.
‡ These patients were not residents of Wuhan.
§ Data regarding the incubation period were missing for 808 patients (73.5%).
¶ The presence of hepatitis B infection was defined as a positive result on testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.
‖ Included in this category is any type of cancer.

Table 2. Radiographic and Laboratory Findings.*

Variable	All Patients (N = 1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N = 926)	Severe (N = 173)	Yes (N = 67)	No (N = 1032)
Radiologic findings					
Abnormalities on chest radiograph — no./total no. (%)	162/274 (59.1)	116/214 (54.2)	46/60 (76.7)	30/39 (76.9)	132/235 (56.2)
Ground-glass opacity	55/274 (20.1)	37/214 (17.3)	18/60 (30.0)	9/39 (23.1)	46/235 (19.6)
Local patchy shadowing	77/274 (28.1)	56/214 (26.2)	21/60 (35.0)	13/39 (33.3)	64/235 (27.2)
Bilateral patchy shadowing	100/274 (36.5)	65/214 (30.4)	35/60 (58.3)	27/39 (69.2)	73/235 (31.1)
Interstitial abnormalities	12/274 (4.4)	7/214 (3.3)	5/60 (8.3)	6/39 (15.4)	6/235 (2.6)
Abnormalities on chest CT — no./total no. (%)	840/975 (86.2)	682/808 (84.4)	158/167 (94.6)	50/57 (87.7)	790/918 (86.1)
Ground-glass opacity	550/975 (56.4)	449/808 (55.6)	101/167 (60.5)	30/57 (52.6)	520/918 (56.6)
Local patchy shadowing	409/975 (41.9)	317/808 (39.2)	92/167 (55.1)	22/57 (38.6)	387/918 (42.2)
Bilateral patchy shadowing	505/975 (51.8)	368/808 (45.5)	137/167 (82.0)	40/57 (70.2)	465/918 (50.7)
Interstitial abnormalities	143/975 (14.7)	99/808 (12.3)	44/167 (26.3)	15/57 (26.3)	128/918 (13.9)
Laboratory findings					
Median Pao_2:Fio_2 ratio (IQR)††	3.9 (2.9–4.7)	3.9 (2.9–4.5)	4.0 (2.8–5.2)	2.9 (2.2–5.4)	4.0 (3.1–4.6)
White-cell count					
Median (IQR) — per mm^3	4700 (3500–6000)	4900 (3800–6000)	3700 (3000–6200)	6100 (4900–11,100)	4700 (3500–5900)
Distribution — no./total no. (%)					
>10,000 per mm^3	58/978 (5.9)	39/811 (4.8)	19/167 (11.4)	15/58 (25.9)	43/920 (4.7)
<4000 per mm^3	330/978 (33.7)	228/811 (28.1)	102/167 (61.1)	8/58 (13.8)	322/920 (35.0)
Lymphocyte count					
Median (IQR) — per mm^3	1000 (700–1300)	1000 (800–1400)	800 (600–1000)	700 (600–900)	1000 (700–1300)
Distribution — no./total no. (%)					
<1500 per mm^3	731/879 (83.2)	584/726 (80.4)	147/153 (96.1)	50/54 (92.6)	681/825 (82.5)

Platelet count					
Median (IQR) — per mm^3	168,000 (132,000–207,000)	172,000 (139,000–212,000)	137,500 (99,000–179,500)	156,500 (114,200–195,000)	169,000 (133,000–207,000)
Distribution — no./total no. (%)					
<150,000 per mm^3	315/869 (36.2)	225/713 (31.6)	90/156 (57.7)	27/58 (46.6)	288/811 (35.5)
Median hemoglobin (IQR) — g/dl‡	13.4 (11.9–14.8)	13.5 (12.0–14.8)	12.8 (11.2–14.1)	12.5 (10.5–14.0)	13.4 (12.0–14.8)
Distribution of other findings — no./total no. (%)					
C-reactive protein ≥10 mg/liter	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)	41/45 (91.1)	440/748 (58.8)
Procalcitonin ≥0.5 ng/ml	35/633 (5.5)	19/516 (3.7)	16/117 (13.7)	12/50 (24.0)	23/583 (3.9)
Lactate dehydrogenase ≥250 U/liter	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)	31/44 (70.5)	246/631 (39.0)
Aspartate aminotransferase >40 U/liter	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)	26/52 (50.0)	142/705 (20.1)
Alanine aminotransferase >40 U/liter	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)	20/49 (40.8)	138/692 (19.9)
Total bilirubin >17.1 μmol/liter	76/722 (10.5)	59/594 (9.9)	17/128 (13.3)	10/48 (20.8)	66/674 (9.8)
Creatine kinase ≥200 U/liter	90/657 (13.7)	67/536 (12.5)	23/121 (19.0)	12/46 (26.1)	78/611 (12.8)
Creatinine ≥133 μmol/liter	12/752 (1.6)	6/614 (1.0)	6/138 (4.3)	5/52 (9.6)	7/700 (1.0)
D-dimer ≥0.5 mg/liter	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)	34/49 (69.4)	226/511 (44.2)
Minerals§					
Median sodium (IQR) — mmol/liter	138.2 (136.1–140.3)	138.4 (136.6–140.4)	138.0 (136.0–140.0)	138.3 (135.0–141.2)	138.2 (136.1–140.2)
Median potassium (IQR) — mmol/liter	3.8 (3.5–4.2)	3.9 (3.6–4.2)	3.8 (3.5–4.1)	3.9 (3.6–4.1)	3.8 (3.5–4.2)
Median chloride (IQR) — mmol/liter	102.9 (99.7–105.6)	102.7 (99.7–105.3)	103.1 (99.8–106.0)	103.8 (100.8–107.0)	102.8 (99.6–105.3)

* Lymphocytopenia was defined as a lymphocyte count of less than 1500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.
† Data regarding the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pa_{O_2}:F_{IO_2}) were missing for 894 patients (81.3%).
‡ Data regarding hemoglobin were missing for 226 patients (20.6%).
§ Data were missing for the measurement of sodium in 363 patients (33.0%), for potassium in 349 patients (31.8%), and for chloride in 392 patients (35.7%).

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Table 3. Complications, Treatments, and Clinical Outcomes.

Variable	All Patients (N = 1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N = 926)	Severe (N = 173)	Yes (N = 67)	No (N = 1032)
Complications					
Septic shock — no. (%)	12 (1.1)	1 (0.1)	11 (6.4)	9 (13.4)	3 (0.3)
Acute respiratory distress syndrome — no. (%)	37 (3.4)	10 (1.1)	27 (15.6)	27 (40.3)	10 (1.0)
Acute kidney injury — no. (%)	6 (0.5)	1 (0.1)	5 (2.9)	4 (6.0)	2 (0.2)
Disseminated intravascular coagulation — no. (%)	1 (0.1)	0	1 (0.6)	1 (1.5)	0
Rhabdomyolysis — no. (%)	2 (0.2)	2 (0.2)	0	0	2 (0.2)
Physician-diagnosed pneumonia — no./total no. (%)	972/1067 (91.1)	800/894 (89.5)	172/173 (99.4)	63/66 (95.5)	909/1001 (90.8)
Median time until development of pneumonia (IQR) — days*					
After initial Covid-19 diagnosis	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–3.5)	0.0 (0.0–1.0)
After onset of Covid-19 symptoms	3.0 (1.0–6.0)	3.0 (1.0–6.0)	5.0 (2.0–7.0)	4.0 (0.0–7.0)	3.0 (1.0–6.0)
Treatments					
Intravenous antibiotics — no. (%)	637 (58.0)	498 (53.8)	139 (80.3)	60 (89.6)	577 (55.9)
Oseltamivir — no. (%)	393 (35.8)	313 (33.8)	80 (46.2)	36 (53.7)	357 (34.6)
Antifungal medication — no. (%)	31 (2.8)	18 (1.9)	13 (7.5)	8 (11.9)	23 (2.2)
Systemic glucocorticoids — no. (%)	204 (18.6)	127 (13.7)	77 (44.5)	35 (52.2)	169 (16.4)
Oxygen therapy — no. (%)	454 (41.3)	331 (35.7)	123 (71.1)	59 (88.1)	395 (38.3)
Mechanical ventilation — no. (%)	67 (6.1)	0	67 (38.7)	40 (59.7)	27 (2.6)
Invasive	25 (2.3)	0	25 (14.5)	25 (37.3)	0
Noninvasive	56 (5.1)	0	56 (32.4)	29 (43.3)	27 (2.6)
Use of extracorporeal membrane oxygenation — no. (%)	5 (0.5)	0	5 (2.9)	5 (7.5)	0
Use of continuous renal-replacement therapy — no. (%)	9 (0.8)	0	9 (5.2)	8 (11.9)	1 (0.1)
Use of intravenous immune globulin — no. (%)	144 (13.1)	86 (9.3)	58 (33.5)	27 (40.3)	117 (11.3)
Admission to intensive care unit — no. (%)	55 (5.0)	22 (2.4)	33 (19.1)	55 (82.1)	0
Median length of hospital stay (IQR) — days†	12.0 (10.0–14.0)	11.0 10.0–13.0)	13.0 (11.5–17.0)	14.5 (11.0–19.0)	12.0 (10.0–13.0)

Clinical outcomes at data cutoff — no. (%)					
Discharge from hospital	55 (5.0)	50 (5.4)	5 (2.9)	1 (1.5)	54 (5.2)
Death	15 (1.4)	1 (0.1)	14 (8.1)	15 (22.4)	0
Recovery	9 (0.8)	7 (0.8)	2 (1.2)	0	9 (0.9)
Hospitalization	1029 (93.6)	875 (94.5)	154 (89.0)	51 (76.1)	978 (94.8)

* For the development of pneumonia, data were missing for 347 patients (31.6%) regarding the time since the initial diagnosis and for 161 patients (14.6%) regarding the time since symptom onset.
† Data regarding the median length of hospital stay were missing for 136 patients (12.4%).

CLINICAL OUTCOMES

None of the 1099 patients were lost to follow-up during the study. A primary composite end-point event occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died (Table 3). Among the 173 patients with severe disease, a primary composite end-point event occurred in 43 patients (24.9%). Among all the patients, the cumulative risk of the composite end point was 3.6%; among those with severe disease, the cumulative risk was 20.6%.

TREATMENT AND COMPLICATIONS

A majority of the patients (58.0%) received intravenous antibiotic therapy, and 35.8% received oseltamivir therapy; oxygen therapy was administered in 41.3% and mechanical ventilation in 6.1%; higher percentages of patients with severe disease received these therapies (Table 3). Mechanical ventilation was initiated in more patients with severe disease than in those with nonsevere disease (noninvasive ventilation, 32.4% vs. 0%; invasive ventilation, 14.5% vs. 0%). Systemic glucocorticoids were given to 204 patients (18.6%), with a higher percentage among those with severe disease than nonsevere disease (44.5% vs. 13.7%). Of these 204 patients, 33 (16.2%) were admitted to the ICU, 17 (8.3%) underwent invasive ventilation, and 5 (2.5%) died. Extracorporeal membrane oxygenation was performed in 5 patients (0.5%) with severe disease.

The median duration of hospitalization was 12.0 days (mean, 12.8). During hospital admission, most of the patients received a diagnosis of pneumonia from a physician (91.1%), followed by ARDS (3.4%) and shock (1.1%). Patients with severe disease had a higher incidence of physician-diagnosed pneumonia than those with nonsevere disease (99.4% vs. 89.5%).

DISCUSSION

During the initial phase of the Covid-19 outbreak, the diagnosis of the disease was complicated by the diversity in symptoms and imaging findings and in the severity of disease at the time of presentation. Fever was identified in 43.8% of the patients on presentation but developed in 88.7% after hospitalization. Severe illness occurred in 15.7% of the patients after admission to a hospital. No radiologic abnormalities

were noted on initial presentation in 2.9% of the patients with severe disease and in 17.9% of those with nonsevere disease. Despite the number of deaths associated with Covid-19, SARS-CoV-2 appears to have a lower case fatality rate than either SARS-CoV or Middle East respiratory syndrome–related coronavirus (MERS-CoV). Compromised respiratory status on admission (the primary driver of disease severity) was associated with worse outcomes.

Approximately 2% of the patients had a history of direct contact with wildlife, whereas more than three quarters were either residents of Wuhan, had visited the city, or had contact with city residents. These findings echo the latest reports, including the outbreak of a family cluster,[4] transmission from an asymptomatic patient,[6] and the three-phase outbreak patterns.[8] Our study cannot preclude the presence of patients who have been termed "super-spreaders."

Conventional routes of transmission of SARS-CoV, MERS-CoV, and highly pathogenic influenza consist of respiratory droplets and direct contact,[18-20] mechanisms that probably occur with SARS-CoV-2 as well. Because SARS-CoV-2 can be detected in the gastrointestinal tract, saliva, and urine, these routes of potential transmission need to be investigated[21] (Tables S1 and S2).

The term Covid-19 has been applied to patients who have laboratory-confirmed symptomatic cases without apparent radiologic manifestations. A better understanding of the spectrum of the disease is needed, since in 8.9% of the patients, SARS-CoV-2 infection was detected before the development of viral pneumonia or viral pneumonia did not develop.

In concert with recent studies,[1,8,12] we found that the clinical characteristics of Covid-19 mimic those of SARS-CoV. Fever and cough were the dominant symptoms and gastrointestinal symptoms were uncommon, which suggests a difference in viral tropism as compared with SARS-CoV, MERS-CoV, and seasonal influenza.[22,23] The absence of fever in Covid-19 is more frequent than in SARS-CoV (1%) and MERS-CoV infection (2%),[20] so afebrile patients may be missed if the surveillance case definition focuses on fever detection.[14] Lymphocytopenia was common and, in some cases, severe, a finding that was consistent with the results of two recent reports.[1,12] We found a lower case fatality rate (1.4%) than the rate that was recently reportedly,[1,12] probably because of the difference in sample sizes and case inclusion criteria. Our findings were more similar to the national official statistics, which showed a rate of death of 3.2% among 51,857 cases of Covid-19 as of February 16, 2020.[11,24] Since patients who were mildly ill and who did not seek medical attention were not included in our study, the case fatality rate in a real-world scenario might be even lower. Early isolation, early diagnosis, and early management might have collectively contributed to the reduction in mortality in Guangdong.

Despite the phylogenetic homogeneity between SARS-CoV-2 and SARS-CoV, there are some clinical characteristics that differentiate Covid-19 from SARS-CoV, MERS-CoV, and seasonal influenza infections. (For example, seasonal influenza has been more common in respiratory outpatient clinics and wards.) Some additional characteristics that are unique to Covid-19 are detailed in Table S3.

Our study has some notable limitations. First, some cases had incomplete documentation of the exposure history and laboratory testing, given the variation in the structure of electronic databases among different participating sites and the urgent timeline for data extraction. Some cases were diagnosed in outpatient settings where medical information was briefly documented and incomplete laboratory testing was performed, along with a shortage of infrastructure and training of medical staff in nonspecialty hospitals. Second, we could estimate the incubation period in only 291 of the study patients who had documented information. The uncertainty of the exact dates (recall bias) might have inevitably affected our assessment. Third, because many patients remained in the hospital and the outcomes were unknown at the time of data cutoff, we censored the data regarding their clinical outcomes as of the time of our analysis. Fourth, we no doubt missed patients who were asymptomatic or had mild cases and who were treated at home, so our study cohort may represent the more severe end of Covid-19. Fifth, many patients did not undergo sputum bacteriologic or fungal assessment on admission because, in some hospitals, medical resources were overwhelmed. Sixth, data generation was clinically driven and not systematic.

Covid-19 has spread rapidly since it was first identified in Wuhan and has been shown to have

a wide spectrum of severity. Some patients with Covid-19 do not have fever or radiologic abnormalities on initial presentation, which has complicated the diagnosis.

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APPENDIX

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Vital Surveillances

The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team

Abstract

Background: An outbreak of 2019 novel coronavirus diseases (COVID-19) in Wuhan, Hubei Province, China has spread quickly nationwide. Here, we report results of a descriptive, exploratory analysis of all cases diagnosed as of February 11, 2020.

Methods: All COVID-19 cases reported through February 11, 2020 were extracted from China's Infectious Disease Information System. Analyses included the following: 1) summary of patient characteristics; 2) examination of age distributions and sex ratios; 3) calculation of case fatality and mortality rates; 4) geo-temporal analysis of viral spread; 5) epidemiological curve construction; and 6) subgroup analysis.

Results: A total of 72,314 patient records—44,672 (61.8%) confirmed cases, 16,186 (22.4%) suspected cases, 10,567 (14.6%) clinically diagnosed cases (Hubei Province only), and 889 asymptomatic cases (1.2%)—contributed data for the analysis. Among confirmed cases, most were aged 30–79 years (86.6%), diagnosed in Hubei (74.7%), and considered mild (80.9%). A total of 1,023 deaths occurred among confirmed cases for an overall case fatality rate of 2.3%. The COVID-19 spread outward from Hubei Province sometime after December 2019, and by February 11, 2020, 1,386 counties across all 31 provinces were affected. The epidemic curve of onset of symptoms peaked around January 23–26, then began to decline leading up to February 11. A total of 1,716 health workers have become infected and 5 have died (0.3%).

Conclusions: COVID-19 epidemic has spread very quickly taking only 30 days to expand from Hubei to the rest of Mainland China. With many people returning from a long holiday, China needs to prepare for the possible rebound of the epidemic.

Introduction

A cluster of pneumonia cases of unknown origin in Wuhan, China caused concern among health officials in late December 2019. On December 31, an alert was issued by the Wuhan Municipal Health Commission, a rapid response team was sent to Wuhan by the Chinese Center for Disease Control and Prevention (China CDC), and a notification was made to the World Health Organization (WHO) (*1*–*4*). Likely potential causes including influenza, avian influenza, adenovirus, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) were ruled out. Epidemiological investigation implicated Wuhan's Huanan Seafood Wholesale Market, which was shut down and disinfected, and active case finding was initiated and vigorously pursued (*2*,*4*–*5*).

On January 7, 2020, the causative pathogen was identified as a novel coronavirus, and genomic characterization and test method development ensued (*2*–*6*). Now named 2019-nCoV, the virus is distinct from both SARS-CoV and MERS-CoV, yet closely related (*5*,*7*). Early cases suggested that COVID-19 (i.e. the new name for disease caused by the novel coronavirus) may be less severe than SARS and MERS. However, illness onset among rapidly increasing numbers of people and mounting evidence of human-to-human transmission suggests that 2019-nCoV is more contagious than both SARS-CoV and MERS-CoV (*3*,*8*–*11*).

On January 20, China's "*National Infectious Diseases Law*" was amended to make 2019-novel coronavirus diseases (COVID-19) a Class B notifiable disease and its "*Frontier Health and Quarantine Law*" was amended to support the COVID-19 outbreak response effort. Then, on January 23, the Chinese Government began to limit movement of people in and out of Wuhan, and two days later, it announced its highest-level commitment and mobilized all sectors to respond to the epidemic and prevent further spread of COVID-19. Characterization of the epidemiological features of COVID-19 is crucial for the development and implementation of effective control strategies. Here, we report the results of a descriptive, exploratory analysis of all cases found through February 11, 2020.

Method

Study Design

This study was a descriptive, exploratory analysis of all cases of COVID-19 diagnosed nationwide in China as of the end of February 11, 2020. As such, it in some respects uses a cross-sectional study design and hence, we have used the STROBE Guidelines (www.equator-network.org) to aid our thorough reporting of this observational study.

A public health emergency was declared, and a formal investigation began on December 31, 2019, supported by city (Wuhan Municipal Health Commission and Wuhan CDC), provincial (Health Commission of Hubei Province and Hubei Provincial CDC), and national (National Health Commission and China CDC) authorities and resources. This study was reviewed by the China CDC Institutional Review Board via a fast-track mechanism. Although individual informed consent was not required for this study, all data were handled as a deidentified set to protect patient privacy and confidentiality.

Data Source

By categorizing COVID-19 as a Class B notifiable disease, Chinese law required all cases to be immediately reported to China's Infectious Disease Information System. Entry of each case into the system was performed by local epidemiologists and public health workers who investigated and collected information on possible exposures. All case records contain national identification numbers, and therefore, all cases have records in the system and no records are duplicated. All data contained in all COVID-19 case records in the Infectious Disease Information System through the end of February 11, 2020 were extracted from the system as a single dataset and were then stripped of all personal identifying information. No sampling was done to achieve a predetermined study size and no eligibility criteria were used—all cases were included.

Variables

Patient characteristics were collected at baseline, meaning the time of diagnosis, epidemiological investigation, and entry into the Infectious Disease Information System. Patients were categorized as health workers for the occupation variable if they had active employment of any kind in a health facility (i.e. this category did not just include physicians and nurses). Patients were categorized as having a Wuhan-related exposure if they had recently resided in or visited Wuhan or if they had close contact with someone who had. The comorbid conditions variable was determined upon epidemiological investigation by patient self-reported medical history, which was not independently verified using medical records for all cases. The severity of symptoms variable was categorized as mild, severe, or critical. Mild included non-pneumonia and mild pneumonia cases. Severe was characterized by dyspnea, respiratory frequency $\geq$ 30/minute, blood oxygen saturation $\leq$93%, PaO_2/FiO_2 ratio <300, and/or lung infiltrates >50% within 24–48 hours. Critical cases were those that exhibited respiratory failure, septic shock, and/or multiple organ dysfunction/failure.

As some variables of interest (i.e., Wuhan-related exposure, comorbid condition, and case severity) are not required fields when creating records in the Infectious Disease Information System, some records have missing data for these variables.

For construction of epidemiological curves, date of onset was defined as the date on which patients self-reported the start of either fever or cough during epidemiological investigation. Cases were categorized as confirmed, suspected, clinically diagnosed (Hubei Province only), or asymptomatic. Confirmed cases were diagnosed based on positive viral nucleic acid test results on throat swab samples (some samples were tested retrospectively). Suspected cases were diagnosed clinically based on symptoms and exposures. Clinically diagnosed cases were suspected cases with lung imaging features consistent with coronavirus pneumonia. Asymptomatic cases were diagnosed based on positive viral nucleic acid test results but without any COVID-19 symptoms (e.g., fever, dry cough). The date of positive viral nucleic acid test result is used as onset date for asymptomatic cases

Analysis

For confirmed cases, demographic and clinical characteristics were summarized using descriptive statistics. Age distribution graphs were constructed using patient age at baseline for confirmed cases diagnosed in Wuhan, Hubei Province (including Wuhan), and China (including Hubei Province). Sex ratio (i.e., male:female [M:F] ratio) was also calculated. Case fatality rates were calculated as the total number of deaths (numerator) divided by the total number of cases (denominator), expressed as a percent. Observed time was summarized using person-days (PD) and

mortality was calculated as the number of deaths (numerator) divided by the total observed time (denominator), expressed per 10 PD.

For geo-temporal analysis, the county-level location of each case at time of diagnosis was used to build color-coded maps of China to indicate the numbers of cases in each province on December 31, 2019; January 10, 2020; January 31, 2020; and February 11, 2020. This analysis was performed using ArcGIS Desktop software (version 10.6; Esri; Redlands, California, USA).

The epidemiological curve for all cases was constructed by plotting the number of cases (y-axis) versus self-reported date of symptom onset (x-axis). Date of symptom onset for confirmed, suspected, clinically diagnosed, and asymptomatic cases were stacked to show total cases over time. The epidemiological curve for confirmed cases was also overlaid with the number of cases versus date of diagnosis to show the delay between onset of symptoms and diagnosis of disease.

Two subgroups were also analyzed separately using epidemiological curves: confirmed cases diagnosed outside of Hubei Province (with and without Wuhan-related exposure) and all cases diagnosed among health workers (confirmed, suspected, clinically diagnosed, and asymptomatic).

Results

Patients

A total of 72,314 unique records were extracted and data from all records were included in the analysis. Thus, all 72,314 individuals diagnosed with COVID-19 as of February 11, 2020, were included in the analysis. Among them, 44,672 cases (61.8%) were confirmed, 16,186 cases (22.4%) were suspected, 10,567 cases (14.6%) were clinically diagnosed, and 889 cases (1.2%) were asymptomatic.

Baseline characteristics of confirmed cases (n=44,672) are presented in Table 1. A majority were aged 30–69 years (77.8%), male (51.4%), farmers or laborers (22.0%), and diagnosed in Hubei Province (74.7%). Most patients reported Wuhan-related exposures (85.8%) and were classified as mild cases (80.9%).

TABLE 1. Patients, deaths, and case fatality rates, as well as observed time and mortality for n=44,672 confirmed COVID-19 cases in Mainland China as of February 11, 2020.

Baseline Characteristics	Confirmed Cases, N (%)	Deaths, N (%)	Case Fatality Rate, %	Observed Time, PD	Mortality, per 10 PD
Overall	44,672	1,023	2.3	661,609	0.015
Age, years					
0–9	416 (0.9)	–	–	4,383	–
10–19	549 (1.2)	1 (0.1)	0.2	6,625	0.002
20–29	3,619 (8.1)	7 (0.7)	0.2	53,953	0.001
30–39	7,600 (17.0)	18 (1.8)	0.2	114,550	0.002
40–49	8,571 (19.2)	38 (3.7)	0.4	128,448	0.003
50–59	10,008 (22.4)	130 (12.7)	1.3	151,059	0.009
60–69	8,583 (19.2)	309 (30.2)	3.6	128,088	0.024
70–79	3,918 (8.8)	312 (30.5)	8.0	55,832	0.056
≥80	1,408 (3.2)	208 (20.3)	14.8	18,671	0.111
Sex					
Male	22,981 (51.4)	653 (63.8)	2.8	342,063	0.019
Female	21,691 (48.6)	370 (36.2)	1.7	319,546	0.012
Occupation					
Service industry	3,449 (7.7)	23 (2.2)	0.7	54,484	0.004
Farmer/laborer	9,811 (22.0)	139 (13.6)	1.4	137,992	0.010
Health worker	1,716 (3.8)	5 (0.5)	0.3	28,069	0.002
Retiree	9,193 (20.6)	472 (46.1)	5.1	137,118	0.034
Other/none	20,503 (45.9)	384 (37.5)	1.9	303,946	0.013

TABLE 1. (continued)

Baseline Characteristics	Confirmed Cases, N (%)	Deaths, N (%)	Case Fatality Rate, %	Observed Time, PD	Mortality, per 10 PD
Province					
Hubei	33,367 (74.7)	979 (95.7)	2.9	496,523	0.020
Other	11,305 (25.3)	44 (4.3)	0.4	165,086	0.003
Wuhan-related exposure*					
Yes	31,974 (85.8)	853 (92.8)	2.7	486,612	0.018
No	5,295 (14.2)	66 (7.2)	1.2	71,201	0.009
Missing	7,403	104	2.8	103,796	0.010
Comorbid condition†					
Hypertension	2,683 (12.8)	161 (39.7)	6.0	42,603	0.038
Diabetes	1,102 (5.3)	80 (19.7)	7.3	17,940	0.045
Cardiovascular disease	873 (4.2)	92 (22.7)	10.5	13,533	0.068
Chronic respiratory disease	511 (2.4)	32 (7.9)	6.3	8,083	0.040
Cancer (any)	107 (0.5)	6 (1.5)	5.6	1,690	0.036
None	15,536 (74.0)	133 (32.8)	0.9	242,948	0.005
Missing	23,690 (53.0)	617 (60.3)	2.6	331,843	0.019
Case severity§					
Mild	36,160 (80.9)	–	–	–	–
Severe	6,168 (13.8)	–	–	–	–
Critical	2,087 (4.7)	1,023 (100)	49.0	31,456	0.325
Missing	257 (0.6)	–	–	–	–
Period (by date of onset)					
Before Dec 31, 2019	104 (0.2)	15 (1.5)	14.4	5,142	0.029
Jan 1–10, 2020	653 (1.5)	102 (10.0)	15.6	21,687	0.047
Jan 11–20, 2020	5,417 (12.1)	310 (30.3)	5.7	130,972	0.024
Jan 21–31, 2020	26,468 (59.2)	494 (48.3)	1.9	416,009	0.012
After Feb 1, 2020	12,030 (26.9)	102 (10.0)	0.8	87,799	0.012

Abreviation: PD, person-days.

* The Wuhan-related exposure variable, only includes a total of 37,269 patients and 919 deaths and these values were used to calculate percentages in the confirmed cases and deaths columns.

† The comorbid condition variable, only includes a total of 20,812 patients and 504 deaths and these values were used to calculate percentages in the confirmed cases and deaths columns.

§ The case severity variable, only includes a total of 44,415 patients and 1,023 deaths and these values were used to calculate percentages in the confirmed cases and deaths columns.

Deaths, Case Fatality Rates, and Mortality

As shown in Table 1, a total of 1,023 deaths have occurred among 44,672 confirmed cases for an overall case fatality rate of 2.3%. Additionally, these 1,023 deaths occurred during 661,609 person-days (PD) of observed time, for a mortality rate of 0.015/10 PD.

The ≥80 age group had the highest case fatality rate of all age groups at 14.8%. Case fatality rate for males was 2.8% and for females was 1.7%. By occupation, patients who reported being retirees had the highest case fatality rate at 5.1%, and patients in Hubei Province had a >7-fold higher case fatality rate at 2.9% compared to patients in other provinces (0.4%). While patients who reported no comorbid conditions had a case fatality rate of 0.9%, patients with comorbid conditions had much higher rates—10.5% for those with cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer. Case fatality rate was also very high for cases categorized as critical at 49.0%.

Age Distribution and Sex Ratio

The age distribution of cases in Wuhan only, in Hubei Province overall, and in China overall are

presented in Figure 1. The proportion of confirmed cases 30–79 years of age at baseline (i.e., date of diagnosis) was 89.8% for cases in Wuhan city versus 88.6% in Hubei overall (which includes Wuhan) and 86.6% in China overall (which includes Hubei Province and all 30 other provincial-level administrative divisions, or PLADs). The male-to-female ratio was 0.99:1 in Wuhan, 1.04:1 in Hubei, and 1.06:1 in China overall.

Geo-Temporal Findings

On January 19, 2020, National Health Commission of the People's Republic of China confirmed that Guangdong Provincial CDC reported first imported cases of COVID-19, via the Chinese Infectious Diseases Reporting System. This was the first time COVID-19 had been reported outside of Hubei Province via the System. As of January 22, 2020, a total of 301 confirmed COVID-19 cases were reported from 83 counties in 23 provinces. On January 30, 2020, Xizang Autonomous Region (Tibet) reported its first confirmed COVID-19 case coming from Hubei Province. Thus, COVID-19 cases have been reported from all 31 PLADs (Figure 2).

As of February 11, 2020, a total 44,672 confirmed cases were reported from 1,386 counties of 31 provinces, autonomous regions, and municipalities and Hubei Province accounted for 74.7% (Figure 2E). Among them, 0.2% of cases had onset of illness before December 31, 2019 and all were from Hubei Province (Figure 2A); 1.7% had onset of illness during January 1–10, 2020, distributed in 113 counties of 22 PLADs and Hubei Province accounted for 88.5% (Figure 2B); 13.8% had onset of illness during January 11–20, 2020, distributed in 627 counties of 30 PLADs and Hubei Province accounted for 77.6% (Figure 2C); 73.1% had onset of illness during January 21–31, 2020, distributed in 1310 counties of 31 PLADs and Hubei Province accounted for 74.7% (Figure 2D).

Epidemiological Curve

Figure 3A shows the COVID-19 epidemic curve with number of cases plotted by date of patient onset of symptoms from December 8, 2019 to February 11, 2020. Confirmed, suspected, clinically diagnosed, and asymptomatic cases are stacked to show total daily cases by date of symptom onset. The inset shows that in December 2019 only 0–22 cases/day began to experience symptoms. The peak onset of symptoms for all cases overall occurred on February 1, 2020. Since then, onset of illness has declined.

Figure 3B shows the same COVID-19 epidemic curve for confirmed cases only with number of cases plotted by date of patients' onset of symptoms from December 8, 2019 to February 11, 2020. These data are overlaid with confirmed cases plotted by date of diagnosis to show the lag between the time patients fall ill and the time they actually are diagnosed and are reported to the Infectious Disease Information System. Although for confirmed cases onset of illness peaked around January 23–27, diagnosis of infection by nucleic acid testing of throat swabs did not peak until February 4.

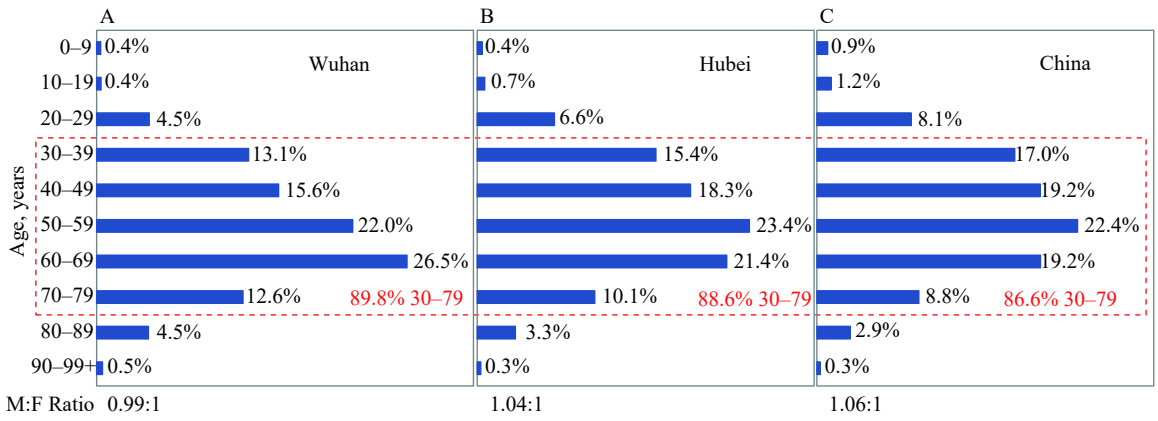

FIGURE 1. Age distribution and sex ratio of all confirmed COVID-19 cases in China through February 11, 2020. (A) patients diagnosed in the city of Wuhan only; (B) patients diagnosed in Hubei Province, which includes Wuhan as its capital city; and (C) patients diagnosed in China overall, including Hubei Province and all 30 other provincial-level administrative divisions (PLADs). Dashed red line highlights the proportion of patients in the 30–79 years age range. Sex ratio (i.e. male-to-female [M:F] ratio) is shown below each graph.

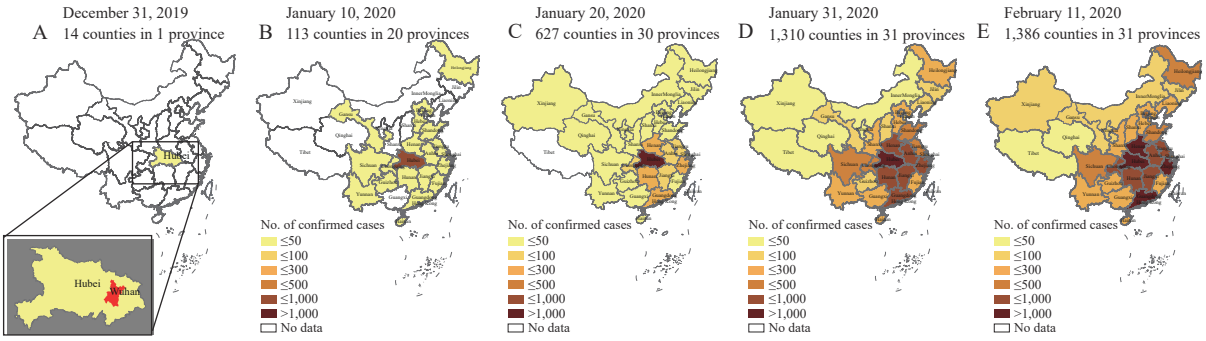

FIGURE 2. Geo-temporal spread of COVID-19 in China through February 11, 2020. (A) a total of 14 county-level administrative areas (hereafter counties) in Hubei Province only (inset) had reported cases as of December 31, 2019; (B) by January 10, 2020, 113 counties in 20 PLADs had reported cases with the highest prevalence still in Hubei Province; (C) nine days later, on January 20, 627 counties in 30 PLADs had reported cases and PLADs neighboring Hubei Province observed increasing prevalence; (D) by the end of January 31, 1310 counties across all 31 PLADs were affected and prevalence in the central, south, and south-central regions had risen dramatically; (E) by the end of February 11, 1,386 counties nationwide were affected and prevalence in the south-central PLADs had risen to the level of Hubei.

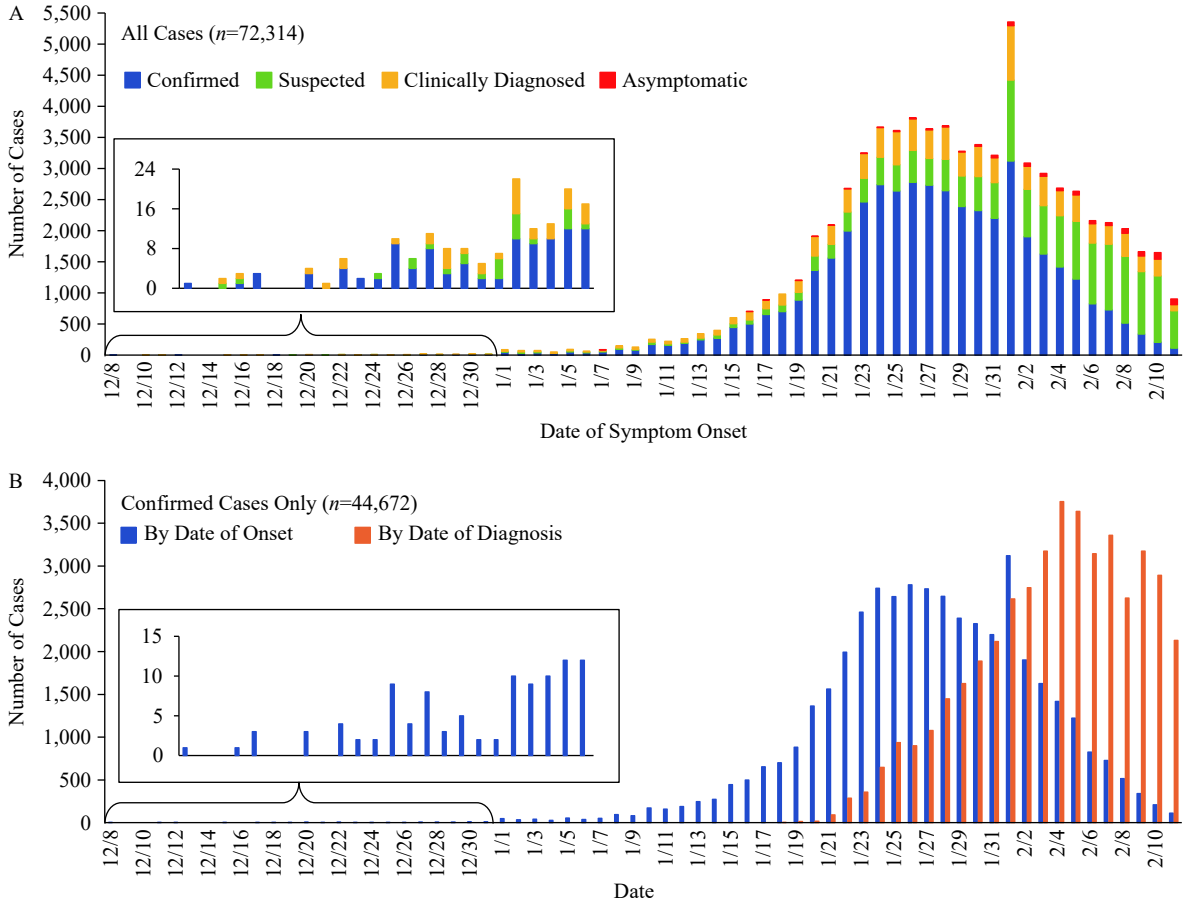

FIGURE 3. Epidemiological curves of COVID-19 in China through February 11, 2020. (A) the epidemiological curve shows the progression of illness in the outbreak over time from December 8, 2019 to February 11, 2020. A total of 72,314 cases are shown and confirmed cases (blue) are compared to suspected cases (green), clinically diagnosed cases (yellow), and asymptomatic cases (red). The inset shows a zoomed-in view of all days in December, when total daily count remained below 24 cases; (B) the epidemiological curve shows the progression of illness in the outbreak over time from December 8, 2019 to February 11, 2020 for confirmed cases only (blue). The number of cases diagnosed each day is also shown for confirmed cases only (orange). The inset shows a zoomed-in view of all days in December, when total daily count remained below 15 cases.

Subgroup Findings

Figure 4 shows the COVID-19 epidemic curve with the number of cases plotted by date of onset of symptoms from December 18, 2019 to February 11, 2020 for two subgroups—confirmed cases found outside of Hubei Province (Figure 4A) and all cases among health workers nationwide (Figure 4B). Peak timing of onset of symptoms among cases outside of Hubei Province occurred on January 27. Most of these cases (85.8%) reported having recently resided in or visited Wuhan or having had close contact with an infected individual from Wuhan. Peak timing of onset of symptoms among health worker cases occurred on February 1. In the 422 medical facilities serving COVID-19 patients, a total of 3,019 health workers have been infected (1,716 confirmed cases), and 5 have died.

Confirmed cases, case severity, and case fatality rates among health workers in different areas of China and different time periods are presented in Table 2. A total of 1,080 confirmed cases among health workers have been found in Wuhan, accounting for 64.0% of

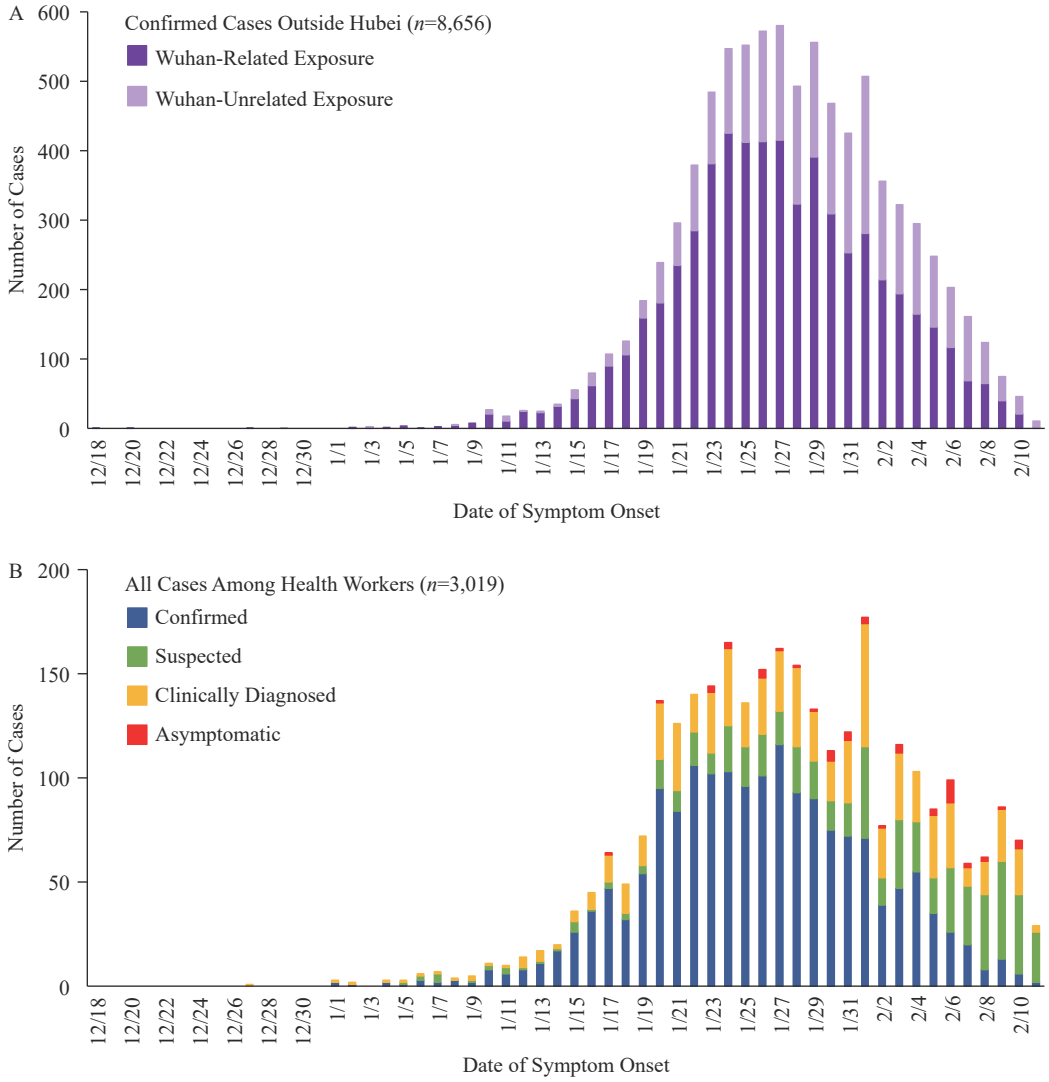

FIGURE 4. Subgroup epidemiological curves of COVID-19 in China through February 11, 2020. (A) subgroup analysis of confirmed cases discovered outside of Hubei Province only. The epidemiological curve shows the progression of illness in the outbreak over time from the onset of symptoms of the first case outside Hubei Province on December 18, 2019 through the end of February 11, 2020. Total confirmed cases outside Hubei Province, and Wuhan-related exposure (dark purple) versus Wuhan-unrelated exposure (light purple), are shown; (B) subgroup analysis of all cases among health workers only. The epidemiological curve shows the progression of illness in the outbreak over time from the onset of symptoms of the first health worker case on December 27, 2019 through the end of February 11, 2020. Total cases among health workers and confirmed (blue) versus suspected (green), clinically diagnosed (yellow), and asymptomatic (red) cases are shown.

national total. An additional 394 health worker cases (23.3%) were found in Hubei Province (excluding Wuhan), and 214 cases (12.7%) were found in the other 30 PLADs. The proportion of health worker cases that were severe or critical was 17.7% in Wuhan, 10.4% in Hubei Province, 7.0% in the remaining 30 PLADs, and 14.6% overall. The proportion of health worker cases in Wuhan classified as severe or critical declined from 38.9% in early January to 12.7% in early February. In China overall, the severe or critical cases among health workers also declined—from 45.0% in early January to 8.7% in early February.

Discussion

A main finding of this characterization and exploratory analysis of the first 72,314 cases of COVID-19 found in China in the 40 days between first recognition of the outbreak of pneumonia with unknown etiology on December 31, 2019 to the end of the study period on February 11, 2020 is that this novel coronavirus is highly contagious. It has spread extremely rapidly from a single city to the entire country within only about 30 days. Moreover, it has achieved such far-reaching effects even in the face of extreme response measures including the complete shutdown and isolation of whole cities, cancellation of Chinese New Year celebrations, prohibition of attendance at school and work, massive mobilization of health and public health personnel as well as military medical units, and rapid construction of entire hospitals.

In light of this rapid spread, it is fortunate that COVID-19 has been mild for 81% of patients and has a very low overall case fatality rate of 2.3%. Among the 1,023 deaths, a majority have been ≥60 years of age and/or have had pre-existing, comorbid conditions such as hypertension, cardiovascular disease, and diabetes. Moreover, the case fatality rate is unsurprisingly highest among critical cases at 49%, and no deaths have occurred among those with mild or even severe symptoms (Table 1).

A major contribution of our study is a first description of the COVID-19 epidemic curves. We interpret the overall curve (Figure 3A) as having a mixed outbreak pattern—the data appear to indicate a continuous common source pattern of spread in December and then from early January through February 11, 2020, the data appear to have a propagated source pattern. This mixed outbreak time trend is consistent with the working theory that perhaps several zoonotic events occurred at Huanan Seafood Wholesale Market in Wuhan allowed 2019-nCoV to be transmitted from a still-unknown animal into humans and, due to its high mutation and recombination rates, it adapted to become capable of and then increasingly efficient at human-to-human transmission (*3*,*8*).

The early days of the outbreak have been reminiscent of SARS and MERS, and indeed, the discovery that the causative agent was a closely-related, never-before-described coronavirus predicted potential for nosocomial transmission and so-called "super-spreader" events (*8*). Unfortunately, 2019-nCoV did indeed infect health workers in China via nosocomial transmission. Here we offer a first description of the 1,716 confirmed cases among health workers. Overall, they also display a likely mixed outbreak pattern—perhaps the data are characterized by a point source curve beginning in late December 2019, which

TABLE 2. Confirmed cases, case severity, and case fatality rates among health workers in different areas of China by time period.

Period (by date of onset)	Wuhan			Hubei (outside Wuhan)			China (outside Hubei)			China (overall)		
	Confirmed Cases, N	Severe + Critical, N (%)	Deaths, N (CFR*, %)	Confirmed Cases, N	Severe + Critical, N (%)	Deaths, N (CFR*, %)	Confirmed Cases, N	Severe + Critical, N (%)	Deaths, N (CFR*, %)	Confirmed Cases, N	Severe + Critical, N (%)	Deaths, N (CFR*, %)
Before Dec 31, 2019	0	0	0	0	0	0	0	0	0	0	0	0
Jan 1–10, 2020	18	7 (38.9)	1 (5.6)	1	1 (100)	0	1	1 (100)	0	20	9 (45.0)	1 (5.0)
Jan 11–20, 2020	233	52 (22.3)	1 (0.4)	48	8 (16.7)	0	29	1 (3.4)	0	310	61 (19.7)	1 (0.3)
Jan 21–31, 2020	656	110 (16.8)	0	250	29 (11.6)	2 (0.8)	130	10 (7.7)	0	1,036	149 (14.4)	2 (0.2)
After Feb 1, 2020	173	22 (12.7)	1 (0.6)	95	3 (3.2)	0	54	3 (5.6)	0	322	28 (8.7)	1 (0.3)
Total	1,080	191 (17.7)	3 (0.3)	394	41 (10.4)	2 (0.5)	214	15 (7.0)	0	1,688	247 (14.6)	5 (0.3)

Abreviation: CFR, case-fatality rate.

* CFR presented here was calculated as number of deaths (numerator) divided by total number of confirmed cases in the row (denominator), expressed as a percent.

was eclipsed by a higher magnitude continuous source curve beginning on January 20, 2020. To date, there is no evidence of a super-spreader event occurring in any of the Chinese health facilities serving COVID-19 patients. However, we do not know whether this is due to the nature of the virus itself or whether these events have been successfully prevented.

It is these authors' sincere hope and intent that this new analysis, on what has become a "public health emergency of international concern," (*12*) helps to inform health and public health workers preparing for or perhaps already experiencing COVID-19 in their populations. This study provides important insight into several crucial open questions on this epidemic and how to design strategies to effectively control it (*3*). For instance, the downward trend in the overall epidemic curve suggests that perhaps isolation of whole cities, broadcast of critical information (e.g., promoting hand washing, mask wearing, and care seeking) with high frequency through multiple channels, and mobilization of a multi-sector rapid response teams is helping to curb the epidemic.

China's response is certainly an echo of lessons learned during SARS and is a tribute to the work China and other low- and middle-income countries have been doing, with the much-needed help of international partners, over the past few decades to build infectious disease surveillance systems and public health infrastructure capable of catching outbreaks early and responding swiftly using evidence-based best practices. The 2019-nCoV and other coronaviruses may continue to adapt over time to become more virulent (*3*), and zoonosis is not going to stop. We must remain vigilant, hone our skills, fund our defenses, and practice our responses, and we must help our neighbors to do the same.

The very large number of cases included in our study was a major strength. Nevertheless, our study did have some important limitations. Firstly, a large proportion of cases included in our analysis (37%) were not confirmed by nucleic acid testing since this process is slow, labor intensive, and requires specialized equipment and skilled technicians. Yet all 72,314 cases were at least diagnosed clinically and investigated by trained epidemiologists. Secondly, some records did have missing data for a few important variables of interest—Wuhan-related exposure, comorbid conditions, and case severity—which limits our ability to draw conclusions from the data.

In conclusion, the present descriptive, exploratory analysis of the first 72,314 cases of COVID-19 reported through February 11, 2020 offers important new information to the international community on the epidemic in China. In particular, this analysis chronicles the extremely rapid spread of the novel coronavirus despite extreme efforts to contain it. However, important questions remain including identification of the animal reservoir, determination of infectiousness period, identification of transmission routes, and effective treatment and prevention methods including further test development, drug development, and vaccine development (*3*–*4*,*8*–*9*). As an international community, we must all be responsible partners in surveillance, communication, response, research, and implementation of evidence-based public health and clinical practice. The massive vigorous actions taken by the Chinese government have slowed down the epidemic in China and curbed spread to the rest of the world. Although the epidemic appears to be in decline in the lead up to February 11, 2020, we may yet face more challenges. Huge numbers of people will soon be returning to work and school after the extended New Year holiday. We need to prepare for a possible rebound of the COVID-19 epidemic in the coming weeks and months.

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In order to share the results of epidemiological characteristics of COVID-19 domestically and internationally, the Chinese Versionis jointly published on the *Chinese Journal of Epidemiology*.

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RESEARCH ARTICLE

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Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis

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Abstract

We aim to systematically review the characteristics of asymptomatic infection in the coronavirus disease 2019 (COVID-19). PubMed and EMBASE were electronically searched to identify original studies containing the rate of asymptomatic infection in COVID-19 patients before 20 May 2020. Then mate-analysis was conducted using R version 3.6.2. A total of 50 155 patients from 41 studies with confirmed COVID-19 were included. The pooled percentage of asymptomatic infection is 15.6% (95% CI, 10.1%-23.0%). Ten included studies contain the number of presymptomatic patients, who were asymptomatic at screening point and developed symptoms during follow-up. The pooled percentage of presymptomatic infection among 180 initially asymptomatic patients is 48.9% (95% CI, 31.6%-66.2%). The pooled proportion of asymptomatic infection among 1152 COVID-19 children from 11 studies is 27.7% (95% CI, 16.4%-42.7%), which is much higher than patients from all aged groups. Abnormal CT features are common in asymptomatic COVID-19 infection. For 36 patients from 4 studies that CT results were available, 15 (41.7%) patients had bilateral involvement and 14 (38.9%) had unilateral involvement in CT results. Reduced white blood cell count, increased lactate dehydrogenase, and increased C-reactive protein were also recorded. About 15.6% of confirmed COVID-19 patients are asymptomatic. Nearly half of the patients with no symptoms at detection time will develop symptoms later. Children are likely to have a higher proportion of asymptomatic infection than adults. Asymptomatic COVID-19 patients could have abnormal laboratory and radiational manifestations, which can be used as screening strategies to identify asymptomatic infection.

KEYWORDS

asymptomatic infection, children coronavirus disease 2019, Coronavirus disease 2019, COVID-19, presymptomatic infection, SARS-CoV-2

1 | BACKGROUND

The current COVID-19 pneumonia pandemic, caused by a novel coronavirus SARS-CoV-2 that belongs to the beta-coronavirus lineage B, is spreading globally at an accelerated rate. First reported in a seafood market in Wuhan province China in December 2019,[1] this disease is now affecting more than 156 countries around the world. As of 5 June 2020, a total number of 4 248 389 laboratory-confirmed cases have been documented globally, leading to 294 046 deaths,[2] which is far more than two previously identified coronaviruses SARS-CoV (2003) and MERS-CoV (2012) that cause Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome (MERS) did.

Clinical manifestation of COVID-19 is protean. Significant clinical presentations of COVID-19 include fever, respiratory and gastrointestinal symptoms, pneumonia,[3] and other symptoms such as myasthenia, ageusia, and anosmia.[4] However, patients infected with SARS-CoV-2 could also be asymptomatic, confirmed by positive Nucleic acid testing results during the illness. As a potential source of COVID-19 infection, asymptomatic patients with subclinical manifestation could be missed by detection strategies and put a threat to infection control via person-to-person contact. Asymptomatic cases inevitably distorting the COVID-19 epidemiologic reality. While a variety of studies on asymptomatic infection have been reported, the proportion of asymptomatic patients in confirmed COVID-19 cases is not well characterized. We conducted this meta-analysis to better understand the asymptomatic infection of COVID-19.

2 | MATERIALS AND METHOD

2.1 | Studies selection

Two databases including PubMed and Embase were searched before 20 May 2020 following the PRISMA guideline. We included the following items:

#1: "COVID-19" OR "2019 novel coronavirus disease" OR "COVID19" OR"COVID-19 pandemic" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "coron121avirus disease-19" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "coronavirus disease 2019" OR "2019-nCoV disease" OR"COVID-19 virus disease"

#2: "Asymptomatic"

#3: #1 AND #2

We included articles reporting a specific number of asymptomatic infection cases in confirmed COVID-19 patients. Information describing the epidemiological and clinical features of COVID-19 asymptomatic infection were extracted from studies to obtain epidemiological and clinical features of asymptomatic infection.

2.2 | Selection criteria

Records were identified through database searching. Confirmed COVID-19 was defined as one that had a throat-swab or other specimen tested positive for SARS-CoV2 using real-time RT-PCR assay. Asymptomatic infection was defined as patients who developed no symptoms such as fever, cough, or diarrhea during illness. A presymptomatic case was defined as a patient who has no symptoms at diagnosis time but developed symptoms during follow-up. Patients with no symptoms at screening point were defined as the number of asymptomatic patients plus the number of presymptomatic patients. Two authors (He and Guo) extracted data independently. Disagreements were resolved by discussion until consensus was reached or by consulting a third author. Including criteria included: (a) Study objectives: Patients confirmed infected with SARS-CoV-2 (including adult, pediatric patients, and pregnant women). (b) Study types: prospective/retrospective cross-section cohort studies. There was no language restriction. Original articles reporting asymptomatic infection in confirmed COVID-19 patients were included for meta-analysis.

The methodological quality of the studies included in meta-analysis was assessed using an 11-item checklist which was recommended by Agency for Healthcare Research and Quality (AHRQ). If an item was answered "NO" or "UNCLEAR" it would be scored "0" and if it was answered "YES," then the item scored "1." Article quality was assessed as follows: low quality = 0 to 3; moderate quality = 4 to 7; high quality = 8 to 11.

2.3 | Data extraction

After removing the duplicates, the abstract review was conducted through titles and abstracts. The following data were extracted: author, date of publication, site of study, study group, total number of people included in the study, age, sex, the number of asymptomatic infections, and the number of presymptomatic infection in patients if available. For detail information of asymptomatic patients, information containing age, sex, conversion time of illness (the time between the first day with a positive reverse transcription-polymerase chain reaction [RT-PCR] result and the day of a second negative RT-PCR result), laboratory analysis results and CT examination results were extracted if available.

2.4 | Data analysis

All statistical analysis was performed using R version 3.6.2 (R Foundation for Statistical Computing) statistical software and Rstudio. Packages "meta," "metafor," and "weightr" were used. The proportion of asymptomatic infection was transformed using the logit transformation to make it conform to the normal distribution. A random effects model was applied to calculate the effect size and its 95% confidence interval (95% CI) by the method of moments (the Dorsmanin and Laird method) and as presented by Forest plot. The tau^2 and I^2 statistic was used to estimate the proportion of the observed heterogeneity. Studies containing the number of presymptomatic patients were extracted to analyze the proportion of presymptomatic infection in patients with no symptoms at screening point. Untransformed proportions and a random effects model by the method of moments (the Dorsmanin and Laird method) were applied to calculate the effect size and its 95% confidence interval (95% CI) and as presented by Forest plot. Leave-one-out diagnostics and regression diagnostics were used to identify influential studies that pronouncedly contribute to heterogeneity in meta-analytic data. Meta-analysis via linear was conducted to find the factor attributing to the overall heterogeneity, which was described in the article published by Wang.[5] Subgroup summary proportion analysis were conducted to explain

the factor contributing to heterogeneity. Then subgroups forest plot was created by different study group: all, children, pregnant women or elderly people, and different place: China or outside of China. Publication bias was detected with funnel plot and Egger's regression test.

3 | RESULTS

3.1 | Study characteristic of meta-analysis

Study process is depicted in Figure S1. Of the 470 studies identified, 40 studies[6-45] and 1 additional study[46] including 50155 patients were included in the meta-analysis. Place where the study was conducted, age, sex, and reported proportion of asymptomatic infection, number of presymptomatic infection, and quality scores were abstracted (Table S1). There were 25 (59.5%) studies from China and 16 from other countries (South Korea: 4, United States of America: 3, Europe region: 3, UK: 2, Brunei: 1, Iraqi Kurdistan: 1, Thailand: 1, and Japan: 1). All studies were of high (27) or moderate (14) quality. There were no articles with low quality rating.

3.2 | Results of meta-analysis

3.2.1 | Pooled proportion of asymptomatic infection

A total of 50 155 patients with confirmed COVID-19 were included. The pooled percentage of all asymptomatic infection is 15.6% (95% CI, 10.1%-23.0%) with significant heterogeneity noted among studies ($P < .01$; Q, 1653.8; tau^2, 2.34; I^2, 97.6%) (Figure 1).

3.2.2 | Proportion of presymptomatic infection

There was a total of 10 studies containing the number of patients who were identified as silent COVID-19 patients but developed symptoms during follow-up. A total of 180 initial no-symptoms COVID-19 patients were included. The pooled percentage of presymptomatic infection among patients with no symptoms at screening point is 48.9% (95% CI, 31.6-66.2%) with heterogeneity noted among studies ($P < .01$; I^2, 85%) (Figure 2).

3.2.3 | Subgroup meta-analysis

Study group

There were 24 studies of 48 868 people in study cohorts from all age groups, 11 studies of 1152 children, 3 studies of 75 elderly people, and 4 studies of 83 pregnant women. The pooled prevalence of asymptomatic infection was 9.0% (95% CI, 5.5%-14.6%), 27.7% (95% CI, 16.4%-42.7%), 28.3% (95% CI, 0.94%-94.2%), and 49.9% (95% CI, 14.9%-84.9%) in studies from all aged group, children, the elderly, and pregnant women respectively (Figure 3). There was a significant subgroup difference between the studies ($P = .0041$).

Study place

The pooled prevalence of asymptomatic infection was 15.5% (95% CI, 8.8%-25.7%) and 14.5% (95% CI, 9.8%-21.1%) in studies from China and other countries respectively (Figure 4). The P value between these two groups is .8313 with no significance. There was significant heterogeneity among the studies conducted in China ($P < .01$; $I^2 = 98.3\%$) and fewer heterogeneity studies from other countries ($P < .01$; $I^2 = 70.1\%$).

3.2.4 | Sensitivity analysis and publication bias

Leave-one-out diagnostics (Figure S2) and regression diagnostics (Figure S3) showed that no specific study has a pronounced impact on the original summary proportion. Meta-analysis via linear was conducted to explaining heterogeneity by different independent variables: study place, study group, quality scores, and the number of confirmed cases. The P values were .96, .0005, .06, and .0028 differently for them. Different study group and sample size may account for the high heterogeneity among studies. The Funnel plot (Figure 5) and Egger's regression test indicate that there may be publication bias ($t = 5.65$; $P < .0001$).

3.3 | Clinical features of asymptomatic infection

Fifty-nine patients from four studies included in the meta-analysis[9,26-28] and one additional case series study[47] were included. A summary of the characterizes of asymptomatic COVID-19 infection is shown in Table 1. Illness duration ranged from 3 to 34 days. CT imaging results could be normal and abnormal. For 36 patients from 4 studies, 15 (41.7%) had bilateral involvement and 14 (38.9%) had unilateral involvement in CT results. Some patients may have abnormal laboratory results. Detail information was available from two studies respectively conducted by Ma et al[26] and Xu et al.[47] In those two studies, 27.3% (3/26) of asymptomatic patients had reduced white blood cell count, 42.3% (11/26) of patients showed increased lactate dehydrogenase, and 11.5% (3/26) of patients recorded increased C-reactive protein. Increased creatine kinase-MB, both decreased lymphocyte count and increased lymphocyte count were also recorded in those two studies.

4 | DISCUSSION

This study conducted a meta-analysis studying the epidemiological and clinical characteristics of asymptomatic COVID19 patients. 50155 confirmed COVID-19 patients from 41 studies were included and the pooled proportion of asymptomatic infection is 15.6%. Meanwhile nearly half of the patients who were asymptomatic at

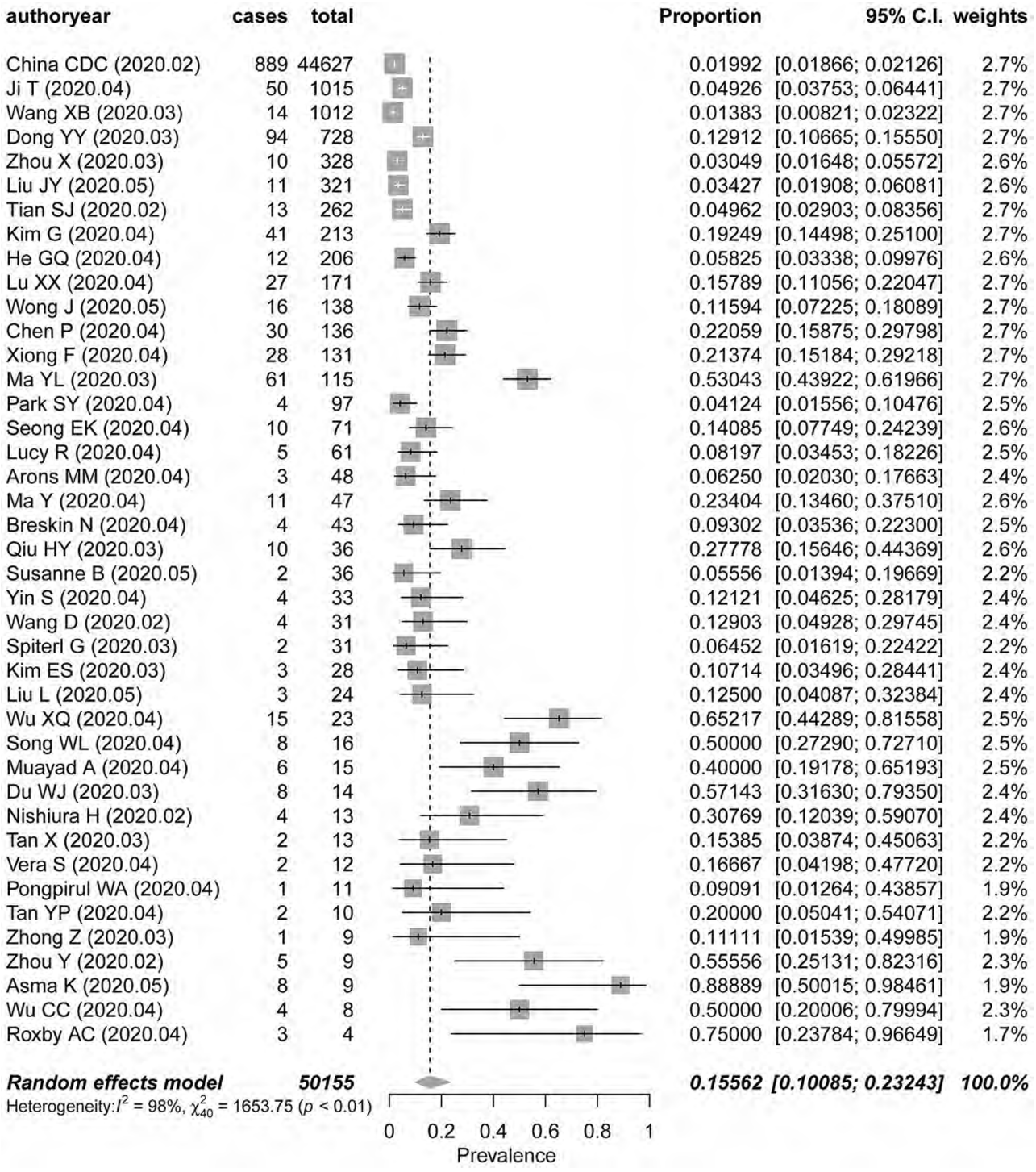

FIGURE 1 Frost plot of the proportion of asymptomatic infection in COVID-19 patients

screening time may develop symptoms during follow-up. Our results also show that there is no significant difference in the percentage of asymptomatic infection between studies conducted in China or other countries. Meantime, 11 studies whose research objects are children, got a pooled asymptomatic proportion of 27.7% among confirmed cases. This result is much higher than the result obtained from all aged groups.

Many viral infections are associated with asymptomatic, subclinical, or very mild symptoms. Influenza was estimated to be 5.2% to 35.5%.[48] Asymptomatic infections were also reported during SARS and MERS. Our result of asymptomatic proportion is lower than in many independent studies. In the study conducted by Nishiura et.al estimating the asymptomatic ratio of COVID-19 by using the information on Japanese chartered flights evacuated from Wuhan, China, this number

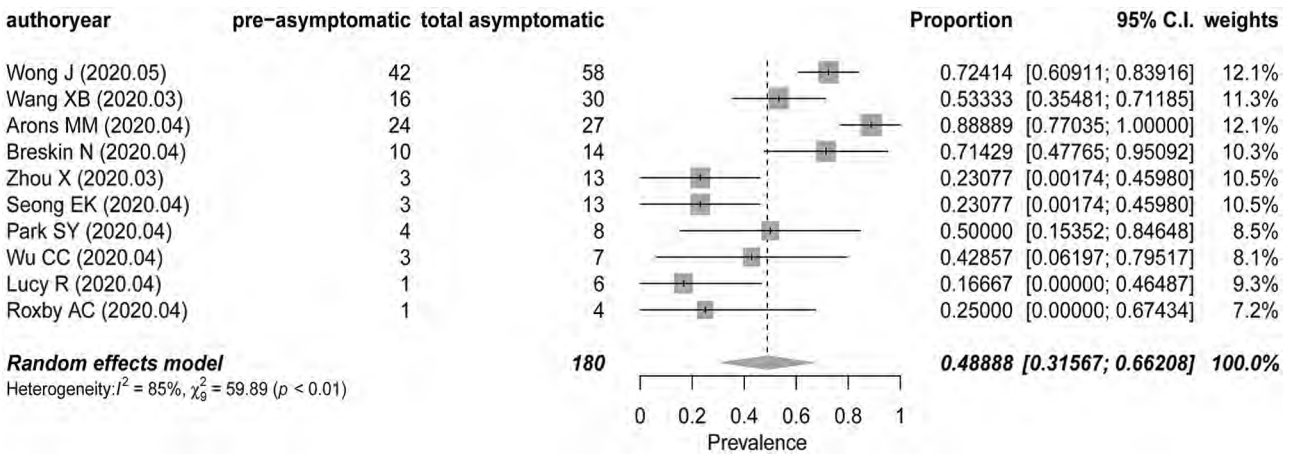

FIGURE 2 Frost plot of the proportion of presymptomatic infection in initial no-symptom COVID-19 patient

was calculated to be 30.8%.[19] This could be explained by the relatively small observation sample size. Presymptomatic is common in patients who had no symptoms at diagnosis. Those patients developed symptoms later during follow-up and are easy to be mistakenly classified as asymptomatic patients if the observation time is not long enough, which disturbs figuring out the true burden of asymptomatic infection. In 10 studies containing the number of presymptomatic infection, the pooled proportion of presymptomatic infection of COVID-19 among no-symptoms patients at screening time is 48.8%. This result indicates that nearly half of the patients who were diagnoses with COVID-19 asymptomatically at screening time may be in their incubation period and develop symptoms later in the nature course of the disease. In a study reporting 55 asymptomatic cases, even admitted asymptomatically, 39 of them developed symptoms and two of them even developed severe COVID-19 during hospitalization.[49] In one extreme case, an asymptomatic patient did not show any symptoms of COVID-19 until her sudden death due to arterial and venous thromboembolic events of COVID-19.[50]

Studies showed that most children's cases were less severe than adults. The main reason why the majority of children had a benign course of illness with mild respiratory symptoms is still unknown. This may be explained by host factors. Angiotensin-converting enzyme 2 (ACE2), the main means of pathogenesis, is significantly lower in children than in adults. Moreover, children's immune function is less mature than adults with a blunt immune response in SARS-CoV2 infection. This may highlight a possible likelihood of underestimation of children COVID-19 patients, owing to the not so ideal performance of current screening strategy relying hugely on clinical symptoms to detect COVID-9. Some studies also showed that the median age of asymptomatic patients is younger than the symptomatic patients.[26] The elderly and pregnant women also showed higher proportions of asymptomatic infection in our subgroup meta-analysis. Reasons may be explained by the relatively small sample size of these two types of patients. Special immune system states may also be a possible reason for this phenomenon.

Clinical manifestations of asymptomatic patients show that most asymptomatic patients were moderate in their clinical manifestations and stay asymptomatic until their RNA testing turned negative. Some transient symptoms were recorded in some studies. In the study conducted by Lee et al, acute anosmia or ageusia was observed in 15.7% (367/2342) patients with asymptomatic-to-mild disease severity owing to damage to the olfactory nerve during invasion and multiplication of SARS-CoV-2.[4] An asymptomatic patient can also have a transient high temperature[51] or a slightly dry cough during illness.[52] COVID-19 patients may show varying degrees of laboratory abnormalities, for example, leukopenia, increased lactate dehydrogenase, lymphocytosis, lymphopenia, etc. We still don't know whether there are differences in laboratory test results between asymptomatic patients and symptomatic patients. Though imaging examination could be a potential approach to identify asymptomatic COVID-19 patients. Even without clinical features, some asymptomatic patients do have abnormal CT features indicating pulmonary involvement,[53] which is mainly patchy shadowing and GGOs, demonstrating that chest CT method could be helpful to screen asymptomatic COVID-19 patients. IgG and IgM levels of the patients showed a gradually increasing trend during COVID-19. Noticeably, one study from Wuhan showed that 98/1021(9.6%) nucleic acid testing negative patients had IgG positive results, suggesting possible recovery from asymptomatic SARS-CoV-2 infection.[54] A study from Germany also demonstrates the importance of serological tests in COVID-19. In 5/316(1.6%) healthcare workers SARS-CoV-2-IgG antibodies could be detected. Four of the five subjects were tested negative for SARS-CoV-2 via PCR. One subject was not tested via PCR since he was asymptomatic.[55] All those results suggest that asymptomatic patients could use serological tests to detect COVID-19 infection.

Asymptomatic infection was believed to be less contagious as a consequence of a decreased virulence throughout the successive transmission, like SARS-CoV. In the study conducted by

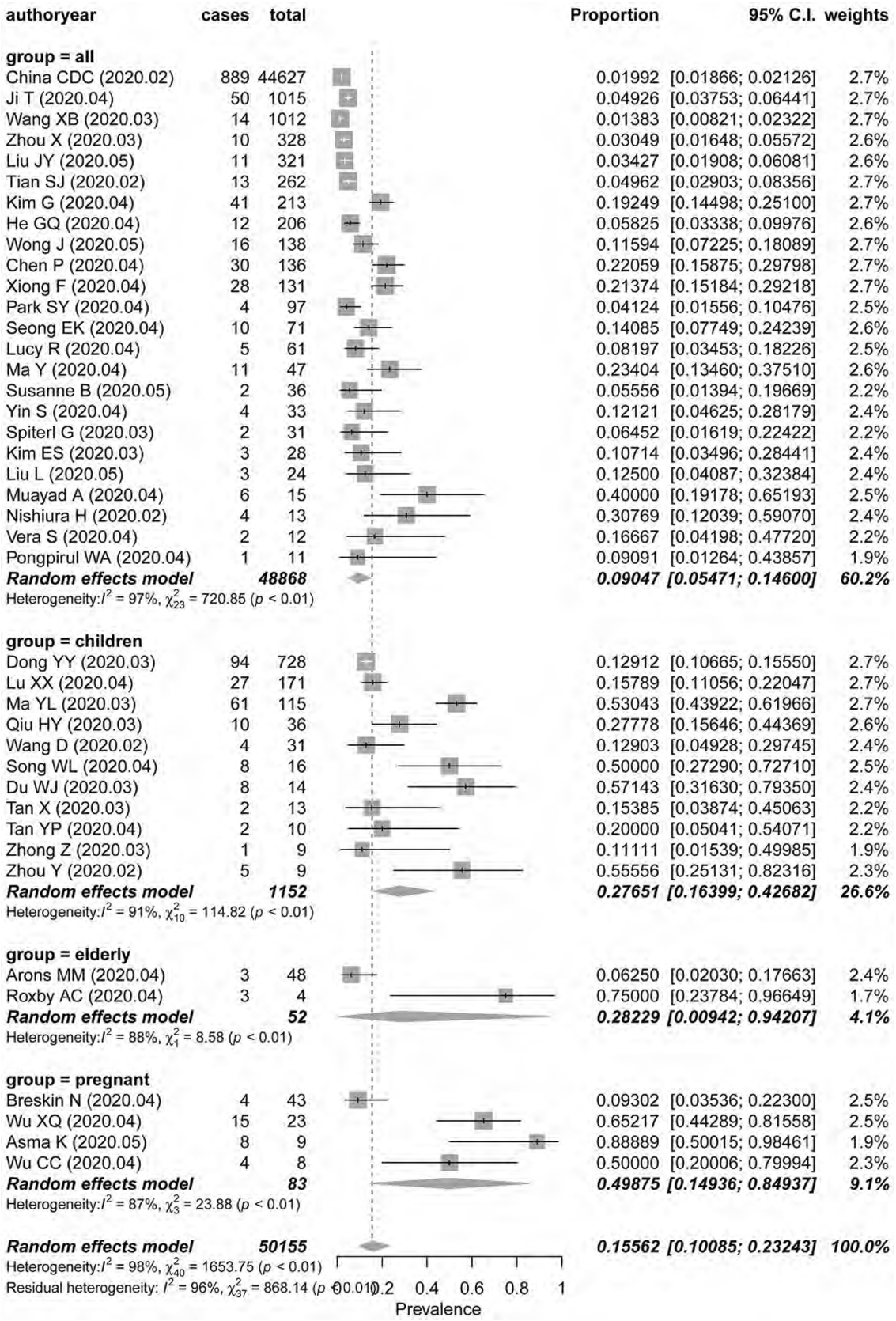

FIGURE 3 Frost plot of the proportion of asymptomatic infection in COVID-19 patients by study group

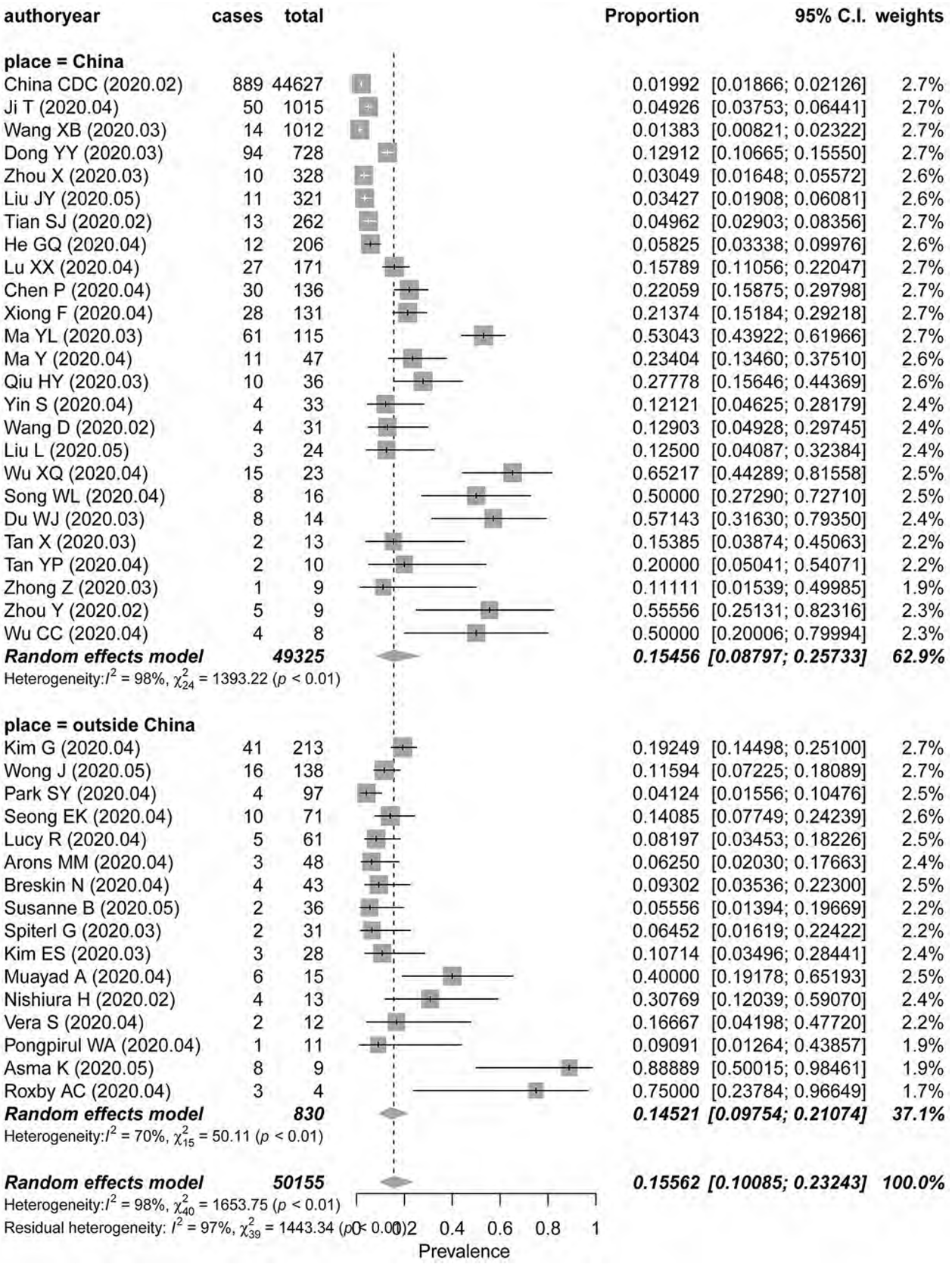

FIGURE 4 Frost plot of the proportion of asymptomatic infection in COVID-19 patients by study place

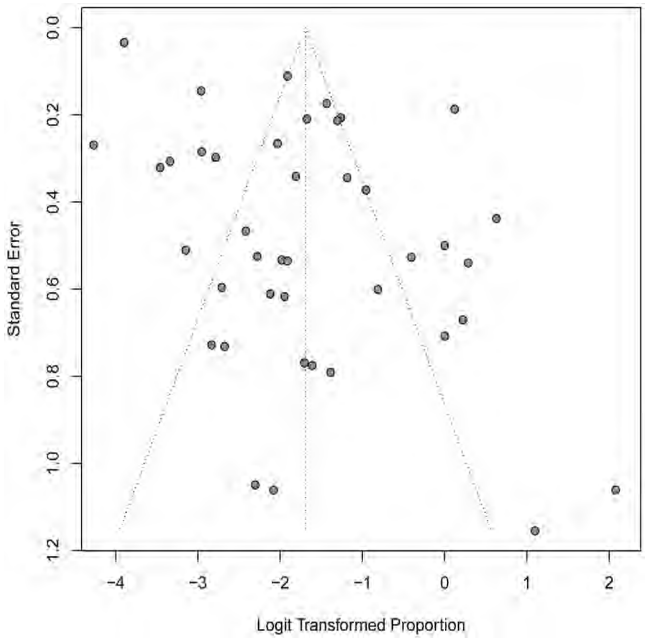

FIGURE 5 Funnel plot based on the proportion of asymptomatic infection for evaluation of publication bias

Schwierzeck et al,[36] the viral load of six asymptomatic patients is lower than six symptomatic cases. This result was supported by a mass screening by Rivett et al of health care workers as well as their contacts in the UK. Viral loads were significantly lower for 31 asymptomatic health care workers screening group than in those 30 individuals tested positive due to the presence of symptoms.[42] However, it's still too early to conclude that asymptomatic patients are less likely to transmit the virus. Relatively high viral load was also detected in asymptomatic patients[51,56] and the stool sample was tested positive in a well infant of COVID-19,[51] a man in his 20s[57] and a 10 years old boy in Zhejiang, China.[58] The role of asymptomatic patients in potential transmission of infection to close contact is still a concern. The study conducted by Hu et al certificated that asymptomatic carriers can result in person-to-person transmission and should be considered a source of COVID-19. Case 13 in that study transmitted the virus to his cohabiting family members and one of the infected individuals developed severe COVID-19 pneumonia.[59] In a family cluster report, the index patient is asymptomatic during hospitalization.[60] A familial cluster of five patients with COVID-19 pneumonia in Anyang, China, had contact with an asymptomatic

TABLE 1 Characteristics of the studies included for clinical characteristics of asymptomatic infection

(ID) Study	(20) Ma Y	(13) Xiong F	(9) He GQ	(32) Du WJ	Xu TM
Number of asymptomatic patients	11	28	12	8	15
Age (range)	23 (1-60)	62.1	31 (24-51)	NA	27
Male (percentage)	6 (54.5%)	15 (53.6%)	6 (50%)	5 (62.5%)	10 (66.7%)
Conversion time, d	10 (3-34)	NA	NA	5.43	NA
Hospital stay, d	14 (10-30)	NA	NA	NA	NA
Abnormal CT result	7 (63.6%)	NA	NA	5 (62.5%)	NA
Bilateral involvement (CT)	4	NA	4	3	4
Unilateral involvement (CT)	3	NA	5	2	4
White blood cell count (109/L)	NA	5.3 (3.5-7.9)	6.1 (4.6-6.9)	7.11	6.3 (4.8-8.1)
Decreased	3 (27.3%)	NA	NA	NA	0
Lymphocyte count (10^9/L)	NA	1.0 (0.8-1.3)	1.9 (1.5-2.1)	4.64	2.3 (1.7-3.4)
Increased	4 (36.4%)	NA	NA	NA	NA
Decreased	0 (0.0%)	NA	NA	NA	1 (6.7%)
Neutrophils count (10^9/L)	NA	4.0 (2.6-6.4)	3.4 (2.6-5.0)	1.93	3.0 (2.7-4.6)
Hemoglobin, g/L	NA	110.0 (91.0-121.0)	136.0 (121.0-144.0)	131.63	138.0 (131.0-162.0)
PLT (10^9/L)	NA	151.5 (108.9-191.0)	272.0 (210.0-311.0)	260.88	214.0 (142.0-277.0)
C-reaction protein, mg/L	NA	NA	0.80 (0.46-1.10)	0.65	NA
Increased	1 (9.1%)	NA	NA	NA	2 (2/14, 14.3%)
Lactate dehydrogenase, U/L	NA	NA	154.0 (134.0-182.0)	333.03	195.0 (166.0-388.0)
Increased	5 (45.5%)	NA	NA	NA	6 (40%)
Creatine kinase, U/L	NA	NA	65.1 (36.0-73.9)	116.85	NA
Increased	6 (54.5%)	NA	NA	NA	NA
Level of D-dimer, μg/mL	NA	NA	NA	0.49	0.2 (0.1- 0.3)
ESR, mg/L	NA	NA	14 (10-15)	NA	NA

family member before their symptom onset.[61] Presymptomatic patient can also transmit the virus by close contact.[62] Laboratory screening tests should be regarded as part of active case monitoring and contact investigations. When asymptomatic patients are identified, it is better to put the patients under monitor.

There are highlights in our studies. First, by using logit transversion of the original data, the pooled proportion of asymptomatic infection was more accurately estimated. Besides, the pooled percentage of presymptomatic infection in patients without symptoms at screening point was also analyzed in the 10 studies containing the detailed information. Meanwhile, there are limitations to our study. First of all, some including studies' observation time were not long enough or did not record negative PCR results of patients. This may lead to some presymptomatic cases to be mistaken for asymptomatic patients. Second, recalling bias may exist, some studies recorded symptoms of patients mainly basing on self-reporting. Some asymptomatic patients may have symptoms before screening and thus symptomatic person might have failed to report mild or subclinical symptoms after symptoms resolved. Third, serum viral conversion time and treatments are not available in many articles, making it's hard to conclude whether asymptomatic patients are more likely to clear virus shedding in organs and whether those patients with slightly clinical manifestations should undergo routine treatment or should only take quarantine till recovery. More studies are needed to get a comprehensive understanding of asymptomatic infection of COVID-19 to guide the prevention measures employed in the real-world.

5 | CONCLUSION

Probing into asymptomatic infection proportion is a useful quantity to understand the true burden of disease transmission. In our meta-analysis, asymptomatic infection is estimated to be 15.6% of all confirmed cases. Nearly half of the patients who have no symptoms at the screening point can develop symptoms during follow-up. Children are likely to have a higher proportion of asymptomatic infection of COVID-19 than adults. One-third of confirmed children with COVID-19 are asymptomatic. A comprehensive analysis of a possible patient's epidemical history, nucleic acid tests, serological tests, and imaging test results are required to identify asymptomatic infections of COVID-19 to intercept the transmission of this virus.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Data curation, methodology, and writing-original draft: JH and YG. Funding acquisition, writing-review, and editing, and supervision: JZ and RM. Software: JH.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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REFERENCE 15

SARS-CoV-2 Infections Among Children in the Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids) Study

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COVID-19, pediatric, community, asymptomatic, viral load

ABSTRACT

BACKGROUND: Children with SARS-CoV-2 infection typically have mild symptoms that do not require medical attention, leaving a gap in our understanding of the spectrum of illnesses that the virus causes in children.

METHODS: We conducted a prospective cohort study of children and adolescents (<21 years of age) with a SARS-CoV-2-infected close contact. We collected nasopharyngeal or nasal swabs at enrollment and tested for SARS-CoV-2 using a real-time PCR assay.

RESULTS: Of 382 children, 293 (77%) were SARS-CoV-2-infected. SARS-CoV-2-infected children were more likely to be Hispanic (p<0.0001), less likely to have asthma (p=0.005), and more likely to have an infected sibling contact (p=0.001) than uninfected children. Children ages 6-13 years were frequently asymptomatic (39%) and had respiratory symptoms less often than younger children (29% vs. 48%; p=0.01) or adolescents (29% vs. 60%; p<0.0001). Compared to children ages 6-13 years, adolescents more frequently reported influenza-like (61% vs. 39%; p<0.0001), gastrointestinal (27% vs. 9%; p=0.002), and sensory symptoms (42% vs. 9%; p<0.0001), and had more prolonged illnesses [median (IQR) duration: 7 (4, 12) vs. 4 (3, 8) days; p=0.01]. Despite the age-related variability in symptoms, we found no differences in nasopharyngeal viral load by age or between symptomatic and asymptomatic children.

CONCLUSIONS: Hispanic ethnicity and an infected sibling close contact are associated with increased SARS-CoV-2 infection risk among children, while asthma is associated with decreased risk. Age-related differences in the clinical manifestations of SARS-CoV-2 infection must be considered when evaluating children for COVID-19 and in developing screening strategies for schools and childcare settings.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for more than 20 million infections and 750,000 deaths as of August 2020. Current epidemiological data suggest children are less susceptible to SARS-CoV-2 infection than adults. Population screening in Iceland found SARS-CoV-2 was detected at a lower rate among children <10 years of age compared with adolescents and adults (6.7% vs. 13.7%).[1] Further, recent mathematical modeling from Asia and Europe estimated susceptibility of individuals <20 years of age to the virus was approximately half that of older adults.[2] Finally, in a household transmission study, the secondary attack rate was lower among children less than 20 years of age (5%) than among adults 20-59 years of age (15%) or 60 years of age or older (18%).[3] The extent to which these findings reflect differences in SARS-CoV-2 exposures among adults and children or age-related biological differences in SARS-CoV-2 susceptibility is unknown. Thus far, few factors that influence infection risk among SARS-CoV-2-exposed children have been identified.

Children infected with SARS-CoV-2 generally have milder illnesses than adults. In a recent meta-analysis of data from 371 children <18 years of age, fever (51%) and cough (37%) were the most frequently reported symptoms, while 17% of children were asymptomatic.[4] To date, studies describing the clinical characteristics of SARS-CoV-2 infections among children have been limited by cross-sectional designs, small sample sizes, or inclusion of only hospitalized or symptomatic children.[5-9] Given that a small minority of children with SARS-CoV-2 infection require hospitalization, the spectrum of illnesses caused by SARS-CoV-2 in children has not been well characterized. Such data are critical for providers evaluating children with possible coronavirus disease 2019 (COVID-19) and for the development of effective screening strategies for children to attend schools and other congregate childcare settings.

We describe risk factors, clinical manifestations, and nasopharyngeal viral loads of SARS-CoV-2 infection among 382 children and adolescents living within the catchment area of a health system in central North Carolina, constituting the largest non-hospitalized pediatric cohort described to date.

METHODS

Study Design

The Duke Biospecimens from RespirAtory Virus-Exposed Kids (BRAVE Kids) study is a prospective cohort study of children and adolescents with confirmed SARS-CoV-2 infection or close contact with an individual with confirmed SARS-CoV-2 infection. This study is being conducted within the Duke University Health System (DUHS) in Raleigh-Durham, North Carolina. The DUHS is a large, integrated health system consisting of three hospitals and over 100 outpatient clinics. This study was approved by the DUHS Institutional Review Board.

Study Participants

Eligible participants were <21 years of age and had close contact with an individual with laboratory-confirmed SARS-CoV-2 infection. Participants were identified either through presentation to the health system themselves or through presentation of a close contact with laboratory-confirmed SARS-CoV-2 infection. We defined close contact as an unprotected exposure within 6 feet to a confirmed case between 2 days before and 7 days after symptom onset or laboratory confirmation of SARS-CoV-2 infection in asymptomatic contacts. Close contacts included, but were not limited to, parents, siblings, other caregivers, partners, and relatives. Informed consent was obtained from study participants or their legal guardians; assent was obtained for children 8-17 years of age. Written consent was provided using an electronic consent document. We obtained a waiver of documentation for participants who did not have an email address or were unable to complete the electronic consent document.

Study Procedures

We collected exposure, sociodemographic, and clinical data at enrollment through review of electronic medical records and a directed caregiver questionnaire conducted by telephone. We recorded symptoms occurring up to 14 days prior to enrollment. Research staff conducted follow-up questionnaires by phone for all participants 7 days after study enrollment to document new symptoms and healthcare encounters. For participants with ongoing symptoms 7 days after study enrollment, additional questionnaires were administered 14 and 28 days after enrollment, or until the participant reported complete symptom resolution. We recorded the results of SARS-CoV-2 testing performed for clinical care. Research staff collected nasopharyngeal swabs from participants who consented to a home visit. Participants who declined a home visit received a kit for self-collection of a mid-turbinate nasal swab. Nasopharyngeal and nasal samples were collected with nylon flocked swabs (Copan Italia, Brescia, Italy) into RNAProtect (Qiagen, Hilden, Germany).

Viral Load Assay

SARS-CoV-2 RNA copies per milliliter (copies/mL) was determined by a two-step real-time quantitative PCR assay developed in the Clinical Laboratory Improvement Amendments-certified Immunology and Virology Quality Assessment Center at the Duke Human Vaccine Institute. DSP Virus/Pathogen Midi Kits (Qiagen, Hilden, Germany) were used to extract viral RNA on a QIAsymphony SP automated sample preparation platform. A reverse primer specific to the SARS-CoV-2 envelope gene was annealed to the extracted RNA and reverse transcribed into cDNA using SuperScript III Reverse Transcriptase and RNaseOut (Thermo Fisher Scientific, Waltham, MA). cDNA was treated with RNase H and then added to a custom 4x TaqMan Gene Expression Master Mix (Applied Biosystems, Foster City, CA) containing envelope gene-specific primers and a fluorescently labeled hydrolysis probe; quantitative PCR was carried out on a QuantStudio 3 Real-Time PCR system (Thermo Fisher Scientific, Waltham, MA).[10] SARS-CoV-

2 RNA copies per reaction were interpolated using quantification cycle data and a serial dilution of a highly characterized custom DNA plasmid containing the SARS-CoV-2 envelope gene sequence. The limit of quantification was 62 RNA copies/mL of sample as determined by an extensive validation process consistent for use in a clinical setting.

Data Analysis

We described characteristics of the study population by SARS-CoV-2 infection status using frequencies and percentages for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. We used chi-square or Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests or ANOVA for continuous variables to compare the characteristics of SARS-CoV-2-infected and uninfected children and to evaluate age-related differences in symptoms among SARS-CoV-2-infected children. We compared nasopharyngeal SARS-CoV-2 viral loads (measured as $\log_{10}$ copies/mL) by age, illness characteristics, and timing of sample collection relative to symptom onset using ANOVA or linear regression. We used a quantile-quantile plot to verify normality of the nasopharyngeal viral load data. Study data were managed using REDCap electronic data capture tools hosted at Duke University.[11] Analyses were performed using R version 3.6.1.[12]

RESULTS

Patient Characteristics

Among the 382 children enrolled between April 7 and July 16, 2020 (**Figure 1**), median (IQR) age was 9.7 (4.8, 15.9) years, 204 (53%) children were female, and 307 (81%) subjects were of Hispanic ethnicity. Most children were healthy, with the most commonly identified comorbidities being obesity (body mass index $\geq 95^{th}$ percentile for age; 28%) and asthma (9%). Two hundred ninety-three (77%) children were SARS-CoV-2-infected and 89 (23%) were SARS-CoV-2-uninfected (**Table 1**). Asthma was less common in

SARS-CoV-2-infected children than in uninfected children (6% vs. 17%; p=0.005). SARS-CoV-2-infected children were more likely to be of Hispanic ethnicity (88% vs. 57%; p<0.0001) and to have an infected sibling contact than uninfected children (49% vs. 29%; p=0.001). Of 145 SARS-CoV-2-infected children with an infected sibling, 46 of 145 (32%) did not have any identified adult close contacts with confirmed SARS-CoV-2 infection. Among these 46 children, median (IQR) age of the infected sibling contacts was 12.0 (8.2, 16.2) years.

Symptoms of SARS-CoV-2 Infection

One or more symptoms were reported by 206 (70%) subjects with confirmed SARS-CoV-2 infection (**Table 2**). The most commonly reported symptoms were fever (42%), cough (34%), and headache (26%). The median (IQR) duration of symptoms was 5 (3-10) days; 90% of symptomatic children reported full symptom resolution within 15 days. The clinical manifestations of SARS-CoV-2 infection varied by age (**Figure 2**). Symptoms were reported at enrollment or in follow-up in 75% of children ages 0-5 years, 61% of children ages 6-13 years, and 76% of adolescents age 14-20 years (p=0.04). Children 6-13 years of age reported respiratory symptoms less often than younger children (29% vs. 48%; p=0.01) and adolescents 14-20 years of age (29% vs. 60%; p<0.0001). Compared to children 6-13 years of age, adolescents 14-20 years of age also more frequently reported influenza-like (61% vs. 39%; p=0.002), gastrointestinal (27% vs. 9%; p=0.002), and sensory symptoms (42% vs. 9%; p<0.0001). Adolescents had more prolonged illnesses than either children ages 0-5 years [median (IQR) duration: 7 (4, 12) vs. 4 (3, 7.5) days; p=0.002] or children ages 6-13 years median (IQR) duration: 7 (4, 12) vs. 4 (3, 8) days; p=0.01]. One infant with a prior history of severe bronchiolitis required hospitalization for respiratory distress and was given remdesivir.

Nasopharyngeal Viral Loads

We performed quantitative SARS-CoV-2 PCR on nasopharyngeal samples from 258 study participants. SARS-CoV-2 was detected in 178 (69%) samples at a median (IQR) viral load of 4.0 (3.0, 5.6) log

copies/mL. We evaluated associations between nasopharyngeal viral load and age, symptoms, and the timing of sample collection relative to symptom onset (**Figure 3**). SARS-CoV-2 viral loads did not differ by age group (p=0.80). Amongst symptomatic children, nasopharyngeal viral loads were highest in the 3 days before and after onset of symptoms and declined with increasing time from symptom onset (p<0.0001). Nasopharyngeal viral loads did not differ in symptomatic and asymptomatic children of any age [median (IQR): 4.1 (3.0, 5.5) vs. 3.8 (2.8, 6.5) log copies/mL; p=0.56]; similarly, we found no association between viral load and the presence of fever, respiratory symptoms, or other reported symptom complexes.

DISCUSSION

We describe the clinical and epidemiological characteristics of 382 children and adolescents who had close contact with a SARS-CoV-2-infected individual. We found that Hispanic ethnicity and a SARS-CoV-2-infected sibling were risk factors for SARS-CoV-2 infection, while asthma was associated with a decreased infection risk. We also report that the characteristics and duration of illnesses among SARS-CoV-2-infected children vary by age. Finally, we demonstrate that nasopharyngeal SARS-CoV-2 viral loads do not differ by age or between symptomatic and asymptomatic children, and decrease sharply after symptom onset in children and adolescents.

More than 80% of children in our cohort were Hispanic, and Hispanic ethnicity was associated with an increased risk of SARS-CoV-2 infection. Individuals of Hispanic ethnicity account for 59-62% of all SARS-CoV-2 cases reported in the study catchment area.[13] Analyses of SARS-CoV-2 infections in New York and Houston identified similar racial and ethnic disparities in infection risk.[14,15] We also found that having an infected sibling was a risk factor for SARS-CoV-2 infection. Early studies suggested that children transmit SARS-CoV-2 less effectively than adults, but evidence for efficient transmission from children has been accumulating.[9,16-18] Further, there have been increasing reports of infections among children as schools,

camps, and other childcare facilities reopen in the United States and other countries.[17,19,20] Nearly one-third of the SARS-CoV-2-infected children who had an infected sibling in our cohort did not have any other known infected close contacts, suggesting probable child-to-child transmission within these households.

Our findings suggest that asthma is associated with a lower susceptibility to SARS-CoV-2 infection among children. Though many viral respiratory infections are associated with asthma exacerbations, a recent study of adults hospitalized with SARS-CoV-2 pneumonia found no difference in disease severity between asthmatic and non-asthmatic patients.[21] Several prior studies reported that individuals with asthma are underrepresented in cohorts of patients with COVID-19.[22-24] In a study of 1590 individuals hospitalized for COVID-19 in China, not a single patient had a history of provider-diagnosed asthma.[24] These observations have led to speculation that asthma may lower SARS-CoV-2 susceptibility, or alternatively protect from severe COVID-19, by promoting a Th2-dominant immune response or through reduced expression of the SARS-CoV-2 receptor (ACE2).[25]

Consistent with prior reports, we found that the majority of SARS-CoV-2-infected children had mild illnesses, with only a single subject requiring hospitalization for COVID-19. Moreover, symptoms reported by children in our cohort were broadly similar to those seen in other pediatric studies.[4,5,7,8] Among 291 SARS-CoV-2-infected children with symptom data reported to the Centers for Disease Control and Prevention (CDC), fever, cough, and headache were most commonly reported.[26] Similar to recent studies of SARS-CoV-2-infected adults, gastrointestinal, and sensory symptoms (anosmia or dysgeusia) were relatively common in our cohort.[27,28] However, we found that the clinical manifestations of SARS-CoV-2 infection among children and adolescents varied markedly by age. Approximately 75% of children <6 years of age had symptomatic infection most frequently characterized by fever or cough. By comparison, only 61% of children 6-13 years of age were symptomatic, and less than one-third of these children reported respiratory symptoms. Symptoms reported by SARS-CoV-2-infected adolescents were generally similar to

those described in adults, with high prevalence of respiratory, influenza-like, gastrointestinal, and sensory symptoms.[29] Illness duration among SARS-CoV-2-infected children in our cohort increased with age. Symptom duration among children <13 years of age was shorter than among older adolescents, and all age groups had shorter illness durations than have generally been reported in adults.[30,31] In a study of 270 outpatient SARS-CoV-2-infected adults in the United States, 35% of adults reported not having returned to their usual state of health 14 to 21 days after SARS-CoV-2 testing.[30]

Recent studies evaluating associations between age and nasopharyngeal viral load reported conflicting results. Among 145 children and adults with symptomatic SARS-CoV-2 infection in Chicago, higher amounts of viral nucleic acid were detected in samples from 46 children <5 years of age than from 51 older children and 48 adults.[32] This study used cycle threshold (Ct) values from a PCR assay that has been approved for clinical use, but has not been calibrated for quantitation.[32] A study conducted in Switzerland showed no difference in nasopharyngeal viral loads between 53 children <11 years of age and adults.[33] In this largest pediatric cohort reported to date, we found no association between age and nasopharyngeal SARS-CoV-2 viral load among children and adolescents <21 years of age. Our findings indicate that, despite marked age-related differences in the clinical manifestations of SARS-CoV-2 infection, viral load in the upper respiratory tract is similar across the age spectrum. Conflicting data have also been reported with regard to associations between nasopharyngeal viral load and illness severity.[34-36] A higher nasopharyngeal viral load predicted a shorter duration of illness among adults presenting for emergency care, while a higher viral load was associated with an increased risk of intubation in hospitalized adults.[35,36] Moreover, a prior study suggested that asymptomatic patients have viral loads that approximate those of patients with symptomatic COVID-19.[37] In our pediatric cohort, nasopharyngeal viral loads were similar across age groups and did not differ based on symptoms. Finally, as previously described in adults, we found a strong association between the timing of symptom onset and nasopharyngeal viral load, with the highest viral loads among children and adolescents observed around the time of symptom onset.[38]

Our study has several limitations. First, study recruitment was influenced by local SARS-CoV-2 testing availability and guidelines, which changed substantially during the study period and may differ from other areas. Given our study design and the relatively high rate of asymptomatic infection among children in our cohort, we were unable to determine the direction of SARS-CoV-2 transmission within households. Nearly one-third (30%) of children in our cohort were tested for SARS-CoV-2 infection at only a single time point, and some children who ultimately developed SARS-CoV-2 infection may have been misclassified as uninfected because of the timing of sample collection. The prevalence of influenza-like and sensory symptoms should be interpreted with caution in children <5 years of age, given that many children in this age group are unable to verbalize these symptoms. Further, viral loads from nasopharyngeal swabs are likely affected by sampling technique. Finally, analyses were limited to detection of viral nucleic acid, although a prior study reported a close correlation between viral load and infectious virus in symptomatic neonates, children, and adolescents.[39]

In summary, we identify risk factors for SARS-CoV-2 infection among children and present further evidence of probable child-to-child transmission within household settings. Moreover, we demonstrate that the clinical manifestations of SARS-CoV-2 infection among children and adolescents are dependent on age. Finally, we show that children and adolescents with SARS-CoV-2 infection have similar nasopharyngeal viral loads. Future studies are needed to elucidate the biological and immunological factors that account for the age-related differences in infection susceptibility and illness characteristics among children.

Declarations

SRP consults for cytomegalovirus vaccine programs at Merck, Sanofi, Moderna, and Pfizer, and receives support for research from Moderna and Merck. EBW is an investigator for clinical trials funded by Pfizer and Moderna. All other authors have no conflicts of interest to declare.

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Table 1. Characteristics of the study population

	Total (n=382)		**SARS-CoV-2-Infected (n=293)**		**SARS-CoV-2-Uninfected (n=89)**		***P***
	N (or median)	% (or IQR)	N (or median)	% (or IQR)	N (or median)	% (or IQR)	
Age, years	9.7	(4.8, 15.9)	10.4	(4.8, 16.4)	8.7	(5.0, 14.4)	0.37
Sex							0.80
Female	204	53%	158	54%	46	52%	
Male	178	47%	135	46%	43	48%	
Race							<0.0001
Black or African-American	26	7%	17	6%	9	10%	
Latino or Hispanic-American	307	81%	256	88%	51	57%	
Non-Hispanic white	45	12%	17	6%	28	31%	
Other	2	<1%	1	<1%	1	1%	
Number of household members	5	(4, 6)	5	(4, 6)	5	(4, 6)	0.97
Close contacts with SARS-CoV-2							
Parent	217	57%	159	54%	134	46%	0.09
Sibling	171	45%	145	49%	26	29%	0.001
Other	103	27%	77	26%	26	29%	0.68
Comorbidities							
Provider-diagnosed asthma	34	9%	19	6%	15	17%	0.005
Obesity (BMI ≥ 95th percentile for age)	108	28%	88	30%	20	22%	0.18

IQR, interquartile range; BMI, body mass index

Table 2. Clinical manifestations of SARS-CoV-2 infection among children and adolescents

	Total (n=293)		0-5 Years (n=87)		6-13 Years (n=109)		14-20 Years (n=97)		*P*
	n (%)		n (%)		n (%)		n (%)		
Asymptomatic infection	87	30%	22	25%	42	39%	23	24%	0.04
Symptomatic infection									
Median (IQR) days of symptoms	5	(3, 10)	4	(3, 7.5)	4	(3, 8)	7	(4, 12)	0.006
Fever	122	42%	45	52%	36	33%	41	42%	0.03
Respiratory symptoms	132	45%	42	48%	32	29%	58	60%	<0.0001
Cough	99	34%	26	30%	25	23%	48	49%	
Difficulty breathing	29	10%	7	8%	9	8%	13	13%	
Nasal congestion	34	12%	12	14%	5	5%	17	18%	
Rhinorrhea	31	11%	14	16%	1	<1%	16	16%	
Influenza-like symptoms	106	36%	5	6%	42	39%	59	61%	<0.0001
Headache	75	26%	4	5%	23	21%	48	49%	
Myalgias	49	17%	1	1%	18	17%	30	31%	
Pharyngitis	44	15%	1	1%	13	12%	30	31%	
Gastrointestinal symptoms	51	17%	15	17%	10	9%	26	27%	0.004
Abdominal pain	20	7%	5	6%	6	6%	9	9%	
Diarrhea	30	10%	11	13%	5	5%	14	14%	
Vomiting	21	7%	4	5%	3	3%	14	14%	
Sensory symptoms	51	17%	0	0%	10	9%	41	42%	<0.0001
Anosmia	43	15%	0	0%	10	9%	33	34%	
Dysgeusia	43	15%	0	0%	9	8%	34	35%	
Other symptoms	57	19%	16	18%	16	15%	25	26%	0.13
Arthralgias	10	3%	2	2%	1	1%	7	7%	
Chest pain	11	4%	0	0%	3	3%	8	8%	
Conjunctivitis	7	2%	2	2%	0	0%	5	5%	
Rash	8	3%	6	7%	0	0%	2	2%	

IQR, interquartile range

Figure 1. Flowchart of enrollment and determination of SARS-CoV-2 infection status in the study population

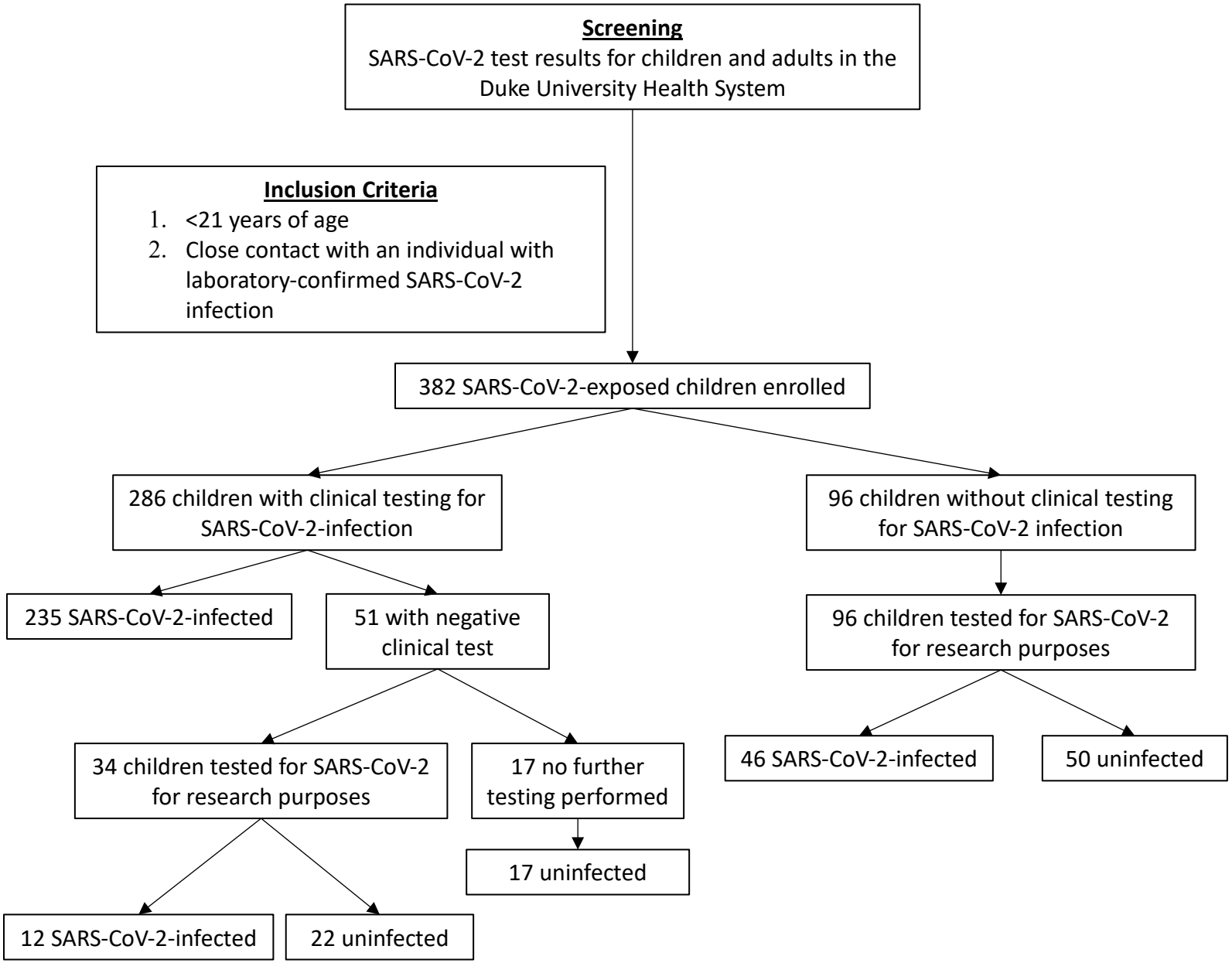


Figure 2. Prevalence of reported symptom complexes in 293 SARS-CoV-2-infected children by age. Age was categorized into three groups (0-5 years, 6-13 years, and 14-20 years), and the prevalence of specific symptom complexes are reported for children in each age group. Symptom complexes include respiratory symptoms (cough, difficulty breathing, nasal congestion, or rhinorrhea), influenza-like symptoms (headache, myalgias, or pharyngitis), gastrointestinal symptoms (abdominal pain, diarrhea, or vomiting), and sensory symptoms (anosmia or dysgeusia). Error bars correspond to the 95% confidence interval for each symptom complex in each age group.

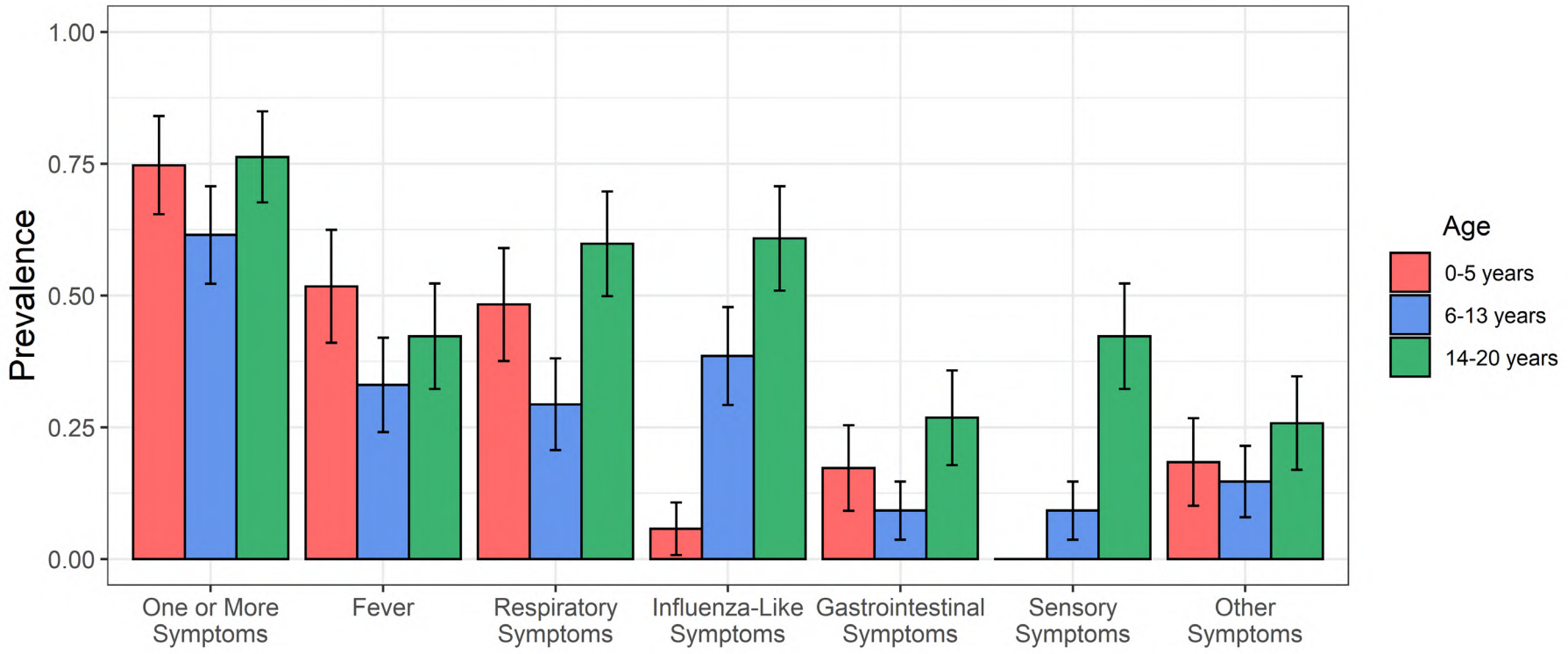
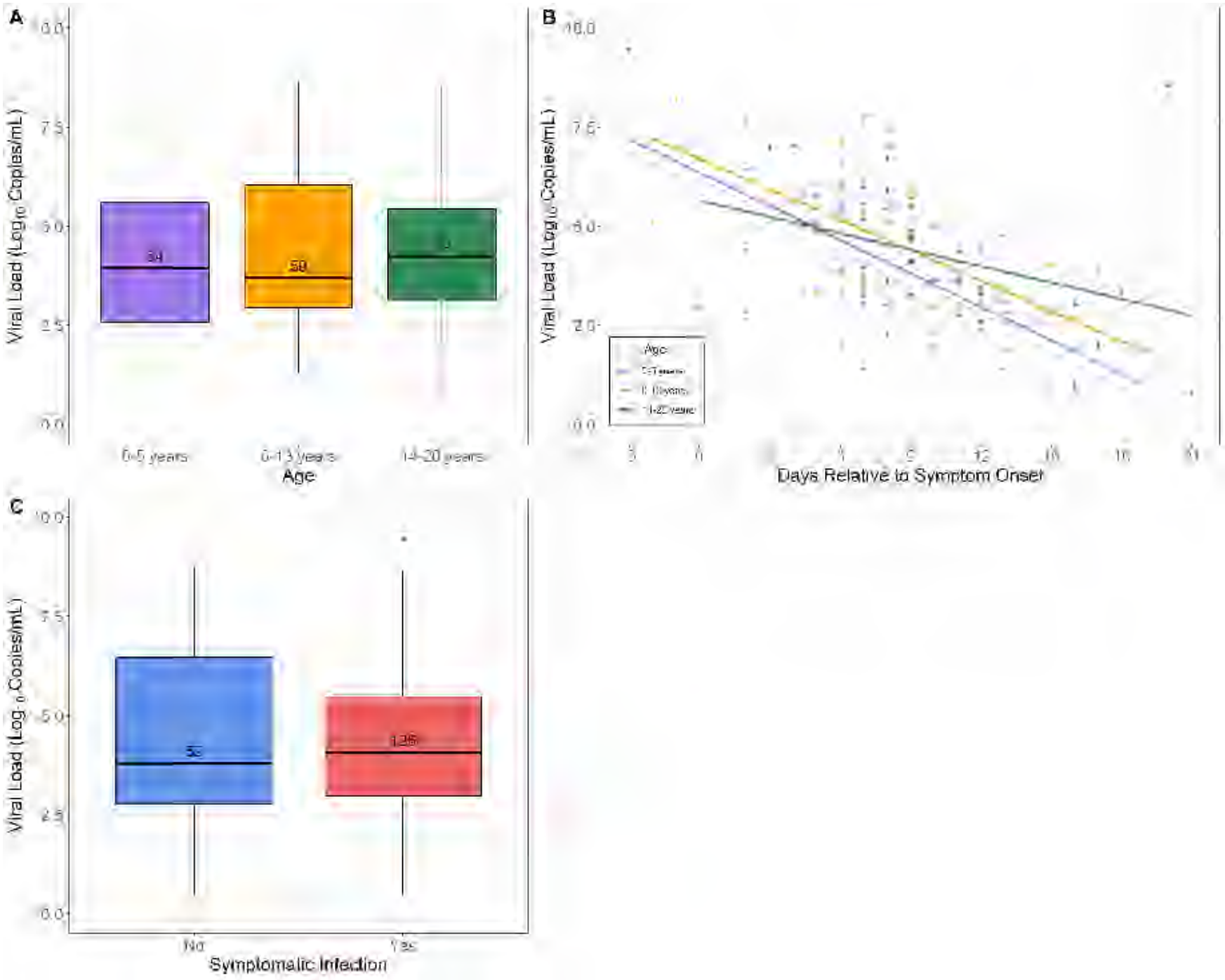


Figure 3. Evaluation of nasopharyngeal SARS-CoV-2 viral load among 178 SARS-CoV-2-infected children by age, symptoms, and timing of sample collection relative to symptom onset. Panel A shows viral loads among SARS-CoV-2-infected children by age group; no difference in viral load was seen with respect to age (p=0.80). Panel B shows viral loads in symptomatic SARS-CoV-2-infected children relative to the timing of symptom onset (days -3 to 21). SARS-CoV-2 viral loads were highest in the 3 days before and after symptom onset [median (IQR): 6.5 (4.4, 7.7) log copies/mL] and declined with increasing time from symptom onset (p<0.0001). Adjusting for the timing of sample collection relative to symptom onset, there were no differences in nasopharyngeal viral load by age group (0-5 years vs. 14-20 years, p=0.27; 6-13 years vs. 14-20 years, p=0.94). Panel C shows viral loads among SARS-CoV-2-infected children who reported one or more symptoms and children who reported no symptoms; viral loads were similar among asymptomatic children and children with symptomatic COVID-19 (p=0.56).


A
Viral Load (Log10 Copies/mL)
0.0
2.5
5.0
7.5
34
50
6-5 years
6-13 years
14-20 years
Age
B
Viral Load (Log10 Copies/mL)
0.0
2.5
5.0
7.5
10.0
Age
Days Relative to Symptom Onset
C
Viral Load (Log10 Copies/mL)
0.0
2.5
5.0
7.5
10.0
No
Yes
Symptomatic Infection

REFERENCE 16

Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020

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Presymptomatic transmission of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), might pose challenges for disease control. The first case of COVID-19 in Singapore was detected on January 23, 2020, and by March 16, a total of 243 cases had been confirmed, including 157 locally acquired cases. Clinical and epidemiologic findings of all COVID-19 cases in Singapore through March 16 were reviewed to determine whether presymptomatic transmission might have occurred. Presymptomatic transmission was defined as the transmission of SARS-CoV-2 from an infected person (source patient) to a secondary patient before the source patient developed symptoms, as ascertained by exposure and symptom onset dates, with no evidence that the secondary patient had been exposed to anyone else with COVID-19. Seven COVID-19 epidemiologic clusters in which presymptomatic transmission likely occurred were identified, and 10 such cases within these clusters accounted for 6.4% of the 157 locally acquired cases. In the four clusters for which the date of exposure could be determined, presymptomatic transmission occurred 1–3 days before symptom onset in the presymptomatic source patient. To account for the possibility of presymptomatic transmission, officials developing contact tracing protocols should strongly consider including a period before symptom onset. Evidence of presymptomatic transmission of SARS-CoV-2 underscores the critical role social distancing, including avoidance of congregate settings, plays in controlling the COVID-19 pandemic.

Early detection and isolation of symptomatic COVID-19 patients and tracing of close contacts is an important disease containment strategy; however, the existence of presymptomatic or asymptomatic transmission would present difficult challenges to contact tracing. Such transmission modes have not been definitively documented for COVID-19, although cases of presymptomatic and asymptomatic transmissions have been reported in China (*1*,*2*) and possibly occurred in a nursing facility in King County, Washington (*3*). Examination of serial intervals (i.e., the number of days between symptom onsets in a primary case and a secondary case) in China suggested that 12.6% of transmission was presymptomatic (*2*). COVID-19 cases in Singapore were reviewed to determine whether presymptomatic transmission occurred among COVID-19 clusters.

The surveillance and case detection methods employed in Singapore have been described (*4*). Briefly, all medical practitioners were required by law to notify Singapore's Ministry of Health of suspected and confirmed cases of COVID-19. The definition of a suspected case was based on the presence of respiratory symptoms and an exposure history. Suspected cases were tested, and a confirmed case was defined as a positive test for SARS-CoV-2, using laboratory-based polymerase chain reaction or serologic assays (*5*). All cases in this report were confirmed by polymerase chain reaction only. Asymptomatic persons were not routinely tested, but such testing was performed for persons in groups considered to be at especially high risk for infection, such as evacuees on flights from Wuhan, China (*6*), or families that experienced high attack rates.

Patients with confirmed COVID-19 were interviewed to obtain information about their clinical symptoms and activity history during the 2 weeks preceding symptom onset to ascertain possible sources of infection. Contact tracing examined the time from symptom onset until the time the patient was successfully isolated to identify contacts who had interactions with the patient. All contacts were monitored daily for their health status, and those who developed symptoms were tested as part of active case finding.

Clinical and epidemiologic data for all 243 reported COVID-19 cases in Singapore during January 23–March 16 were reviewed. Clinical histories were examined to identify symptoms before, during, and after the first positive SARS-CoV-2 test.

Records of cases that were epidemiologically linked (clusters) were reviewed to identify instances of likely presymptomatic transmission. Such clusters had clear contact between a source patient and a patient infected by the source (a secondary patient), had no other likely explanations for infection, and had the source patient's date of symptom onset occurring after the date of exposure to the secondary patient who was subsequently infected. Symptoms considered in the review included respiratory, gastrointestinal (e.g., diarrhea), and constitutional symptoms. In addition, the source patient's exposure had to be strongly attributed epidemiologically to transmission from another source. This reduced the likelihood that an unknown source was involved in the cases in the cluster.

Summary

What is already known about this topic?

Preliminary evidence indicates the occurrence of presymptomatic transmission of SARS-CoV-2, based on reports of individual cases in China.

What is added by this report?

Investigation of all 243 cases of COVID-19 reported in Singapore during January 23–March 16 identified seven clusters of cases in which presymptomatic transmission is the most likely explanation for the occurrence of secondary cases.

What are the implications for public health practice?

The possibility of presymptomatic transmission increases the challenges of containment measures. Public health officials conducting contact tracing should strongly consider including a period before symptom onset to account for the possibility of presymptomatic transmission. The potential for presymptomatic transmission underscores the importance of social distancing, including the avoidance of congregate settings, to reduce COVID-19 spread.

Seven Clusters of COVID-19 Cases Suggesting Presymptomatic Transmission

Investigation of COVID-19 cases in Singapore identified seven clusters (clusters A–G) in which presymptomatic transmission likely occurred. These clusters occurred during January 19–March 12, and involved from two to five patients each (Figure). Ten of the cases within these clusters were attributed to presymptomatic transmission and accounted for 6.4% of the 157 locally acquired cases reported as of March 16.

Cluster A. A woman aged 55 years (patient A1) and a man aged 56 years (patient A2) were tourists from Wuhan, China, who arrived in Singapore on January 19. They visited a local church the same day and had symptom onset on January 22 (patient A1) and January 24 (patient A2). Three other persons, a man aged 53 years (patient A3), a woman aged 39 years (patient A4), and a woman aged 52 years (patient A5) attended the same church that day and subsequently developed symptoms on January 23, January 30, and February 3, respectively. Patient A5 occupied the same seat in the church that patients A1 and A2 had occupied earlier that day (captured by closed-circuit camera) (*5*). Investigations of other attendees did not reveal any other symptomatic persons who attended the church that day.

Cluster B. A woman aged 54 years (patient B1) attended a dinner event on February 15 where she was exposed to a patient with confirmed COVID-19. On February 24, patient B1 and a woman aged 63 years (patient B2) attended the same singing class. Two days later (February 26), patient B1 developed symptoms; patient B2 developed symptoms on February 29.

Cluster C. A woman aged 53 years (patient C1) was exposed to a patient with confirmed COVID-19 on February 26 and likely passed the infection to her husband, aged 59 years (patient C2) during her presymptomatic period; both patients developed symptoms on March 5.

Cluster D. A man aged 37 years (patient D1) traveled to the Philippines during February 23–March 2, where he was in contact with a patient with pneumonia who later died. Patient D1 likely transmitted the infection to his wife (patient D2), aged 35 years, during his presymptomatic period. Both patients developed symptoms on March 8.

Cluster E. A man aged 32 years (patient E1) traveled to Japan during February 29–March 8, where he was likely infected, and subsequently transmitted the infection to his housemate, a woman aged 27 years (patient E2), before he developed symptoms. Both developed symptoms on March 11.

Cluster F. A woman aged 58 years (patient F1) attended a singing class on February 27, where she was exposed to a patient with confirmed COVID-19. She attended a church service on March 1, where she likely infected a woman aged 26 years (patient F2) and a man aged 29 years (patient F3), both of whom sat one row behind her. Patient F1 developed symptoms on March 3, and patients F2 and F3 developed symptoms on March 3 and March 5, respectively.

Cluster G. A man aged 63 years (patient G1) traveled to Indonesia during March 3–7. He met a woman aged 36 years (patient G2) on March 8 and likely transmitted SARS-CoV-2 to her; he developed symptoms on March 9, and patient G2 developed symptoms on March 12.

Investigation of these clusters did not identify other patients who could have transmitted COVID-19 to the persons infected. In four clusters (A, B, F, and G), presymptomatic transmission exposure occurred 1–3 days before the source patient developed symptoms. For the remaining three clusters (C, D, and E), the exact timing of transmission exposure could not be ascertained because the persons lived together, and exposure was continual.

Discussion

This investigation identified seven clusters of COVID-19 in Singapore in which presymptomatic transmission likely occurred. Among the 243 cases of COVID-19 reported in Singapore as of March 16, 157 were locally acquired; 10 of the 157 (6.4%) locally acquired cases are included in these clusters and were attributed to presymptomatic transmission. These findings are supported by other studies that suggest that presymptomatic transmission of COVID-19 can occur (*1*–*3*). An examination of transmission events among cases in Chinese patients outside of Hubei province, China, suggested that

FIGURE. Seven COVID-19 clusters with evidence of likely presymptomatic SARS-CoV-2 transmission from source patients to secondary patients — Singapore, January 19–March 12, 2020

Cluster A	Dates of likely transmission, symptom onset, and other exposure																	Symptoms
	Jan													Feb				
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	
Patient A1 ★																		Fever
Patient A2 ★																		Fever
Patient A3																		Fever
Patient A4																		Fever, cough
Patient A5																		Fever, sore throat

Cluster B	Dates of likely transmission, symptom onset, and other exposure															Symptoms
	Feb															
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
Patient B1 ★																Cough, headache, myalgia
Patient B2																Fever, cough, headache, myalgia

Cluster C	Dates of likely transmission, symptom onset, and other exposure									Symptoms
	Feb				Mar					
	26	27	28	29	1	2	3	4	5	
Patient C1 ★										Itchy throat, chills
Patient C2										Cough

Cluster D	Dates of likely transmission, symptom onset, and other exposure															Symptoms
	Feb							Mar								
	23	24	25	26	27	28	29	1	2	3	4	5	6	7	8	
Patient D1 ★																Cough, blocked nose
Patient D2																Fever, sore throat, sneezing

★ **Source patient**

Other exposure (clusters B, C and F: known COVID-19 case; cluster A: unknown exposure in Wuhan, China; cluster D: patient in Philippines with pneumonia; cluster E: unknown exposure in Japan; cluster G: unknown exposure in Indonesia)

Likely period of transmission from source patient to secondary patients

Symptom onset date

FIGURE. (*Continued*) Seven COVID-19 clusters with evidence of likely presymptomatic SARS-CoV-2 transmission from source patients to secondary patients — Singapore, January 19–March 12, 2020

Cluster E	Dates of likely transmission, symptom onset, and other exposure												Symptoms
	Feb	Mar											
	29	1	2	3	4	5	6	7	8	9	10	11	
Patient E1 ★													Fever
Patient E2													Cough

Cluster F	Dates of likely transmission, symptom onset, and other exposure								Symptoms
	Feb			Mar					
	27	28	29	1	2	3	4	5	
Patient F1 ★									Sore throat, blocked nose
Patient F2									Cough
Patient F3									Cough, runny nose, sore throat, myalgia

Cluster G	Dates of likely transmission, symptom onset, and other exposure										Symptoms
	Mar										
	3	4	5	6	7	8	9	10	11	12	
Patient G1 ★											Fever
Patient G2											Sore throat

★ **Source patient**

Other exposure (clusters B, C and F: known COVID-19 case; cluster A: unknown exposure in Wuhan, China; cluster D: patient in Philippines with pneumonia; cluster E: unknown exposure in Japan; cluster G: unknown exposure in Indonesia)

Likely period of transmission from source patient to secondary patients

Symptom onset date

12.6% of transmissions could have occurred before symptom onset in the source patient (*3*).

Presymptomatic transmission might occur through generation of respiratory droplets or possibly through indirect transmission. Speech and other vocal activities such as singing have been shown to generate air particles, with the rate of emission corresponding to voice loudness (*7*). News outlets have reported that during a choir practice in Washington on March 10, presymptomatic transmission likely played a role in SARS-CoV-2 transmission to approximately 40 of 60 choir members.*

*https://www.latimes.com/world-nation/story/2020-03-29/coronavirus-choir-outbreak.

Environmental contamination with SARS-CoV-2 has been documented (*8*), and the possibility of indirect transmission through fomites by presymptomatic persons is also a concern. Objects might be contaminated directly by droplets or through contact with an infected person's contaminated hands and transmitted through nonrigorous hygiene practices.

The possibility of presymptomatic transmission of SARS-CoV-2 increases the challenges of COVID-19 containment measures, which are predicated on early detection and isolation of symptomatic persons. The magnitude of this impact is dependent upon the extent and duration of transmissibility while a patient is presymptomatic, which, to date, have

not been clearly established. In four clusters (A, B, F, and G), it was possible to determine that presymptomatic transmission exposure occurred 1–3 days before the source patient developed symptoms. Such transmission has also been observed in other respiratory viruses such as influenza. However, transmissibility by presymptomatic persons requires further study.

The findings in this report are subject to at least three limitations. First, although these cases were carefully investigated, the possibility exists that an unknown source might have initiated the clusters described. Given that there was not widespread community transmission of COVID-19 in Singapore during the period of evaluation and while strong surveillance systems were in place to detect cases, presymptomatic transmission was estimated to be more likely than the occurrence of unidentified sources. Further, contact tracing undertaken during this period was extensive and would likely have detected other symptomatic cases. Second, recall bias could affect the accuracy of symptom onset dates reported by cases, especially if symptoms were mild, resulting in uncertainty about the duration of the presymptomatic period. Finally, because of the nature of detection and surveillance activities that focus on testing symptomatic persons, underdetection of asymptomatic illness is expected. Recall bias and interviewer bias (i.e., the expectation that some symptoms were present, no matter how mild), could have contributed to this.

The evidence of presymptomatic transmission in Singapore, in combination with evidence from other studies (*9*,*10*) supports the likelihood that viral shedding can occur in the absence of symptoms and before symptom onset. This study identified seven clusters of cases in which presymptomatic transmission of COVID-19 likely occurred; 10 (6.4%) of such cases included in these clusters were among the 157 locally acquired cases reported in Singapore as of March 16. Containment measures should account for the possibility of presymptomatic transmission by including the period before symptom onset when conducting contact tracing. These findings also suggest that to control the pandemic it might not be enough for only persons with symptoms to limit their contact with others because persons without symptoms might transmit infection. Finally, these findings underscore the importance of social distancing in the public health response to the COVID-19 pandemic, including the avoidance of congregate settings.

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REFERENCE 17

Factors that make an infectious disease outbreak controllable

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The aim of this study is to identify general properties of emerging infectious agents that determine the likely success of two simple public health measures in controlling outbreaks, namely (*i*) isolating symptomatic individuals and (*ii*) tracing and quarantining their contacts. Because these measures depend on the recognition of specific disease symptoms, we investigate the relative timing of infectiousness and the appearance of symptoms by using a mathematical model. We show that the success of these control measures is determined as much by the proportion of transmission occurring prior to the onset of overt clinical symptoms (or via asymptomatic infection) as the inherent transmissibility of the etiological agent (measured by the reproductive number R_0). From published studies, we estimate these quantities for two moderately transmissible viruses, severe acute respiratory syndrome coronavirus and HIV, and for two highly transmissible viruses, smallpox and pandemic influenza. We conclude that severe acute respiratory syndrome and smallpox are easier to control using these simple public health measures. Direct estimation of the proportion of asymptomatic and presymptomatic infections is achievable by contact tracing and should be a priority during an outbreak of a novel infectious agent.

epidemiology | severe acute respiratory syndrome | HIV | smallpox | influenza

The global spread of severe acute respiratory syndrome (SARS) in early 2003 caused at least 800 deaths and substantial morbidity and had a significant economic cost for the worse affected countries (1–4). Despite rapid early spread, the epidemic eventually was contained, reflecting in part a highly effective global public health response. However, containment was aided also by specific epidemiological and biological characteristics of the SARS virus. Evaluating whether the methods used to control SARS are likely to be equally effective for future outbreaks of other emerging infectious diseases requires a more detailed understanding of the factors that make containment feasible even when effective vaccines or treatment are not available.

In the first instance, two basic public health policy options exist for controlling the spread of an infectious disease in the absence of effective vaccines or treatment: (*i*) effective isolation of symptomatic individuals and (*ii*) tracing and quarantining of the contacts of symptomatic cases. Both measures rely on rapid dissemination of information to facilitate accurate diagnosis of the symptoms of the disease based on a clear and precise case definition.

For SARS, the timing of the onset of symptoms relative to peak infectivity is likely to have been a crucial factor in the success of simple public health interventions aimed at reducing transmission. In SARS patients, viremia (as measured in both fecal material and respiratory tract exudates) seems to peak between 5 and 10 days after the onset of illness and overt clinical symptoms such as elevated temperature (5). Although viremia does not always predict infectivity, the very low levels measured in the days immediately after the onset of symptoms suggest that peak infectivity occurs somewhat later. Also, no confirmed cases of transmission from asymptomatic patients have been reported to date in detailed epidemiological analyses of clusters of SARS cases (6, 7), which suggests that, for SARS, there is a period after symptoms develop during which people can be isolated before their infectiousness increases. Actions taken during this period to isolate or quarantine ill patients can effectively interrupt transmission.

Modeling Infectious Disease Outbreaks

We develop a mathematical model of infectious disease outbreak dynamics that captures the distributions of times to symptoms and infectiousness for the etiological agent concerned and provides an alternative approach to earlier theoretical studies (8). This model can be used to evaluate the impact of simple public health control measures. By exploring different distributions and different intervention strategies, we aim to establish a general quantitative framework that can help predict whether simple control measures can be successful in reversing epidemic growth if applied efficaciously at an early stage of an outbreak.

In our analyses, we focus on an infectious disease outbreak in its early stages within a community. We assume that the people in the community mix homogeneously; i.e., all susceptible individuals are equally likely to become infected. We characterize individuals in terms of their infectiousness as a function of the time (τ) since they were infected, $\beta(\tau)$, and also the probability that they have not yet developed symptoms, $S(\tau)$; example distributions are illustrated in Fig. 1. [Note that in the examples we illustrate, all patients eventually develop symptoms, because $S(\tau)$ tends to zero as the time since infection τ becomes large. More generally, if $S(\tau)$ tends to a fixed value $S_\infty > 0$, then a proportion S_∞ of infections are totally asymptomatic.]

From this description of the course of infection in the individual, illustrated in Fig. 1, we identify three important parameters:

- The basic reproduction number (9), R_0, defined as the number of secondary infections generated by a primary infection in a susceptible population and which thus measures the intrinsic transmissibility of an infectious agent; it can be calculated as the area under the infectiousness curve (see Fig. 1 and Eq. **3**). For an epidemic to expand in the early stages of spread, more than one secondary case has to be generated by the primary case, and hence we need $R_0 > 1$.
- The disease generation time T_g, which is the mean time interval between infection of one person and infection of the people that individual infects; together with R_0, T_g sets the time scale of epidemic growth and thereby the speed with which intervention measures need to be put in place to avoid a large outbreak. Specifically, the doubling time for the number of cases in a growing outbreak is of order $\ln(2)\, T_g/(R_0 - 1)$.
- The proportion of transmission occurring prior to symptoms (or asymptomatically), θ, which determines the potential for symptom-based public health control measures to reduce the number of infections.

We base the analysis on an idealized optimal intervention, without delays in implementation of isolation and quarantining, so

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Abbreviation: SARS, severe acute respiratory syndrome.

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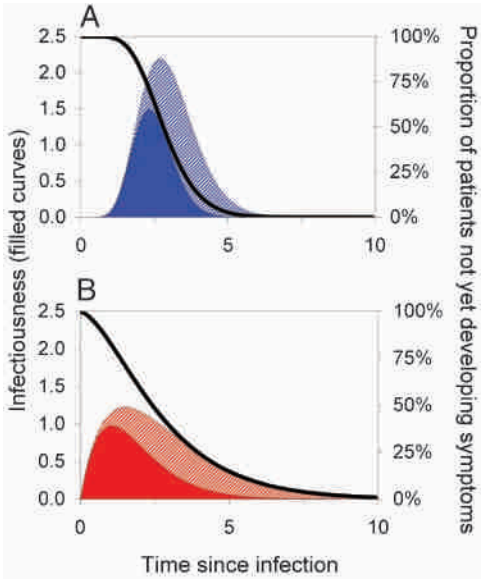

Fig. 1. Key epidemiological determinants. These determinants describe the pattern of typical disease progression for an individual patient as a function of time since infection (measured in arbitrary units). Filled curves represent infectiousness through time (left axis). The black curve represents $S(\tau)$, the probability of a person not having developed symptoms by a certain time (right axis). The basic reproduction number R_0 is the area under the infectiousness curve (solid color plus cross-hatched section). The solid-colored area represents transmission arising prior to symptoms such that θ, the proportion of presymptomatic transmission, is the proportion of the total area under the infectiousness curve that is solid-colored. (*A* and *B*) Low- and high-variance incubation and infectiousness distributions, respectively. Both cases have $R_0 = 5$, $T_g = 3$ (in arbitrary time units), and $\theta = 0.5$; *A* shows a low variance of $0.1 \times \text{mean}^2$, whereas *B* shows a high variance of $0.5 \times \text{mean}^2$.

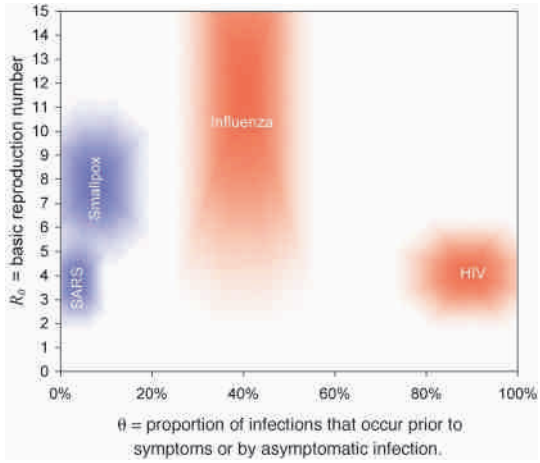

Fig. 2. Parameter estimates. Plausible ranges for the key parameters R_0 and θ (see main text for sources) for four viral infections of public concern are shown as shaded regions. The size of the shaded area reflects the uncertainties in the parameter estimates. The areas are color-coded to match the assumed variance values for $\beta(\tau)$ and $S(\tau)$ of Fig. 1 appropriate for each disease, for reasons that are apparent in Fig. 3.

that T_g does not play an important role in our analysis. However, the framework can account for a distributed delay between onset of clinical symptoms and admission to hospital for isolation (in other words, delays in implementation), within the definition of θ. The effect of delays is always to increase θ. In the SARS epidemic, for example, there were significant delays between onset of symptoms and isolation in settings such as Hong Kong. These delays shortened over the course of the epidemic because of public health announcements to encourage early reporting to a health care setting (4). Obviously the definition of θ also depends on the clinical definition of symptoms: for example, for smallpox, different values will be obtained depending on whether prodromal fever or overt rash are used to determine isolation measures. Such uncertainties need to be incorporated into the estimation of θ.

The choice of parameter θ has the key advantage that at the start of an outbreak it can readily be estimated by using contact tracing since it is the proportion of infections occurring with an asymptomatic or presymptomatic infector.

Once public health interventions are implemented, a person is isolated immediately after symptoms with an efficacy ε_I, and a proportion of the people he or she infected prior to isolation are contact-traced and quarantined with efficacy ε_T. The two parameters ε_I and ε_T together determine the efficacy of implementation of the public health measures.

By analysis and simulation of the mathematical formulation of this model (discussed in detail in the next section), we find that the interventions are sufficient to control outbreaks of infections for combinations of values of parameters R_0 and θ falling below a certain critical line. Estimated ranges of the parameters for four infections we consider here are shown as shaded areas in Fig. 2. The critical values of R_0 and θ will depend on the intervention efficacies, as well as other parameters, and are shown for some selected cases in Fig. 3. Additional assumptions about the interpatient variability of the time to symptoms and the variance of the infectiousness function are made as appropriate and are color-coded into the three figures.

Mathematical Model Formulation and Analysis‡

The basic model of disease transmission determines the dynamics of $Y(t,\tau)$, the current number of people, at time t, who were infected time τ ago. The cumulative epidemic size by time t is given by $Y(t) = \int_0^\infty Y(t,\tau)\, d\tau$, whereas the incidence of infection (i.e., rate of people acquiring infection) at time t is $\Lambda(t) = Y(t,0)$. The model predicts that an outbreak will be controlled if the incidence declines to zero, i.e., $\Lambda(t) \to 0$ as t becomes large. The model of disease spread is determined by the Von Foerster equations (15),

$$\frac{\partial Y(t,\tau)}{\partial t} + \frac{\partial Y(t,\tau)}{\partial \tau} = 0 \qquad [1]$$

$$Y(t,0) = \int_0^t \beta(\tau) Y(t,\tau)\, d\tau, \qquad [2]$$

together with the boundary conditions $Y(0,0) = Y_i$ and $Y(t,\tau) = 0$ when $t < \tau$. Here $\beta(\tau)$ represents infectiousness at time τ since infection. The reproduction number for this model is defined by

$$R_0 = \int_0^\infty \beta(\tau)\, d\tau, \qquad [3]$$

whereas the generation time (or serial interval), denoted T_g, is given by the mean of the infectiousness distribution $\beta(\tau)$,

$$T_g = \int_0^\infty \tau\beta(\tau)\, d\tau \Big/ \int_0^\infty \beta(\tau)\, d\tau. \qquad [4]$$

The asymptotic behavior of the model (in the limit $t \to \infty$) is either exponential growth or decline: by substituting an exponential function $Y(t,\tau) = K(\tau)\exp(rt)$ into Eqs. **1** and **2**, we see that $r > 0$,

‡Reading this section is not essential to an understanding of the results in this article.

i.e., epidemic growth, occurs when $R_0 > 1$, and $r < 0$, i.e., epidemic decline, occurs when $R_0 < 1$, confirming the empirical definition of R_0 in Eq. **3**.

Other quantities are of practical importance in determining the extent and rapidity of control measures needed to control an outbreak. In any novel outbreak, a detailed description of clinical symptoms should be publicized as soon as possible to facilitate the rapid isolation (self-imposed or otherwise) of symptomatic individuals. We define ε_I as the efficacy of this isolation measure, which could equally be thought of as the fraction of people isolated or the degree by which their infectiousness is reduced. Isolation of symptomatic individuals modifies the model by changing Eq. **2** to

$$Y(t,0) = \int_0^t \beta(\tau)[1 - \varepsilon_I + \varepsilon_I S(\tau)]Y(t,\tau)\, d\tau. \qquad [5]$$

Here, $S(\tau)$ is the proportion of people not having symptoms by time τ, i.e., the cumulative density function of the incubation period distribution (see Fig. 1).

It follows that isolation reduces the reproduction number from R_0 to

$$R_I = \int_0^\infty \beta(\tau)[1 - \varepsilon_I + \varepsilon_I S(\tau)]\, d\tau = R_0[1 - \varepsilon_I + \varepsilon_I \theta]. \qquad [6]$$

Here, the parameter θ is the proportion of transmission occurring before symptoms develop or by asymptomatic infection:

$$\theta = \int_0^\infty \beta(\tau)S(\tau)\, d\tau \Big/ \int_0^\infty \beta(\tau)\, d\tau. \qquad [7]$$

Isolation will lead to the control of the outbreak when $R_I < 1$. If isolation is perfect (i.e., $\varepsilon_I = 1$) and instantaneous (after symptoms), this measure can contain outbreaks when $\theta < 1/R_0$. Conditions of this general form are familiar in other contexts of infectious disease control (see ref. 9). This sets a biological upper bound for the efficacy of isolation. An intuitive interpretation of this condition is that isolating symptomatic individuals can only control an outbreak for which, on average, each person infects less than one person prior to symptoms appearing.

A more intuitive definition θ is obtained by noting that we can define the contributions of symptomatic and asymptomatic infection to R_0 as $R_0^{syx} = \int_0^\infty \beta(\tau)[1 - S(\tau)]d\tau$ and $R_0^{asyx} = \int_0^\infty \beta(\tau)S(\tau)d\tau$, respectively. θ then is just the proportion $\theta = R_0^{asyx}/(R_0^{asyx} + R_0^{syx})$. This definition may also make it easier to generalize our analysis to models in which there is greater granularity or heterogeneity in contact processes and can be used directly for empirical estimators of R_0^{asyx} and R_0^{syx}.

To capture the additional effect of tracing and quarantining the contacts of an isolated individual, we extend the model and define $Y(t, \tau, \tau')$ as the total number of people, at time t, who were infected time τ ago by people who themselves were infected time τ' ago. We define ε_T as the efficacy of contact tracing. An approximate model for $Y(t, \tau, \tau')$ is obtained by assuming that isolation and contact tracing are independent events, which will overestimate the efficacy of contact tracing, because more realistically it is performed on isolated individuals, creating a correlation between the events. To derive the equations for the model, we first define $I(t, \tau, \tau')$ as the number of infected people who are neither quarantined nor isolated [note that $Y(t, \tau, \tau')$ includes both quarantined and isolated individuals]. The hazard of being isolated then is

$$h(\tau) = -\frac{1}{S(\tau)}\frac{dS(\tau)}{d\tau} \Leftrightarrow S(\tau) = \exp\left(-\int_0^\tau h(u)du\right). \qquad [8]$$

We subdivide $I(t, \tau, \tau')$ into four groups of individuals: there are $I_{\bar{I}\bar{T}}(t, \tau, \tau')$ individuals who will never be isolated or contact-traced; $I_{I\bar{T}}(t, \tau, \tau')$ individuals who will be isolated but never contact-traced; $I_{\bar{I}T}(t, \tau, \tau')$ individuals who will never be isolated but will be contact-traced; and $I_{IT}(t, \tau, \tau')$ individuals who will be either isolated or contact-traced (competing hazards). If we define the differential operator $\Delta = \partial_t + \partial_\tau + \partial_{\tau'}$, then the equations of state are

$$\begin{aligned}
\Delta I_{\bar{I}\bar{T}}(t, \tau, \tau') &= 0 \\
\Delta I_{I\bar{T}}(t, \tau, \tau') &= -h(\tau)I_{I\bar{T}}(t, \tau, \tau') \\
\Delta I_{\bar{I}T}(t, \tau, \tau') &= -h(\tau')I_{\bar{I}T}(t, \tau, \tau') \\
\Delta I_{IT}(t, \tau, \tau') &= -[h(\tau) + h(\tau')]I_{IT}(t, \tau, \tau'),
\end{aligned} \qquad [9]$$

which represents the removal of people by isolation or contact tracing, and

$$\begin{aligned}
I_{\bar{I}\bar{T}}(t, 0, \tau) &= (1 - \varepsilon_I)(1 - \varepsilon_T)\Lambda(t, \tau) \\
I_{I\bar{T}}(t, 0, \tau) &= \varepsilon_I(1 - \varepsilon_T)\Lambda(t, \tau) \\
I_{\bar{I}T}(t, 0, \tau) &= (1 - \varepsilon_I)\varepsilon_T\Lambda(t, \tau) \\
I_{IT}(t, 0, \tau) &= \varepsilon_I\varepsilon_T\Lambda(t, \tau) \\
\Lambda(t, \tau) &= \beta(\tau)\int_\tau^t I(t, \tau, \tau')\, d\tau' \\
I &= I_{\bar{I}\bar{T}} + I_{I\bar{T}} + I_{\bar{I}T} + I_{IT},
\end{aligned} \qquad [10]$$

which represents the efficacy of isolation and contact tracing in terms of the proportions of people entering into each subgroup, occurring at a total rate proportional to the incidence $\Lambda(t, \tau)$ of people infected by people who themselves have been infected for a time τ. The dynamics of $Y(t, \tau, \tau')$ then are recovered by the following transformation:

$$\begin{aligned}
I_{\bar{I}\bar{T}}(t, \tau, \tau') &= Y_{\bar{I}\bar{T}}(t, \tau, \tau') \\
I_{I\bar{T}}(t, \tau, \tau') &= \exp\left[-\int_0^\tau h(u)\, du\right]Y_{I\bar{T}}(t, \tau, \tau') = S(\tau)Y_{I\bar{T}}(t, \tau, \tau') \\
I_{\bar{I}T}(t, \tau, \tau') &= \exp\left[-\int_{\tau'-\tau}^{\tau'} h(u)\, du\right]Y_{\bar{I}T}(t, \tau, \tau') \\
&= \frac{S(\tau')}{S(\tau' - \tau)}Y_{\bar{I}T}(t, \tau, \tau') \\
I_{IT}(t, \tau, \tau') &= \exp\left[-\int_0^\tau h(u)\, du\right]\exp\left[-\int_{\tau'-\tau}^{\tau'} h(v)\, dv\right]Y_{IT}(t, \tau, \tau') \\
&= \frac{S(\tau)S(\tau')}{S(\tau' - \tau)}Y_{IT}(t, \tau, \tau')
\end{aligned} \qquad [11]$$

such that

$$\begin{aligned}
\Delta Y_{\bar{I}\bar{T}}(t, \tau, \tau') &= 0, \qquad \Delta Y_{I\bar{T}}(t, \tau, \tau') = 0, \\
\Delta Y_{\bar{I}T}(t, \tau, \tau') &= 0, \qquad \Delta Y_{IT}(t, \tau, \tau') = 0.
\end{aligned} \qquad [12]$$

The incidence $\Lambda(t, \tau)$ can be rewritten

$$\Lambda(t,\tau) = \beta(\tau)\int_\tau^t I(t, \tau, \tau')\, d\tau'$$

$$= \beta(\tau)\int_{\tau}^{t}\left(\begin{array}{l} Y_{\bar{I}\bar{T}}(t-\tau, 0, \tau'-\tau) + S(\tau)Y_{I\bar{T}}(t-\tau, 0, \tau'-\tau) \\ \quad + \dfrac{S(\tau')}{S(\tau'-\tau)}Y_{\bar{I}T}(t-\tau, 0, \tau'-\tau) \\ \quad + \dfrac{S(\tau)S(\tau')}{S(\tau'-\tau)}Y_{IT}(t-\tau, 0, \tau'-\tau) \end{array}\right)d\tau'$$

$$= \beta(\tau)[1-\varepsilon_I+\varepsilon_I S(\tau)]\int_{\tau}^{t} Y(t, \tau, \tau')\left(1-\varepsilon_T+\varepsilon_T\frac{S(\tau')}{S(\tau'-\tau)}\right)d\tau'. \quad [13]$$

The final model for the number of infected people with isolation and contact tracing then is given simply by

$$\Delta Y(t, \tau, \tau') = 0 \quad [14]$$

and

$$Y(t, 0, \tau) = \beta(\tau)[1-\varepsilon_I+\varepsilon_I S(\tau)] \cdot\int_{\tau}^{t}\left[1-\varepsilon_T+\varepsilon_T\frac{S(\tau')}{S(\tau'-\tau)}\right]Y(t, \tau, \tau')\,d\tau'. \quad [15]$$

The threshold condition that separates exponential growth from decline is found when the eigenvalue of the next generation operator is 1. The eigenvector then is the stationary distribution of infection generation times. From Eq. **15**, we see that the operator is

$$\beta(\tau)[1-\varepsilon_I+\varepsilon_I S(\tau)]\int_{0}^{\infty}\left[1-\varepsilon_T+\varepsilon_T\frac{S(\rho+\tau)}{S(\rho)}\right](\cdot)\,d\rho \quad [16]$$

Eq. **16** can be solved for simple functions $\beta(\tau)$ and $S(\tau)$.

A similar result to Eq. **16** was derived by Müller *et al.* (8), although for a different set of assumptions regarding the contact-tracing process; in ref. 8, contact tracing was assumed to be an immediately recursive process, such that contacts of infected contacts would be screened and traced before symptoms develop, in a continuing chain until all infected contacts have been isolated. Their approach is mathematically convenient but perhaps not as realistic for when no screening tools are available or for pathogens with short infectious periods.

The calculation simplifies dramatically when the distribution of time to symptoms is exponential, i.e., $S(\tau) = \exp(-\nu\tau)$, because in that case $S(\rho+\tau)/S(\rho) = S(\tau)$, and Eq. **16** reduced to the algebraic equation

$$\int_{0}^{\infty}\beta(\tau)[1-\varepsilon_I+\varepsilon_I S(\tau)][1-\varepsilon_T+\varepsilon_T S(\tau)]\,d\tau = 1. \quad [17]$$

If, in addition, we make the unrealistic but simplifying assumption that the infectiousness distribution is exponential, i.e., $\beta(\tau) = R_0 e^{-\tau}$, such that the proportion of presymptomatic or asymptomatic transmission is $\theta = 1/(\nu+1)$, then the critical line dividing outbreak control from epidemic growth is determined by

$$R_0\left\{\left[(1-\varepsilon_I)(1-\varepsilon_T)+\varepsilon_I(1-\varepsilon_T)\theta + (1-\varepsilon_I)\varepsilon_T\theta+\varepsilon_I\varepsilon_T\frac{\theta}{2+\theta}\right]\right\} = 1. \quad [18]$$

We investigated the validity of the approximation underlying the model defined by Eqs. **14** and **15**, namely that quarantining and contact tracing are separate independent processes determined by the same distribution $S(\tau)$, by investigating the dynamics of an individual-based, discrete-time simulation defined by the following, more realistic rules:

1. At time $t = 0$, a number Y_i of people are infected with $\tau = 0$.

Thereafter, at each time step of size δ:

2. Each τ value is incremented by δ.
3. If an individual is not isolated, he or she infects a random number of new people, drawn from a Poisson distribution of mean $\beta(\tau)\,\delta$.
4. Newly infected people are assigned a τ value of 0 and a time to onset of symptoms of $S^{-1}(\rho)$, where ρ is a uniform random number between 0 and 1.
5. When an individual becomes symptomatic, he or she is isolated with probability ε_I. Symptomatic individuals who have been isolated have their contacts traced, and the people they have infected are themselves quarantined with probability ε_T. Contacts of individuals who are nonsymptomatic when quarantined are only themselves traced after symptoms develop.

The time step δ was reduced until convergence of model results was achieved, at which point the model can be expected to reproduce the dynamics of the comparable continuous time model. In the absence of contact tracing, this stochastic individual-based model was exactly equivalent in its mean behavior (dynamic as well as steady-state) to the deterministic model defined by Eqs. **14** and **15**.

Once contact tracing was introduced, the analytic solution given above overestimated (sometimes substantially) the efficacy of contact tracing when isolation is <100% effective (i.e., $\varepsilon_I < 1$). To understand the mismatch, we note that the analytical solution agreed exactly with a modified form of the individual-based simulation in which in step 4, newly infected people are instead assigned two independent times to symptoms, both drawn from the same distribution S, the first time being the time at which a person is isolated and the second time being the time at which their contacts are traced and quarantined. The distribution of time to isolation and time to contact tracing are unchanged for this modified model, but the correlation between the two events is removed. We leave the development of an analytically tractable approach to capturing this correlation for future study.

When isolation is 100% effective, i.e., $\varepsilon_I = 1$, the correlation no longer becomes important, so that once again agreement between the deterministic model and the individual-based simulation was exact (at least for the exponential and simple gamma distributions we tested).

Parameter Estimates for a Selection of Viral Infections

We estimated R_0 and θ values from published studies for four viral infections of interest. These estimates are plotted as shaded regions in Fig. 2 to compare with the scenario analysis created from the model, plotted in Fig. 3.

SARS. The basic reproduction number R_0 for SARS has been estimated in a number of ways. For the Hong Kong outbreak, we fitted a detailed transmission model to the incidence time series, which gave estimates of 2–4 (2). Lipsitch et al (3) estimated R_0 from exponential doubling times of several epidemics, which resulted in a wider range of just in excess of 1–7. To estimate θ, we first looked at the time to symptoms and infectiousness distributions, $S(\tau)$ and $\beta(\tau)$. $S(\tau)$ was determined from detailed analysis of clinical patient records (4). Up-to-date estimates based on Donnelly *et al.* (4) indicate a mean of 4.25 days and a variance of 14.25 days^2. $\beta(\tau)$ can be inferred from viral shedding data (5), which peaks 5–10 days after onset of symptoms. To maximize θ, we chose a low variance distribution (var = 0.1 × mean^2) and a peak at 9.25 days after infection, yielding $\theta < 11\%$. Because there is no evidence of presymptomatic transmission having occurred, no minimum value is given.

Smallpox. R_0 and θ have been determined from a detailed analysis of an outbreak in Nigeria by Eichner and Dietz (10). They concluded $4 < R_0 < 10$ and $0 < \theta < 20\%$ (defining symptoms as the appearance of rash). The reported incubation distributions (10) suggest that our low variance model is appropriate for smallpox.

Pandemic Influenza. A maximum bound for R_0 can be obtained by analyzing the case data from an outbreak of the 1978 H1N1 flu in a boys boarding school (11), yielding an upper bound of $R_0 < 21$. No lower bound can be defined for a novel recombinant influenza strain. β (τ) can be estimated from experimental infections. Rvachev and Longini (12) suggest, by analyzing an unpublished experiment from a Soviet laboratory, a mean of 3 days (when variance = $0.5 \times \text{mean}^2$), whereas viral shedding peaking at 2 days suggests that S (τ) has an estimated mean of 2 days (13). This results in a range of θ estimates of $30\% < \theta < 50\%$.

HIV. In populations for which spread into the general population has been seen (e.g., sub-Saharan Africa), R_0 is by definition >1. We are not aware of published estimates of R_0 for these generalized heterosexual epidemics; however, based on the formulas shown by Anderson and May (9), an upper bound of ≈5 can be obtained. If most transmission occurs during primary infection, then $\theta \approx 100\%$. If transmission is more uniform, then the distribution of time to AIDS (14) leads to a lower bound: $\theta > 80\%$.

Intervention Strategies

We investigated six intervention strategies chosen to demonstrate the impact of the biology of the etiological agent, as characterized by R_0 and θ, on the efficacy of the public health intervention. First, we considered three scenarios with no contact tracing: one with 100% effective isolation of symptomatic patients (i.e., $\varepsilon_I = 1$); one with 90% effective isolation (i.e., $\varepsilon_I = 0.9$); and one with 75% effective isolation (i.e., $\varepsilon_I = 0.75$) (Fig. 3). To these, we added three more scenarios by adding 100% effective contact tracing, which results in effective isolation of all the infected contacts of those who have been identified as symptomatic cases.

The model required two more assumptions to be made to be fully parametrized, namely characterization of the variance of the key distributions $\beta(\tau)$ and $S(\tau)$. We considered two cases that qualitatively matched the viral infections we describe below: a low variance case illustrated in Fig. 1*A*, for which the distributions are derived from gamma distributions with variance $= 0.1 \times \text{mean}^2$, chosen to match SARS and smallpox, and a high variance case illustrated in Fig. 1*B*, for which the distributions are derived from gamma distributions with variance $= 0.5 \times \text{mean}^2$, chosen to match influenza and (very approximately) HIV.

To summarize the predictions of the model, we illustrated for each scenario the critical line of R_0 and θ values that separates epidemic growth (above the line) from outbreak control (below the line) (Fig. 3). In the absence of contact tracing, the line was determined analytically by Eq. **6**, i.e., $R_0(1 - \varepsilon_I + \varepsilon_I\theta) = 1$, and was independent of which variances were chosen (i.e., Fig. 1*A* or *B*). For the cases with contact tracing, a range of R_0 and θ values was explored with the stochastic simulation repeated 100 times to determine critical parameter combinations for which, on average, infection incidence neither grew nor declined. The results depended on the variances of the distributions, and thus the analysis was repeated for the two cases of interest. In total we have nine critical lines, corresponding to six possible public health measures, and two possible variances for the distributions $\beta(\tau)$ and $S(\tau)$. The lines are plotted in Fig. 3, which is color-coded to match the assumed variances for $\beta(\tau)$ and $S(\tau)$ of Figs. 1 and 2.

Effect of Delays in Isolation

In reality, delays will occur between a patient becoming ill and being isolated. This delay obviously will reduce the efficacy of the control measures. Defining patient isolation in this context may not be straightforward, because self-isolation may arise prior to a patient presenting to the hospital and being isolated formally. This will depend on the nature of symptoms, the concomitant severity of illness, and also on the time scales involved. For influenza, for example, a person with flu-like symptoms at a workplace may not self-isolate before the end of the working day, which will be a substantial delay on influenza's rapid time scale of development and spread. For smallpox, on the other hand, the main rash is preceded by prodromal fever, and in an outbreak situation, it is plausible that most people would isolate themselves prior to or very near the start of the infectious period. For SARS, our analysis of patient reports in Hong Kong has shown that substantial delays of ≥2 days before patient hospitalization persisted during the outbreak, but these delays were substantially shorter than in the start of the outbreak (4). The effectiveness of self-isolation after fever is

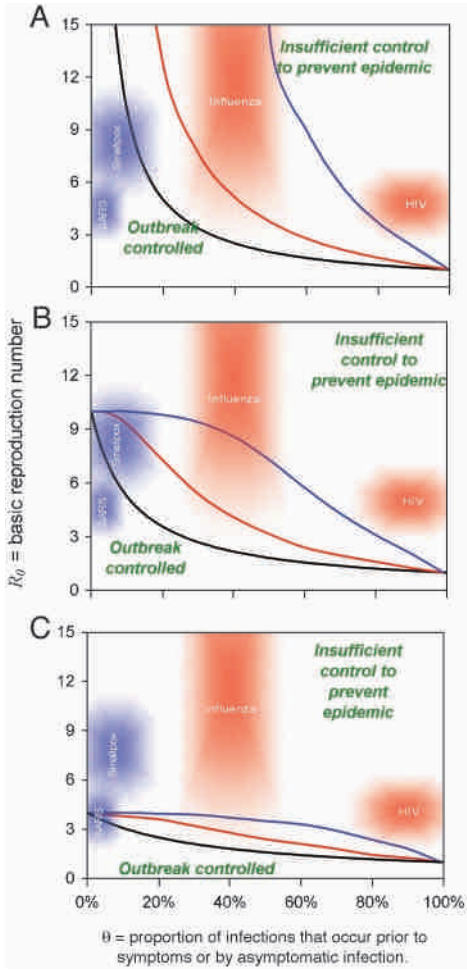

Fig. 3. Criteria for outbreak control. Each curve represents a different scenario, consisting of a combination of interventions and a choice of parameters. For each scenario, if a given infectious agent is below the R_0–θ curve, the outbreak is always controlled eventually. Above the curve, additional control measures (e.g., movement restrictions) would be required to control spread. Black lines correspond to isolating symptomatic individuals only. Colored lines correspond to the addition of immediate tracing and quarantining of all contacts of isolated symptomatic individuals. The black (isolation only) line is independent of distributional assumptions made (low or high variance), whereas the colored (isolation + contact tracing) lines match the variance assumptions made in Fig. 1 (red = high variance; blue = low variance). The efficacy of isolation of symptomatic individuals is 100% in *A*, 90% in *B*, and 75% in *C*. Contact tracing and isolation is always assumed 100% effective in the scenarios in which it is implemented (colored lines). Curves are calculated by using a mathematical model of outbreak spread incorporating quarantining and contact tracing (see main text).

not known in that context. It is straightforward to implement these delays in our modeling framework by replacing the distribution $S(\tau)$ by a new distribution $\Sigma(\tau)$, which we define as the probability that a person has not been isolated by time τ since infection. Mathematically, $\Sigma(\tau)$ then can be expressed as the convolution of the time from infection to symptoms distribution $S(\tau)$ and the time from symptoms to isolation distribution $F(\tau)$. Specifically, if $\sigma(\tau) = -d\Sigma(\tau)/d\tau$, $s(\tau) = -dS(\tau)/d\tau$, and $f(\tau) = -dF(\tau)/d\tau$ are the corresponding probability density functions, then they are related by $\sigma(\tau) = \int_0^\tau f(\tau - u)s(u)\,du$. The parameter θ then must be interpreted as the proportion of infections that arise prior to a person being isolated, defined by the equation $\theta = \int_0^{+\infty} \beta(\tau)\Sigma(\tau)d\tau$. Implementation of additional delays between a patient being isolated and his or her contacts being traced and quarantined also may be important and can be implemented in the individual-based model. The effect of delays in isolation can be envisaged in Fig. 3 by displacing the shaded areas to the right, whereas delays between isolation and contact tracing will simply bring the isolation-plus-contact-tracing lines closer to the isolation-only line. In this article, we focus on providing an estimate of what may be achieved in the best-case scenario.

Results and Conclusions

We propose that the proportion of transmission that occurs before the onset of symptoms or via asymptomatic transmission, which we call θ, is a useful new statistic for summarizing the likely feasibility of isolation- or contact-tracing-based intervention measures in controlling an epidemic outbreak. For control through isolation alone, we need $\theta < 1/R_0$. For diseases in which $\theta > 1/R_0$, contact tracing needs to be added to the set of control measures used. Fig. 3 shows how the two key parameters R_0 and θ can be used to predict whether control policies involving isolation and contact tracing will lead to outbreak containment. In general, the curves show that for very high values of θ, neither contact tracing nor isolation make any impact in preventing an epidemic; for low values of θ, only isolation is effective. Contact tracing can be important, however, to counter the effect of delays in implementation of patient isolation, because these would effectively increase θ. For intermediate values of θ, the impact of contact tracing depends on the efficacy of reporting and isolation of symptomatic cases. For efficient (i.e., >90% effective) isolation, Fig. 3 shows that contact tracing can give substantial (up to 4-fold) additional reductions in transmission.

One key advantage of using R_0 and θ as summary statistics for emerging pathogens is that, in principle, they can be readily estimated from detailed contact tracing and data collected from the first few hundred people infected in a novel disease outbreak. In addition, once the pathogen has been identified, θ can be inferred from longitudinal data on clinical symptoms and pathogen load within the infected patient. The framework presented here could be used to assess the likely success or failure of simple public health measures earlier than might be possible otherwise.

Comparing R_0 and θ estimates for SARS, smallpox, "pandemic" influenza, and HIV (Fig. 2), it is clear that SARS is the easiest of the four infections to control because of its low R_0 and θ values. Indeed, for SARS, our analysis indicates that effective isolation of symptomatic patients is sufficient to control an outbreak. The second most readily controlled infection of the four examined is smallpox. Here isolation even at the 90% level is insufficient to guarantee control, but effective contact tracing together with isolation of symptomatic cases is predicted to readily control an outbreak even for the highest feasible R_0 values. This prediction contradicts other recent modeling studies of smallpox control (16, 17), largely because those studies assumed unrealistically high values of θ for smallpox (18). Influenza, on the other hand, is predicted to be very difficult to control even with 90% quarantining and contact tracing because of the high level of presymptomatic transmission. In addition, quarantining and contact tracing for influenza would probably be unfeasible because of the very short incubation (2 days) and infectious (3–4 days) periods of that disease. Last, despite its relatively low transmissibility (outside high-risk groups), our analysis predicts that effective "self-isolation" (i.e., cessation of risk behaviors) and contact tracing of AIDS patients would have done little to control the early stages of the HIV pandemic, again because of the high level of presymptomatic transmission. However, we note that we have not considered backward contact tracing for HIV in which infectious individuals may be identified by those they have infected as well as by those who infected them, which may be important for HIV because of the high mean and variance of the incubation-time distribution (8).

The analysis presented here highlights the need for the development of a more robust analytical framework for capturing the impact of contact tracing and other reactive, locally targeted control policies on disease-transmission dynamics, particularly when realistic infectiousness and incubation distributions are being modeled. Naive analytical approaches fail to capture the correlation structure between disease generations induced by contact tracing and thus can tend to overestimate its efficacy at reducing transmission. Additional development of the model structure introduced here and alternative approaches (8, 19) is needed, together with investigation of the impact of heterogeneity of transmission. Such heterogeneity could be important in diseases for which infectiousness and time to symptoms are strongly correlated. In the case of SARS, a few superspread events resulted in a large proportion of all cases (2): early isolation of these cases would have had a dramatic impact on the course of the epidemic. Similarly, for a sexually transmitted infection, reductions in risk-taking by the most sexually active members of the population can have a disproportionately large impact on an outbreak.

Nonetheless, the lesson from the SARS outbreak is that θ, the proportion of transmission that occurs before the onset of clinical symptoms or in asymptomatic infection, may be equally as important for determining the ease of control of a novel outbreak as the intrinsic transmissibility, R_0. Both need to be considered when assessing the risks posed by emerging infectious agents. We conclude that the control of SARS through the use of simple public health measures was achieved because of the efficacy with which those measures were introduced and the moderate transmissibility of the pathogen coupled with its low infectiousness prior to clinical symptoms.

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Sex- and Age-Specific Differences in COVID-19 Testing, Cases, and Outcomes: A Population-Wide Study in Ontario, Canada

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in late 2019 and spread globally, resulting in the COVID-19 pandemic. During the two previous coronavirus epidemics, severe acute respiratory syndrome and Middle East respiratory syndrome, male sex was associated with worse clinical outcomes.[1] Emerging COVID-19 incidence and outcome data indicate that men, especially older men, may also be more affected.[2-6] It is unclear whether these findings may be skewed because of unreported sex-based differences in SARS-CoV-2 testing and the age distributions of study populations.[7,8]

METHODS

This population-wide cohort study included all residents of Ontario, Canada, who received a nasopharyngeal swab for SARS-CoV-2 between January 23, 2020 (date swab was performed for first reported case of COVID-19 in Canada) and May 26, 2020. We excluded individuals with unknown sex. Ontario is Canada's most populous province and home to nearly 15 million residents who receive universal access to medically necessary services including laboratory testing for SARS-CoV-2 under a publicly funded provincial health insurance program. We obtained data for this study from the Ontario Ministry of Health as part of the province's emergency "modeling table," including deidentified line level data on all SARS-CoV-2 testing via the Ontario Laboratories Information System and from the integrated Public Health Information System for all reported COVID-19 cases and related clinical outcomes.

We reported sex- and age-disaggregated data on SARS-CoV-2 testing, COVID-19 cases and related rates of hospitalization, intensive care unit (ICU) admission, and death. We used census data from Statistics Canada to compare sex-based testing by age with the sex and age distribution of the Ontario population. Among laboratory-confirmed COVID-19 cases, we used logistic regression to estimate sex-based odds ratios for hospitalization, ICU admission, and death, adjusting for 10-year age intervals, with the level of statistical significance set at $\alpha = .05$. All analyses were performed using SAS statistical software, v.9.4 (SAS Institute Inc). The study was approved by the research ethics board of the University of Toronto.

RESULTS

A total of 233,566 unique Ontario residents (150,195 females [64.3%] vs 83,371 males [35.7%]) received testing for SARS-CoV-2 between January 23, 2020, and May 26, 2020 (Table 1). With the exception of two age groups (ages 0–9 years and 70–79 years), males received less testing for SARS-CoV-2 than would be expected for their age-based representation in the Ontario population (Table 1).

Table 1. Sex- and Age-Disaggregated SARS-CoV-2 Testing and Positivity in Ontario, Canada (January 23–May 26, 2020)

	SARS-CoV-2 testing (n = 233,566)			Test positivity (n = 25,963)	
Age, y	Females, n (%)	Males, n (%)	Percentage of males in Ontario, 2019[a]	Females, n (%)	Males, n (%)
All ages, n (%)	150,195 (64.3)	83,371 (35.7)	49.4	14,678 (9.8)	11,285 (13.5)
0–9	2,073 (45.7)	2,465 (54.3)	51.1	116 (5.6)	122 (4.9)
10–19	3,520 (58.3)	2,522 (41.7)	51.1	290 (8.2)	316 (12.5)
20–29	17,857 (65.9)	9,224 (34.1)	51.9	1,754 (9.8)	1,546 (16.8)
30–39	21,019 (65.8)	10,915 (34.2)	49.9	1,778 (8.5)	1,547 (14.2)
40–49	23,043 (69.2)	10,255 (30.8)	48.7	2,056 (8.9)	1,576 (15.4)
50–59	26,092 (67.4)	12,638 (32.6)	49.6	2,493 (9.6)	1,843 (14.6)
60–69	16,632 (59.0)	11,559 (41.0)	48.3	1,571 (9.4)	1,562 (13.5)
70–79	11,236 (53.3)	9,831 (46.7)	46.6	1,085 (9.7)	1,114 (11.3)
≥80	28,723 (67.3)	13,962 (32.7)	40.0	3,535 (12.3)	1,659 (11.9)

[a]Census-data from Statistics Canada (Statistics Canada. Table 17-10-0005-01 Population estimates on July 1, by age and sex. https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1710000501).

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0002-8614/20/$15.00

Table 2. Sex- and Age-Disaggregated COVID-19 Clinical Outcomes in Ontario, Canada (January 23–May 26, 2020)

	Females, n (%)	Males, n (%)	aOR (95% CI) males vs females	*P* value
All ages	n = 14,678	n = 11,285		
Hospitalization	1,520 (10.4)	1,764 (15.6)	1.76 (1.63–1.90)	<.001
ICU admission	256 (1.7)	458 (4.1)	2.24 (1.91–2.62)	<.001
Death	1,116 (7.6)	980 (8.7)	1.70 (1.54–1.88)	<.001
Age 0–59 y	n = 8,487	n = 6,950		
Hospitalization	430 (5.1)	560 (8.1)	1.76 (1.54–2.00)	<.001
ICU admission	95 (1.1)	173 (2.5)	2.44 (1.90–3.15)	<.001
Death	30 (.4)	63 (.9)	2.82 (1.82–4.36)	<.001
Age 60–79 y	n = 2,656	n = 2,676		
Hospitalization	527 (19.8)	746 (27.9)	1.57 (1.38–1.78)	<.001
ICU admission	121 (4.6)	246 (9.2)	2.12 (1.69–2.65)	<.001
Death	206 (7.8)	343 (12.8)	1.77 (1.47–2.13)	<.001
Age ≥ 80 y	n = 3,535	n = 1,659		
Hospitalization	563 (15.9)	458 (27.6)	2.01 (1.75–2.32)	<.001
ICU admission	40 (1.1)	39 (2.4)	2.10 (1.35–3.28)	.0011
Death	880 (24.9)	574 (34.6)	1.60 (1.41–1.81)	<.001

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit.

Compared with females, males had a higher rate of laboratory-confirmed COVID-19 infection (11,285 males [13.5%] vs 14,678 females [9.8%]), a finding consistent across all age groups (Table 1). Among all individuals with COVID-19 infection, males had higher rates of hospitalization (1,764 males [15.6%] vs 1,520 females [10.4%]), ICU admission (458 males [4.1%] vs 256 females [1.7%]), and death (980 males [8.7%] vs 1,116 females [7.6%]) (Table 2). In age-adjusted analyses, male sex was associated with a higher odds of hospitalization (adjusted odds ratio [aOR] = 1.76; 95% confidence interval [CI] = 1.63–1.90; $P < .001$), ICU admission (aOR = 2.24; 95% CI = 1.91–2.62; $P < .001$), and death (aOR = 1.70; 95% CI = 1.54–1.88; $P < .001$) (Table 2).

DISCUSSION

We found that although more females than males were tested for SARS-CoV-2, males had a higher rate of laboratory-confirmed COVID-19 infection, hospitalization, ICU admission, and death. These findings were consistent even with age adjustment, suggesting that the observed differences in outcomes between females and males were not explained by age or systematic differences in testing by sex. Instead, they may be due to sex-based immunological or other gendered differences, such as higher rates of smoking leading to cardiovascular disease.[4-6,9]

The study is limited to a single region and could not control for underlying differences in sociodemographic characteristics and comorbidities between females and males. A recent multinational analysis reported that compared with women, men had higher COVID-19 case fatality rates that were not completely explained by their higher prevalence of comorbidities.[10] We also could not identify healthcare workers, most of whom are women, which could explain some of the sex-based differences in SARS-CoV-2 testing. With most regional health systems failing to report fully sex-disaggregated data on COVID-19, our study highlights how sex-specific reporting can guide a more gender-responsive approach to the global pandemic.[1,2,9] In particular, our findings can inform pathways for COVID-19 care including targeting older men as a particularly at-risk group that may benefit from intensified prevention and earlier intervention.[1,5,8]

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REFERENCE 19

Derivation and Validation of Clinical Prediction Rule for COVID-19 Mortality in Ontario, Canada

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Abstract

Background: SARS-CoV-2 is currently causing a high mortality global pandemic. However, the clinical spectrum of disease caused by this virus is broad, ranging from asymptomatic infection to cytokine storm with organ failure and death. Risk stratification of individuals with COVID-19 would be desirable for management, prioritization for trial enrollment, and risk stratification. We sought to develop a prediction rule for mortality due to COVID-19 in individuals with diagnosed infection in Ontario, Canada.

Methods: Data from Ontario's provincial iPHIS system were extracted for the period from January 23 to May 15, 2020. Both logistic regression-based prediction rules, and a rule derived using a Cox proportional hazards model, were developed in half the study and validated in remaining patients. Sensitivity analyses were performed with varying approaches to missing data.

Results: 21,922 COVID-19 cases were reported. Individuals assigned to the derivation and validation sets were broadly similar. Age and comorbidities (notably diabetes, renal disease and immune compromise) were strong predictors of mortality. Four point-based prediction rules were derived (base case, smoking excluded as a predictor, long-term care excluded as a predictor, and Cox model based). All rules displayed excellent discrimination (AUC for all rules ≥ 0.92) and calibration (both by graphical inspection and $P > 0.50$ by Hosmer-Lemeshow test) in the derivation set. All rules performed well in the validation set and were robust to random replacement of missing variables, and to the assumption that missing variables indicated absence of the comorbidity or characteristic in question.

Conclusions: We were able to use a public health case-management data system to derive and internally validate four accurate, well-calibrated and robust clinical prediction rules for COVID-19 mortality in Ontario, Canada. While these rules need external validation, they may be a useful tool for clinical management, risk stratification, and clinical trials.

Key words

COVID-19; SARS-CoV-2; ageing; logistic models; clinical epidemiology

Introduction

Since the COVID-19 pandemic was declared by the World Health Organization on March 12, 2020 (1), the spread of SARS-CoV-2 has taken a fearsome toll on global mortality. As of June 11, 2020, over 400,000 deaths worldwide have been attributed to SARS-CoV-2, with many more excess deaths likely related either to infection with the virus or disruption of health systems by epidemics (2). While most infections with SARS-CoV-2 are mild or even asymptomatic, approximately 20% of recognized infections are sufficiently severe to require hospitalization (3, 4). Among those hospitalized, 10-20% have an intensive care requirement, usually related to respiratory failure (3-5), though multiorgan system failure (6), clotting abnormalities (7) and angioneogenesis (8) with resultant bleeding are increasingly recognized as severe complications of COVID-19.

Numerous studies have identified clinical factors associated with requirements for intensive care and death among those with COVID-19 infection (9-11). Published prediction models to date have evaluated case-level factors that might predict care diagnosis, more severe disease requiring hospitalization, and poor outcomes (critical illness or death) (9). A recent review identified 16 prediction models focused on prognosis; 14 were based on the COVID-19 epidemic in China and the other two used aggregated public data from a variety of sources (9). The generalizability of these rules to the North American context is unclear. Furthermore, few of these efforts included conversion of prediction models into parsimonious, simple, score-based tools that can be used easily for risk stratification in clinical settings. In the context of COVID-19, a such rules might have important implications for risk-stratification of patients, streamlining decisions around hospital care vs. self-isolation (12), and prioritizing

individuals for enrollment in clinical trials of emerging therapies (e.g., convalescent plasma or antiviral drugs), as has been the case with similar tools developed for community acquired pneumonia (13).

Ontario, Canada, had identified over 30,000 virologically confirmed cases of COVID-19 in the province as of June 11, 2020 (14). Each confirmed case is the subject of epidemiological investigation by local public health authorities, who enter epidemiological, clinical and outcome data into the Province's Integrated Public Health Information System (iPHIS). Our objective was to make use of iPHIS data to develop and validate parsimonious, sensitive and specific prediction rules for infection-related death in individuals with COVID-19 in Ontario.

Methods

Study population and data collection

Ontario is Canada's most populous province, with a current population of 14.7 million (15) . The Province identified imported COVID-19 cases from China, and Iran, in January and February 2020 (16); local epidemic spread of SARS-CoV-2 has been evident since late February 2020 (17). Each of Ontario's 34 public health units is responsible for local case investigation and uploading of case information into the iPHIS data system, which is used for surveillance and case management of notifiable diseases in the Province (18). Ontario's case definition for a confirmed case of requires a positive laboratory test using a validated nucleic acid amplification test, including real-time PCR and nucleic acid sequencing (19).

Information on patient characteristics – including age group (by 10-year intervals), sex, medical comorbidities, long-term care residence, healthcare and emergency service work, case symptoms, dates of symptom onset, testing and reporting, hospitalization and intensive care admission, and mortality was collected for cases. Approximately 80% of all deaths during the Ontario COVID-19 epidemic have occurred in long term care facilities (20), and there has been little transfer of long-term care residents to intensive care units (17).

Statistical analysis

We randomly assorted cases into derivation and validation sets. Characteristics of the two sets are presented in **Table 1**. Univariable logistic regression was used to

identify factors associated with mortality in the derivation group. Continuous variables were dichotomized to facilitate score generation and ease of application in clinical settings. When a factor was found to be protective, the covariate evaluated was *absence* of the factor, so that resultant odds ratios were > 1.

Risk factors significant at $P < 0.2$, or which were thought a priori to confer important increases in risk (age and sex) were included in model building using a forward stepwise selection algorithm, with covariates selected for $P < 0.05$, and retained in the model for $P < 0.15$. We did not include interaction terms in efforts to keep a final prediction rule as simple as possible. The final regression model was transformed to a point-based rule, with each regression coefficient divided by half of the smallest coefficient and rounded to the nearest integer to obtain weighted values. Risk scores were calculated by summing the individual point values of all applicable risk factors. Risk of death can then be approximated from a graph of model-predicted probability versus calculated score (**Figure 1**) using the relation $p = 1/(e^{-(I + CS)}+1)$ where S is the individual's score, C is the prediction rule's coefficient in a logit model using score as a predictor of death, I is the intercept from the same model.

The discriminatory ability of the prediction rule in the derivation group was quantified through the area under the receiver-operating characteristic curve (ROC AUC), with 95% confidence intervals estimated through 1000 bootstrap replicates. Calibration was assessed visually and using the Hosmer-Lemeshow test for goodness of fit, which evaluates expected and observed probabilities in population deciles (21).

Survival Analytic Approach and Alternate Rules

Some analysts have expressed concern that failure to account for right censoring in could lead to bias in COVID-19 clinical prediction rules (9). As such we created a second prediction rule using Cox-proportional hazards analysis, by identifying factors associated with increased hazard of death using the same selection algorithm as applied to the logistic model described above. Log transformed hazard ratios were converted to point scores using the approach described above. Discriminative ability of the rule was evaluated using Harrell's C-statistic after constructing a Cox proportional hazards model with the score as the sole covariate in both the derivation and validation sets. ROC analysis, and score calibration, were performed by using the Cox-model-derived score as a predictor in a logistic model.

Smoking status emerged as a protective effect in our base case prediction model; this is likely to be controversial with some users. Furthermore, it might be argued that the known high mortality associated with COVID-19 in long term care settings favors creation of a rule for non-long-term care residents. As such, we made additional rules which excluded smoking status, and which excluded long-term care residents, using the approach described above.

Sensitivity Analyses

In the base case, models were built using only observations from individuals with complete data; we tested the robustness of our models by evaluating the discriminative ability and calibration of rules in datasets in which missing fields were replaced at random, and in datasets where an attribute was assumed not present if a field was left blank (e.g., if an individual had no record of presence or absence cardiac disease, they were assumed not to have cardiac disease). All analyses were performed

using Stata version 14.0 (Stata Corporation, College Station, TX). The study was approved by the research ethics board of the University of Toronto.

Results

Of 21,922 COVID-19 cases reported between January 23 and May 15, 2020, 57% were female, and 43% were aged > 59 years. The median time from symptom onset to case reporting was 5 days (IQR 4 to 10 days). Fourteen percent of cases were residents of long-term care facilities; 17% were healthcare workers. Thirteen percent of cases were hospitalized; 2% had record of intubation and/or mechanical ventilation, and case-fatality was 8%. Individuals assigned to the derivation and validation sets were broadly similar, but were significantly more likely to be smokers, less likely to have a history of chronic liver disease, and less likely to die (**Table 1**).

Derivation of the Prediction Rule

In univariable analyses, death was associated with a broad array of demographic characteristics and comorbid conditions. No association was seen between risk of death and mean neighborhood income or asthma which were not included in subsequent model building (**Table 2**). As age was provided as ordinal, 10-year age groupings (0 to 9, 10 to 19, 20 to 29, etc.) the age coefficient in models represents increased risk per increase in (age/10). Using a forward selection algorithm, we identified 7 independent predictors of death in the derivation group: age, long-term care residence, a history of renal disease, diabetes, chronic obstructive pulmonary disease, and immune compromise, and non-smoking. (**Table 3**).

The point-based prediction rule was well-calibrated between quantiles of observed and expected risk (Hosmer-Lemeshow x^2=1.58; p=0. 0.90) in the derivation group and discriminated extremely well between those who did and did not develop die (ROC AUC in the derivation group=0.95; 95% CI, 0.91-0.96). The median score (interquartile

range) was 13 (6) for survivors and 25 (6) for those who died ($p<0.001$ by the Wilcoxon rank-sum test). The rule displayed good calibration to outcomes in the validation set (Hosmer-Lemeshow $x^2=9.16$; $p=0.16$), as well as excellent discrimination (AUC 0.92, 95% CI 0.89 to 0.94) (**Figure 1** and **Figure 2**).

Alternate Prediction Rules

Three alternate rules (based on a Cox proportional hazards model, a logistic model excluding smoking status, and a model with long-term care residents excluded) were created. These models had excellent discrimination. We statistical found evidence for poor calibration of the model that excluded long-term care residents in the validation set ($P = 0.04$). The Harrell's C-statistic for a Cox model including age, male sex, diabetes, COPD, and immune compromise was 0.97 in the derivation set, and 0.96 in the validation set. Other fit statistics, and c-statistics for AUC, as well as values of the model intercept and smallest logit model coefficient (for calculation of death probability) are presented in **Table 3** and presented graphically in the **Supplement.**

Sensitivity Analyses

We re-evaluated all four prediction rules in datasets in which missing variables were assumed to not be present, and in which missing variables were replaced randomly. Discriminative ability remained good for both randomly replaced datasets (ROC curve AUC 0.84-0.90 for missing observations replaced with zeroes; AUC 0.79-0.83 for missing observations replaced randomly). The large number of observations in datasets with all missings replaced ($N = 21,922$) resulted in statistically significant differences between observed and expected mortality probabilities ($P < 0.001$ for all

analyses by Hosmer-Lemeshow test), but visual inspection suggested that calibration of rules remained very good (**Supplement**).

Discussion

Accurate prediction of mortality from COVID-19 has a number of potential applications, including rational decision making for hospital admission, prioritization of high-risk individuals for inclusion in trials of novel therapeutic agents, and to identify high risk individuals for policy purposes (e.g., to inform decisions around risks and benefits of remote work). We demonstrate here that COVID-19 mortality in identified cases can be predicted with remarkable accuracy based on the limited, readily available demographic and chronic health information available in public health line lists. The large number of COVID-19 cases that have occurred in Ontario provided sufficient statistical power for both model derivation and validation without resorting to bootstrap resampling. The discriminative ability of our rules (as reflected in AUC > 0.9 in both derivation and validation sets) places them among the upper tier of current COVID-19 prediction rules; the parsimoniousness of these rules and their conversion to an easy-to-calculate point score allows easy incorporation into clinical care.

While many of our predictors (age and comorbidities) could have been anticipated based on established epidemiology of COVID-19 (22-24), some (e.g., non-smoking as a predictor of mortality) are likely to be controversial, and it is for this reason that we derived alternate rules that exclude non-smoking. Apparent protective effects of smoking against COVID-19 acquisition (25) as well as under-representation of smokers among COVID-19 patients have been noted by others (26). However, other investigators have suggested higher risk of progression of COVID-19 in smokers(26, 27), and increased density of ACE-2 (a viral receptor) is present in the lungs of smokers (28), suggesting that apparent protective effects might result from selection

bias (e.g., individuals predisposed to very mild COVID-19 infection as a result of young age or good general health might be over-represented among those tested for COVID-19 due to smoking-related health concerns like cough). Regardless, a non-causal association with risk may still be useful for clinical prediction; if this association reflects peculiarities of Ontario's approach to COVID-19 testing we expect that it may not be generalizable to other jurisdictions that test more widely.

Similarly, the strong effect of long-term care residence on mortality is unsurprising, given the high fraction of long-term care deaths seen during the Canadian COVID-19 epidemic to date (20). As such we created alternate rules that exclude smoking and long-term care residence; these rules can be used in place of our base case rule, as they have similar discriminative ability. Lastly, to avoid biases that might be introduced by right-censoring (i.e., lack of mortality in individuals in the study cohort as a result of insufficient follow up time) we derived an additional rule using survival methods, which also performed well. There was substantial overlap between all four prediction rules in included covariates: notably, age, diabetes, and immune compromise were included in all four rules we derived, and renal or chronic obstructive pulmonary disease were included in 3 of four rules.

Our analysis had many limitations; the use of a public health record system not explicitly designed as a research tool means that we lack laboratory and radiological results that have been useful in other prediction models (23, 29). Furthermore, missing data was a significant limitation of our dataset, although our models appeared robust even with random replacement of predictors and outcomes that should bias associations towards the null. In that sense, the ability to derive simple, accurate and parsimonious rules, which perform well in split-halves validation, despite limitations

in our dataset, may suggest generalizability of application outside Ontario. We hope that other groups will evaluate our rules in other settings.

In summary, we developed and internally validated a prediction rule for COVID-19 mortality using a large and detailed public health line list in the Canadian province of Ontario. The rule was well calibrated and discriminated well and was robust in sensitivity analyses to assess the impact of missing information on predictor variables. If externally validated, this rule might facilitate decision making during future epidemic waves.

Figure Legends

Figure 1. Observed and Predicted Risk of Death by Score, Base-Case Rule

Plot of predicted probability of death (Y-axis) by model score (X-axis) for base case prediction rule. Curve represents model predictions, circles represent observed proportion who died. Circle size proportionate to number of deaths at a given score. Top panel: derivation set; bottom panel: validation set.

Figure 2. Receiver Operator Characteristic Curve, Base-Case Rule.

Sensitivity of rule (Y-axis) is plotted against false positive rate (1-specificify, X-axis) for different positivity criteria available from score. Confidence intervals for area under the curve derived via boostrapping. Top panel: derivation set; bottom panel: validation set.

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Table 1. Characteristics of Confirmed COVID-19 Cases in Ontario, Canada to May 15, 2020

Covariate	Overall (% or Median, IQR)	Derivation (% or Median, IQR)	Validation (% or Median, IQR)	P-value
All	21922 (100)	10957 (50)	10965 (50)	
Age > 59	9398 (43)	4672 (43)	4705 (43)	0.63
FSA Income*	$64,869 ($26,402)	$64,986 ($26,937)	$64,869 ($26,402)	0.73
Male gender	9389 (43)	4708 (43)	4681 (43)	0.68
Time from symptom onset to report	5 (6)	5 (6)	5 (6)	0.81
Long-term care resident	3102 (14)	1539 (14)	1563 (14)	0.50
Outbreak-associated case†	9438 (43)	4772 (44)	4666 (43)	0.14
Healthcare worker	3780 (17)	1888 (17)	1892 (17)	0.55
Homeless shelter worker	106 (0.4)	61 (0.6)	45 (0.4)	0.13
Homeless	226 (1)	102 (0.9)	124 (1)	0.11
Smoker (recorded)	515 (2)	285 (3)	230 (2)	0.01
Pregnant or post-partum	91 (0.4)	58 (0.5)	45 (0.4)	0.21
Comorbidity history				
Anemia or hemoglobinopathy	370 (2)	177 (2)	193 (2)	0.42

Chronic liver disease	94 (0.4)	38 (0.3)	56 (0.5)	0.06
Renal disease	358 (2)	185 (2)	173 (2)	0.55
Diabetes	1294 (6)	623 (6)	671 (6)	0.22
Chronic obstructive pulmonary disease	267 (1)	134 (1)	133 (1)	0.97
Asthma	880 (4)	409 (4)	390 (4)	0.58
Cardiovascular disease	2032 (9)	979 (9)	1053 (10)	0.15
Malignancy	460 (2)	211 (2)	249 (2)	0.06
Immune compromise	318 (1)	162 (1)	156 (1)	0.69
Tuberculosis	52 (0.2)	32 (0.2)	20 (0.2)	0.10
Obesity	295 (1)	137 (1)	158 (1)	0.16
Outcomes				
Hospitalized	2779 (13)	1355 (12)	1424 (13)	0.17
Record of intubation and/or mechanical ventilation	408 (2)	195 (2)	213 (2)	0.31
Died	1825 (8)	862 (8)	963 (9)	0.02

NOTE: Proportions compared with chi-squared test, continuous variables compared with Wilcoxon rank-sum test.

*Based on mean after tax income by FSA (2016 Canadian Census).

†Defined as case or cases with outbreak number signifying part of an outbreak investigation by a public health unit.

Table 2. Univariable and Multivariable Analyses, and Point Score Derivation, Base Case Prediction Rule

Covariate	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	Logit	Points
Age (per 10-year increment)	3.48 (3.28 to 3.70)	<0.001	2.42 (1.78 to 3.29)	0.88	2
Low income*	1.04 (0.92 to 1.18)	0.55	---	---	---
Male gender	1.13 (1.02 to 1.25)	0.02	---	---	---
Time from symptoms to diagnosis $\leq$ 3 days†	1.27 (1.14 to 1.42)	<0.001	---	---	---
Long-term care resident	22.62 (19.08 to 26.83)	<0.001	6.24 (2.95 to 13.21)	1.83	4
Outbreak-associated case	9.15 (8.10 to 10.33)	<0.001	---	---	---
Non-healthcare worker‡	30.56 (15.77 to 59.22)	<0.001	---	---	---
Non-homeless shelter worker‡	5.79 (0.80 to 41.96)	0.08	---	---	---
Non-homeless‡	2.31 (0.94 to .712143	0.07	---	---	---
Non-smoker‡	1.65 (0.98 to 2.77)	0.06	6.86 (0.73 to 64.27)	1.93	4

Pregnant or post-partum	No deaths	---	---	---	---
Comorbidity history					
Anemia or hemoglobinopathy	5.08 (3.68 to 7.02)	<0.001	---	---	---
Chronic liver disease	6.06 (3.50 to 10.46)	<0.001	---	---	---
Renal disease	9.85 (7.31 to 13.26)	<0.001	2.37 (0.97 to 5.77)	0.86	2
Diabetes	6.49 (5.22 to 8.06)	<0.001	2.19 (1.08 to 4.42)	0.78	2
Chronic obstructive pulmonary disease	11.22 (8.14 to 15.44)	<0.001	3.26 (1.15 to 9.26)	1.18	3
Asthma	1.01 (0.71 to 1.44)	0.96	---	---	---
Cardiovascular disease	11.38 (9.12 to 14.20)	<0.001	---	---	---
Malignancy	6.36 (4.80 to 8.44)	<0.001	---	---	---
Immune compromise	4.12 (2.94 to 5.79)	<0.001	3.56 (1.12 to 11.35)	1.27	3
Tuberculosis	0.88 (0.21 to 3.70)	<0.001	---	---	---
Obesity	2.63 (1.78 to 3.89)	<0.001	---	---	---

*Residence in FSA in lowest quartile of income

†Lowest quartile lag between symptoms and diagnosis

‡Non-exposure status evaluated as risk factor to maintain positive covariate.

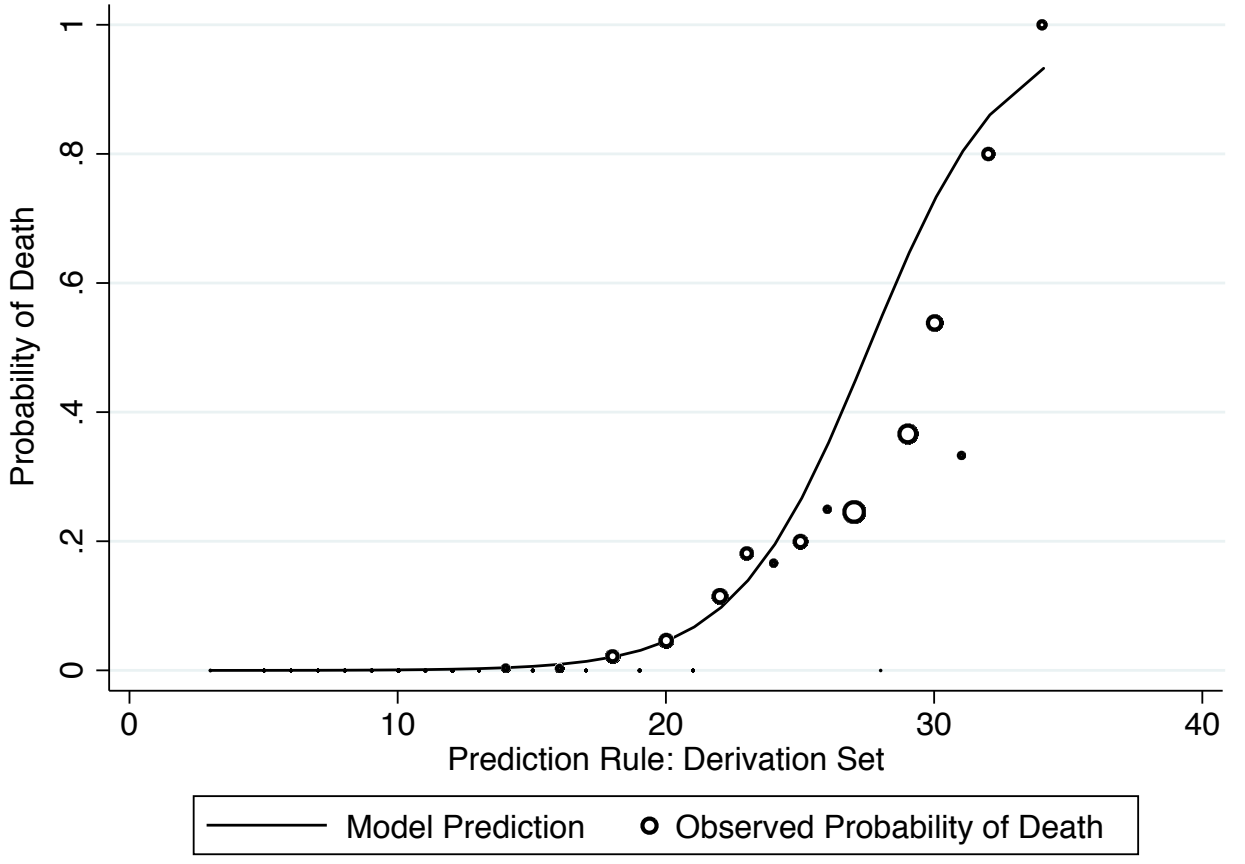
Table 3. Base Case and Alternate Clinical Prediction Rules

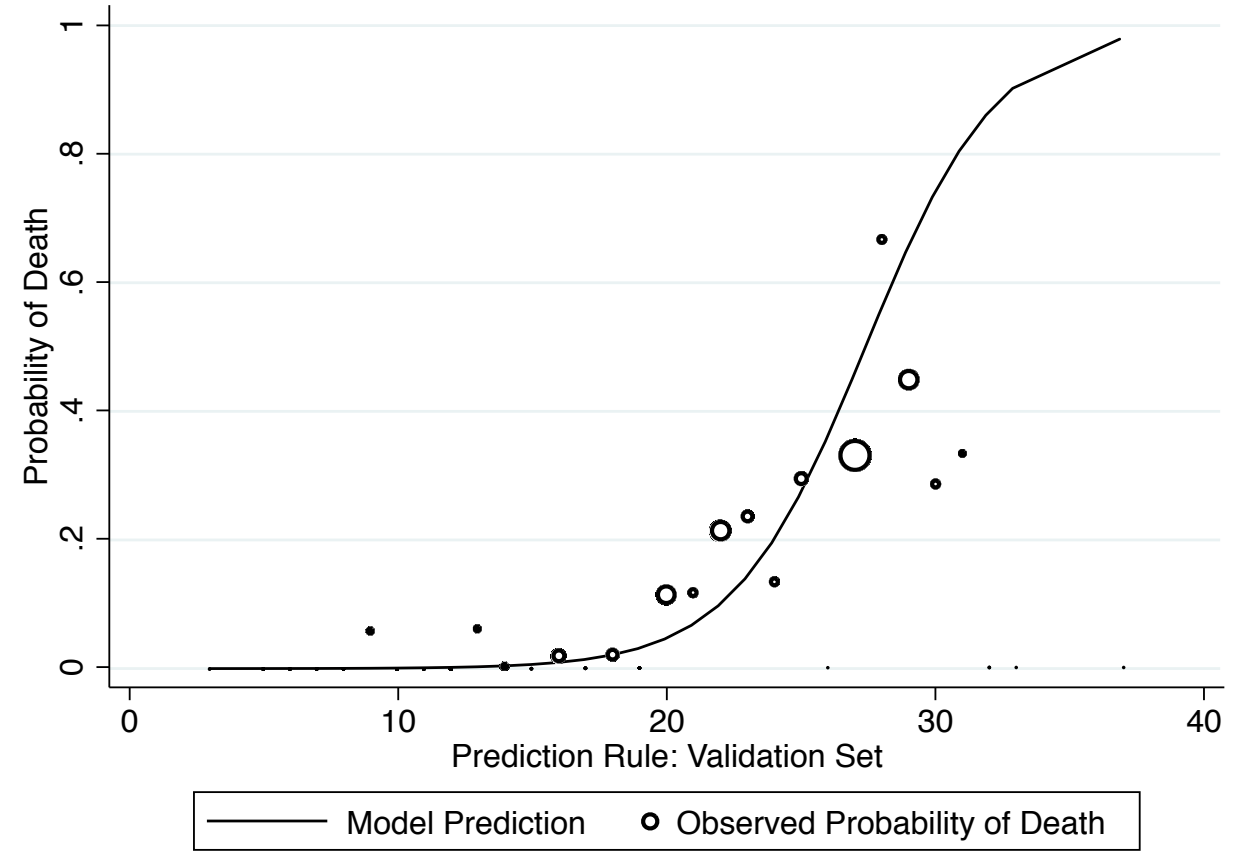
Covariate	Rule 1: Base Case	Rule 2: Cox model-based*	Rule 3: Non-smokers Excluded	Rule 4: Long term care residents excluded
Age	2	3	3	2
Male sex	---	2	---	---
Renal disease	2	---	2	3
Immune compromised	3	4	5	4
Diabetic	2	4	3	2
COPD	3	3	3	---
Cardiovascular disease	---	---	2	4
Long-term care resident	5	---	7	---
Non-smoker	5	---	---	---
Time from symptoms to diagnosis $\leq$ 3 days	---	---	---	2
Maximum points	40	40	50	40
Smallest logit model coefficient (C)*	0.36	0.34	0.25	0.52
Model intercept (I)*	-9.81	-9.99	-8.33	-12.51

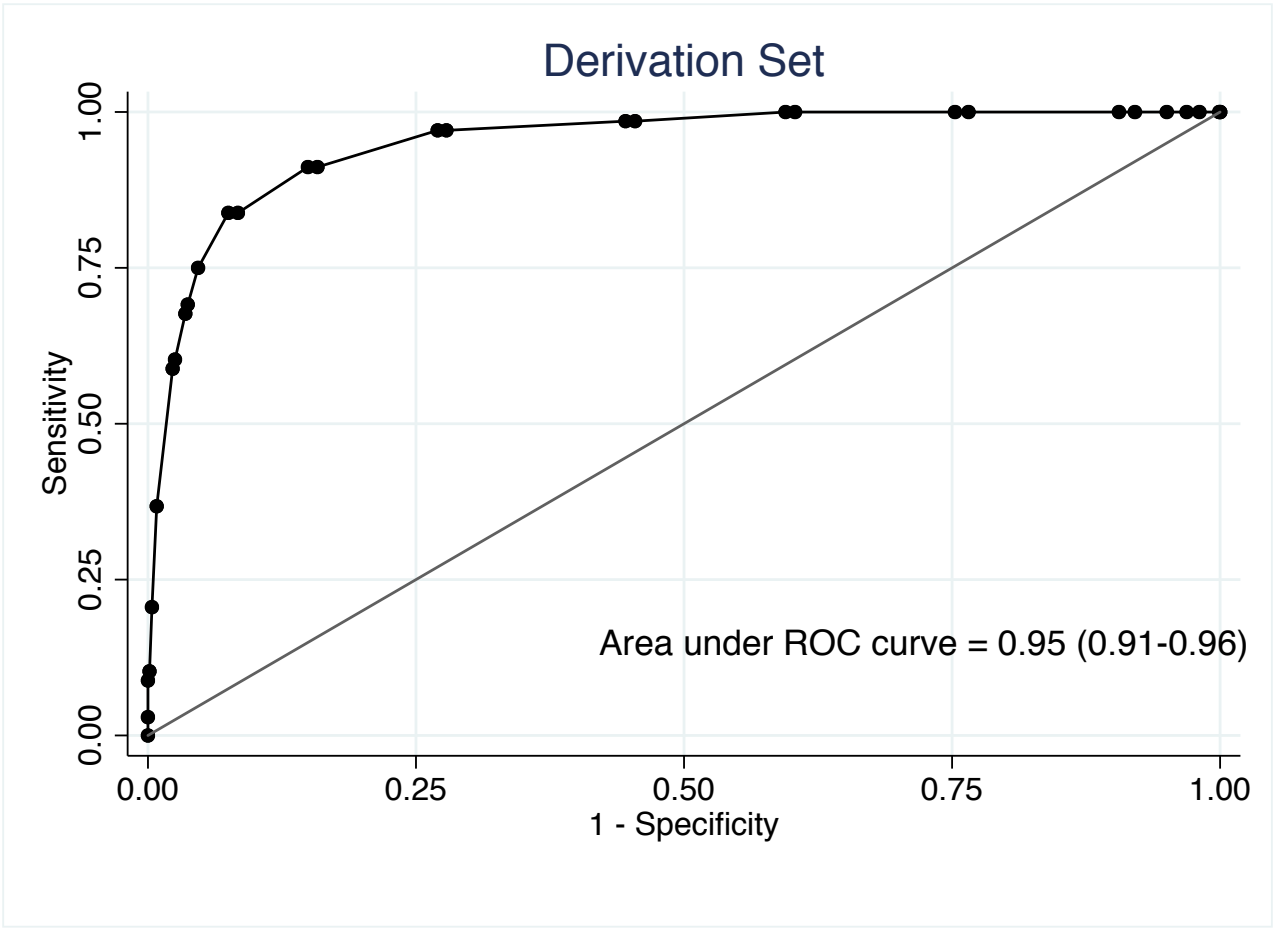
AUC in derivation set (validation set)	0.95 (0.92)	0.93 (0.91)	0.95 (0.92)	0.92 (0.91)
Hosmer-Lemeshow goodness-of-fit test P-value in derivation set (validation set)	0.85 (0.20)	0.50 (0.24)	0.99 (0.40)	0.59 (0.04)

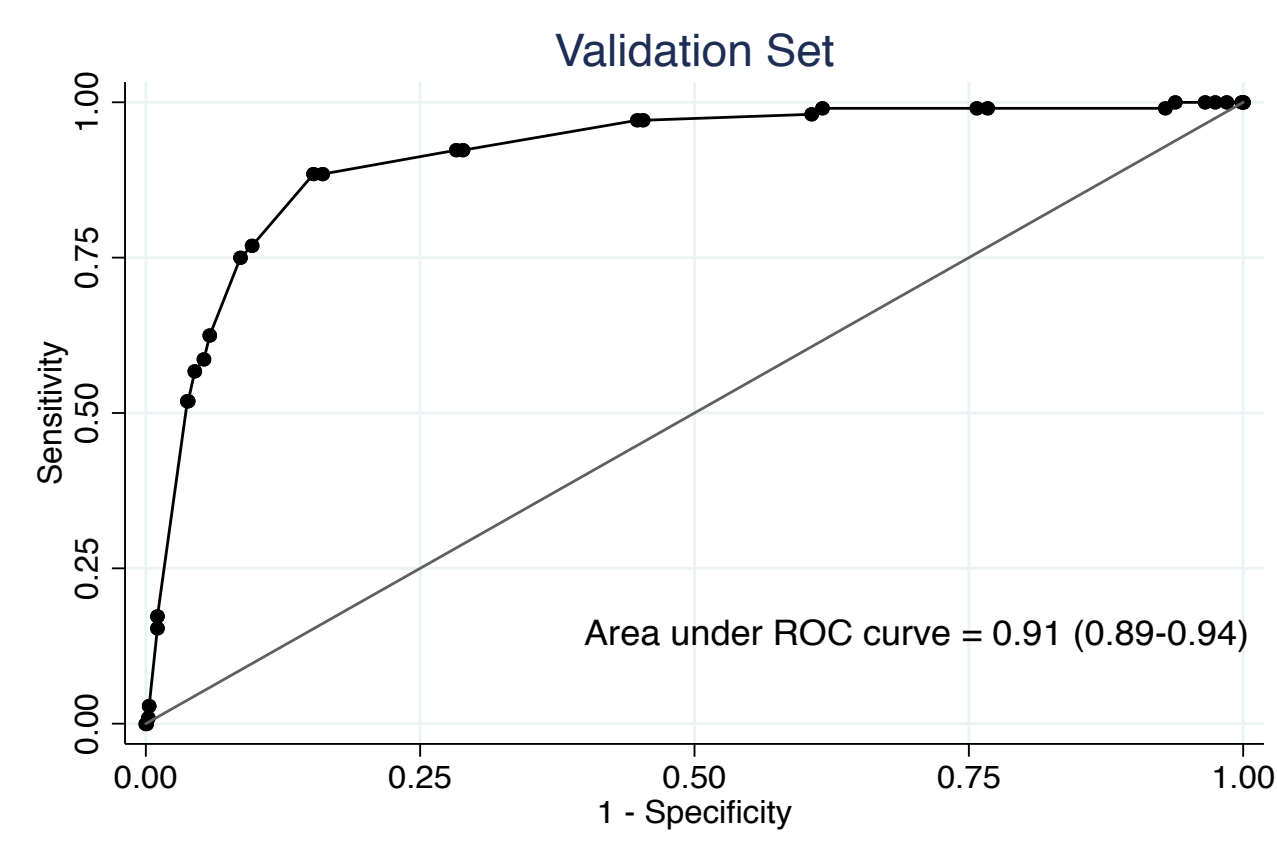
NOTE: AUC, area under the ROC curve; Hosmer-Lemeshow test based on deciles of risk score.

* Can be used to calculate probability of death as per text.


Probability of Death
0
.2
.4
.6
.8
1
0
10
20
30
40
Prediction Rule: Derivation Set
Model Prediction
Observed Probability of Death


Probability of Death
0
.2
.4
.6
.8
1
0
10
20
30
40
Prediction Rule: Validation Set
Model Prediction
Observed Probability of Death


Derivation Set
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Area under ROC curve = 0.95 (0.91-0.96)


Validation Set
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Area under ROC curve = 0.91 (0.89-0.94)

Supplement: Derivation and Validation of Clinical Prediction Rule for COVID-19 Mortality in Ontario, Canada

1. Cox-model derived prediction rule.

As noted in the text, we used a Cox proportional hazards model to derive point scores for a prediction score. The use of Cox models was intended to avoid bias that might be introduced as a result of incomplete follow up and right censoring. Point scores were derived based on log-hazard ratios. The scores, and values for I and C necessary to predict mortality probability are presented in Table 3. The score itself was then evaluated as a single covariate in a logit model predicting mortality. Model calibration in derivation (top panel) and validation (bottom panel) sets are presented in Figure S1 below. Figure S2 presents the ROC curves for the derivation (top panel) and validation

(bottom panel) sets.

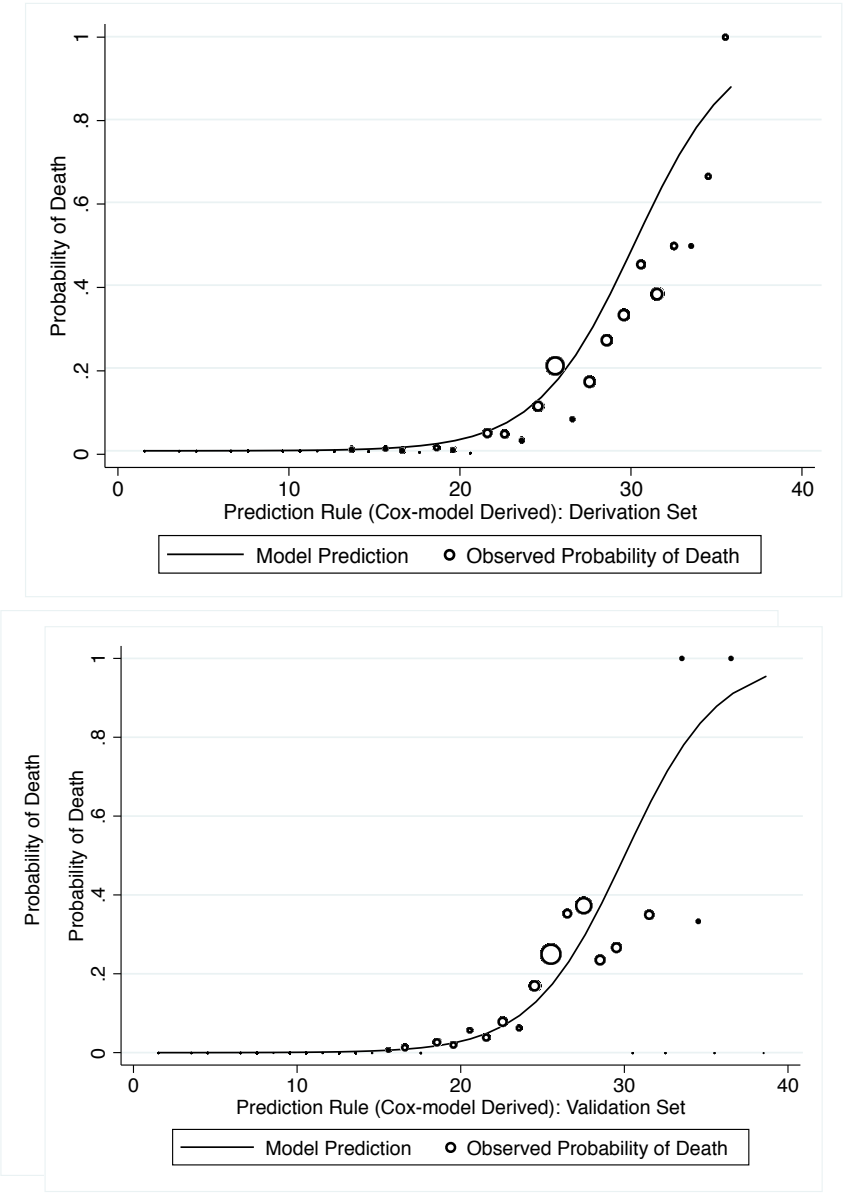


Figure S1. Observed (circles) and predicted (curve) probability of death in Cox model-derived alternate prediction rule. Circle size is proportionate to number of deaths for each score.

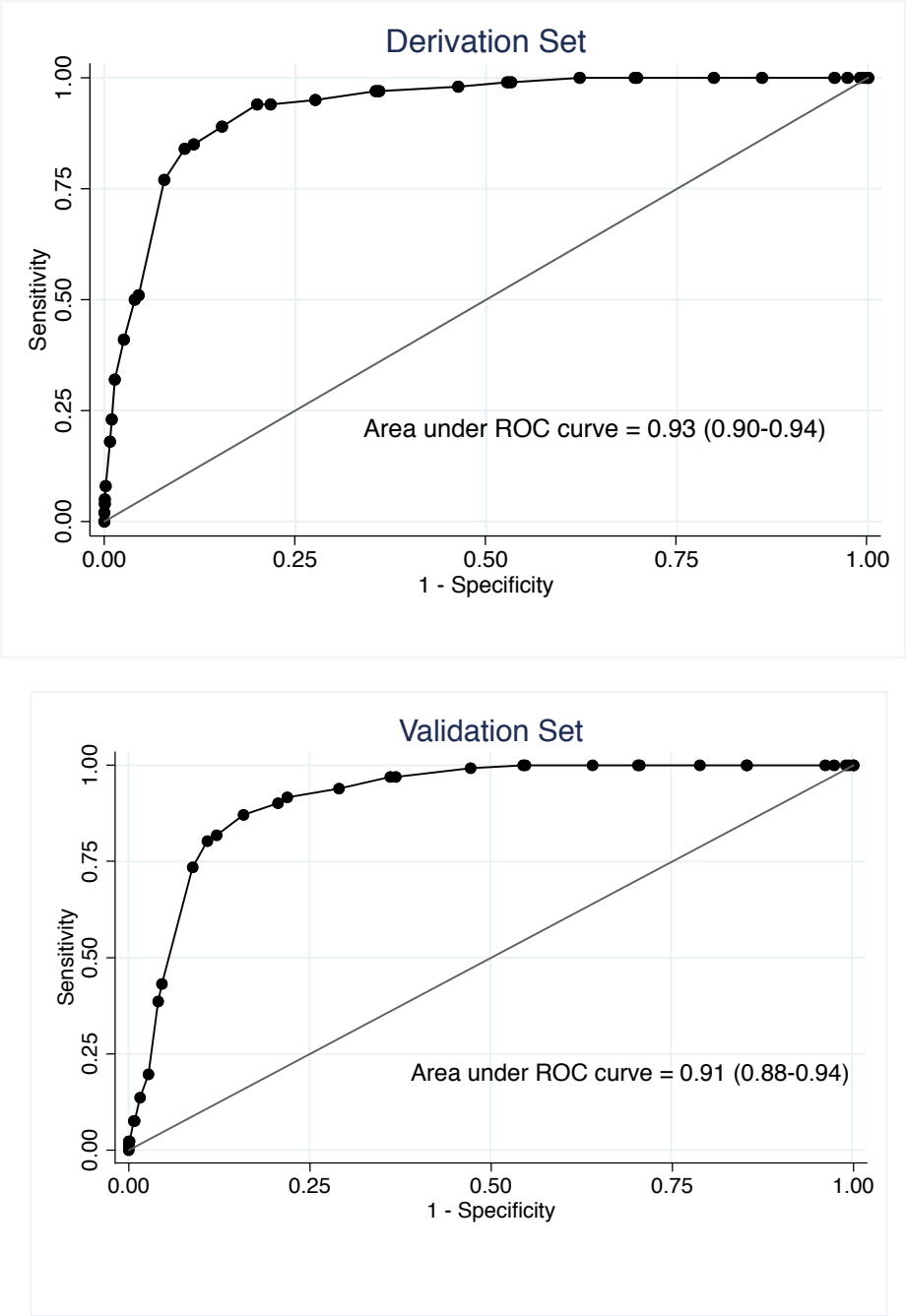
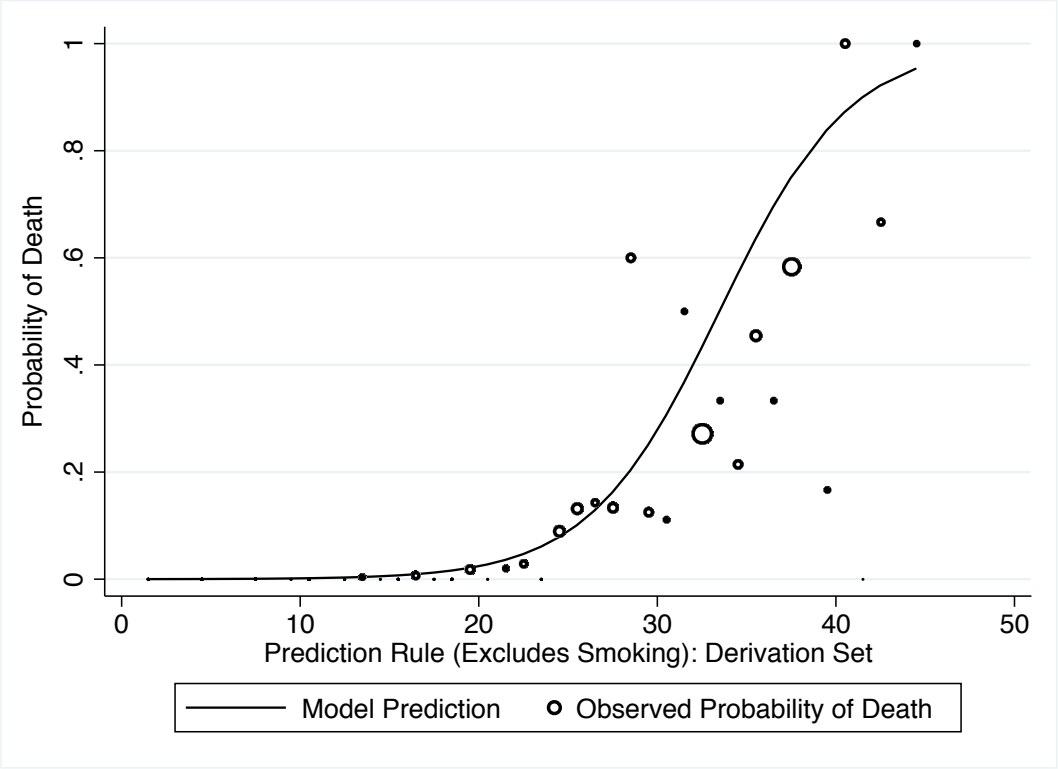


Figure S2. ROC curves for derivation (top) and validation (bottom) sets, Cox model-based prediction rule. Confidence intervals derived via bootstrapping.

2. Logit model-derived prediction rule with smoking excluded.

We anticipated that a prediction rule incorporating non-smoking as a risk factor for mortality would be controversial. As such, we created an alternate rule with non-smoking excluded. Again, rule-based scores, and values for I and C necessary to predict mortality probability are presented in Table 3. As above model calibration in derivation (top panel) and validation (bottom panel) sets are presented in Figure S3 below. Figure S4 presents the ROC curves for the derivation (top panel) and validation (bottom panel) sets.



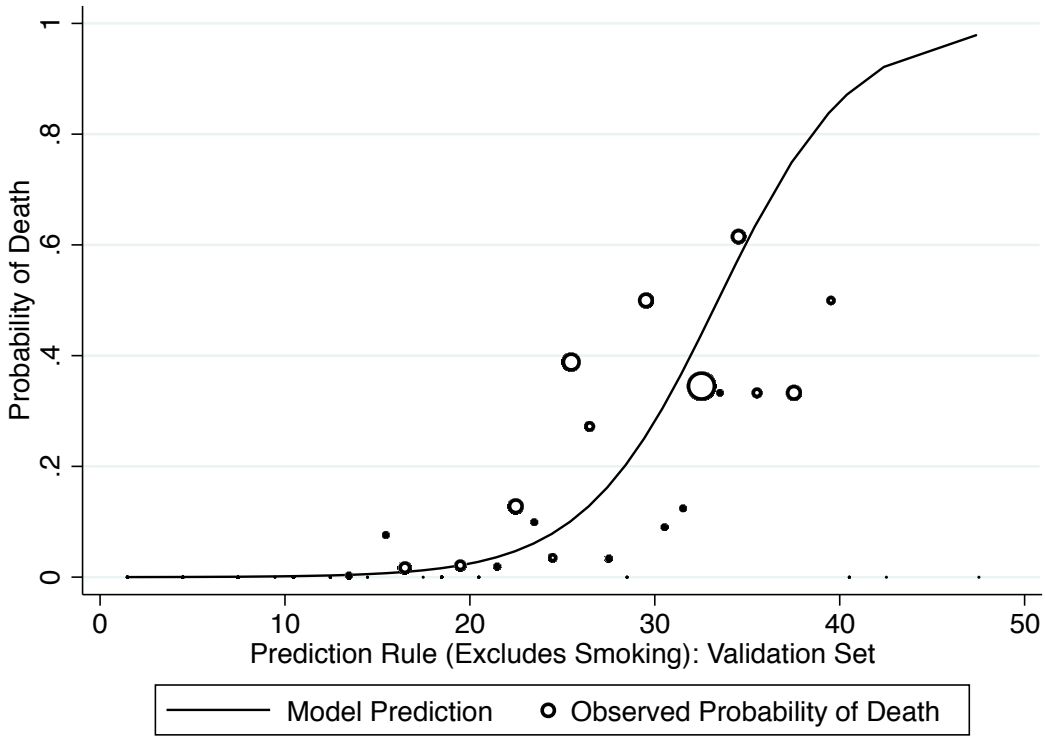


Figure S3. Observed (circles) and predicted (curve) probability of death in logit model-derived alternate prediction rule that excludes smoking status. Circle size is proportionate to number of deaths for each score.

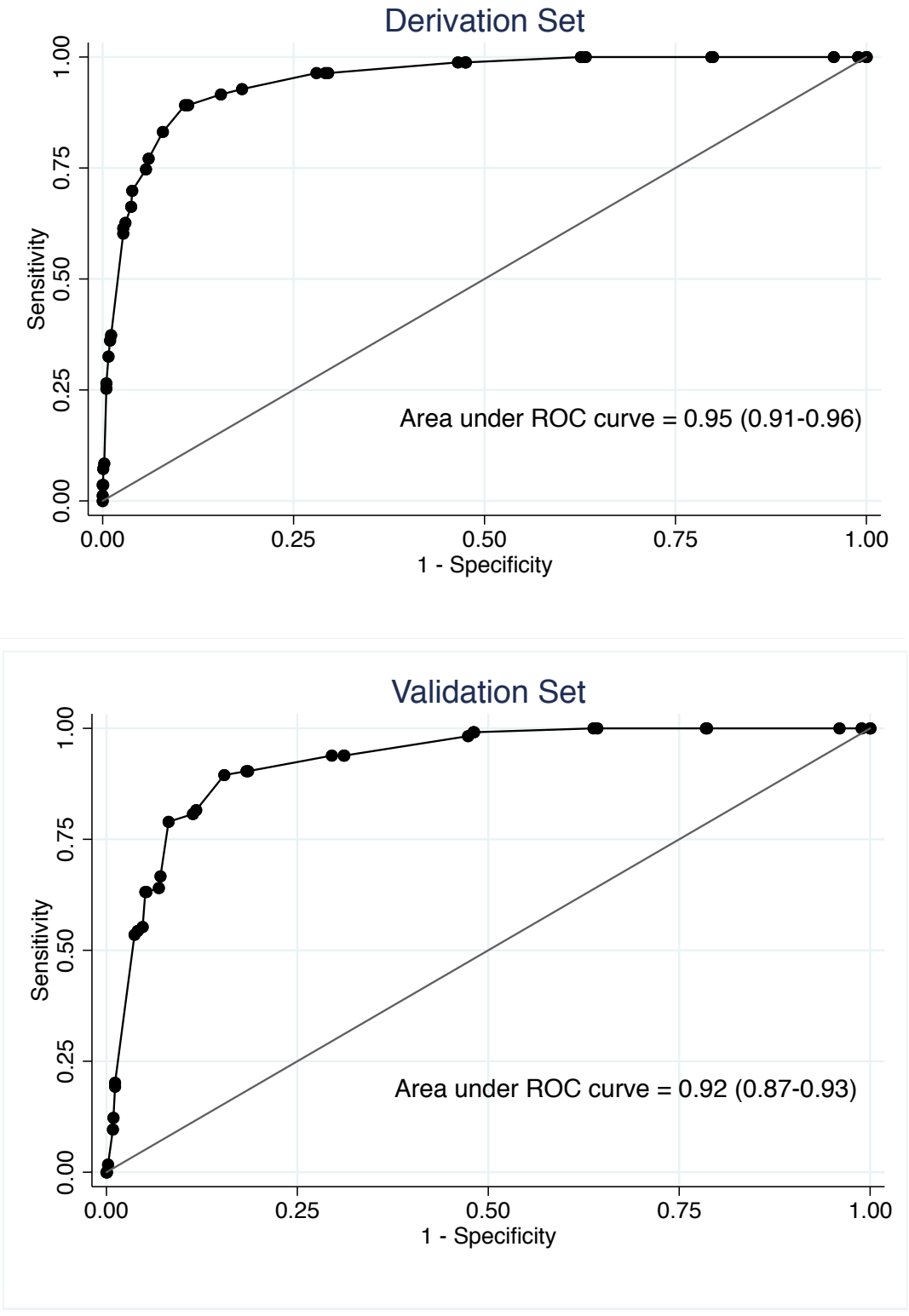
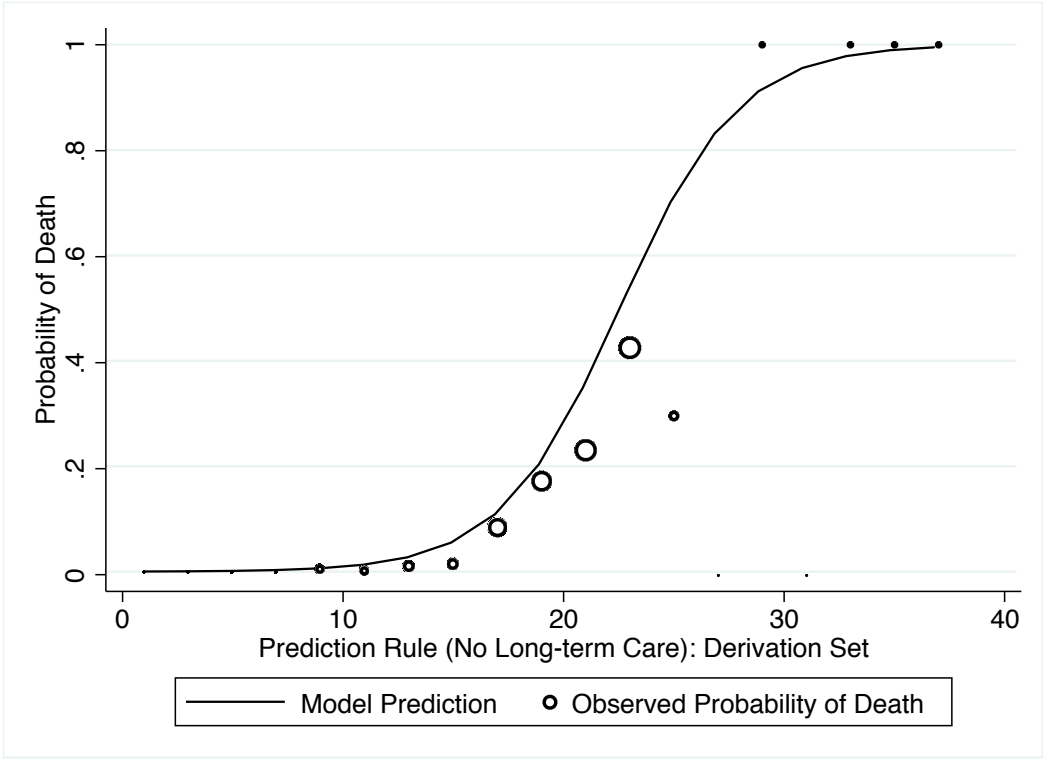


Figure S4. ROC curves for derivation (top) and validation (bottom) sets in logit model-derived alternate prediction rule that excludes smoking status. Confidence intervals derived via bootstrapping.

3. Logit model-derived prediction rule with long-term care residents excluded.

The extremely high mortality in the long-term care setting might make a prediction rule unhelpful. As such, we created an alternate rule with long-term care residents excluded. Again, rule-based scores, and values for I and C necessary to predict mortality probability are presented in Table 3. As above model calibration in derivation (top panel) and validation (bottom panel) sets are presented in Figure S5 below. Figure S6 presents the ROC curves for the derivation (top panel) and validation (bottom panel) sets.



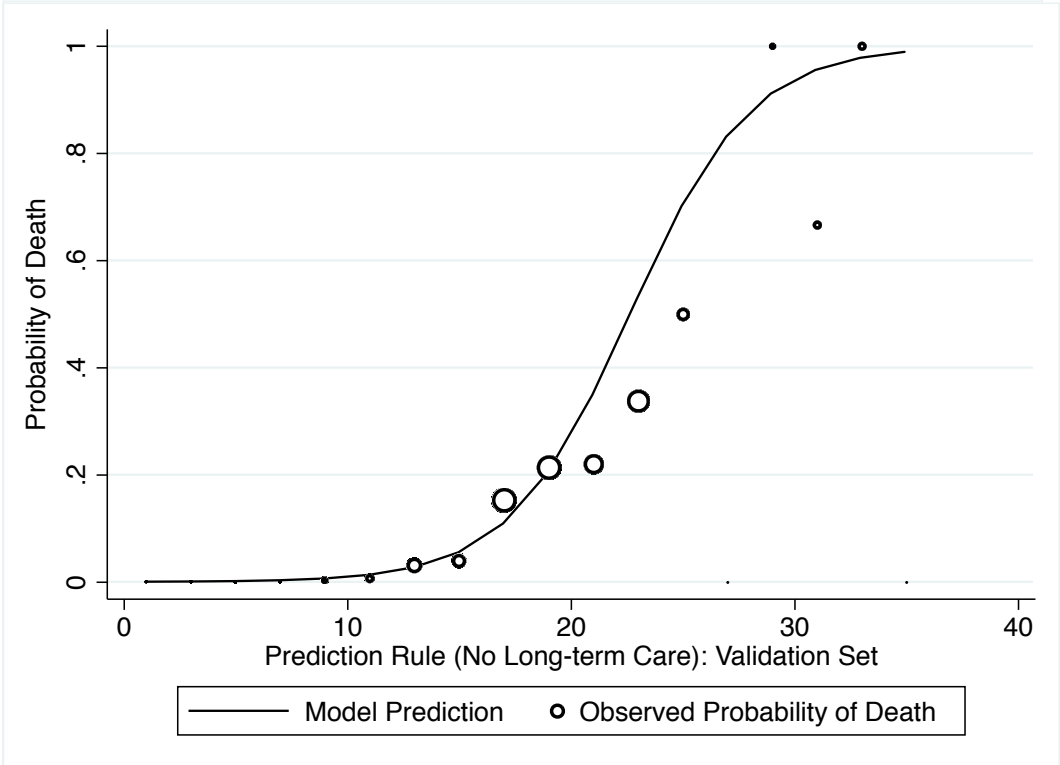
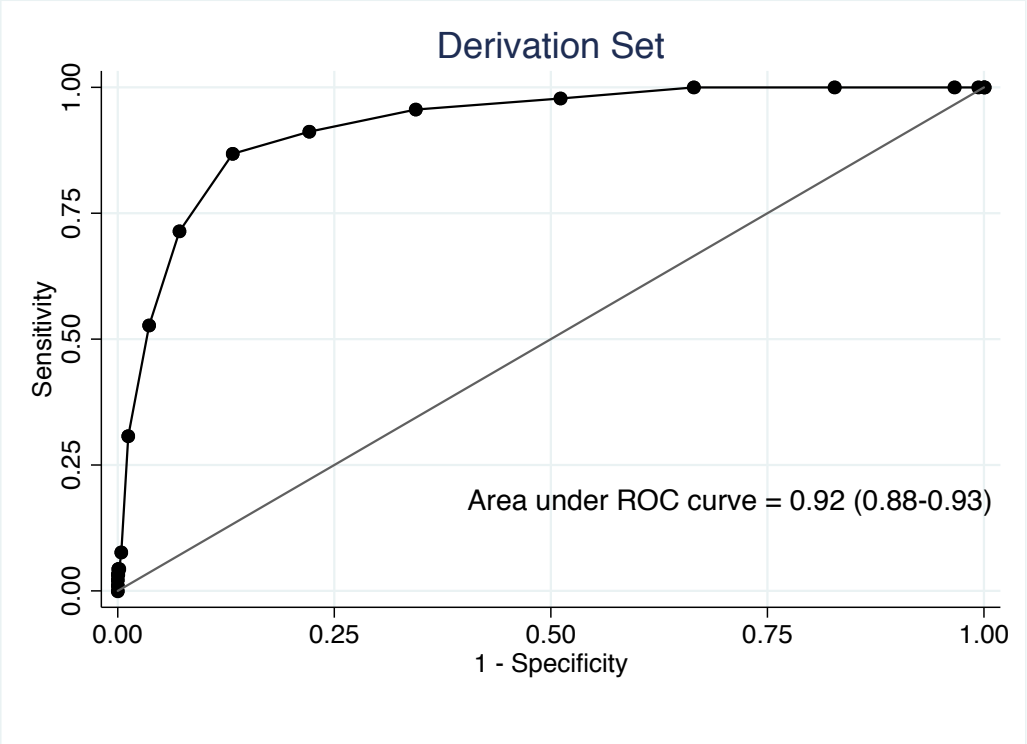


Figure S5. Observed (circles) and predicted (curve) probability of death in logit model-derived alternate prediction rule that excludes long term care residents. Circle size is proportionate to number of deaths for each score.



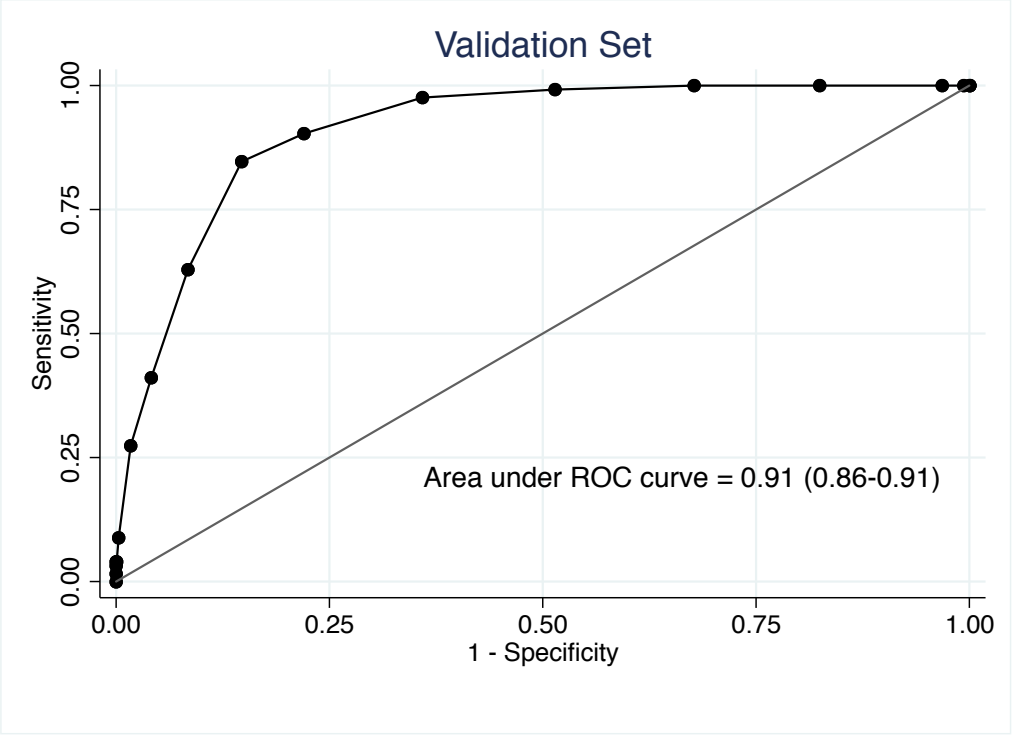


Figure S6. ROC curves for derivation (top) and validation (bottom) sets in logit model-derived alternate prediction rule that excludes smoking status. Confidence intervals derived via bootstrapping.

4. Sensitivity Analyses with Replacement of Missing Data

The iPHIS dataset was limited by substantial data missingness. To assess the robustness of our rules, we replaced missing variables in two ways: first, by assuming that missingness (for covariates or death) indicated that they were not present or did not occur (i.e., replaced missing values as zero); and second, by assuming that variables were missing completely at random, and replacing missing values randomly based on their frequency of observation among non-missings. The latter approach had the effect of substantially increasing the number of deaths available in the dataset. Notwithstanding the likely introduction of misclassification via both of these approaches, model calibration (based on visual inspection) and discrimination remained very good. Calibration (left sided panels) and discrimination (right sided panels) are presented graphically for all four prediction rules with missing values replaced as zeroes (Figure S7) and missing values replaced at random (Figure S8).

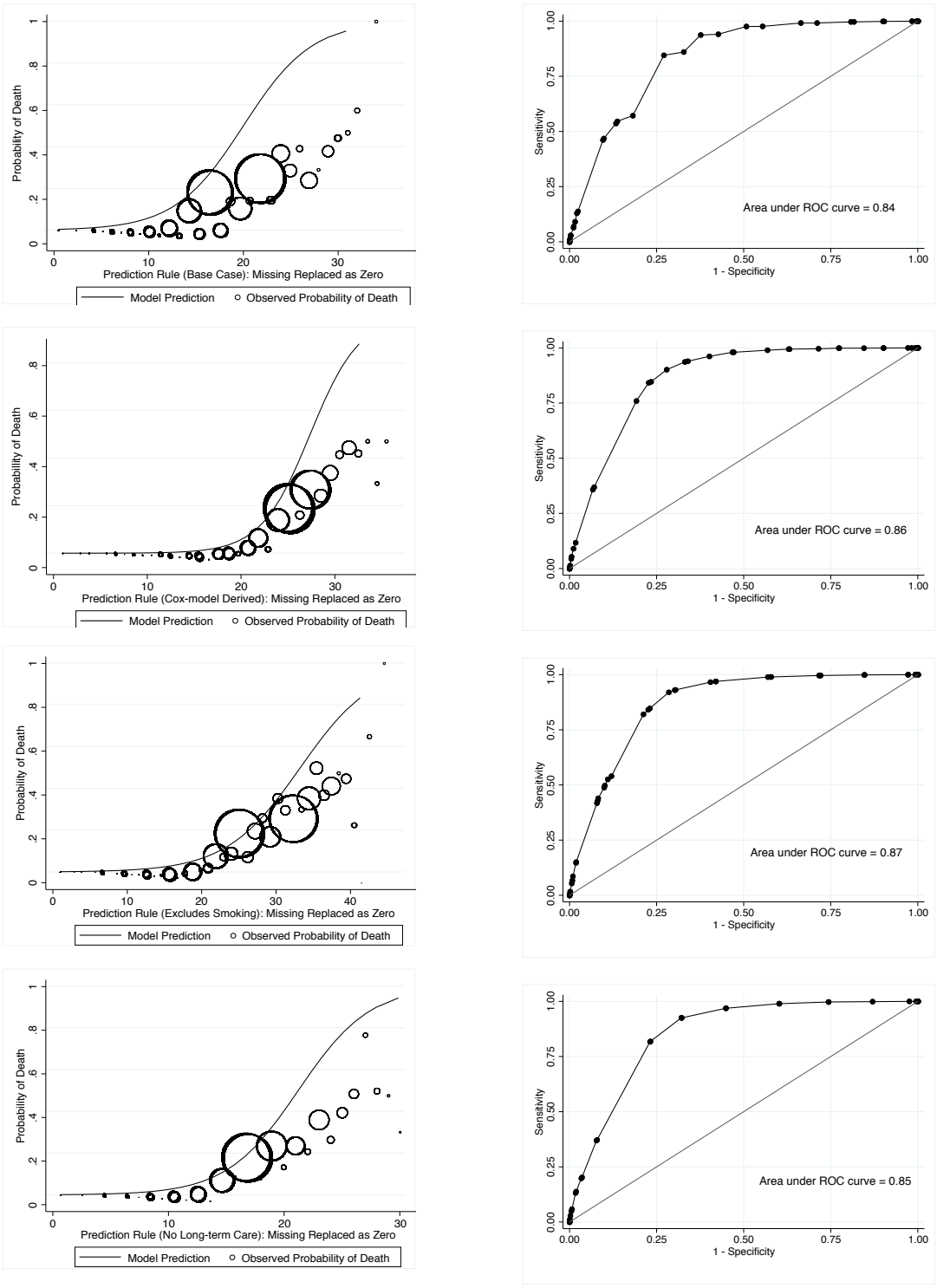


Figure 7S. Left panel figures present model calibration for all four prediction rules with missing variables replaced as zeroes. Lines represent model predictions and circles represent observed probability of death; circle size is proportionate to observed

numbers of deaths at each score level. Right panel figures represent ROC curves for the same prediction rules with missing variables replaced as zeroes.

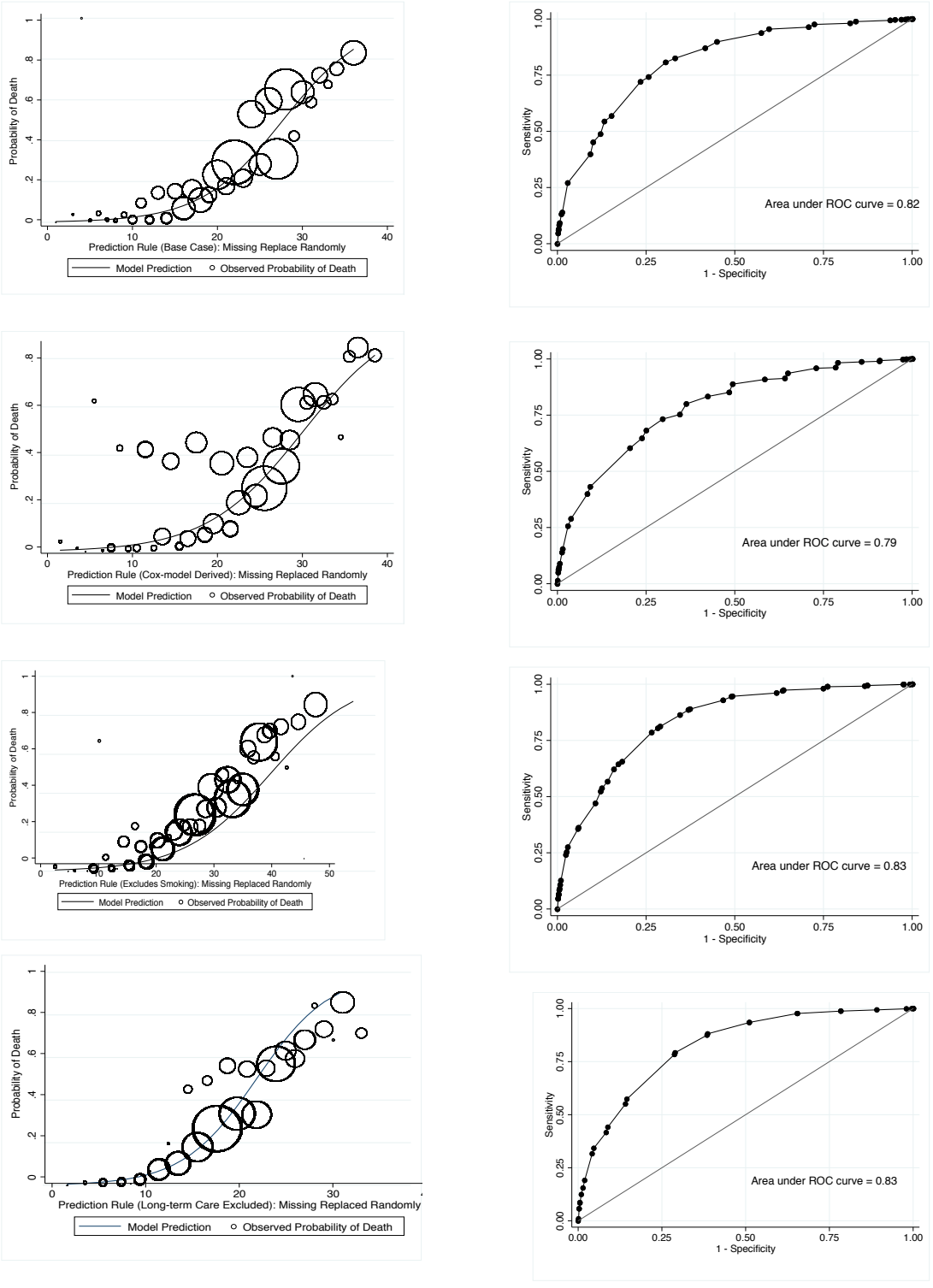


Figure 8S. Left panel figures present model calibration for all four prediction rules with missing variables replaced at random. Lines represent model predictions and circles represent observed probability of death; circle size is proportionate to observed numbers of deaths at each score level. Circles are large because missing death data has been replaced as either present or

absent, with the result that death numbers are far higher than in other analyses. Right panel figures represent ROC curves for the same prediction rules with missing variables replaced at random.

REFERENCE 20

Ontario

Ministry of Education

Operational Guidance During COVID-19 Outbreak

Child Care Re-Opening

Version 2 – July 2020

Contents

Highlights of Changes:

- Revised cohort size to maximum of 15 children, as of July 27, 2020 (see section: Maximum Cohort Size and Ratio)
- Revised deadline for certification required by the Workplace Safety and Insurance Board (see section: Staffing)
- Additional guidance around cleaning washroom facilities (see section: Cleaning Child Care Centres/Homes)
- Revised guidance around how screening must be conducted (see section: Screening for Symptoms)
- Additional information about how long to exclude staff/providers/children from the program depending on test results (see section: Testing Requirements)
- Revised protocols for when a child/staff/provider shows symptoms or becomes sick (see section: Protocols When a Child or Staff/Home Child Care Provider Demonstrates Symptoms of Illness or Becomes Sick)
- Revised language about physical barriers (see section: Space Set-Up and Physical Distancing)

INTRODUCTION AND PURPOSE

This guidance document is intended to support the following child care sector partners:

- Consolidated Municipal Service Managers and District Social Service Administration Boards (CMSMs and DSSABs);
- child care licensees and staff;
- home child care agencies and providers; and,
- district school boards.

The information found within this guidance document is meant to support partners in meeting requirements set out under the *Child Care and Early Years Act, 2014* (CCEYA) and to provide clarification on operating child care programs with enhanced health and safety guidelines and/or restrictions in place to re-open. This guidance document will be modified as applicable when these restrictions can be lifted and/or amended to reflect new advice at that time.

This guidance document has been designed for use in conjunction with the Child Care Centre and Home Child Care Agency Licensing Manuals, the CCEYA and its regulations. **In the event of a conflict between this document and the licensing manuals, this document will prevail. Advice of the local public health unit must be followed, even in the event that it contradicts this guidance document.**

To support preparations for re-opening, child care operators may begin accessing their centres immediately. Starting June 12, once centres are prepared to operate including having enhanced health and safety measures in place, they are permitted to re-open. Home-based child care providers must also operate with the enhanced health and safety measures in place.

The ministry is requesting school boards, Consolidated Municipal Service Managers/District Social Services Administration Boards and child care partners, in collaboration with local public health units, work together to ensure full-day licensed child care programs located in schools are able to re-open. The ministry understands that district school board protocols may differ from those of licensed child care and recommends that partners work together to align protocols where needed (i.e., in a shared space).

While the focus of this guidance document is on the new health, safety and operational measures that are required in order to safely re-open child care, please note that every effort should continue to be made to uphold the welcoming and caring environment that child care provides for children and families. More information regarding the early years pedagogy, including helpful resources can be found on the ministry website.

The Early Years Portal contains a wealth of information to help licensees, staff and home child care providers understand the requirements of the CCEYA and its regulations.

You may wish to visit the provincial COVID-19 website regularly for current pandemic information, as well as the Public Health Ontario public resources page for information to help stop the spread, find sector specific resources, including helpful posters, mental health resources, and other information.

If you have further questions or require clarification, please contact your Ministry of Education program advisor directly or contact the Licensed Child Care Unit at information.met@ontario.ca.

LICENSING REQUIREMENTS

Licensing Processes and Renewals

- Licences are required to be amended, if necessary, to ensure director approvals and conditions on the licence align with new restrictions.
- To support the operational needs of licensees, the ministry will prioritize and expedite the review of requests to revise and amend licences.
- Licensees are required to meet all the requirements set out in the *Child Care and Early Years Act*, *2014* (CCEYA) and its regulations and to obtain all necessary municipal approvals to support licence revision requests.
- Licensees must follow all current ministry and CMSM/DSSAB policies and guidelines.
- Licences that expire during the emergency period will be automatically extended by six months.
- Renewal, revision and application fees are set at zero for the period of the emergency and during the 60 days after the end of the emergency period.

Inspections

- Ministry staff will conduct in-person monitoring and licensing inspections of child care centres, home child care agencies, home child care premises and in-home services where necessary.
- Ministry staff must:
    - be screened prior to entering the premises following the protocol determined by the licensee (see screening section below);
    - wear personal protective equipment; and,
    - follow any other protocols requested by the licensee or home child care or in-home service provider.
- Ministry staff will use technology (e.g., telephone, video conferencing) to complete virtual monitoring and licensing inspections where appropriate.

Maximum Cohort Size and Ratio

- For the purposes of this document, a cohort is defined as a group of children and the staff members assigned to them, who stay together throughout the duration of the program for minimum 7 days.
- As of July 27, 2020, maximum cohort size for each room in a child care centre (including each family age group) will consist of no more than 15 children, space permitting. Staff are not included in this number, but should still be considered part of the cohort that stays together (e.g., 15 toddlers + at least 3

staff). For more guidance on cohorts and staff scheduling, please see the Staffing section.

- Children attending on a part-time basis (e.g., half days, only Mondays and Wednesdays) should be counted in the total number of individuals in the cohort, even on the days when they are not physically attending the program.
    - For example, if one child only attends the program in the morning, they should still be considered part of the cohort of 15 children, even when they are not in the program in the afternoon.
- Maximum capacity rules do not apply to Special Needs Resource staff on site (i.e., if they are not counted towards staff to child ratios they are not included in the maximum capacity rules).
- For any play activity room that is currently licensed for a maximum group size of less than 15 children due to square footage requirements (e.g., infant room 1 is licensed for 6 children), licensees can only have the number of children listed on the licence.
    - In addition, infant groups can have a maximum group size of 10 children, as this age group has never been permitted to include more than 10 children in a group.
- Each cohort must stay together throughout the day and is not permitted to mix with other cohorts.
- Licensees are required to maintain ratios set out under the CCEYA. Licensee can increase staff to child ratio as long as the group does not exceed the maximum of 15 children.
- Mixed age grouping is permitted as set out under the CCEYA where a director approval has been granted on the licence.
- Reduced ratios are permitted as set out under the CCEYA provided that cohorts are not mixed with other cohorts. Reduced ratios are not permitted at any time for infants.

Maximum Capacity of Building

- More than one child care program or day camp can be offered per building as long as they are able to maintain separation between the programs and cohorts, and follow all health and safety requirements that apply to those programs.
- There are no changes to the maximum group size for home child care which allows for a maximum of 6 children, not including the providers own children who are 4 years or older.

Staffing

- Staff should work at only one location.
- Supervisors and/or designates should limit their movement between rooms, doing so when absolutely necessary.
- Supply/replacement staff should be assigned to a specific cohort so as to limit staff interaction with multiple cohorts.
- Qualified Staff
    - Licensees are required to ensure each group has the required number of qualified staff as set out in the CCEYA. Licensees may submit requests for staff director approval (DAs) to the ministry.
    - Staff DAs can be transferred from one child care centre to another child care centre that is operated by the same licensee.
    - Licensees can also request a staff DA for multiple age groups.
- Certification in Standard First Aid Training, including Infant and Child CPR
    - Staff that are included in ratios and all home child care providers are required to have valid certification in first aid training including infant and child CPR, unless exempted under the CCEYA or the certification has been extended by the Workplace Safety and Insurance Board (WSIB).
    - The WSIB has indicated that all certifications that expire after March 1, 2020 are automatically temporarily extended until December 31, 2020.
    - Licensees are encouraged to monitor the WSIB website for any updates on First Aid/CPR certificate extensions for any staff, home child care providers or in-home service providers whose certification would have expired after March 1, 2020.
- Vulnerable Sector Checks (VSCs)
    - Licensees are required to obtain VSCs from staff and other persons who are interacting with children at a premises.
    - A licensee is not required to obtain a new VSC from staff or persons interacting with children where the fifth anniversary of the staff or person's most recent VSC falls within the emergency period, until 60 days after the emergency period ends.

HEALTH AND SAFETY REQUIREMENTS

Working with Local Public Health

- While the ministry is providing guidance on how to operate child care during the COVID-19 pandemic, CMSMs/DSSABs, licensees, and home child care providers must follow the advice of local public health officials when establishing health and safety protocols, including how to implement the provincial direction that the maximum cohort size for each room in a child care centre consist of no more than 15 children plus the appropriate number of staff to maintain ratios.
- The ministry recognizes that this may result in regional differences in these protocols, but given the different impact of COVID-19 in different communities it is important to follow the advice of local public health officials to keep children and families safe in their respective communities.
- Contact information for local public health units.

Health and Safety Protocols

- Every licensee must ensure that there are written policies and procedures outlining the licensee's health and safety protocols. Licensees must submit an attestation to the Ministry that confirms new policies and procedure have been developed and reviewed with employees and providers. These policies and procedures must be consistent with any direction of a medical officer of health and include information on how the child care setting will operate during and throughout the recovery phase following the pandemic including:
    - sanitization of the space, toys and equipment;
    - how to report illness;
    - how physical distancing will be encouraged;
    - how shifts will be scheduled, where applicable;
    - rescheduling of group events and/or in-person meetings; and,
    - parent drop off and pick up procedures.

Cleaning Child Care Centres/Homes

- Frequently touched surfaces should be cleaned and disinfected at least twice a day as they are most likely to become contaminated (for example, doorknobs, water fountain knobs, light switches, toilet and faucet handles, electronic devices, and tabletops).

- Please refer to Public Health Ontario's Environmental Cleaning fact sheet and the Public Services Health and Safety Association's Child Care Centre Employer Guideline for information on cleaning.
- Information from Public Health Ontario provides best practices for cleaning and disinfecting, including:
    - which products to use;
    - how to clean and disinfect different materials
    - other items to remember, including checking expiry dates of cleaning and disinfectant products and following the manufacturer's instructions.
- It is recommended that operators keep a cleaning and disinfecting log to track and demonstrate cleaning schedules.
- Only one cohort should access the washroom at a time and it is recommended that the facilities be cleaned in between each use, particularly if different cohorts will be using the same washroom.

Guidance On the Use of Masks and Personal Protective Equipment (PPE)

- The Ontario Together Portal has a Workplace PPE Supplier Directory that lists Ontario businesses that provide personal protective equipment.
- Masks are not recommended for children, particularly those under the age of two (see information about the use of face coverings on the provincial COVID-19 website).
- Follow local public health guidelines regarding the use of masks and PPE. You may want to consider the use of PPE:
    - in the screening area and when accompanying children into the program from the screening area. See the screening section of this guidance document for more information;
    - when cleaning and disinfecting blood or bodily fluid spills if there is a risk of splashing. Please refer to the Public Services Health and Safety Association's Child Care Centre Employer Guideline for more information on working safely in a child care setting. Note that there is also a resource document for Child Care Providers; and,
    - when caring for a sick child or a child showing symptoms of illness. See the section in this guidance document on protocols when an individual is sick for more information.
- When wearing a mask, you should wash your hands before donning the mask and before and after removing the mask. Refer to Public Health Ontario resources for how to properly wear and take off masks and eye protection.

- Child care licensees and home child care providers should secure and sustain an amount of PPE and cleaning supplies that can support their current and ongoing operations.
- Perform and promote frequent, proper hand hygiene (including supervising or assisting participants with hand hygiene). Hand washing using soap and water is recommended over alcohol-based hand rub for children. Refer to Public Health Ontario's How to Wash Your Hands fact sheet.

Screening for Symptoms

- All individuals including children attending child care, staff and child care providers, parents/guardians, and visitors must be screened each day before entering the child care setting.
- Home child care providers and residents must also be screened each day before receiving children into care.
- Where possible, daily screening should be done electronically (e.g., via online form, survey, or e-mail) prior to arrival at the child care setting. Where operationally feasible, include temperature checks as part of screening.
- Parents and guardians should be reminded of this requirement when children are first registered for the program and through visible signage at the entrances and drop-off areas.
- If children are screened at the child care setting, screeners should take appropriate precautions when screening and escorting children to the program, including maintaining a distance of at least 2 meters (6 feet) from those being screened, or being separated by a physical barrier (such as a plexiglass barrier), and wearing personal protective equipment (PPE) (i.e., surgical/procedure mask and eye protection (goggles or face shield)).
- Please follow advice from your local public health office regarding precautions to have in place.
    - Refer to Public Health Ontario resources for how to properly wear and take off masks and eye protection.
- Alcohol-based hand sanitizer containing at least 60% alcohol content should be placed at all screening stations. Dispensers should not be in locations that can be accessed by young children.
- All child care licensees must maintain daily records of screening results.
    - Records are to be kept on the premises (centre or home).
- You may wish to consult the Province's COVID-19 website for information and resources on COVID-19 symptoms, protections, and seeking health care.

Attendance Records

- All child care licensees are responsible for maintaining daily records of anyone entering the child care facility/home and the approximate length of their stay (such as cleaners, people doing maintenance work, people providing supports for children with special needs, those delivering food).
    - Records are to be kept on the premises (centre or home).
- Records (e.g. name, contact information, time of arrival/departure, screening completion/result, etc.) must be kept up-to-date and available to facilitate contact tracing in the event of a confirmed COVID-19 case or outbreak.

Testing Requirements

- Symptomatic children or staff/home child care providers should be referred for testing.
    - Those who test negative for COVID-19 must be excluded from the program until 24 hours after symptom resolution.
    - Those who test positive for COVID-19 must be excluded from the program for 14 days after the onset of symptoms and/or clearance has been received from the local public health unit.
- Testing of asymptomatic persons should only be performed as directed by the local public health unit as part of case/contact and outbreak management.
- Please refer to the provincial testing guidance for updated information regarding the requirement for routine testing in a child care setting.
- A list of symptoms, including atypical signs and symptoms, can be found in the COVID-19 Reference Document for Symptoms on the Ministry of Health's COVID-19 website.
- Please see the protocols when a child or staff/home child care provider becomes sick for information on testing in the event of a suspected case.

Protocols When a Child or Staff/Home Child Care Provider Demonstrates Symptoms of Illness or Becomes Sick

- A single, symptomatic, laboratory confirmed case of COVID-19 in a staff member, home child care provider or child must be considered a confirmed COVID-19 outbreak, in consultation with the local public health unit. Outbreaks should be declared in collaboration between the program and the local public health unit to ensure an outbreak number is provided.
- Staff, home child care providers, parents/guardians, and children who are symptomatic or have been advised to self-isolate by the local public health unit, must not attend the program. Asymptomatic individuals awaiting results may not need to be excluded and should follow the advice of public health.

    - Symptoms to look for include but are not limited to: fever, cough, shortness of breath, sore throat, runny nose, nasal congestion, headache, and a general feeling of being unwell.
    - Children in particular should be monitored for atypical symptoms and signs of COVID-19. For more information, please see the symptoms outlined in the 'COVID-19 Reference Document for Symptoms' on the Ministry of Health's COVID-19 website.
- If a child or child care staff/provider becomes sick while in the program, they should be isolated and family members contacted for pick-up.
- If a separate room is not available, the sick person should be kept at a minimum of 2 meters from others.
- The sick person should be provided with tissues and reminded of hand hygiene, respiratory etiquette, and proper disposal of tissues.
- If the sick person is a child, a child care staff/provider should remain with the child until a parent/guardian arrives. If tolerated and above the age of 2, the child should wear a surgical/procedure mask. The child care staff/provider should wear a surgical/procedure mask and eye protection at all times and not interact with others. The child care staff/provider should also avoid contact with the child's respiratory secretions.
- All items used by the sick person should be cleaned and disinfected. All items that cannot be cleaned (paper, books, cardboard puzzles) should be removed and stored in a sealed container for a minimum of 7 days.
- Public health should be notified, and their advice should be followed.
- For home-based programs: if a person who resides in the home becomes symptomatic and/or tests positive for COVID-19, the local public health unit should be notified and their advice on next steps should be followed (including closing the program and notifying all families if necessary).
- If the child care program is located in a shared setting (for example in a school), follow public health advice on notifying others using the space of the suspected illness.
- Where a child, staff or home child care provider is suspected of having or has a confirmed case of COVID-19, licensees must report this to the ministry as a serious occurrence.
    - When a person becomes sick the home child care agency will report to public health, the ministry, and where public health advises, families.
- Other children, including siblings of the sick child, and child care staff/providers in the program who were present while the child or staff member/provider became ill should be identified as a close contact and further cohorted (i.e., grouped together). The local public health unit will provide any further direction on testing and isolation of these close contacts.

Serious Occurrence Reporting

- Child care centre licensees have a duty to report suspected or confirmed cases of COVID-19 under the *Health Protection and Promotion Act*. The licensee should contact their local public health unit to report a child suspected to have COVID-19. The local public health unit will provide specific advice on what control measures should be implemented to prevent the potential spread and how to monitor for other possible infected staff members and children.
- Where a child, parent, staff or home child care provider is suspected (i.e. has symptoms and has been tested) of having or has a confirmed case of COVID-19, licensees must report this to the ministry as a serious occurrence.
- Where a room, centre or premises closes due to COVID-19, licensees must report this to the ministry as a serious occurrence.
- Licensees are required to post the serious occurrence notification form as required under the CCEYA, unless local public health advises otherwise.

OPERATIONAL GUIDANCE

PRE-PROGRAM CONSIDERATIONS

Communication with Families

- Communication with families regarding the enhancement of health and safety measures facilitates transparency of expectations. New policies should be shared with families, for their information and to ensure they are aware of these expectations, including keeping children home when they are sick, which are aimed at helping to keep all children and staff/providers safe and healthy.
- Licensees must share with parents, the policies and procedures regarding health and safety protocols to COVID-19.
- Licensees are not required as part of re-opening to revise their program statement, full parent handbook and other policies.
- Licensees may want to consider providing links to helpful information, as well as detailed instructions regarding screening and protocols if a child or child care staff/provider becomes ill.
- Priority/waitlist policies may need to be updated to account for limited capacity when re-opening. Any changes to policies should be communicated to families so they are aware of the changes. An equitable approach should be implemented to assess priority for care.
- Where possible, the use of in-person communication should be limited.

Parent Fees

- In an effort to stabilize parent fees when re-opening, child care operators should set fees at the level they were at prior to the closure. Home child care providers that closed should also hold parent fees to the level they were at prior to when they closed.
- Additionally, until the ministry is able to amend these enhanced measures, when re-opening:
    - operators are prohibited from charging or accepting fees or deposits to add families to a priority list for preferred access to spaces;
    - operators are prohibited from charging fees to parents if they do not have access to a space or decide not to accept a space; and,
    - licensed home child care providers must give parents 30 days to indicate whether they want to keep their space. After the 30 days, payments would be required to secure the space, whether the child attends or not.

- Emergency child care, including associated provincial funding, ended on June 26, 2020.

Access to Child Care Spaces and Prioritizing Families

- When determining prioritization of limited child care spaces, CMSMs/DSSABs, licensees, and home child care agencies and providers may wish to consider the following:
    - Returning children served through emergency child care to their original placement and continuity of service for these families;
    - Care for families where parents must return to work and that work outside of the home;
    - Families with special circumstances that would benefit from children returning to care, such as children with special needs; and
    - Other local circumstances.
- CMSMs/DSSABs, licensees, and home child care agencies and providers should also consider that some families they used to serve may no longer require care, or require a different level of care (i.e., part time child care).
- Assessing demand for care prior to re-opening, for example via conducting a survey, is recommended.

Fee Subsidy Eligibility and Assessment

- CMSMs/DSSABs may need to consider changes to the way in which child care fee subsidy assessments for eligibility are conducted in order to incorporate virtual assessments and records where possible.

Licensed Child Care Programs in Schools

- The ministry recognizes that there are additional considerations for licensed child care programs located in schools.
- School boards are required to find safe ways to provide child care operators with sufficient time to enter their centres located in schools, in order to prepare their space and ensure they meet the operational guidelines provided by the ministry. School boards should familiarize themselves with this guide to optimally facilitate child care reopening in schools.
- School boards, CMSMs/DSSABs and child care partners should work together collaboratively to ensure that full day licensed child care programs located in schools are able to re-open and that health and safety policies and requirements for child care programs and schools are complementary and aligned with the advice of local public health officials.

Staff Training

- CMSMs/DSSABs must ensure that training that is aligned with local public health direction is provided to all child care staff/providers on the health, safety and other operational measures outlined in this document plus any additional local requirements in place as close to re-opening as possible.
- You may wish to consult the Public Services Health and Safety Association's Child Care Centre Employer Guideline for information on other measures to consider for child care staff/providers. Note that there is also a resource document for Child Care Providers.
- This may include instruction on how to properly clean the space and equipment, how to safely conduct daily screening and keep daily attendance records, and what to do in the case that someone becomes sick.
- It may be useful to draw on the approaches adopted by those who operated emergency child care sites as well as any lessons learned they can offer.

Liability and Insurance

- All requirements under the CCEYA must be met in addition to the enhanced health and safety measures outlined in this document and by local public health.
- Licensees and child care providers may wish to consult with their legal counsel or insurance advisor about any other considerations for operating and providing child care during this period.

IN-PROGRAM CONSIDERATIONS

Drop-Off and Pick-up Procedures

- Licensees should develop procedures that support physical distancing and separate groups as best as possible (i.e., children of one room enter door A and children of another room enter door B, or staggered entrance times).
- As much as possible, parents should not go past the screening area.
- All entrances should have hand sanitizer and if in an enclosed space and physical distance of 2 meters cannot be maintained, parents/guardians and staff/providers may want to use face coverings.
- Consider using signage/markings on the ground to direct families through the entry steps.
- Personal belongings (e.g., backpack, clothing, etc.) should be minimized. If brought, belongings should be labeled and kept in the child's cubby/ designated area.

- You may want to consider a specific policy/protocol for stroller storage if this typically takes place inside the child care setting (for example, designating a space outside of the child care setting so that parents do not need to enter the building to leave the stroller).

Visitors

- There should be no non-essential visitors at the program.
- The provision of special needs services may continue and operators may use their discretion to determine whether the services being provided are essential and necessary at this time.
- Use of video and telephone interviews should be used to interact with families where possible, rather than in person.
- Ministry staff and other public officials (e.g. fire marshal, public health inspectors) are permitted to enter and inspect a child care centre, home child care agency and premises at any reasonable time.
- As much as possible, parents should not go past the screening area.
- Licensees must ensure that there are no volunteers or students at the program.

Space Set-Up and Physical Distancing

- The ministry recognizes that physical distancing between children in a child care setting is difficult and encourages child care staff and providers to maintain a welcoming and caring environment for children.
- Each cohort must have their own assigned indoor space, separated from all other cohorts by a physical barrier. The purpose of the barrier is to reduce the spread of respiratory droplets that are thought to transmit COVID-19 and to reinforce physical distancing requirements between cohorts. The physical barrier must begin at the floor and reach a minimum height of 8 feet to ensure that it will always be 12 inches taller than the tallest person in the facility. It must be as wide as the space/room will allow.
- When in the same common space (e.g., entrances, hallways) physical distancing of at least 2 metres must be maintained between different cohorts and should be encouraged, where possible, between children within the same cohort by:
    - spreading children out into different areas, particularly at meal and dressing time;
    - incorporating more individual activities or activities that encourage more space between children; and
    - using visual cues to promote physical distancing.

- In shared outdoor space, cohorts must maintain a distance of at least 2 metres between groups and any other individuals outside of the cohort.
- Licensees and home child care providers are encouraged to increase the distance between cots/resting mats/playpens or place the children head to toe or toe to toe if the space is limited.
- Shared spaces and structures that cannot be cleaned and disinfected between cohorts should not be used.
- Recognizing that physical distancing is difficult with small children and infants, additional suggestions include:
    - planning activities that do not involve shared objects or toys;
    - when possible, moving activities outside to allow for more space; and
    - avoiding singing activities indoors.

Equipment and Toy Usage and Restrictions

- Licensees and home child care providers are encouraged to provide toys and equipment which are made of materials that can be cleaned and disinfected (e.g., avoid plush toys).
- Toys and equipment should be cleaned and disinfected at a minimum between cohorts.
- Mouthed toys should be cleaned and disinfected immediately after the child is finished using it.
- Licensee and home child care providers are encouraged to have designated toys and equipment (e.g., balls, loose equipment) for each room or cohort. Where toys and equipment are shared, they should be cleaned and disinfected prior to being shared.
- If sensory materials (e.g., playdough, water, sand, etc.) are offered, they should be provided for single use (i.e. available to the child for the day) and labelled with child's name, if applicable.
- Play structures can only be used by one cohort at a time. Please consult with your local public health unit regarding the use of playground equipment onsite.

Program Statement/Activities

- Licensees are encouraged to continue to implement their program statement.
- The ministry recognizes that there may be approaches outlined in the program statement which may not be possible due to physical distancing.
- Licensees are not required to make updates to their program statement during this time.

Outdoor Play

- Licensees should schedule outdoor play in small groups/by cohort in order to facilitate physical distancing. Where the outdoor play area is large enough to accommodate multiple groups, licensees may divide the space with physical markers to ensure cohorts remain separated by at least 2 metres.
- If play structures are to be used by more than one cohort, the structures can only be used by one cohort at a time and should be cleaned and disinfected before and after each use by each cohort.
- Licensees and home child care providers are encouraged to have designated toys and equipment (e.g., balls, loose equipment) for each room or cohort. Where toys and equipment are shared, they should be cleaned and disinfected prior to being shared.
- Licensees and home child care providers should find alternate outdoor arrangements (e.g., community walk), where there are challenges securing outdoor play space. Providers should follow physical distancing practices when possible.
- Children should bring their own sunscreen where possible and it should not be shared.
    - Staff may provide assistance to apply sunscreen to any child requiring it and should exercise proper hand hygiene when doing so (for example washing hands before and after application).

Interactions with Infants/Toddlers

- Licensees should continue to encourage staff and home child care providers to supervise and hold bottles for infants not yet able to hold their own bottle to reduce the risk of choking.
- When holding infants and toddlers use blankets or cloths over clothing and change the blankets or cloths between children.
- Licensees and home child care providers should consider removing cribs or placing infants in every other crib, and mark the cribs that should not be used in order to support physical distancing.
- Recognizing that physical distancing is difficult with small children and infants, suggestions to support physical distancing include:
    - planning activities that do not involve shared objects or toys; and,
    - when possible, moving activities outside to allow for more space.
- Children must not share food, feeding utensils, soothers, bottles, sippy cups, etc. Mouthed toys must be removed immediately for cleaning and disinfecting and must not be shared with other children.
    - Label these items with the child’s name to discourage accidental sharing.

Food Provision

- Licensees and home child care providers should change meal practices to ensure there is no self-serve or sharing of food at meal times.
    - Utensils should be used to serve food.
    - Meals should be served in individual portions to the children.
    - There should be no items shared (i.e., serving spoon or salt shaker).
- There should be no food provided by the family/outside of the regular meal provision of the program (except where required and special precautions for handling and serving the food must be put in place).
- Children should neither prepare nor provide food that will be shared with others.
- Ensure proper hand hygiene is practiced when staff are preparing food and for all individuals before and after eating.
- Where possible, children should practice physical distancing while eating.
- There should be no sharing of utensils.

Provision of Special Needs Resources (SNR) Services

- The ministry recognizes that children with special needs and their families continue to require additional supports and services in child care settings.
- The provision of in-person special needs services in child care settings should continue where appropriate. Should questions arise in respect of which service providers are permitted to enter the premises, please consult with your local public health unit. Please work with special needs service providers to explore alternative modes of service delivery where in-person delivery is not possible.
- Maximum capacity rules do not apply to SNR staff (consultants and enhanced staff) on site (i.e., if they are not counted towards staff to child ratios they are not included in the maximum capacity rules).
- Where SNR services are provided through external staff/service providers, licensees and home child care providers should inform all families of this fact, and record attendance for contact tracing purposes.
- All SNR staff must be screened before entering the child care setting, as per the protocol in the screening section above.

REFERENCE 21

Ontario

Ministry of Education

Operational Guidance During COVID-19 Outbreak

Child Care Re-Opening

Version 3 – August 2020

Contents

Highlights of Changes:

- Revised cohort size to maximum group sizes set out under the *Child Care are Early Years Act, 2014* (CCEYA), as of September 1, 2020 (see section: Maximum Group Size and Ratio)
- Revised guidance around who must review Health and Safety Protocols (see section: Health and Safety Protocols)
- Revised guidance around the use of masks to specify that all children in grade 4 and above are required to wear a non-medical or cloth mask, and all school-aged children are encouraged but not required to wear a mask. Additionally, all adults in a child care setting are required to wear a medical mask and eye protection (i.e., face shield) (see section: Guidance On the Use of Masks, Personal Protective Equipment (PPE), and Handwashing)
- Updated guidance around when an individual does not pass the screening to indicate this does not need to be reported to the local public health unit (see section: Screening for Symptoms)
- Revised guidance around reporting a serious occurrence related to COVID-19 (see section: Serious Occurrence Reporting)
- Revised guidance around parent fees to provide 14 days for parents to decide to accept a space before resuming fees, whether the space is used or not (see section: Parent Fees)
- Additional guidance to allow students completing post-secondary educational placements in child care settings (see section: Visitors)
- Additional guidance on staff training to clarify training should be available for all staff/providers at least once (see section: Staff Training)
- Revised guidance to remove the use of blankets or cloths over clothing when holding infants and toddlers (see section: Interactions with Infants/Toddlers)

INTRODUCTION AND PURPOSE

This guidance document is intended to support the following child care and early years sector partners:

- Consolidated Municipal Service Managers and District Social Service Administration Boards (CMSMs and DSSABs);
- child care licensees and staff;

- home child care agencies and providers; and,
- district school boards.

The information found within this guidance document is meant to support partners in meeting requirements set out under the *Child Care and Early Years Act, 2014* (CCEYA) and to provide clarification on operating child care programs with enhanced health and safety guidelines and/or restrictions in place. This guidance document will be modified as applicable when these restrictions can be lifted and/or amended to reflect new advice at that time.

This guidance document has been designed for use in conjunction with the Child Care Centre and Home Child Care Agency Licensing Manuals, the CCEYA and its regulations. **In the event of a conflict between this document and the licensing manuals, this document will prevail. Advice of the local public health unit must be followed, even in the event that it contradicts this guidance document.**

As of September 1, 2020, child care and early years programs may return to maximum group sizes as set out under the CCEYA (i.e., licensed age groups prior to the COVID-19 outbreak). All child care settings must operate with enhanced health and safety measures in place. New measures include but are not limited to the guidance that all adults in a child care setting are required to wear medical masks and eye protection (i.e., face shield), children in grades 4 and above are required to use non-medical or cloth masks, and all school-aged children are encouraged, but not required to wear masks. Home-based child care providers must also operate with these health and safety measures in place.

As always, **the top priority for the ministry will be the health and safety of the children and child care staff/providers** and we will monitor the COVID-19 outbreak situation closely. Should there be a need to return to stricter health and safety measures, the ministry will revise this guidance under the advice of the Chief Medical Officer of Health.

The ministry is requesting school boards, Consolidated Municipal Service Managers/District Social Services Administration Boards and child care partners, in collaboration with local public health units, work together to ensure full-day licensed child care programs located in schools are able to re-open. The ministry understands that district school board protocols may differ from those of licensed child care and recommends that partners work together to align protocols where needed (i.e., in a shared space).

While the focus of this guidance document is on the health, safety and operational measures that are required in order to safely operate child care, please note that every effort should continue to be made to uphold the welcoming and caring environment that

child care provides for children and families. More information regarding the early years pedagogy, including helpful resources can be found on the ministry website. The ministry has also created a guidance document with ideas on how to provide an engaging environment while physically distancing: *Building On How Does Learning Happen?*

Additionally, EarlyON Centres and Before and After School Programs are also permitted to operate as of September 1, 2020 and the *2020-21 Before and After School Kindergarten to Grade 6 Policies and Guidelines* has been updated, and *operational guidance for the re-opening of EarlyON Child and Family Centres* has also been created. The health and safety guidance aligns with this document and includes program specific guidance as well.

The Early Years Portal contains a wealth of information to help licensees, staff and home child care providers understand the requirements of the CCEYA and its regulations.

You may wish to visit the provincial COVID-19 website regularly for current information, as well as the Public Health Ontario public resources page for information to help stop the spread, find sector specific resources, including helpful posters, mental health resources, and other information.

If you have further questions or require clarification, please contact your Ministry of Education program advisor directly or contact the Licensed Child Care Unit at information.met@ontario.ca.

LICENSING REQUIREMENTS

Licensing Processes and Renewals

- Licences are required to be amended, if necessary, to ensure director approvals and conditions on the licence align with new restrictions.
- To support the operational needs of licensees, the ministry will prioritize and expedite the review of requests to revise and amend licences.
- Licensees are required to meet all the requirements set out in the *Child Care and Early Years Act, 2014* (CCEYA) and its regulations and to obtain all necessary municipal approvals to support licence revision requests.
- Licensees must follow all current ministry and CMSM/DSSAB policies and guidelines.
- Licences that expire during the emergency period will be automatically extended by six months.
- Renewal, revision and application fees are set at zero for the period of the emergency and during the 60 days after the end of the emergency period.

Inspections

- Ministry staff will conduct in-person monitoring and licensing inspections of child care centres, home child care agencies, home child care premises and in-home services where necessary.
- Ministry staff must:
    - be screened prior to entering the premises following the protocol determined by the licensee (see screening section below);
    - wear a medical mask and eye protection (i.e., face shield); and,
    - follow any other protocols requested by the licensee or home child care or in-home service provider.
- Ministry staff will use technology (e.g., telephone, video conferencing) to complete virtual monitoring and licensing inspections where appropriate.

Maximum Group Size and Ratio

- As of September 1, 2020, child care settings may return to maximum group sizes as set out under the CCEYA (i.e., licensed age groups prior to theCOVID-19 outbreak).
- Staff and students are not included in the maximum group size, but should be assigned to a specific group where possible. Please see the *Staffing* section for more information. Children are permitted to attend on a part time basis, and as with children attending full time, should be included in one group and should not mix with other groups.

- Maximum group size rules do not apply to Special Needs Resource staff on site.
- While groups are permitted to return to the previous maximum group size under the CCEYA (i.e., maximum group size prior to the COVID-19 outbreak), each group should stay together throughout the day and as much as possible should not mix with other groups.
    - Please see the *Health and Safety Requirements* section of this document for more information on limiting interactions between groups, particularly in shared spaces, and programming to support physical distancing.
- Licensees are required to maintain ratios set out under the CCEYA. Please see the group size and ratio charts below for reference.
- Mixed age grouping is permitted as set out under the CCEYA where a director approval has been granted on the licence.
- Reduced ratios are permitted as set out under the CCEYA provided that groups are not mixed and that reduced ratios are not permitted at any time for infants.

Group Size/Ratio Charts

Age category	Age range of age category	Ratio of employees to children	Maximum number of children in group
Infant	Younger than 18 months	3 to 10	10
Toddler	18 months or older but younger than 30 months	1 to 5	15
Preschool	30 months or older but younger than 6 years	1 to 8	24
Kindergarten	44 months or older but younger than 7 years	1 to 13	26
Primary/junior school age	68 months or older but younger than 13 years	1 to 15	30
Junior school age	9 years or older but younger than 13 years	1 to 20	20

LICENSED FAMILY AGE GROUPS

Item	Age range of age category	Ratio of employees to children
1.	Younger than 12 months	1 to 3
2.	12 months or older but younger than 24 months	1 to 4
3.	24 months or older but younger than 13 years	1 to 8

Maximum Capacity of Building

- More than one child care or early years program or day camp can be offered per building as long as they are able to maintain separation between the groups and/or programs, and follow all health and safety requirements that apply to those programs.
- There are no changes to the maximum group size for home child care which allows for a maximum of 6 children, not including the providers own children who are 4 years or older.

Staffing

- Staff and students should work at only one location.
- Supervisors and/or designates should limit their movement between rooms, doing so when absolutely necessary.
- Supply/replacement staff should be assigned to a specific group so as to limit staff interaction with multiple groups of children.
- Students on field placement should be assigned to a specific licensed age group.
- Qualified Staff
    - Licensees are required to ensure each group has the required number of qualified staff as set out in the CCEYA. Licensees may submit requests for staff director approval (DAs) to the ministry.
    - Staff DAs can be transferred from one child care centre to another child care centre that is operated by the same licensee.
    - Licensees can also request a staff DA for multiple age groups.
- Certification in Standard First Aid Training, including Infant and Child CPR
    - Staff that are included in ratios and all home child care providers are required to have valid certification in first aid training including infant

and child CPR, unless exempted under the CCEYA or the certification has been extended by the Workplace Safety and Insurance Board (WSIB).
    - The WSIB has indicated that all certifications that expire after March 1, 2020 are automatically temporarily extended until December 31, 2020.
    - Licensees are encouraged to monitor the WSIB website for any updates on First Aid/CPR certificate extensions for any staff, home child care providers or in-home service providers whose certification would have expired after March 1, 2020.
- Vulnerable Sector Checks (VSCs)
    - Licensees are required to obtain VSCs from staff and other persons who are interacting with children at a premises, including students.
    - A licensee is not required to obtain a new VSC from staff or persons interacting with children where the fifth anniversary of the staff or person's most recent VSC falls within the emergency period, until 60 days after the emergency period ends.

HEALTH AND SAFETY REQUIREMENTS

Working with Local Public Health

- While the ministry is providing guidance on how to operate child care during the COVID-19 outbreak, CMSMs/DSSABs, licensees, and home child care providers must follow the advice of the local public health unit when establishing health and safety protocols, including how to maintain separation between groups.
- The ministry recognizes that this may result in regional differences in these protocols, but given the different impact of COVID-19 in different communities it is important to follow the advice of local public health officials to keep children and families safe in their respective communities.
- Contact information for local public health units.

Health and Safety Protocols

- Every licensee must ensure that there are written policies and procedures outlining the licensee's health and safety protocols. Licensees must submit an attestation to the Ministry that confirms new policies and procedures have been developed and reviewed with employees, home child care providers, home child care visitors and students. These policies and procedures must be consistent with any direction of a medical officer of health and include information on how the child care setting will operate during and throughout the recovery phase following the COVID-19 outbreak including:
    - disinfection of the space, toys and equipment;
    - how to report illness;
    - how physical distancing will be encouraged;
    - how shifts will be scheduled, where applicable;
    - rescheduling of group events and/or in-person meetings; and,
    - parent drop off and pick up procedures.

Cleaning Child Care Centres/Homes

- Frequently touched surfaces should be cleaned and disinfected at least twice a day as they are most likely to become contaminated (for example, doorknobs, water fountain knobs, light switches, toilet and faucet handles, electronic devices, and tabletops).
- Please refer to Public Health Ontario's Environmental Cleaning fact sheet and the Public Services Health and Safety Association's Child Care Centre Employer Guideline for information on cleaning.

- Information from Public Health Ontario provides best practices for cleaning and disinfecting, including:
    - which products to use;
    - how to clean and disinfect different materials
    - other items to remember, including checking expiry dates of cleaning and disinfectant products and following the manufacturer's instructions.
- It is recommended that operators keep a cleaning and disinfecting log to track and demonstrate cleaning schedules.
- Only one group should access the washroom at a time and it is recommended that the facilities be cleaned in between each use, particularly if multiple groups will be using the same washroom.

Guidance on the Use of Masks, Personal Protective Equipment (PPE) and Handwashing

- All adults in a child care setting (i.e., child care staff, home child care providers, home child care visitors, and students) are required to wear medical masks and eye protection (i.e., face shield) while inside in the child care premises, including in hallways.
- All children in grades 4 and above are required to wear a non-medical or cloth mask while inside in the child care premises, including in hallways.
- All school-aged children are encouraged but not required to wear a mask while inside in the child care premises, including in hallways (see information about the use of masks on the provincial COVID-19 website or the Public Health Ontario factsheet on non-medical masks). Parents/guardians are responsible for providing their school-aged child(ren) with a mask(s).
- The use of masks is not required outdoors for adults or children if physical distancing of a least 2-metres can be maintained between individuals.
- Reasonable exceptions to the requirement to wear masks are expected to be put in place by licensees. Exceptions to wearing masks indoors could include circumstances where a physical distance of at least 2 metres can be maintained between individuals, situations where a child cannot tolerate wearing a mask, reasonable exceptions for medical conditions, etc.
- Licensees should document their requirements and exceptions related to masks.
- Masks are not recommended for children under the age of two (see information about the use of masks on the provincial COVID-19 website).

- Child care licensees and home child care providers should secure and sustain an amount of PPE (including but not limited to face shields, medical masks, gloves, etc.), and cleaning supplies that can support their current and ongoing operations.
- The Ontario Together Portal has a Workplace PPE Supplier Directory that lists Ontario businesses that provide personal protective equipment and other supplies.
- When wearing a medical mask, you should wash your hands before putting on the mask and before and after removing the mask. Refer to Public Health Ontario resources for how to properly wear and take off masks and eye protection.
- Perform and promote frequent, proper hand hygiene (including supervising or assisting participants with hand hygiene). Hand washing using soap and water is recommended over alcohol-based hand rub for children. Refer to Public Health Ontario's How to Wash Your Hands fact sheet.

Screening for Symptoms

- All individuals including children attending child care, staff, students and child care providers, parents/guardians, and visitors must be screened each day before entering the child care setting.
- Home child care providers and residents must also be screened each day before receiving children into care.
- Where possible, daily screening should be done electronically (e.g., via online form, survey, or e-mail) prior to arrival at the child care setting.
- Parents and guardians should be reminded of this requirement when children are first registered for the program and through visible signage at the entrances and drop-off areas.
- If children are screened at the child care setting, screeners should take appropriate precautions when screening and escorting children to the program, including maintaining a distance of at least 2 metres (6 feet) from those being screened, or being separated by a physical barrier (such as a plexiglass barrier). If a 2 metre distance or physical distancing cannot be maintained, personal protective equipment (PPE) (i.e., medical mask and eye protection (i.e., face shield)) should be worn.
- Where an individual does not pass the screening and is not permitted to attend the program, this does not need to be reported to the local public health unit.
- Please follow advice from your local public health unit regarding precautions to have in place.

    - Refer to Public Health Ontario resources for how to properly wear and take off masks and eye protection.
- Alcohol-based hand rub containing 60% to 90% alcohol content should be placed at all screening stations. Dispensers should not be in locations that can be accessed by young children.
- All child care licensees must maintain daily records of screening results.
    - Records are to be kept on the premises (centre or home).
- You may wish to consult the Province's COVID-19 website for information and resources on COVID-19 symptoms, protections, and seeking health care.

Attendance Records

- All child care licensees are responsible for maintaining daily records of anyone entering the child care facility/home and the approximate length of their stay (such as cleaners, people doing maintenance work, people providing supports for children with special needs, those delivering food).
    - Records are to be kept on the premises (centre or home).
- Records (e.g. name, contact information, time of arrival/departure, screening completion/result, etc.) must be kept up-to-date and available to facilitate contact tracing in the event of a confirmed COVID-19 case or outbreak.

Testing Requirements

- Children, child care centre staff, students, home child care providers and those ordinarily resident/regularly at the home child care premises should be referred for testing when demonstrating symptoms of illness.
    - Those who test negative for COVID-19 must be excluded from the program until 24 hours after symptom resolution.
    - Those who test positive for COVID-19 must be excluded from the program for 14 days after the onset of symptoms and/or clearance has been received from the local public health unit.
- Testing of asymptomatic persons should only be performed as per provincial testing guidance.
- Please refer to the provincial testing guidance for updated information regarding the requirement for routine testing in a child care setting.
- A list of symptoms, including atypical signs and symptoms, can be found in the COVID-19 Reference Document for Symptoms on the Ministry of Health's COVID-19 website.
- Please see the protocols when a child, child care centre staff, student, home child care provider and those ordinarily resident/regularly at the home child care premises becomes sick for information on testing in the event of a suspected case.

Protocols When Someone in a Child Care Setting Demonstrates Symptoms of Illness

- A single, symptomatic, laboratory confirmed case of COVID-19 in a staff member, home child care provider or child must be considered a confirmed COVID-19 outbreak, in consultation with the local public health unit. Outbreaks should be declared in collaboration between the program and the local public health unit to ensure an outbreak number is provided.
- Children, child care centre staff, students, home child care providers and those ordinarily resident/regularly at the home child care premises who are symptomatic or have been advised to self-isolate by the local public health unit, must not attend the program. Asymptomatic individuals awaiting results may not need to be excluded and should follow the advice of the local public health unit.
    - Symptoms to look for include but are not limited to: fever, cough, shortness of breath, sore throat, runny nose, nasal congestion, headache, and a general feeling of being unwell.
    - Children in particular should be monitored for atypical symptoms and signs of COVID-19. For more information, please see the symptoms outlined in the 'COVID-19 Reference Document for Symptoms' on the Ministry of Health's COVID-19 website.
- If a child, child care centre staff, student, home child care provider and those ordinarily resident/regularly at the home child care premises becomes symptomatic while in the program, they should be isolated in a separate room and family members contacted for pick-up.
- If a separate room is not available, the person who is symptomatic should be kept at a minimum of 2 metres from others.
- The person who is symptomatic should be provided with tissues and reminded of hand hygiene, respiratory etiquette, and proper disposal of tissues.
- If the person who is symptomatic is a child, a child care staff/provider should remain with the child until a parent/guardian arrives. If tolerated and above the age of 2, the child should wear a medical mask. The child care staff/provider should wear a medical mask and eye protection (i.e., face shield) at all times and not interact with others. The child care staff/provider should also avoid contact with the child's respiratory secretions.
- All items used by the person who is symptomatic should be cleaned and disinfected. All items that cannot be cleaned (paper, books, cardboard puzzles) should be removed and stored in a sealed container for a minimum of 7 days.

- The local public health unit should be notified, and their advice should be followed.
- For home-based programs: if a person who resides in the home becomes symptomatic and/or tests positive for COVID-19, the local public health unit should be notified and their advice on next steps should be followed (including closing the program and notifying all families if necessary).
- If the child care program is located in a shared setting (for example in a school), follow public health advice on notifying others using the space of the suspected illness.
- Where a child, staff, parent, student, home child care provider, person who is ordinarily a resident at a home child care premises or a person who is regularly at a home child care premises is suspected of having or has a confirmed case of COVID-19, licensees must report this to the ministry as a serious occurrence (see *Serious Occurrence Reporting* section below).
    - When a person becomes symptomatic the home child care agency will report to the local public health unit, the ministry, and where public health advises, families.
- Other children, including siblings of the symptomatic child, and child care staff/providers in the program who were present while the child or staff member/provider became ill should be identified as a close contact and grouped together. The local public health unit will provide any further direction on testing and isolation of these close contacts.

Serious Occurrence Reporting

- Child care centre licensees have a duty to report suspected or confirmed cases of COVID-19 under the *Health Protection and Promotion Act*. The licensee should contact their local public health unit to report a child suspected to have COVID-19. The local public health unit will provide specific advice on what control measures should be implemented to prevent the potential spread and how to monitor for other possible infected staff members and children.
- Where a child, parent, staff, student, home child care provider, home child care visitor or a person who is ordinarily a resident at/regularly present at a home child care premises is suspected (i.e. has one or more symptoms and has been tested) of having or has a confirmed case of COVID-19, licensees must report this to the ministry as a serious occurrence.
- Where a room, centre or premises closes due to COVID-19, licensees must report this to the ministry as a serious occurrence.
- Licensees are required to post the serious occurrence notification form as required under the CCEYA, unless the local public health unit advises otherwise.

OPERATIONAL GUIDANCE

PRE-PROGRAM CONSIDERATIONS

Communication with Families

- Communication with families regarding the enhancement of health and safety measures facilitates transparency of expectations. New policies should be shared with families, for their information and to ensure they are aware of these expectations, including keeping children home when they are sick, which are aimed at helping to keep all children and staff/providers safe and healthy.
- Licensees must share with parents, the policies and procedures regarding health and safety protocols to COVID-19, including requirements and exceptions related to masks.
- Licensees are not required as part of re-opening to revise their program statement, full parent handbook and other policies.
- Licensees may want to consider providing links to helpful information, as well as detailed instructions regarding screening and protocols if a child or individual in the program becomes ill.
- Priority/waitlist policies may need to be updated as health and safety measures change to account for any resulting limited capacity. Any changes to policies should be communicated to families so they are aware of the changes. An equitable approach should be implemented to assess priority for care.
- Where possible, the use of in-person communication should be limited.

Parent Fees

- In an effort to stabilize parent fees when re-opening, the ministry encourages child care operators to set fees at the level they were at prior to the closure, where possible. Home child care providers are also encouraged to hold parent fees to the level they were at prior to the COVID-19 outbreak (March 2020), where possible.
- Where a child who was receiving care in a child care centre immediately prior to the closure is offered a child care space for September 1, 2020, or later, parents will have 14 days to accept or decline the placement.
    - If the placement is accepted, child care operators may charge a fee to use or hold the space as of September 1, 2020, whether the child attends or not.

    - If the placement is declined, child care operators may offer the placement to another child.
- operators continue to be prohibited from charging or accepting fees or deposits to add families to a priority list for preferred access to spaces;
- Per the operational guidance first released in mid-June, for children who received child care at a home child care premises immediately before the closure, licensed home child care providers are still required to give parents 30 days to indicate whether they want to keep their space. After the 30 days, payments would be required to secure the space, whether the child attends or not.

Access to Child Care Spaces and Prioritizing Families

- Given the strict health and safety measures in place and the advice of local public health units, some child care licensees/providers may continue to operate at reduced capacity for a period of time. When determining prioritization of limited child care spaces, CMSMs/DSSABs, licensees, and home child care agencies and providers may wish to consider the following:
    - Returning children served through emergency child care to their original placement and continuity of service for these families;
    - Care for families where parents must return to work and that work outside of the home;
    - Families with special circumstances that would benefit from children returning to care, such as children with special needs; and
    - Other local circumstances.
- CMSMs/DSSABs, licensees, and home child care agencies and providers should also consider that some families they used to serve may no longer require care, or require a different level of care (i.e., part time child care).
- Assessing demand for care as the COVID-19 outbreak and health and operational advice changes, is recommended.

Fee Subsidy Eligibility and Assessment

- CMSMs/DSSABs may need to consider changes to the way in which child care fee subsidy assessments for eligibility are conducted in order to incorporate virtual assessments and records where possible.

Licensed Child Care Programs in Schools

- The ministry recognizes that there are additional considerations for licensed child care programs located in schools.
- School boards are required to find safe ways to allow child care operators to enter their centres located in schools, in order to prepare their space and

ensure they meet the operational guidelines provided by the ministry. School boards should familiarize themselves with this guide to optimally facilitate child care operating in schools.
- School boards, CMSMs/DSSABs and child care partners should work together collaboratively to ensure that full day licensed child care programs located in schools are able to operate and that health and safety policies and requirements for child care programs and schools are complementary and aligned with the advice of local public health officials.

Staff Training

- CMSMs/DSSABs must ensure that training that is aligned with local public health unit direction is provided to all child care staff/providers on the health, safety and other operational measures outlined in this document plus any additional local requirements in place as close to re-opening as possible.
    - New training is not required with each iteration of this guidance but should be offered in a way that includes child care staff/providers at least once, whether they have re-opened through the summer or later into the fall.
- You may wish to consult the Public Services Health and Safety Association's Child Care Centre Employer Guideline for information on other measures to consider for child care staff/providers. Note that there is also a resource document for Child Care Providers.
- This may include instruction on how to properly clean the space and equipment, how to safely conduct daily screening and keep daily attendance records, and what to do in the case that someone becomes sick.
- It may be useful to draw on the approaches adopted by those who operated emergency child care sites as well as any lessons learned from those operating through early phases of re-opening.

Liability and Insurance

- All requirements under the CCEYA must be met in addition to the enhanced health and safety measures outlined in this document and by local public health.
- Licensees and child care providers may wish to consult with their legal counsel or insurance advisor about any other considerations for operating and providing child care during this period.

IN-PROGRAM CONSIDERATIONS

Drop-Off and Pick-up Procedures

- Licensees should develop procedures that support physical distancing and separate groups of children as best as possible (i.e., children of one room enter door A and children of another room enter door B, or staggered entrance times).
- As much as possible, parents should not go past the screening area.
- All entrances should have alcohol-based hand rub.
- Consider using signage/markings on the ground to direct families through the entry steps.
- Personal belongings (e.g., backpack, clothing, etc.) should be minimized. Belongings should be labeled and kept in the child's cubby/designated area.
- You may want to consider a specific policy/protocol for stroller storage if this typically takes place inside the child care setting (for example, designating a space outside of the child care setting so that parents do not need to enter the building to leave the stroller).

Visitors

- There should be no non-essential visitors at the program.
- Students completing post-secondary educational placements will be permitted to enter child care settings and should only attend one child care setting and be assigned to one group of children.
- Students will also be subject to the same health and safety protocols as other staff members such as screening, and the use of PPE when on the child care premises, and must also review the health and safety protocols.
- The provision of special needs services may continue and operators may use their discretion to determine whether the services being provided are essential and necessary at this time.
- Use of video and telephone interviews should be used to interact with families where possible, rather than in person.
- Ministry staff and other public officials (e.g. fire marshal, public health inspectors) are permitted to enter and inspect a child care centre, home child care agency and premises at any reasonable time.
- As much as possible, parents should not go past the screening area.
- Licensees must ensure that there are no volunteers at the program.

Space Set-Up and Physical Distancing

- The ministry recognizes that physical distancing between children in a child care setting is difficult and encourages child care staff and providers to maintain a welcoming and caring environment for children. Please see the document *Building On How Does Learning Happen?* For more support and ideas on how to provide an engaging environment while physically distancing.
- Each group of children must have their own assigned indoor space, separated from all other groups by a physical barrier. The purpose of the barrier is to reduce the spread of respiratory droplets that are thought to transmit COVID-19 and to reinforce physical distancing requirements between groups. The physical barrier must begin at the floor and reach a minimum height of 8 feet to ensure that it will always be 12 inches taller than the tallest person in the facility. It must be as wide as the space/room will allow.
- When in the same common space (e.g., entrances, hallways) physical distancing of at least 2 metres must be maintained between different groups and should be encouraged, where possible, between children within the same group by:
    - spreading children out into different areas, particularly at meal and dressing time;
    - incorporating more individual activities or activities that encourage more space between children; and
    - using visual cues to promote physical distancing.
- In shared outdoor space, a distance of at least 2 metres must be maintained between groups and any other individuals outside of the group at all times.
- Licensees and home child care providers are encouraged to increase the distance between cribs/cots/resting mats/playpens or place the children head to toe or toe to toe if the space is limited.
- Shared spaces and structures that cannot be cleaned and disinfected between groups should not be used.
- Recognizing that physical distancing is difficult with small children and infants, additional suggestions include:
    - planning activities that do not involve shared objects or toys;
    - when possible, moving activities outside to allow for more space; and
    - avoiding singing activities indoors.

Equipment and Toy Usage and Restrictions

- Licensees and home child care providers are encouraged to provide toys and equipment which are made of materials that can be cleaned and disinfected (e.g., avoid plush toys).

- Mouthed toys should be cleaned and disinfected immediately after the child is finished using it.
- Licensees and home child care providers are encouraged to have designated toys and equipment (e.g., balls, loose equipment) for each room or group of children. Where toys and equipment are shared, they should be cleaned and disinfected prior to being shared, including between groups.
- If sensory materials (e.g., playdough, water, sand, etc.) are offered, they should be provided for single use (i.e. available to the child for the day) and labelled with child's name, if applicable.
- Play structures can only be used by one group of children at a time. Please consult with your local public health unit regarding the use of playground equipment onsite.

Program Statement/Activities

- Licensees are encouraged to continue to implement their program statement.
- The ministry recognizes that there may be approaches outlined in the program statement which may not be possible due to physical distancing.
- Licensees are not required to make updates to their program statement during this time.

Outdoor Play

- Licensees should schedule outdoor play by groups in order to facilitate physical distancing. Where the outdoor play area is large enough to accommodate multiple groups, licensees must separate the groups by at least 2 metres.
- If play structures are to be used by more than one group:
    - the structures can only be used by one group at a time
    - the structures should be cleaned and disinfected before and after each use by each group.
- Licensees and home child care providers are encouraged to have designated toys and equipment (e.g., balls, loose equipment) for each room or group. Where toys and equipment are shared, they should be cleaned and disinfected prior to being shared.
- Licensees and home child care providers should find alternate outdoor arrangements (e.g., community walk), where there are challenges securing outdoor play space. Providers should follow physical distancing practices when possible.
- Children should bring their own sunscreen where possible and it should not be shared.

- Staff may provide assistance to apply sunscreen to any child requiring it and should exercise proper hand hygiene when doing so (for example washing hands before and after application).

Interactions with Infants/Toddlers

- Licensees should continue to encourage staff and home child care providers to supervise and hold bottles for infants not yet able to hold their own bottle to reduce the risk of choking.
- Licensees and home child care providers should consider removing cribs or placing infants in every other crib and mark the cribs that should not be used in order to support physical distancing.
- Recognizing that physical distancing is difficult with small children and infants, suggestions to support physical distancing include:
  - planning activities that do not involve shared objects or toys; and,
  - when possible, moving activities outside to allow for more space.
- Children must not share food, feeding utensils, soothers, bottles, sippy cups, etc. Mouthed toys must be removed immediately for cleaning and disinfecting and must not be shared with other children.
  - Label these items with the child's name to discourage accidental sharing.

Food Provision

- Licensees and home child care providers should change meal practices to ensure there is no self-serve or sharing of food at meal times.
  - Utensils should be used to serve food.
  - Meals should be served in individual portions to the children.
  - There should be no items shared (i.e., serving spoon or salt shaker).
- There should be no food provided by the family/outside of the regular meal provision of the program (except where required and special precautions for handling and serving the food must be put in place).
- Children should neither prepare nor provide food that will be shared with others.
- Ensure proper hand hygiene is practiced when staff are preparing food and for all individuals before and after eating.
- Where possible, children should practice physical distancing while eating.
- There should be no sharing of utensils.

Provision of Special Needs Resources (SNR) Services

- The ministry recognizes that children with special needs and their families continue to require additional supports and services in child care settings.
- The provision of in-person special needs services in child care settings should continue where appropriate. Should questions arise in respect of which service providers are permitted to enter the premises, please consult with your local public health unit. Please work with special needs service providers to explore alternative modes of service delivery where in-person delivery is not possible.
- Maximum group size rules do not apply to SNR staff (consultants and enhanced staff) on site.
- Where SNR services are provided through external staff/service providers, licensees and home child care providers should inform all families of this fact, and record attendance for contact tracing purposes.
- All SNR staff must be screened before entering the child care setting, as per the protocol in the screening section above.

REFERENCE 22

Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases

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Abbreviations: BE, Belgium; DE, Germany; FI, Finland; GB, Great Britain; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland

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ABSTRACT

Background

Mathematical modelling of infectious diseases transmitted by the respiratory or close-contact route (e.g., pandemic influenza) is increasingly being used to determine the impact of possible interventions. Although mixing patterns are known to be crucial determinants for model outcome, researchers often rely on a priori contact assumptions with little or no empirical basis. We conducted a population-based prospective survey of mixing patterns in eight European countries using a common paper-diary methodology.

Methods and Findings

7,290 participants recorded characteristics of 97,904 contacts with different individuals during one day, including age, sex, location, duration, frequency, and occurrence of physical contact. We found that mixing patterns and contact characteristics were remarkably similar across different European countries. Contact patterns were highly assortative with age: schoolchildren and young adults in particular tended to mix with people of the same age. Contacts lasting at least one hour or occurring on a daily basis mostly involved physical contact, while short duration and infrequent contacts tended to be nonphysical. Contacts at home, school, or leisure were more likely to be physical than contacts at the workplace or while travelling. Preliminary modelling indicates that 5- to 19-year-olds are expected to suffer the highest incidence during the initial epidemic phase of an emerging infection transmitted through social contacts measured here when the population is completely susceptible.

Conclusions

To our knowledge, our study provides the first large-scale quantitative approach to contact patterns relevant for infections transmitted by the respiratory or close-contact route, and the results should lead to improved parameterisation of mathematical models used to design control strategies.

The Editors' Summary of this article follows the references.

Introduction

Preparing for outbreaks of directly transmitted pathogens such as pandemic influenza [1–3] and SARS [4–9], and controlling endemic diseases such as tuberculosis and meningococcal diseases, are major public health priorities. Both can be achieved by nonpharmaceutical interventions such as school closure, travel restrictions, and contact tracing, or by health-care interventions such as vaccination and use of antiviral or antibiotic agents [2,10–13]. Mathematical models of infectious disease transmission within and between population groups can help to predict the impact of such interventions and inform planning and decision making. Contact rates between individuals are often critical determinants of model outcomes [14]. However, few empirical studies have been conducted to determine the patterns of contact between and within groups and in different social settings.

In comparison to HIV and sexually transmitted diseases [15–17] and drug/needle sharing networks [18], where a number of large-scale empirical studies have been conducted on contact patterns, relatively little effort has been devoted to infections spread by respiratory droplets or close contact. Instead, the contact structure for these infections has been assumed to follow a predetermined pattern governed by a small number of parameters that are then estimated using seroepidemiological data [19,20]. A small number of studies have attempted to directly quantify such contact patterns, but they were conducted in small or nonrepresentative populations [14,21–25]. Hence, it is unclear to what extent the results can be generalized to an overall population and across different geographical areas. To address this lack of empirical knowledge, we present here results from, to our knowledge the first, large-scale, prospectively collected, population-based survey of epidemiologically relevant social contact patterns. The study was conducted in eight different European countries using a common paper diary approach and covering all age groups. We use these data to assess how an emerging infection could spread in a wholly susceptible population if it were transmitted by the social contacts measured here.

Methods

Survey Methodology

Information on social contacts was obtained using cross-sectional surveys conducted by different commercial companies or public health institutes in Belgium (BE), Germany (DE), Finland (FI), Great Britain (GB), Italy (IT), Luxembourg (LU), The Netherlands (NL), and Poland (PL). The recruitment and data collection were organised at the country level according to a common agreed quota sampling methodology and diary design. The surveys were conducted between May 2005 and September 2006 with the oral informed consent of participants and approval of national institutional review boards following a small pilot study to test feasibility of the diary design and recruitment [26].

Survey participants were recruited in such a way as to be broadly representative of the whole population in terms of geographical spread, age, and sex. In BE, IT, and LU, survey participants were recruited by random digit dialling using land line telephones; in GB, DE, and PL survey participants were recruited through a face-to-face interview; survey participants in NL and FI were recruited via population registers and linked to a larger national sero-epidemiology survey in NL. Children and adolescents were deliberately oversampled, because of their important role in the spread of infectious agents. For more details on the survey methodology in the various countries, see Table S1.

Briefly, only one person in each household was asked to participate in the study. Paper diaries were either sent by mail or given face to face to participants. Participants were coached by telephone or in person on how to fill in the diary.

Diaries recorded basic sociodemographic information about the participant, including employment status, level of completed education, household composition, age, and sex. Participants were assigned a random day of the week to record every person they had contact with between 5 A.M. and 5 A.M. the following morning. Participants were instructed to record contacted individuals only once in the diary. A contact was defined as either skin-to-skin contact such as a kiss or handshake (a physical contact), or a two-way conversation with three or more words in the physical presence of another person but no skin-to-skin contact (a nonphysical contact). Participants were also asked to provide information about the age and sex of each contact person. If the age of a contact person was not known precisely, participants were asked to provide an estimate of the age range (the midpoint was used for data analysis). For each contact, participants were asked to record location (home, work, school, leisure, transport, or other), the total duration of time spent together (less than 5 min, 5–15 min, 15 min to 1 h, 1–4 h, or 4 h or more) as well as the frequency of usual contacts with this individual (daily or almost daily, about once or twice a week, about once or twice a month, less than once a month, or for the first time).

Diaries were translated into local languages (see Text S1 for the diary used in GB) and are available on request in the following languages: Dutch, English, French, Finnish, German, Italian, Polish, Portuguese, and Swedish. Diaries for young children were filled in by a parent or guardian on their behalf. Older children who obtained parental consent were given diaries with simplified language to fill in on their own (see Table S1 for more details).

Data Analysis

Main effects of covariates (age, sex, household size, and country) on numbers of contacts were assessed using multiple censored negative binomial regression [27]. The data were right censored at 29 contacts for all countries because of a limited number of possible diary entries in some countries. Additionally, a sensitivity analysis was performed to assess the effects of different handling of professional contacts between the countries.

The log-likelihood function ll for the censored negative binomial was

$$ll = \sum_{i=1}^{n} w_i(\delta_i \log(P(Y = y_i|\mathbf{X}_i)) + (1-\delta_i)\log(1 - \sum_{j=0}^{28} P(Y = j|\mathbf{X}_i))),$$

where w_i is the weight of observation i, $\delta_i = \begin{cases} 1 \text{ if } y_i < 29 \\ 0 \text{ if } y_i \geq 29 \end{cases}$ is an indicator variable for censoring, y_i is the number of observed

contacts, $\mathbf{X}_i$ is the vector of explanatory variables, and P is the probability function of the negative binomial distribution:

$$P(Y = y_i|\mathbf{X}_i) = \frac{\Gamma(y_i + 1/\alpha)}{\Gamma(y_i + 1)\Gamma(1/\alpha)} \left(\frac{1}{1 + \alpha\mu}\right)^{1/\alpha} \left(\frac{\alpha\mu}{1 + \alpha\mu}\right)^{y_i},$$

where $\mu = \exp(\mathbf{X}_i\beta)$; β is the vector of coefficients and α is the overdispersion parameter.

Sampling weights—the inverse of the probability that an observation is included because of the sampling design—were calculated for each country separately, based on official age and household size data of the year 2000 census round data published by Eurostat (http://epp.eurostat.ec.europa.eu/) (see Table S2) and used to correctly estimate population-related quantities. Overall statistics should be considered indicative of general trends and levels, but specific statistical representativity for the whole of Europe is not claimed, since participating countries, although geographically and socially diverse, are not a representative or random selection at the European level.

Association Rule Analysis

Mining association rules is a tool for discovering patterns between variables in large databases [28]. Let X,Y denote disjoint nonempty items in the contact survey, such as daily frequency, duration of more than 4 h, and physical contact. Association rules are rules of the form $X \rightarrow Y$ that measure how likely the event Y is, given X. In this context X is called antecedent while Y is called consequent. Rules are typically extended to include more items in the antecedent but are restricted to include only one item in the consequent. The length of the rule is defined as the total number of items in both antecedent and consequent.

Selecting interesting rules from the set of all possible rules is based on various measures of significance and interest. The best-known are support, confidence, and lift. The support of an association rule $X \rightarrow Y$ is defined as the relative frequency of $X \cap Y$. Finding rules with high support can be seen as a simplification of the learning problem called "mode finding" or "bump hunting." The confidence of a rule is the conditional probability $P(Y|X)$ indicating what percentage of times the rule holds and thus measuring the association between $\{X,X^c\}$ and $\{Y,Y^c\}$. Using both constraints, the set of rules can further be filtered by the lift, which is defined as the ratio of the relative frequency of $X \cap Y$ and the product of relative frequencies of X and Y. The lift can be interpreted as the ratio of the rule's observed support to the support expected under independence. Greater lift values indicate stronger associations. Additionally, a Chi-square test for the rule-corresponding two-by-two table consisting of cells $X \cap Y$, $X^c \cap Y$, $X \cap Y^c$, $X^c \cap Y^c$, where ^{c} refers to the complementing set of items, can be used to test statistical significance of the association. Whenever the Chi-square distribution seemed inappropriate due to small sample size, a Fisher exact test was used. For a more extensive overview of applying association rules on contact data see [29].

Contact Surface Smoothing

Contact surface smoothing was performed by applying a negative binomial model on the aggregated number of contacts (both physical and nonphysical) over 5 y age bands for both responders and contacts using a tensor product spline as a smooth interaction term [30,31].

Epidemiological Modelling: Simulating the Initial Phase of an Epidemic

We explore the age-specific incidence of infection during the initial phase of an epidemic of an emerging infectious disease agent that spreads in a completely susceptible population. We focus on the generic features of epidemic spread along the transmission route that is specified by physical and nonphysical contacts as defined here. We partition the population into 5 y age bands, and we group all individuals aged 70 y and older together. This process results in 15 age classes. We denote the number of at-risk contacts of an individual in age class j with individuals in age class i by k_{ij}. We take k_{ij} as proportional to the observed number of contacts (both physical and nonphysical) that a respondent in age band j makes with other individuals in age band i. The matrix with elements k_{ij} is known in infectious disease epidemiology as the next generation matrix $\mathbf{K}$ [32]. The next generation matrix can be used to calculate the distribution of numbers of new cases in each generation of infection from any arbitrary initial number of introduced infections. For example, when infection is introduced by one single 65-y-old infected individual into a completely susceptible population, we can denote the number of initial cases in generation 0 by the vector $\mathbf{x}_0 = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0)^T$. The expected numbers of new cases in the ith generation are denoted by the vector $\mathbf{x}_i$, and this vector is calculated by applying the next generation matrix $\mathbf{K}$ i times to the initial numbers of individuals $\mathbf{x}_0$, that is, $\mathbf{x}_i = \mathbf{K}^i\,\mathbf{x}_0$. For large i, the vector $\mathbf{x}_i$ will be proportional to the leading eigenvector of $\mathbf{K}$. We find that, in practice, the distribution of new cases is stable after five generations; that is, the distribution no longer depends on the precise age of the initial case. The incidence of new infections per age band is obtained by dividing the expected number of new cases per age class by the number of individuals in each age class. To facilitate comparison among countries, we normalized the distribution of incidence over age classes such that for each country the age-specific incidences sum to one.

Results

Description of Sample

A total of 7,290 diaries covering all contacts made by respondents during a full day were collected in eight countries ranging from 267 in NL to 1,328 in DE (see Table 1). 37.6% of participants in our survey were under 20 y of age, 12.4% of participants were over 60 y of age, and the medians were 28 y in BE (the lowest) to 33 y in DE (the highest). Returns of diaries by female participants showed a slight excess in all countries (ranging from 50.8% in FI to 55.7% in DE). In all countries except DE, single-person households were underrepresented in our sample (Table S2). This can be partially explained by the fact that children and adolescents were deliberately oversampled, and they are more likely to live in larger households.

Overall, 35.3% of the participants were in full-time education, 32.6% employed, 11% retired, 6.1% homemakers, 3.6% unemployed or seeking employment, whereas 8.6% recorded "other," and 2.8% failed to record their occupation. The proportion employed or in full-time education was fairly consistent across the eight countries; the other categories differed somewhat between countries.

Table 1. Number of Recorded Contacts per Participant per Day by Different Characteristics and Relative Number of Contacts from the Weighted Multiple Censored Negative Binomial Regression Model

Category	Covariate	Number of Participants	Mean (Standard Deviation) of Number of Reported Contacts	Relative Number of Reported Contacts (95% Confidence Interval)[a]
Age of participant, y	0–4	660	10.21 (7.65)	1.00
	5–9	661	14.81 (10.09)	1.42 (1.28–1.55)
	10–14	713	18.22 (12.27)	1.73 (1.57–1.90)
	15–19	685	17.58 (12.03)	1.68 (1.52–1.84)
	20–29	879	13.57 (10.60)	1.45 (1.33–1.57)
	30–39	815	14.14 (10.15)	1.45 (1.34–1.57)
	40–49	908	13.83 (10.86)	1.38 (1.27–1.50)
	50–59	906	12.30 (10.23)	1.31 (1.20–1.42)
	60–69	728	9.21 (7.96)	1.06 (0.96–1.16)
	70+	270	6.89 (5.83)	0.81 (0.73–0.88)
	Missing value	65	9.63 (9.05)	0.91 (0.66–1.17)
Sex of participant	Female	3,808	13.39 (10.57)	1.00
	Male	3429	13.51 (10.67)	0.99 (0.96–1.02)
	Missing value	53	10.92 (8.60)	1.57 (1.09–2.05)
Household size	1	749	8.87 (8.27)	1.00
	2	1,645	10.65 (9.14)	1.17 (1.11–1.24)
	3	1,683	12.87 (10.26)	1.20 (1.13–1.27)
	4	2,041	15.84 (11.17)	1.36 (1.28–1.44)
	5	814	16.47 (11.21)	1.46 (1.35–1.56)
	6+	358	17.69 (10.98)	1.56 (1.43–1.70)
Day of the week	Sunday	862	10.10 (8.76)	1.00
	Monday	1,032	13.32 (10.31)	1.33 (1.24–1.41)
	Tuesday	1,116	14.17 (10.83)	1.39 (1.31–1.48)
	Wednesday	1,017	14.58 (11.14)	1.38 (1.29–1.47)
	Thursday	1,069	14.70 (11.23)	1.41 (1.32–1.50)
	Friday	1,122	14.72 (11.25)	1.43 (1.34–1.52)
	Saturday	936	11.63 (9.11)	1.20 (1.12–1.28)
	Missing value	136	12.48 (10.66)	1.24 (1.08–1.40)
Country[b]	BE	750	11.84 (9.85)	1.00
	DE	1,341	7.95 (6.26)	0.70 (0.65–0.74)
	FI	1,006	11.06 (7.89)	0.94 (0.88–1.00)
	GB	1,012	11.74 (7.67)	0.99 (0.92–1.05)
	IT	849	19.77 (12.27)	1.66 (1.55–1.78)
	LU	1,051	17.46 (12.81)	1.42 (1.33–1.51)
	NL	269	13.85 (10.54)	1.34 (1.20–1.47)
	PL	1,012	16.31 (11.45)	1.37 (1.28–1.47)

[a]Dispersion parameter alpha = 0.36 (95% CI 0.34–0.37); alpha = 0 would correspond to no overdispersion, i.e., a censored Poisson distribution.
[b]Direct comparisons between countries are difficult because of different approaches to recording frequent professional contacts. In BE, DE, FI, and NL, participants were instructed not to record professional contacts in the diary if they had more than 20 (BE) or 10 (DE, FI, NL) of them per day.
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Number of Contacts

A total of 97,904 contacts with different persons were recorded (mean = 13.4 per participant per day) in the diaries. On average, German participants reported the fewest daily number of contacts (mean = 7.95, standard deviation [SD] = 6.26) and Italians the highest number (mean = 19.77, SD = 12.27). The contact distributions in all countries are slightly skewed, the skewness statistics ranging from 0.62 in IT to 2.96 in DE (Figure S1). Analysis of the total number of reported contacts with a multiple regression model shows a consistent pattern of contact frequency by age, with a gradual rise in the number of contacts in children, a peak among 10- to 19-y-olds, followed by a fall to a lower plateau in adults until the age of 50 and a sharp decrease after that age (Table 1). Living in a larger household size was associated with higher number of reported contacts. Weekdays were associated with 30%–40% more contacts than Sundays. The influence of the country in which the survey was performed was also apparent (Table 1), even when adjusting for the main different recording formats we used in different countries (diary sizes and estimates of professional contacts) (see Table S3). The overdispersion parameter in the model was significantly different from zero, indicating the necessity to use a negative binomial model as opposed to a Poisson model.

Frequency, Intensity, and Location of Contacts

The intensity of contacts was measured in a number of ways, all of which were found to be highly correlated with each other (see Figure 1 for pooled data from all countries, Figure S2 for country-specific data). Contacts of long duration or of daily frequency were much more likely to involve physical contact. Approximately 70% of contacts made on a daily basis last in excess of an hour, whereas approximately 75% of contacts made with individuals who have never been contacted before lasted for less than 15 min. Approximately 75% of contacts at home and 50% of school and leisure contacts were physical, whereas only a third of contacts recorded in other settings were physical; approximately two-thirds of the persons contacted in multiple

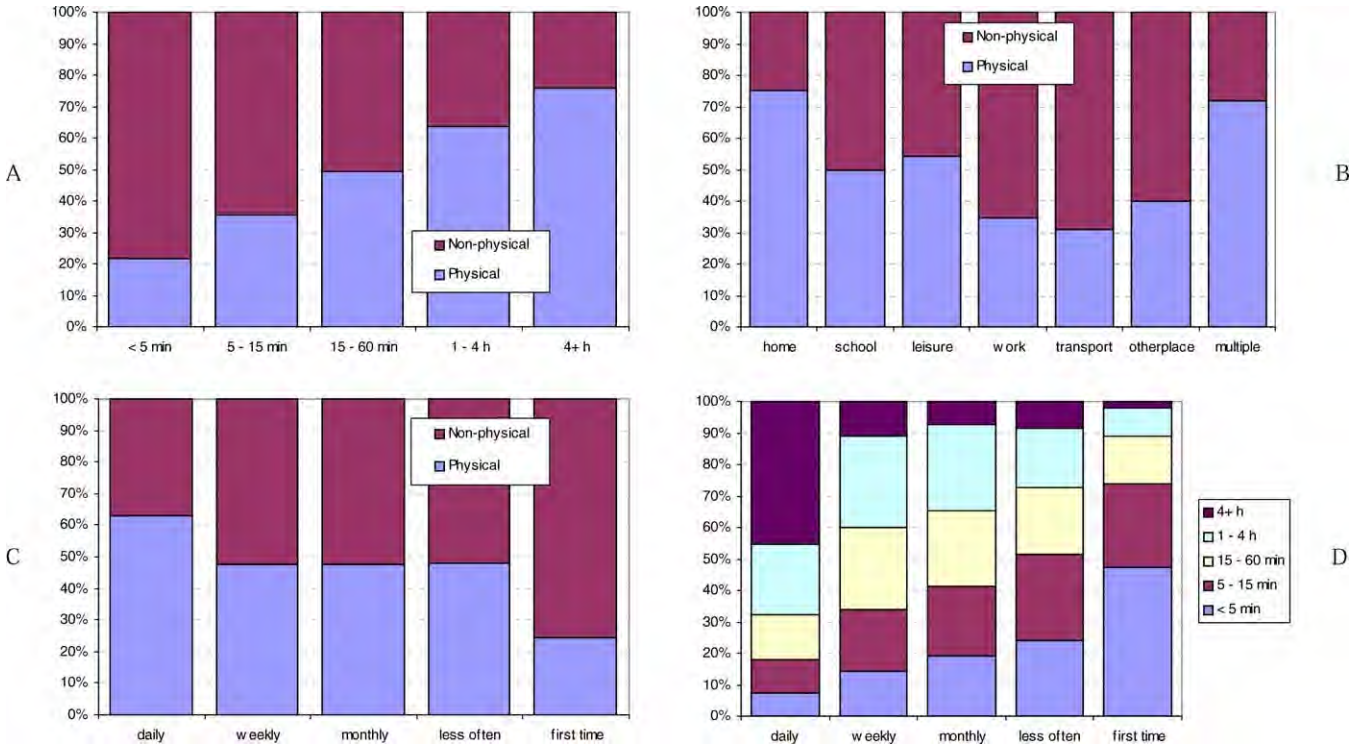

Figure 1. The Mean Proportion of Contacts That Involved Physical Contact, by Duration, Frequency, and Location of Contact in All Countries

Graphs show data by (A) duration, (B) location, and (C) frequency of contact; the correlation between duration and frequency of contact is shown in (D). All correlations are highly significant ($p < 0.001$, χ^2-test). The figures are based on pooled contact data from all eight countries and weighted according to sampling weights as explained in the Methods (based on household size and age).

doi:10.1371/journal.pmed.0050074.g001

settings involved a contact at home, and so a high proportion were physical.

Mining the contact data for frequency, duration, and type of contact based on association rules of maximum length 3 using thresholds of 0.5% (about 500 contacts) on the occurrence, positive dependence, and a 5% significance level on the Chi-square test of dependence resulted in a total of 99 rules of which 46 were of length 2 (see Table S4). 75% of the contacts lasting 4 h or more involved physical contact and occurred on a daily basis (83%), while 83% of the first-time contacts lasting less than 5 min were nonphysical. First time and occasional contacts mostly lasted less than 15 min (lift values 3.3 and 1.8, respectively) and, when nonphysical, this association was intensified (lift values 3.6 and 2.6, respectively). Whether contacts were physical or not did not influence the association between contacts lasting at least four hours and occurring on a daily basis nor did it influence the association between contacts lasting from five minutes up to one hour and occurring on a weekly or monthly basis. Physical contacts and contacts lasting 1–4 h were the only characteristics that were symmetric—that is, they had the same level of confidence in both directions (66% and 64%, respectively). Overall, 67% of all physical contacts lasted for at least 1, while 56% of all physical contacts occurred on a daily basis. All previously reported rules had high lift-values and were significant at the 1% significance level. Due to the high degree of correlation between physical contact and other measures of intimate contact, in the remainder of the paper we use physical contacts as a proxy measure for high-intensity contacts.

Of all pooled reported contacts, 23%, 21%, 14%, 3%, and 16% are made at home, at work, at school, while travelling, and during leisure activities, respectively (Figure 2A). More than half of all reported contacts occur at home, at work, or at school. It is interesting to note, however, that on a population level the overall number of reported contacts made during leisure activities is very close to the number of reported contacts made at school. A higher proportion of physical contacts are made at home, and leisure settings are the second most frequently reported location for such high intensity contacts (Figure 2B).

Age-Related Mixing Patterns

Figure 3 shows the average number of contacts reported per participant with individuals of different age groups for each of the eight countries for all reported (Figure 3A) and physical contacts (Figure 3B) only (full contact matrix data can be found in Table S5). Apart from the remarkable similarity of the general contact pattern structure in the different countries, three main features are apparent from the data. First, the dominant feature is the strong diagonal element: individuals in all age groups tend to mix assortatively (i.e., preferentially with others of similar age). This pattern is most pronounced in those aged 5–24 years, and least pronounced in those aged 55–69.

Second, two parallel secondary diagonals starting at roughly 30–35 years for both contacts and participants are offset from the central diagonal. This pattern represents children mixing with adults in the 30–39 age range (mainly at home, see Figure S3) and vice versa. Older children mix with

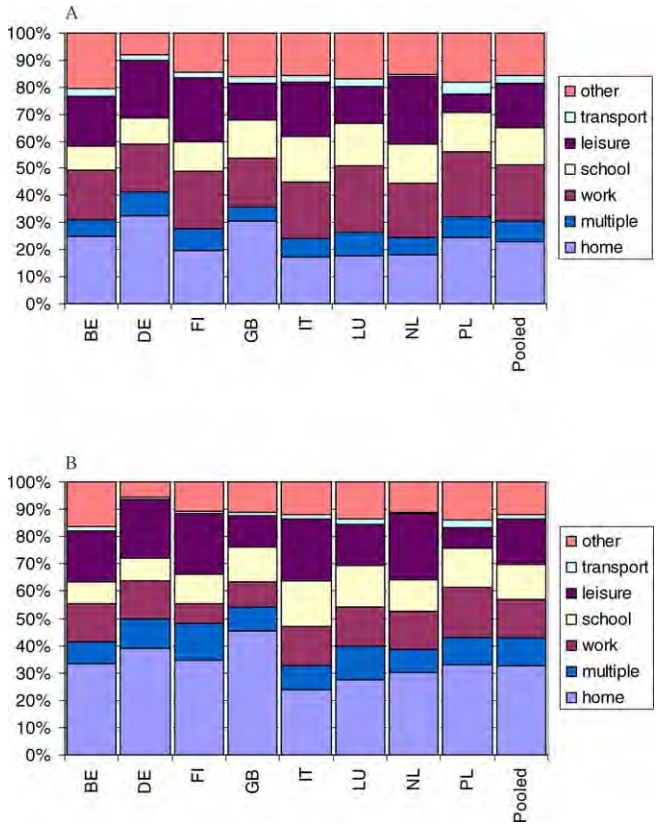

Figure 2. The Distribution by Location and by Country of (A) All Reported Contacts and (B) Physical Contacts Only

Sampling weights were used for each country. "Other" refers to contacts made at locations other than home, work, school, travel, or leisure. "Multiple" refers to the fact that the person was contacted during the day in multiple locations, not just a single location.

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middle-aged adults. Note, though, that the contact rates of the secondary diagonals at 30–35 years offset are an order of magnitude lower than the main assortative diagonal. Mixing between middle-aged adults and the elderly (above 60 y) was also apparent (see Figure S3).

The third feature is more apparent in the data for all reported contacts (Figure 3A) than for physical contacts only: a wider contact "plateau" of adults with other adults primarily due to low-intensity contacts, with many of these contacts occurring at work (see also Figure S4).

Simulated Initial Phase of an Epidemic

According to our mathematical model, the age distribution of cases during the initial phase of an epidemic of a new, emerging infection that spreads according to the reported social contacts in a completely susceptible population reveals a typical pattern that is similar across countries (see Figure 4). The highest incidence occurs among schoolchildren (ranging from 5- to 9-y-olds in NL to 5- to 19-y-olds in IT), and a less pronounced second peak in incidence occurs among adults (ranging from 30- to 34-y-olds in PL to 40- to 44-y-olds in FI). The high incidence among school-aged children results from their high number of contacts relative to other groups, and their tendency to make contacts within their own age group. The tendency to contact others within the same age group could potentially lead to a slow dispersion of infection across age groups. However, the contacts outside age groups are often with others about 30–35 years older or younger, and this tendency results in fairly rapid dispersion of infection across all age groups. Therefore, the observed contact patterns reveal that schoolchildren drive the epidemic in all age groups during the initial phase of spread for infections transmitted by droplets and through close contacts.

Discussion

Mathematical models are increasingly used to evaluate and inform infectious disease prevention and control policy. At their heart all models must make assumptions about how individuals contact each other and transmit the infectious agent. Until now, modellers have relied on proxy measures of contacts and calibration to epidemiological data. For instance, household size, class size, transport statistics, and workplace size distribution have been used in recent models to define the contact structure [2,3,33,34]. Our study complements those relying on proxy measures by using direct estimates of the number, age, intimacy levels, and distribution of actual contacts within various settings. The analysis of population-based contact patterns can help inform the structure and parameterisation of mathematical models of close-contact infectious diseases.

One of the most important findings of our study is that the age and intensity patterns of contact are remarkably similar across different European countries even though the average number of contacts recorded differed. This similarity implies that the results may well be applicable to other European countries, and that the initial phase of spread of newly emerging infections in susceptible populations, such as SARS was in 2003, is likely to be very similar across Europe and in countries with similar social structures.

Another major insight gained from our study comes from the observation that the contacts made by children and adolescents are more assortative than contacts made by other age groups. That is, most of the individuals contacted by children and teenagers are of very similar age, and these contacts tend to be of long duration. This pattern is likely to be the main reason why children and teenagers are and have been an important conduit for the initial spread of close-contact infections in general and for influenza in particular [11,14] and our preliminary modelling work confirms this.

Our study allows us to assess and quantify the risk of transmission in different settings. We took a number of different measures of "closeness of contact," including duration and frequency of contact and whether skin-to-skin contact occurred. These measures correlated highly with each other, such that the longer-duration contacts tended to be frequent and to involve physical contact (and vice versa). More-intimate contacts are likely to carry a greater risk of transmission. Furthermore, these types of contact tend to occur in distinct social settings: the most-intimate contacts occur at home or in leisure settings, whereas the least-intimate tend to occur while travelling. Thus, the risk of infection in these settings can be inferred to vary. This variation has important implications for contact tracing during outbreaks of a new infection. Our results suggest that if efforts concentrate on locating contacts in the home, school, workplace, and leisure settings, on average more than 80% of all contacts would be found.

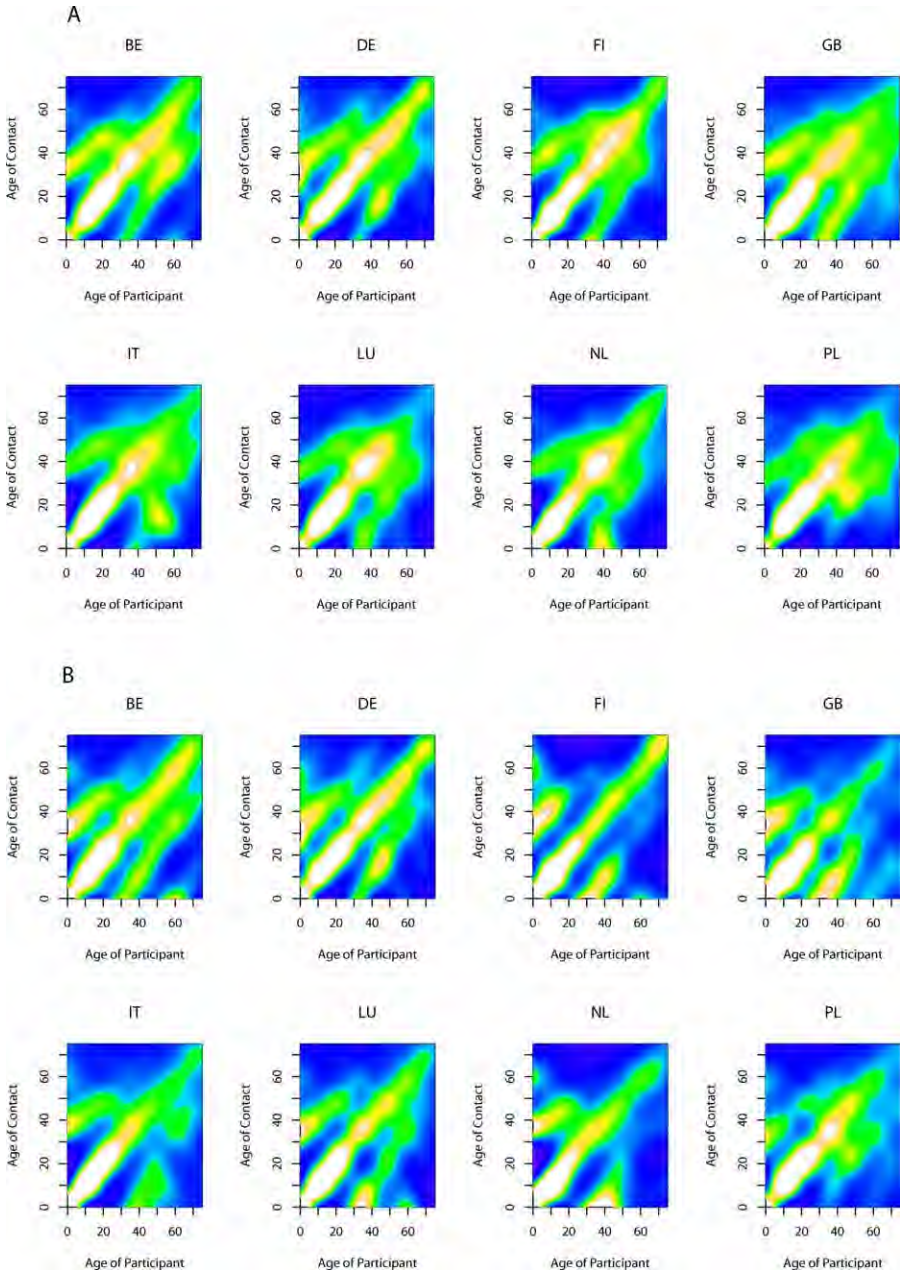

Figure 3. Smoothed Contact Matrices for Each Country Based on (A) All Reported Contacts and (B) Physical Contacts Weighted by Sampling Weights
White indicates high contact rates, green intermediate contact rates, and blue low contact rates, relative to the country-specific contact intensity. Fitting is based on a tensor-product spline to contact matrix data using a negative binomial distribution to account for overdispersion.
doi:10.1371/journal.pmed.0050074.g003

We have used simulations to expand on two particular types of contacts (physical and nonphysical) and to sketch the consequences of the observed contact patterns on the age distribution of incidence in the initial phase of an epidemic, when a new infectious disease is introduced into a completely susceptible population. As shown clearly by our simulations, the highest incidence of infection will occur among the younger age classes (5–19 y) for all countries. It is tempting to link such contact patterns to the observation during the 1957 Asian influenza A H2N2 pandemic that the first few generations of infection primarily affected those aged 11–18 y [35]. However, we note that our survey did not address the clustering of contacts; such clustering of contacts might result in less-pronounced differences in age-specific incidence than suggested by our calculations. Addressing the frequency of clustered contacts, duration and type of contact, differential impact of pathogen on different age groups, time correlation of contacts, and assortative mixing by demographic factors other than age should be key priorities for future research.

One of the major assumptions behind our approach is that talking with or touching another person constitutes the main at-risk events for transmitting infectious diseases. There may be other at-risk events that our methodology does not capture, such as being in a confined space or in close physical proximity with other individuals and not talking to them [23].

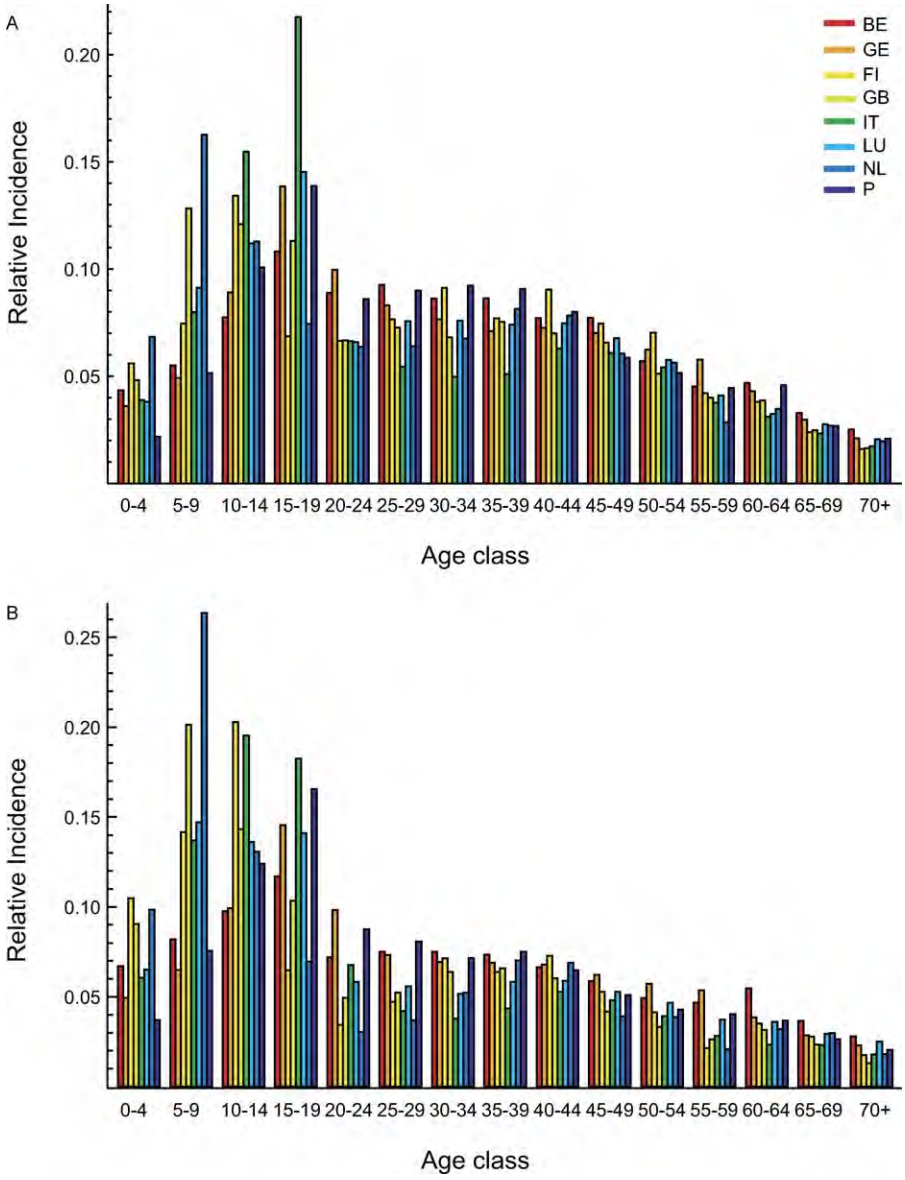

Figure 4. Relative Incidence of a New Emerging Infection in a Completely Susceptible Population, When the Infection Is Spread between and within Age Groups by the Contacts as Observed in Figure 3

For each country, we monitored incidence five generations of infection after the introduction of a single infected individual in the 65–70 age group; the incidence is normalized such that height of all bars sums to one for each country. (A) Results for all reported contacts; (B) for physical contacts only.
doi:10.1371/journal.pmed.0050074.g004

Such events are difficult to record or to measure without using intrusive and expensive surveillance methods, and are probably of lower risk than the communication events captured by our approach. Similarly, our framework does not apply to pathogens that, in addition to the respiratory route, can be also spread by other means, for example, the sewage contamination events for SARS [8]. Although we believe that it is plausible that the contact patterns observed in our study are predictive of disease transmission, further work is clearly needed to establish the types of contacts that represent transmission risks for different diseases and to determine the circumstances under which lower-intensity contacts could be epidemiologically relevant. The data reported in this study should not be considered a substitute for epidemiological studies that quantify, for instance, the intensity of transmission of influenza in households, schools, or other settings. However, this study does provide invaluable data on the relative importance of "leisure" and "other" contacts, which are very difficult to assess in other ways, and it highlights the relatively small contribution of personal contacts during travel based on our approach of defining a contact.

Using contact diaries in the general population was a feasible method for our specific study objectives, but as with all self-reported data, future research should validate our findings with different approaches, including interviews or direct observation. The latter might be particularly useful in assessing contacts of young children who spend time in day-care centres and kindergartens, because parental proxy reporting for young children is likely to be problematic.

Despite the limitations of self-reported egocentric data [36], contact diaries can provide extensive details regarding contact structures and have been used successfully for social network analysis [37]. Our contact diaries yielded detailed information about intimacy, frequency, and epidemiological relevance of contacts with an acceptable burden on respondents. In five countries, participants were given the opportunity to report whether they had any problems filling in the diary. The low proportion reporting problems (4% in adults, 4.9% in older children self-reporting contacts, and 4.9% in parents as proxy for children) suggest that the contact diary was readily accepted and understood by responding participants.

A further limitation of our study is that the comparison of contact patterns between countries is complicated by the variations of diary design (see Table S1), recruitment, and follow-up methodology (see Table S1). Our surveys were conducted in each country by different commercial companies with different recruitment and follow-up methods. Conducting surveys on contact behaviour and networks that entail a certain burden on participants and follow identical methodology in different countries is a challenging task, given that cultural factors in response also play a role. Further research is definitely warranted to determine optimal survey methodologies in different international settings, including developing countries, to improve comparability of contact data. Diaries used in BE, DE, FI, and NL instructed respondents not to record all of their professional contacts, but to provide an estimate if they had a lot of them. The reason for this instruction was to try to capture information from those people who make very large numbers of contacts (shop assistants and bus drivers, for instance), given that it might be very difficult or impossible for such people to fill out the full contact diary. This instruction may have lead to some underreporting of contact frequencies and thus have affected the distribution of age and circumstance of contacts for these four countries, although we have taken account of this possibility to some extent using a censored model. Additional analyses for these countries that combine and compare the estimated frequency of professional contacts with the diary data will provide additional insights about the number of contacts for all countries. The differences between diaries do not, however, affect the age-specific pattern, nor the similarity in age-specific patterns found across countries.

Our survey is, to our knowledge, the first population-based prospective survey of mixing patterns pertinent to the spread of airborne and close-contact infectious diseases performed in several European countries using a similar diary methodology. The quantification of these mixing patterns shows a remarkable similarity in degree of assortativeness, which likely results in similar patterns of spread in different populations. This finding represents a significant advance in our understanding of the spread of these infectious diseases and should help to improve the parameterisation of mathematical models used to design control strategies.

Supporting Information

Figure S1. Histogram of Number of Reported Contacts by Country

Found at doi:10.1371/journal.pmed.0050074.sg001 (7.7 KB PDF).

Figure S2. The Proportion of Contacts That Involved Physical Contact, by (a) Duration, (b) Frequency, (c) Location of Contact; and (d) Correlation between Duration and Frequency of Contact

Contacts were weighted by country-specific sampling weights in BE (A), DE (B), FI (C), GB (D), IT (E), LU (F), NL (G), and PL (H).

Found at doi:10.1371/journal.pmed.0050074.sg002 (84 KB DOC).

Figure S3. Smoothed Weighted Contact Matrices for Each Country Based on Reported Contacts Occurring in the Home Setting

White indicates high contact rates, green intermediate contact rates, and blue low contact rates. Fitting is based on a tensor-product spline to contact matrix data using a negative binomial distribution to account for overdispersion.

Found at doi:10.1371/journal.pmed.0050074.sg003 (282 KB PDF).

Figure S4. Smoothed Weighted Contact Matrices for Each Country Based on Reported Contacts Occurring in the Work Setting

White indicates high contact rates, green intermediate contact rates, and blue low contact rates. Fitting is based on a tensor-product spline to contact matrix data using a negative binomial distribution to account for overdispersion.

Found at doi:10.1371/journal.pmed.0050074.sg004 (254 KB PDF).

Table S1. Details of Survey Methodology in Each Country

Found at doi:10.1371/journal.pmed.0050074.st001 (52 KB DOC).

Table S2. Comparison of Household Size and Age Distribution of Census Data (2000) and Sample in BE, DE, FI, GB, IT, LU, NL, and PLRatio C/S (census versus sample), corresponds to the sampling weights used in the statistical analysis.

Found at doi:10.1371/journal.pmed.0050074.st002 (715 KB DOC).

Table S3. Relative Number of Reported Contacts Estimated by Different Negative Binomial Models (95% Confidence Interval in Brackets)

The results of this model comparison show that neither the censored nature of the data, nor the differences in how professional contacts were handled, substantially changes the model outcome. Note that all covariates have overlapping confidence intervals for models A and B, which are directly comparable, although censoring does improve model fit.

Found at doi:10.1371/journal.pmed.0050074.st003 (282 KB PDF).

Table S4. Association Rules of Length 2 for Type, Duration, and Location of Contacts with Minimal Support of 0.5%, Significant Positive Dependence (0.01 Significance Level)

Support, confidence, lift, and χ^2 values are given.

Found at doi:10.1371/journal.pmed.0050074.st004 (254 KB PDF).

Table S5. Contact Matrices of All Reported and Physical Contacts Consisting of the Average Number of Contact Persons Recorded per Day per Survey Participant Separately for Each Country

Found at doi:10.1371/journal.pmed.0050074.st005 (714 KB DOC).

Text S1. Example of the Diary Used in Great Britain

Found at doi:10.1371/journal.pmed.0050074.sd001 (49 KB PDF).

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Author contributions. JM, NH, MJ, JW, and WJE drafted the manuscript in consultation with all the other authors; the original idea and contact diary were conceived by WJE. JM conducted a pilot study on an adapted diary, and coordinated overall survey design and data collection. JM, MJ, PB, KA, RM, MM, GST, JW, JH, MST, and MR conducted the surveys in their respective countries. NH conducted the data mining and surface smoothing. JW and JH conducted the epidemic modelling. All authors approved the final manuscript.

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Editors' Summary

Background To understand and predict the impact of infectious disease, researchers often develop mathematical models. These computer simulations of hypothetical scenarios help policymakers and others to anticipate possible patterns and consequences of the emergence of diseases, and to develop interventions to curb disease spread. Whether to prepare for an outbreak of infectious disease or to control an existing outbreak, models can help researchers and policy makers decide how to intervene. For example, they may decide to develop or stockpile vaccines or antibiotics, fund vaccination or screening programs, or mount health promotion campaigns to help citizens minimize their exposure to the infectious agent (e.g., handwashing, travel restrictions, or school closures).

Respiratory infections, including the common cold, flu, and pneumonia, are some of the most prevalent infections in the world. Much work has gone into modeling how many people would be affected by respiratory diseases under various conditions and what can be done to limit the consequences.

Why Was This Study Done? Mathematical models have tended to use contact rates (the number of other people that a person encounters per day) as one of their main elements in predicting the outcomes of epidemics. In the past, contact rates were not based on direct observations, but were assumed to follow a certain pattern and calibrated against other indirect data sources such as serological or case notification data. This study aimed to estimate contact rates directly by asking people who they have met during the course of one day. This allowed the researchers to study in more detail different *patterns* of contacts, such as those between different groups of people (such as age groups) and in different social settings. This is particularly important for respiratory diseases, which are spread through the air and by close contact with an infected individual or surface.

What Did the Researchers Do and Find? The researchers wanted to examine the social contacts that people have in order to better understand how respiratory infections might spread. They recruited 7,290 people from eight European countries (Belgium, Germany, Finland, Great Britain, Italy, Luxembourg, The Netherlands, and Poland) to participate in their study. They asked the participants to fill out a diary that documented their physical and nonphysical contacts for a single day. Physical contacts included interactions such as a kiss or a handshake. Nonphysical contacts were situations such as a two-way conversation without skin-to-skin contact. Participants detailed the location and duration of each contact. Diaries also contained basic demographic information about the participant and the contact.

They found that these 7,290 participants had 97,904 contacts during the study, which averaged to 13.4 contacts per day per person. There was a great deal of diversity among the contacts, which challenges the idea that contact rates alone provide a complete picture of transmission dynamics. The researchers identified varied types of contacts, duration of contacts, and mixing patterns. For example, children had more contacts than adults, and those living in larger households had more contacts. Weekdays resulted in more daily contacts than Sundays. More intense contacts (of longer duration or more frequent) tended to be physical. Approximately 70% of contacts made on a daily basis lasted longer than an hour, whereas three-quarters of contacts with people who were not previously known lasted less than 15 minutes. While mixing patterns were very similar across the eight countries, people of the same age tended to mix with each other.

Analyzing these contact patterns and applying mathematical and statistical techniques, the researchers created a model of the initial phase of a hypothetical respiratory infection epidemic. This model suggests that 5- to 19-year-olds will suffer the highest burden of respiratory infection during an initial spread. The high incidence of infection among school-aged children in the model results from these children having a large number of contacts compared to other groups and tending to make contacts within their own age group.

What Do These Findings Mean? This work provides insight about contacts that can be supplemental to traditional measurements such as contact rates, which are usually generated from household or workplace size and transportation statistics. Incorporating contact patterns into the model allowed for a deeper understanding of the transmission patterns of a hypothetical respiratory epidemic among a susceptible population. Understanding the patterning of social contacts—between and within groups, and in different social settings—shows how diverse contacts and mixing between individuals really are. Physical exposure to an infectious agent, the authors conclude, is best modeled by taking into account the social network of close contacts and its patterning.

Additional Information. Please access these Web sites via the online version of this summary at doi:10.1371/journal.pmed.0050074.

- Wikipedia has technical discussions on the assumptions used in mathematical models of epidemiology (note that Wikipedia is a free online encyclopedia that anyone can edit; available in several languages)
- Plans for pandemic influenza are explained for the Government of Canada, the United Kingdom's Health Protection Agency, and the United States Department of Health and Human Services

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Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK

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Abstract

Background: To mitigate and slow the spread of COVID-19, many countries have adopted unprecedented physical distancing policies, including the UK. We evaluate whether these measures might be sufficient to control the epidemic by estimating their impact on the reproduction number (R_0, the average number of secondary cases generated per case).

Methods: We asked a representative sample of UK adults about their contact patterns on the previous day. The questionnaire was conducted online via email recruitment and documents the age and location of contacts and a measure of their intimacy (whether physical contact was made or not). In addition, we asked about adherence to different physical distancing measures. The first surveys were sent on Tuesday, 24 March, 1 day after a "lockdown" was implemented across the UK. We compared measured contact patterns during the "lockdown" to patterns of social contact made during a non-epidemic period. By comparing these, we estimated the change in reproduction number as a consequence of the physical distancing measures imposed. We used a meta-analysis of published estimates to inform our estimates of the reproduction number before interventions were put in place.

Results: We found a 74% reduction in the average daily number of contacts observed per participant (from 10.8 to 2.8). This would be sufficient to reduce R_0 from 2.6 prior to lockdown to 0.62 (95% confidence interval [CI] 0.37–0.89) after the lockdown, based on all types of contact and 0.37 (95% CI = 0.22–0.53) for physical (skin to skin) contacts only.

Conclusions: The physical distancing measures adopted by the UK public have substantially reduced contact levels and will likely lead to a substantial impact and a decline in cases in the coming weeks. However, this projected decline in incidence will not occur immediately as there are significant delays between infection, the onset of symptomatic disease, and hospitalisation, as well as further delays to these events being reported. Tracking behavioural change can give a more rapid assessment of the impact of physical distancing measures than routine epidemiological surveillance.

Keywords: COVID-19, Contact survey, Pandemic, Disease outbreak, Reproduction number, nCov

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Background

Over 1.8 million cases and over 110,000 deaths from COVID-19 have been recorded worldwide as of 13 April 2020 [1]. A major route of transmission of SARS-CoV2 is via droplet spread which requires close contact [2]. In an attempt to mitigate the COVID-19 pandemic, many countries have adopted unprecedented physical distancing policies [3]. On March 23, with just over 6000 confirmed cases, the UK Government implemented strict physical distancing measures instructing individuals to stay at home and avoid leaving their house except for essential work, to take one form of exercise a day, and to buy essential items such as food and medicines. This followed the closure of sporting events, schools, restaurants, bars, gyms, and other leisure or hospitality-related businesses the previous week [4] and an increase in social distancing among the population that had been taking place for several days before the announcement [5].

Physical distancing interventions attempt to reduce contacts relevant to infectious disease spread between individuals. Multiple surveys have been instigated on the uptake of different physical distancing measures during this current pandemic, but these have not explicitly measured contacts between people [6–8]. To make accurate predictions on the impact of these measures, quantitative data on relevant contact patterns is required [9–12]. Many governments have adopted physical distancing measures to mitigate the impact of the COVID-19 pandemic. However, it is unclear to what extent these measures reduce the number of contacts and therefore transmission. Only one previous survey—conducted in two Chinese cities, Wuhan and Shanghai, in February 2020—quantified the impact of these measures on individuals' contact patterns during the COVID-19 pandemic [13].

Changes in human contact behaviour drive respiratory infection rates. Understanding these changes at different stages of the COVID-19 pandemic allows us to rapidly quantify the impact of physical distancing measures on the transmission of pathogens. In this paper, we describe a survey of contact patterns and compliance with physical distance measures and present results from a sample of adults in the UK. We evaluate whether these measures might be sufficient to control the epidemic by estimating their impact on the reproduction number (the average number of secondary cases generated per case).

Methods

Ethics statement

Participation in this opt-in study was voluntary, and all analyses were carried out on anonymised data. The study was approved by the ethics committee of the London School of Hygiene & Tropical Medicine reference number 21795.

Survey methodology

We commissioned the market research company Ipsos to conduct a survey of UK adults (referred to here as the CoMix survey). Adults (≥ 18 years) were recruited into the survey by sending email invitations to existing members of their online panel. Representativeness of the general UK population was ensured by setting quotas on age, gender, geographical location, and socioeconomic status. This cohort of individuals will be requested to answer the survey every 2 weeks for a total of 16 weeks to track changes in their self-reported behaviour. The first surveys were sent on Tuesday, 24 March, 1 day after a lockdown was announced for the UK.

Participants were asked about their attitudes towards COVID-19 and the effect of physical distancing interventions, whether they or any of their household members experienced any recent symptoms, whether they were tested for COVID-19, whether they had had any contact with known COVID-19 cases, and whether they were affected by physical distancing measures.

Participants reported (i) if any person in their household were advised to quarantine, isolate, or limit time in their workplace or educational facility in the preceding 7 days due to COVID-19 and (ii) if they heeded the advice and isolated, quarantined, or stayed away from their workplace or educational facility. In the survey, we defined quarantine as limiting contacts and staying at home, with restricted allowance for movement outside the home after a potential exposure with a COVID-19 case. We defined isolation as completely separating from uninfected contacts, including household members, either in the home or in a health facility. To assess the impact of advice and policy changes regarding physical distancing, we asked participants to indicate if they had planned to participate in a set of events in the preceding week. For each event type, they reported (i) whether they proceeded with their plan, or (ii) if it was cancelled or they decided not to go, and (iii) the frequency of the event type in the previous 7 days. Additional questions were asked about preventive behaviours, such as handwashing or wearing masks, and about the use of public transport in the previous 7 days.

In addition, we asked participants to record all direct contacts made between 5 am the day preceding the survey and 5 am the day of the survey. A direct contact was defined as anyone who was met in person and with whom at least a few words were exchanged, or anyone with whom the participants had any sort of skin-to-skin contact. We were unable to ask parents to provide contact information for their children due to lack of ethical approval; however, participants were able to list contacts who were under 18.

For every recorded contact, participants documented the age and gender of the contact, relationship to the

contact, the frequency with which they usually contact this person, whether contact was physical (skin to skin) or not, and the setting where the contact occurred (e.g. at home, work, school, or whilst undertaking leisure activities), including whether contact occurred in- or outside an enclosed building. Questions on social contacts were consistent with those from the UK arm of the POLYMOD survey [14], which was used as the baseline pre-pandemic comparison dataset. Details on survey methodology, the study protocol, and a copy of the questionnaire used are provided in Additional files 1 and 2.

Statistical analysis

R version 3.6.3 was used for all analyses; the code and data are available on github (see the "Availability of data and materials" section) [15–17].

We grouped study participants and contacts into the following age bands: 18–29, 30–39, 40–49, 50–59, 60–69, and 70+. Age, gender, and locations of participants were compared to the 2018 mid-year estimates provided by the UK Office of National Statistics (ONS) to assess the representativeness of the study sample [18]. We descriptively analysed answers related to symptoms, attitudes, exposure to physical distancing measures, and individual preventative measures. We present the number and percentage or mean and standard deviation where appropriate (Table 3).

We calculated the average number of social contacts per person per day overall, and stratified by age category, sex, household size, location of contact, type of contact, and day of the week. We then compared the mean total number of daily contacts by age group to POLYMOD stratified by contact location.

We calculated social contact matrices for the age-specific daily frequency of direct social contacts, adjusting for the age distribution in the study population and reciprocity of contacts, using the socialmixr package in R [19].

As children (< 18 years) were not included as survey participants, we imputed contacts for younger age groups (child-child and child-adult contacts) using the POLYMOD UK data. Specifically, for those child contact groups that were missing, we used a scaled version of the POLYMOD social contact matrix. Following previous methods developed by Klepac et al. [20], as the scaling factor, we took the ratio of the dominant eigenvalues of the POLYMOD and CoMix matrices, for all age groups present in both studies, stratified by setting. Furthermore, to reflect school closures during the collection of our survey, we removed school contacts from the POLYMOD data from our analysis.

The basic reproduction number, or R_0, is the average number of secondary infections arising from a typical single infection in a completely susceptible population and can be estimated as the dominant eigenvalue of the next generation matrix [21]. The exact form of the next generation matrix is model dependent. For respiratory infections, such as SARS-CoV-2 (the pathogen causing COVID-19), this is usually a function of the age-specific number of daily contacts, the probability that a single contact leads to transmission, and the total duration of infectiousness. Therefore, R_0 is proportional to the dominant eigenvalue of the contact matrix [19].

We assumed that contact patterns prior to physical distancing were similar to those observed in the POLYMOD data and that the duration of infectiousness and the probability that a single contact leads to transmission did not change during the study period. We also assume that all age groups contribute equally to transmission. Under these assumptions, the relative reduction in R_0 is equivalent to the reduction in the dominant eigenvalue of the contact matrices. By multiplying the value of R_0 prior to the interventions by the ratio of the dominant eigenvalues from the POLYMOD and CoMix contact matrices, we were able to calculate R_0 under the physical distancing interventions. Prior to interventions, we assumed R_0 followed a normal distribution with mean 2.6 and standard deviation of 0.54 based on a meta-analysis of the literature presented in Additional file 3 [22–34].

To assess uncertainty, we repeated the age imputation process by taking 10,000 bootstrapped samples from both POLYMOD and CoMix matrices. For every bootstrap sample, we calculated the ratio between the dominant eigenvalues for the sampled POLYMOD and CoMix matrices. This sampling provided a distribution of relative change in R_0 from the contact patterns observed in POLYMOD and CoMix. Subsequently, we scaled the initial distribution of R_0 with the distribution of bootstrap samples to estimate R_0 under physical distancing interventions.

Recent results of the BBC Pandemic study [20] suggested a decrease of nearly 50% in the average number of contacts made by teenagers (13–18 years) compared with the POLYMOD data. We assessed the sensitivity of our results to a potential reduction in contacts over time by taking a conservative reduction of 50% between 5 and 18 year olds in the POLYMOD study and repeating our approach to estimate the reduction in R_0.

Results

Participant characteristics

We surveyed 1356 UK participants who recorded 3849 contacts. The average age of participants was 47.2 years (standard deviation (SD) = 15, max = 86), and 45% (608/1356) were female (see Table 1). The average household size was 2.8 (SD = 1.4, max = 10). Data were collected between Tuesday 24 and Friday 27 March 2020 inclusive.

Table 1 Participant characteristics in the CoMix survey, and comparison with 2018 mid-year UK population estimates provided by the Office of National Statistics. The CoMix survey does not include children under the age of 18

	Number of participants (%)*	UK ONS mid-year Estimate
Location ($N = 1240$)		
North of England	198 (16.0%)	23.2%
Midlands and East of England	328 (26.5%)	25.4%
London	205 (16.5%)	13.4%
South of England	302 (24.4%)	22.2%
Wales	54 (4.4%)	4.7%
Scotland	121 (9.8%)	8.2%
Northern Ireland	32 (2.6%)	2.8%
Missing	116	–
Age group ($N = 1356$)**		
0–9	0	–
10–19	28 (2.1%)	–
20–29	185 (13.6%)	17.1%
30–39	275 (20.3%)	17.4%
40–49	249 (18.4%)	16.7%
50–59	233 (17.2%)	17.6%
60–69	280 (20.7%)	13.9%
70+	106 (7.8%)	17.3%
Missing	0	–
Gender ($N = 1356$)		
Males	748 (55.2%)	49.4%
Females	608 (44.8%)	50.6%
Missing	0	–

*Within-group percentages

**There are no individuals aged less than 18 in the survey participants; therefore, we only compare the percentages of age groups that are fully observed in the study from the ONS mid-year estimates

Participants were recruited from across the UK. The sample included participants from London (16.5%), North of England (16.0%), Midlands and East of England (26.5%), South of England (24.4%), Wales (4.4%), Scotland (9.8%), and Northern Ireland (2.6%), whilst 116 participants did not report their region (Table 1). Further details of participant demographics and the average number of contacts stratified by age, gender, household size, and location are presented in Table 2. Compared to the mid-year ONS population estimates taken from 2018, individuals over 70 years and individuals between the ages of 20–29 years were undersampled.

Thirteen participants reported having been tested for COVID-19 with seven testing positive, and two participants still waiting for their results. Forty-one participants stated they had been in contact with a known COVID-19 case. In terms of perceived risk, 26.4% (359/1356) thought that it was likely that they would develop coronavirus and 48.0% (652/1356) agreed or strongly agreed that COVID-19 would be a serious disease for them if they acquired the infection.

Impact of physical distancing measures

Participants reported data on a total of 3824 household members, including themselves, of whom 508 (13.2%) had been asked to quarantine and 826 (21.6%) had been asked to isolate. Nearly a quarter (921; 24.1%) of household members lived in a house with someone who had at least one symptom of fever, aches, shortness of breath, or cough. Roughly 50% of the 2122 employed individuals had either been asked to limit their time at work, had their work closed, and/or did not visit their work in the preceding 7 days (Table 3). Of those household members who attend educational establishments, 67.2% (818/1217) had their institution closed with 63.3% not visiting during the previous 7 days.

There were clear suggestions that physical distancing in the previous week had impacted planned activities for survey participants with 51.3% of participants that intended to go to a concert being unable as the event was cancelled, 40.6% intending to go to the cinema were unable as the cinema was closed, and 32.5% of participants having to cancel plans to visit a pub (Table 3). Contrastingly, only a small percentage of participants

Table 2 Number of recorded contacts per participant per day stratified by age, gender, household size, and day of the week

Category	Value	Number of participants	CoMix reported contacts, mean (IQR)	POLYMOD reported contacts, mean (IQR)
Overall	Overall	1356	2.8 (1, 4)	10.8 (6, 14)
	18–29	213	3.0 (1, 4)	12.1 (7, 16)
	30–39	275	3.1 (1, 4)	11.3 (6, 15)
	40–49	249	3.1 (1, 4)	12.0 (6, 17)
	50–59	233	3.0 (1, 4)	9.5 (5, 13)
	60–69	280	2.5 (1, 3)	9.0 (5, 12)
	70+	106	2.0 (1, 3)	7.6 (4, 12)
Gender of participant	Female	608	2.9 (1, 4)	11.3 (6, 15)
	Male	748	2.8 (1, 4)	10.2 (5, 13)
Household size	1	203	1.6 (1, 2)	7.4 (3, 11)
	2	431	2.3 (1, 3)	10.1 (5, 13)
	3	363	2.7 (2, 3)	11.2 (6, 15)
	4	207	4 (3, 4)	12.1 (7, 16)
	4+	152	4.7 (4, 6)	14.2 (9, 17)
Date				
24 March 2020	Tuesday	178	3.0 (1, 43)	–
25 March	Wednesday	1014	2.8 (1, 4)	–
26 March	Thursday	162	2.9 (1, 3)	–
27 March	Friday	2	5.0 (5, 5)	–

(2.5%) who intended to go to the supermarket were unable due to COVID-19.

Contact patterns

The mean number of physical (skin to skin) and non-physical contacts per person measured during this study was 2.8 (interquartile range [IQR] = 1–4) which was 74% lower than was measured in POLYMOD (10.8; 6–14). The reduction in mean contacts between POLYMOD and CoMix was consistent across age, gender, and household size (Table 2). The respective social contact matrices (including physical and non-physical contacts)

Table 3 Indicators of adherence with public health interventions and behaviour changes for all household members reported by participants

Measure	Asked to	Have been in	At least with COVID-19 symptom	
Quarantine ($N = 3824$)	508 (13.2%)	778 (20.3%)	Living in a household	921 (24.1%)
Isolation ($N = 3824$)	826 (21.6%)	1264 (33.1%)	People	462 (12.1%)
Setting	Asked to limit time	Reported as closed	Did not visit	
Work ($N = 2122$)	1006 (47.4%)	996 (46.9%)	1149 (54.1%)	
School or university ($N = 1217$)	651 (47.4%)	818 (67.2%)	771 (63.3%)	
Event	Intended to visit	Visited	Cancelled	Chose not to visit
Concert	111	6 (5.4%)	57 (51.3%)	20 (18.1%)
Cinema	133	11 (8.3%)	54 (40.6%)	43 (32.3%)
Sporting event				
Participant	105	14 (13.3%)	46 (43.8%)	33 (31.4%)
Attendee	100	9 (9.0%)	54 (54.0%)	20 (20.0%)
Restaurant	271	28 (10.3%)	118 (43.5%)	100 (36.9%)
Religious event	105	14 (13.3%)	68 (64.7%)	33 (31.4%)
Pub	366	105 (28.6%)	119 (32.5%)	24 (6.6%)
Supermarket	1127	967 (85.8%)	28 (2.5%)	112 (10.0%)

also reflected a much lower number of mean contacts across the age strata as presented in Fig. 1.

The majority of contacts (57.6%) occurred at home, contrasting with 33.7% reported in the POLYMOD survey. Figure 2 displays the average number of contacts across age groups for all, physical, home, work, school, and other contacts. The matrices are consistent with the majority of contacts being in the home, with work, and other contributing very little to the overall number of contacts.

Estimated the basic reproduction number of COVID-19 under physical distancing

We estimated the current R_0 under physical distancing measures to be 0.62 (95% confidence interval [CI] 0.37–0.89) based on all types of contact (Fig. 1). Based on physical contacts only, we estimated R_0 to be 0.37 (95% CI = 0.21–0.52). The average pre- to post-intervention ratio in R_0 was 0.24 (min = 0.21, max = 0.27) for all contacts and 0.14 (min = 0.12, max = 0.17) for physical (skin to skin) contacts only. Based on these values, the physical distancing measures would have reduced the mean estimate of R_0 to below one even if the initial R_0 had been as high as 3.6 assuming all contacts are equally risky or 4.2 assuming only physical contacts result in transmission.

In a sensitivity analysis, reducing contacts made by 5–17 year olds by 50% made little difference to the results. Under this assumption, the estimated value of R_0 for all contacts would be 0.69 (95% CI 0.42–0.98) and 0.37 (95% CI 0.22–0.53) if physical contacts alone result in transmission.

Discussion

The measures introduced by the UK Government appear to have high levels of uptake among participants and

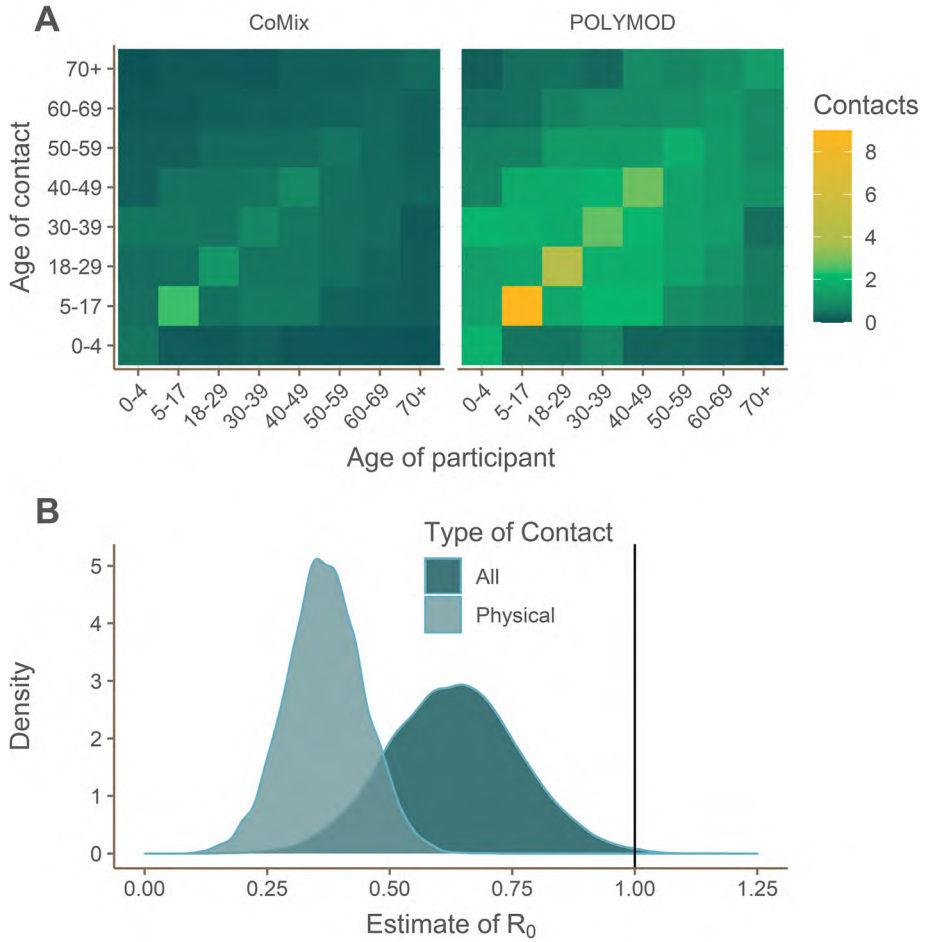

Fig. 1 Comparison of CoMix and POLYMOD contact matrices and estimated reduction in reproduction number due to physical distancing for all and physical (skin to skin) contacts separately. **a** Social contact matrices showing the average total number of daily reported contacts made by participants in different age groups with individuals in other age groups, with results shown for all contacts reported in the CoMix and POLYMOD data. Participants' contacts in CoMix for age groups 0–4 and 5–17 are imputed using the POLYMOD data. **b** The estimated value of R_0 at the time of the survey, assuming values of $R_0 \sim$ Norm (2.6, SD = 0.54) prior to physical distancing reducing all contacts for all and physical (skin to skin) contacts

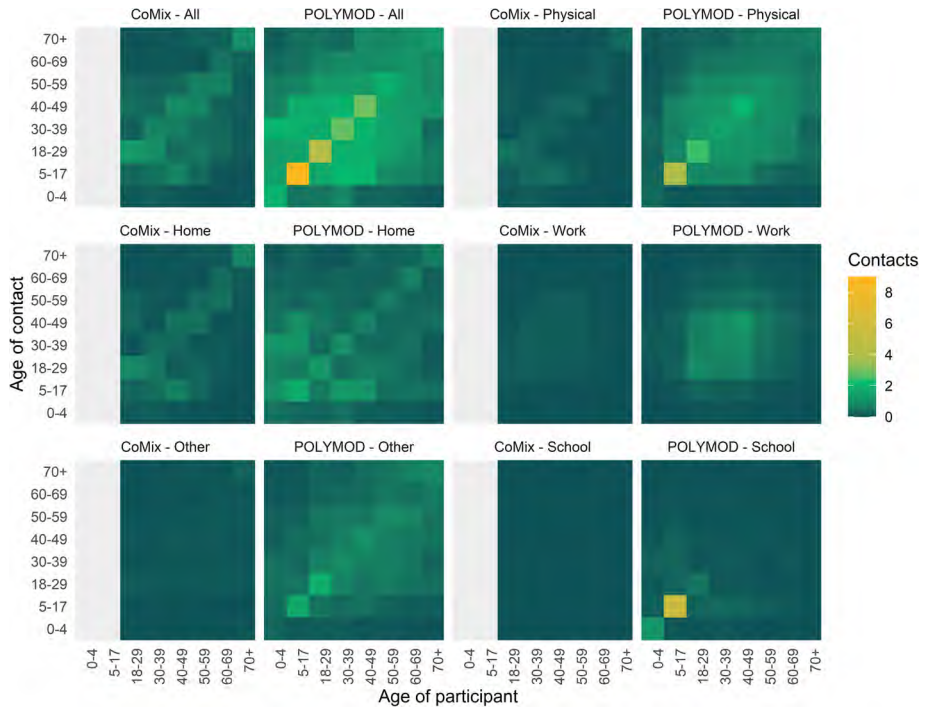

Fig. 2 Contact matrices for all reported contacts made in different settings, comparing CoMix to POLYMOD

have resulted in very large (74%) reductions in the total number of contacts. If similar changes are observed across the UK population, we would expect the basic reproduction number to now be below 1 (0.62; 95% CI 0.37–0.89) and that these physical distancing measures will lead to a decline in cases in the coming weeks. However, this projected decline in incidence will not result in an immediate decline in reported cases, as there are significant delays between infection and the onset of symptomatic disease and hospitalisation, as well as further delays to these events being reported. Hence, routine surveillance data are unlikely to show a decline in cases for some time. However, by directly measuring individuals' contact patterns and estimating the corresponding basic reproduction number, we are able to rapidly quantify the impact of physical distancing on transmission.

The total number of daily contacts (mean of 2.8 per person) was significantly reduced compared to patterns previously estimated in the POLYMOD study (10.7; excluding children < 18 years old) and more recently by the BBC Pandemic study (10.5; excluding under 13 year olds) [20]. The observed reduction appears to be unlikely due to chance given the large difference in average contacts and is consistent with a recent study conducted in Wuhan, China, that estimated a reduction in the average number contacts per day from 14.6 prior to the outbreak to 2.0 under physical distancing interventions [13]. Whilst we are unaware of any directly comparable data from the UK, our findings are certainly consistent with other reports from the UK of a dramatic reduction in social contacts, with, for example, only half of respondents in one survey reporting having left the house at all in the past 24 h [5].

There are several limitations to this survey. Asking individuals to report their contacts from the day before may result in recall bias. Moreover, individuals who are adhering to physical distancing measures may have been more likely to respond to this survey, potentially resulting in selection bias and in an overestimate of the impact of these measures. The POLYMOD survey used paper-based diaries whereas CoMix utilises an online form, which may have resulted in different numbers of contacts being reported in CoMix. However, it is unlikely that the large differences observed would be due only to the reporting methodology of the surveys. Furthermore, we were not able to sample any children, so child-child contacts had to be imputed from the POLYMOD survey. This weakens the comparability of the two studies, and future work is planned to directly measure child-child contacts which will help assess the impact of this limitation.

We were not able to quantify any additional effect from the interventions on transmission, such as reduction in infectiousness by increased handwashing. In addition, we were not able to calculate the net reproductive number, R, as we did not account for the proportion of the population that is no longer susceptible. These could all reduce the net reproductive number to

values lower than estimated in our analysis. This approach further assumes that all age groups contribute equally to transmission, which may not be the case. Assuming flu-like transmission where children are the group most responsible for transmission, the contribution of adults to overall R_0 would be lower [9]. However, if children do not play a significant role in transmission, the significance of adult transmission will be higher. Therefore, although this survey provides evidence of overall contacts in the population reducing which will considerably lower R_0, lack of knowledge of the relative contributions of different age groups to overall transmission reduces our ability to precisely determine the exact reduction in transmission.

Our analysis assumed that direct contacts are an appropriate proxy for effective contacts, and thus, that transmissibility is equal across age groups (e.g. contact between a single infected child and susceptible adult is as likely to result in transmission as contact between a single infected adult and a susceptible adult). We further assume that the reduction in non-school contacts in children is similar to that observed in adults. Furthermore, we assume that the contact patterns prior to interventions are consistent and of similar magnitude. A recent study has found significantly lower numbers of contacts reported by teenagers compared with the POLYMOD survey [20]. Decreasing mixing among 5–17 years by 50%, whilst reducing the magnitude of reduction in R_0, did not affect the qualitative conclusions from the analysis.

As of 13 April, the growth rate of reported cases in the UK appears to be slowing, declining from a 20% increase per day for the 5 days prior to 24 March to a 7% increase per day for the 5 days prior to 13 April [1]. This is consistent with a reduction in the reproduction number; however, it is difficult to correlate the magnitude of this reduction with the estimated value of R_0. Our approach assumes that individuals within an age group behave the same, and does not account for hospitals and other institutions which will have different disease dynamics. Moreover, due to the UK testing algorithm being focused on people in hospitals and as there seems to be an increasing problem of nosocomial infection, any decline in community infection may be counterbalanced by an increase in nosocomial infections. Given that the confirmed cases are primarily hospital based, this can have a disproportionate effect on the estimated reproduction number using crude data (i.e. not split by route of transmission). Future work is planned to compare the estimates of R_0 with the growth rate of the epidemic, accounting for changes in levels of testing, reporting, delays, and transmission context.

This study is planned to continue in the UK for the next 15 weeks and will be extended to other countries including Belgium and the Netherlands. Future analyses will be able to explore changes in contact patterns during different interventions and may provide early warning signs of changes in contact patterns due to interventions being lifted or decreasing adherence with restrictions.

Conclusions

We have shown that behavioural monitoring can give a rapid insight into transmission of COVID-19 and have provided the first evidence that the restrictions adopted by the UK Government have led to a decrease in transmission of COVID-19.

Table 3 shows compliances with different social distancing measures due to COVID-19. *N* symptoms shows the total number of household members who were living in a household where someone had any of the following symptoms (fever, aches, shortness of breath, cough), and how many individuals reported having COVID-19 symptoms themselves. The column *Asked to* refers to the total number of people who reported being asked to quarantine or isolate. The column *Have been in* shows the total number of people who reported having been in quarantine or isolation for at least 1 day in the 7 days before the survey.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12916-020-01597-8.

Additional file 1. CoMix study questions.

Additional file 2. CoMix study Protocol.

Additional file 3. CoMix additional analyses.

Abbreviations

CI: Confidence interval; IQR: Interquartile range; ONS UK: Office of National Statistics; SD: Standard deviation

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Authors' contributions

WJE, GJR, CIJ, and KvZ conceived of and designed the study. CIJ, KvZ, and WJE conceived of the analysis. CIJ, KvZ, AG, and KP conducted the analysis. CIJ and KvZ wrote the manuscript with input and guidance from WJE, AG, KP, GJR, and PK. The CMMID COVID-19 working group members contributed to the processing, cleaning, and interpretation of data; interpreted the study findings; contributed to the manuscript; and approved the work for publication. All authors interpreted the findings, contributed to writing the manuscript, and approved the final version for publication.

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Availability of data and materials

The code and data used to conduct these analyses are found at https://github.com/jarvisc1/comix_covid-19-first_wave

Ethics approval and consent to participate

Participation in this opt-in study was voluntary, and all analyses were carried out on anonymised data. The study and method of informed consent were approved by the ethics committee of the London School of Hygiene & Tropical Medicine reference number 21795.

Consent for publication

Not applicable

Competing interests

WJE is a member of the Editorial Board of this Journal. Other authors declare that they have no competing interests.

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Publisher's Note

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Physical distancing interventions and incidence of coronavirus disease 2019: natural experiment in 149 countries

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ABSTRACT

OBJECTIVE

To evaluate the association between physical distancing interventions and incidence of coronavirus disease 2019 (covid-19) globally.

DESIGN

Natural experiment using interrupted time series analysis, with results synthesised using meta-analysis.

SETTING

149 countries or regions, with data on daily reported cases of covid-19 from the European Centre for Disease Prevention and Control and data on the physical distancing policies from the Oxford covid-19 Government Response Tracker.

PARTICIPANTS

Individual countries or regions that implemented one of the five physical distancing interventions (closures of schools, workplaces, and public transport, restrictions on mass gatherings and public events, and restrictions on movement (lockdowns)) between 1 January and 30 May 2020.

MAIN OUTCOME MEASURE

Incidence rate ratios (IRRs) of covid-19 before and after implementation of physical distancing interventions, estimated using data to 30 May 2020 or 30 days post-intervention, whichever occurred first. IRRs were synthesised across countries using random effects meta-analysis.

RESULTS

On average, implementation of any physical distancing intervention was associated with an overall reduction in covid-19 incidence of 13% (IRR 0.87, 95% confidence interval 0.85 to 0.89; n=149 countries). Closure of public transport was not associated with any additional reduction in covid-19 incidence when the other four physical distancing interventions were in place (pooled IRR with and without public transport closure was 0.85, 0.82 to 0.88; n=72, and 0.87, 0.84 to 0.91; n=32, respectively). Data from 11 countries also suggested similar overall effectiveness (pooled IRR 0.85, 0.81 to 0.89) when school closures, workplace closures, and restrictions on mass gatherings were in place. In terms of sequence of interventions, earlier implementation of lockdown was associated with a larger reduction in covid-19 incidence (pooled IRR 0.86, 0.84 to 0.89; n=105) compared with a delayed implementation of lockdown after other physical distancing interventions were in place (pooled IRR 0.90, 0.87 to 0.94; n=41).

CONCLUSIONS

Physical distancing interventions were associated with reductions in the incidence of covid-19 globally. No evidence was found of an additional effect of public transport closure when the other four physical distancing measures were in place. Earlier implementation of lockdown was associated with a larger reduction in the incidence of covid-19. These findings might support policy decisions as countries prepare to impose or lift physical distancing measures in current or future epidemic waves.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In the absence of evidence for effective treatment regimens or a successful vaccine for coronavirus disease 2019 (covid-19), the most pragmatic recommendation has been to advise physical distancing to minimise transmission

The broader aim of this recommendation was to reduce the burden from covid-19 on public health and healthcare services, and to allow time for the prevention and management of the disease

Evidence on the effectiveness of these interventions to date is largely based on modelling studies, and empirical population level data on effectiveness is scarce globally

WHAT THIS STUDY ADDS

Data from 149 countries showed that the incidence of covid-19 decreased by an average of 13% in association with physical distancing interventions

No evidence was found of additional benefits from closure of public transport when four other physical distancing measures (school closures, workplace closures, restrictions on mass gatherings, and lockdown) were in place

Earlier implementation of lockdown was associated with a larger reduction in the incidence of covid-19

Introduction

As of 8 June 2020, the coronavirus disease 2019 (covid-19) pandemic has been responsible for more than seven million confirmed cases worldwide, including more than 400 000 deaths. In many countries, healthcare facilities have been overwhelmed by a surge in cases, especially patients requiring intensive care. In the absence of evidence for effective treatment regimens or a successful vaccine, the most pragmatic recommendation has been to advise physical distancing (referred to by some as social distancing) to minimise person-to-person transmission[1] with a view to flattening the epidemic curve.[2-4] The main aim of physical distancing is to prevent more rapid spread of covid-19 and to allow more time for public health and healthcare services to become better prepared for the prevention and management of the disease.[4 5] Although most countries have implemented some policy interventions aimed at physical distancing (eg, closure of schools, workplaces, and public

transport, and cancellation of public events), data on the effectiveness of, and adherence to, those policy interventions is scarce. To date, little evidence exists on the comparative effectiveness of specific combinations or sequences of interventions.

Most of the evidence on the postulated effectiveness of physical distancing interventions comes from modelling studies.[2-4] A recent Cochrane systematic review[6] reported that all evidence of physical distancing interventions on covid-19 related morbidity and mortality comes from modelling studies, and only four observational studies focused on severe acute respiratory syndrome and Middle East respiratory syndrome. The UK Department of Health also highlighted the limited availability of robust data on the effectiveness of these measures on influenza.[7] Two recent studies from Wuhan, China[8] and Hong Kong[9] reported a reduction in the number of confirmed cases and transmission of covid-19 associated with physical distancing policy interventions. The data on global effectiveness of these interventions are, however, limited.

Given the impact of the covid-19 pandemic on health and economies worldwide, evidence is urgently needed to inform policy responses. In this natural experimental study across 149 countries we used interrupted time-series analyses to compare the change in incidence of covid-19 before and after implementation of policy interventions for physical distancing.

Methods

Data sources

We obtained data on policy interventions for physical distancing from the Oxford covid-19 Government Response Tracker, a study that tracks national government policy measures in response to the covid-19 pandemic globally (to 30 May 2020).[10] The details of this database, the first such initiative in the context of the covid-19 pandemic, have been described in a working paper.[10] Briefly, a dedicated team of public policy and governance experts based at the University of Oxford collects official data on public policy measures adopted by governments around the world to deal with the covid-19 global pandemic, including physical distancing policies and economic and other healthcare related measures. Our primary interventions of interest were those aimed at physical distancing. These include closures of schools and workplaces, restrictions on mass gatherings (a combination of two variables: cancellation of public events and restrictions on gathering), public transport closure, and lockdown (a combination of two variables: stay at home regulations and restrictions on movements within a country). We merged similar variables related to restrictions on mass gatherings and lockdown because effectively the same concepts are measured and because in most of the countries these restrictions were implemented together, or within a short interval, making it difficult to separate the individual effects. To check the robustness of our primary analysis, we conducted a sensitivity analysis with the seven variables separately.

From the European Centre for Disease Prevention and Control, we collected data on the number of reported cases of covid-19 (to 30 May 2020), as well as the 2019 population estimates.[11] Other population and demographic data—for example, percentages of populations aged 65 years or older (2018 estimates) were from the World Bank data portal.[12] Gross domestic product (GDP) per capita (2018 estimates) were from the International Monetary Fund.[13] The 2019 Global Health Security Index (HSI), a measure of a country's emergency pandemic preparedness developed by the Johns Hopkins University, was from the official report.[14] Data on covid-19 testing (per million) were collected from a variety of sources (see appendix, pp6-7).

Statistical analysis

We used an interrupted time series analysis of each country's data to model the population incidence of covid-19 over time and to estimate the impact of each intervention on the change in incidence of covid-19. This approach allows each country to act as its own control (pre-intervention being the control). Counts of covid-19 cases were modelled using Poisson regression, with the log of the total population size as an offset. The model was used to estimate the incidence rate ratio for development of covid-19 after versus before each intervention within each country.

In this analysis we used an interrupted time series regression model, using the equation:

$$log(Y_t)=\beta_0+\beta_1 T+\beta_2 X_t+\beta_3 Z+\beta_4(log(total\ population))$$

where Y_t represents the number of covid-19 cases at time t, T represents the number of days since the start of follow-up (ie, days since first reported case), X_t is a dummy variable that equates to 0 for the pre-intervention period and 1 for the post-intervention period, and Z represents days since the intervention (equates to 0 for the pre-intervention period). Here, β_0 represents the baseline level of the outcome (number of covid-19 cases) at t=0, β_1 represents the change in the outcome each day pre-intervention, β_2 represents the change in the level of outcome immediately post-intervention, and β_3, our primary parameter of interest, represents the difference in the slope post-intervention (slope B in appendix, pp2-3) compared with the pre-intervention period (slope A in appendix, pp2-3).

Since these policy interventions are not expected to have immediate effects,[15] we hypothesised a seven day lag time (decided a priori) for each intervention to take effect, to coincide with the approximate incubation period of severe acute respiratory coronavirus 2 (SARS-CoV-2),[16] the virus responsible for covid-19, and a recent empirical study.[17] Therefore, we considered the first seven days of the implementation of the intervention as part of the pre-intervention period along with any period before the policy intervention (see appendix, pp2-3). To be eligible for the analysis, countries had to have seven days or more of data after the reported date of intervention implementation, and 30 cases or more by 30 May 2020 (for model convergence).

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Because the epidemic curves are different across the countries studied, use of specific calendar time (eg, 30 May) in the statistical analysis will result in some countries having a substantially longer post-intervention follow-up time than others. As the incidence inevitably decreases with the decline in the epidemic curve, such an approach might show the efficacy of the intervention with greater certainty but could also overestimate the intervention effect. We therefore restricted the post-intervention follow-up time to 30 days since the implementation of a policy, or 30 May 2020, whichever occurred first. This analytical approach also maintains comparability across the countries analysed in meta-analysis.

We also added a scale parameter to the regression equation set as the Pearson χ^2 statistic divided by the residual degrees of freedom,[18] to deal with overdispersion (when the variance is larger than the mean, which is a violation of an assumption of Poisson regression) associated with count data.[19] Models were also checked for autocorrelation.

Random effects meta-analysis was then used to combine these rate ratios (the incidence rate of covid-19 post-intervention compared with the incidence rate pre-intervention) estimated for individual countries.[20] This analysis ascertains whether implementation of any of the physical distancing interventions was associated with an effect on the incidence of covid-19.

Since many country level characteristics might affect both the policy intervention and the incidence of covid-19, we assessed several of these factors in meta-regression, including days between the first reported case and implementation of the first intervention (representing a delay in introduction of the policy), GDP per capita (representing a measure of economic standing, as it is known that covid-19 disproportionately affects those in lower income groups),[21 22] percentage of population aged 65 years or older (to account for population demographics, given the substantially increased risk shown with age),[23] and diagnostic testing rate for covid-19 (because testing has varied within individual countries, and across countries at the same time).

We used random effects meta-analysis to examine the comparative effectiveness of different combinations and sequences of policy interventions. Because the combinations and sequence of interventions do not differentiate between being implemented together or apart, we considered interventions to occur together only if they were implemented within a seven day timeframe. The eligibility criteria to be included in this analysis are the same as those for the primary analysis (ie, at least seven days of data after the intervention and at least 30 cases of covid-19 by 30 May 2020). Additional inclusion criteria include at least a seven day interval between two successive interventions (or combinations of interventions) for valid estimation of the incidence rates and corresponding 95% confidence intervals. We also expanded our time series model to separate out the intervention effects (see appendix, pp2-3). By separating out the effects of interventions implemented in a staggered way, this model also allowed us to examine the comparative effectiveness of early compared with late lockdown. For each specified policy intervention, we report the effect measures as rate ratios comparing the rates of development (slope) of covid-19 before and after each intervention.

All statistical analyses were performed using Stata statistical software (version 14.2)[24] or Python (version 3.6).[25]

Sensitivity analysis

We tested the robustness of our primary analysis using a series of sensitivity analyses. Firstly, we conducted a sensitivity analysis with all seven components of physical distancing interventions separated (as opposed to merging related variables). Then we examine the robustness of our primary seven day lagged analysis, using two additional sensitivity analyses for a five day and a 10 day lagged time frame. Finally, as larger countries might have greater within country variability in the implementation of these interventions, we conducted a sensitivity analysis excluding Brazil, Canada, China, India, Russia, the United Kingdom, and the United States.

Patient and public involvement

This study did not involve patients and the public directly and, given the rapidity of the research, patient and public involvement was not considered viable in this case. However, our findings will be widely disseminated to the public through official (press release, institutional websites, and repositories), personal, and social communication tools.

Results

Overall, 149 countries implemented at least one of the five physical distancing policies between 1 January and 30 May 2020 (flowchart in appendix, p9), with at least seven days of data on incidence of covid-19 post-intervention available for analysis. Figure 1 shows each country and its physical distancing policies. The appendix provides the trajectory of confirmed covid-19 incidence, along with the timeline of policy implementation for each country, as well as the model predicted covid-19 incidence rates for individual countries (pp33-330). In most countries there was little evidence of residual autocorrelation.

Overall impact of physical distancing interventions

All the countries included in the analysis (except Belarus and Tanzania) had implemented at least three of the five physical distancing measures by 30 May 2020. All five measures were in place in 118 countries, whereas 25 countries had four policy measures and four countries had three. On average, policies were first implemented 9 days (SD 13 days) after the first reported case. Countries with the longest interval until first implementation of any of the physical distancing policies were Thailand (58 days), Australia (51 days), Canada (46 days), Sri Lanka and the UK (45 days), Finland and Malaysia (42 days), and Cambodia, Sweden, and the US (40 days).

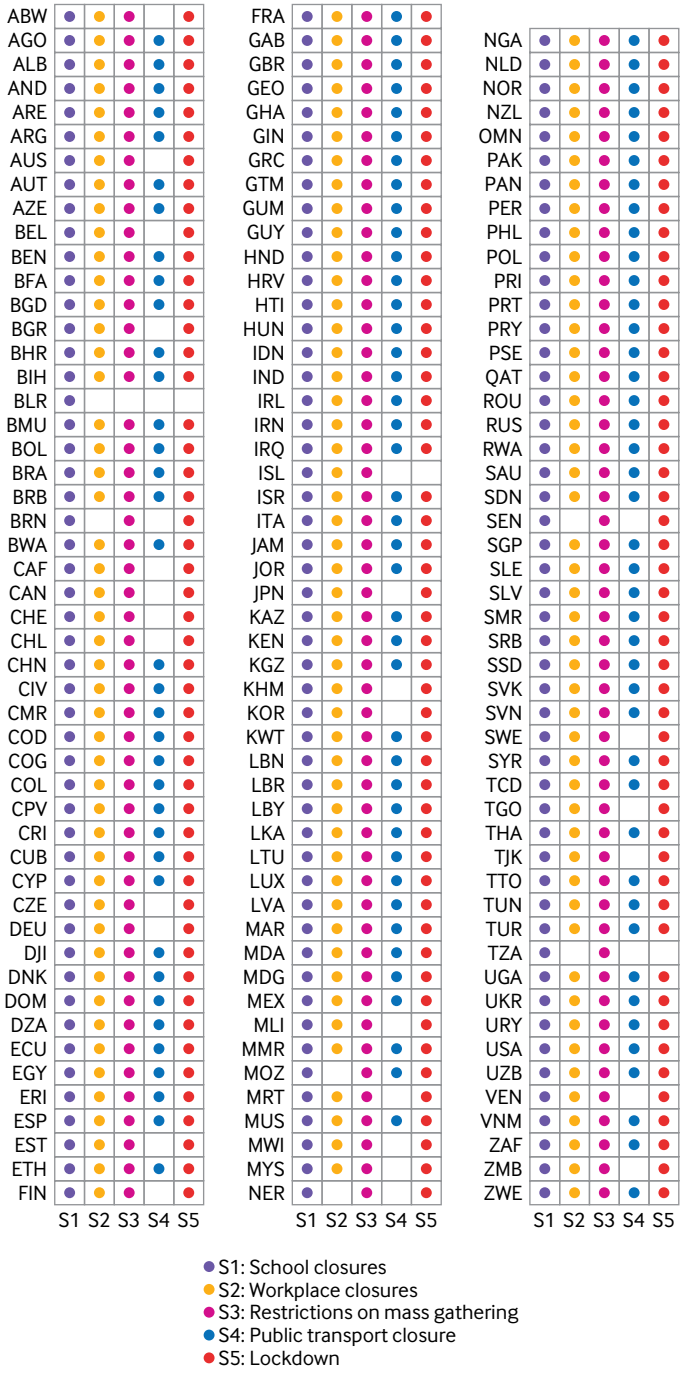

Fig 1 | Physical distancing policies implemented by countries globally. Country codes used are based on the Alpha-3 codes by International Organization for Standardization (see appendix, pp4-5)[25]

The pooled estimates from 149 countries showed an overall decrease of 13% (pooled incidence rate ratio (IRR) 0.87, 95% confidence interval 0.85 to 0.89; P<0.001) in the incidence of covid-19 associated with implementation of any of the physical distancing policies (fig 2). Heterogeneity across countries was low (I^2=19%).

Meta-regression did not identify any effects on the IRR of days since the first reported case of covid-19 until the first implementation of physical distancing policies (P=0.57) and covid-19 testing rate (P=0.71; n=112). However, a higher GDP per capita (P=0.09), higher percentage of population aged 65 years or older (P<0.001), and higher country health security index (P=0.008) were associated with a greater reduction in the pooled IRR (see appendix, p268).

Comparative effectiveness of physical distancing interventions

Number of interventions

Compared with the pre-intervention period, the rate of reduction in incidence of covid-19 was similar with the five physical distancing measures implemented together (pooled IRR 0.87, 0.85 to 0.90; n=118 countries) compared with changes in incidence in countries with four measures implemented (pooled IRR 0.85, 0.82 to 0.89; n=25 countries) (fig 2). A smaller change in incidence of covid-19 was associated with a three intervention combination (pooled IRR 0.88, 0.77 to 1.00) even though this applied to only four countries.

Combination of interventions

Figure 3 details the association between incidence of covid-19 and combinations of physical distancing interventions, implemented together within a seven day time frame (see appendix pp10-15 for detailed results of the meta-analysis). The decrease in incidence of covid-19 associated with a combination of school closures, workplace closures, restrictions on mass gatherings, and lockdowns (pooled IRR 0.87, 0.84 to 0.91; n=32 countries) was similar when closure of public transport was additionally implemented—that is, all five measures were in place (pooled IRR 0.85, 0.82 to 0.88; n=72 countries). A combination of school closures, workplace closures, and restrictions on mass gatherings with or without closure of public transport was consistently associated with a beneficial effect of a decrease in incidence of covid-19. Evidence was insufficient to determine the association between covid-19 incidence and other combinations of interventions without restrictions on mass gathering (fig 3).

Sequence of interventions

Figure 4 shows the association between the sequence of interventions and the change in the incidence of covid-19 (also see appendix, pp16-25). No consistent pattern of association was found for any specific sequence of interventions. When the effect estimates from all the countries were pooled together, however, a greater reduction in incidence of covid-19 was associated with earlier implementation of lockdown (pooled IRR 0.86, 0.84 to 0.89; n=105 countries) as opposed to later implementation (pooled IRR 0.90, 0.87 to 0.94; n=41 countries) (see appendix, pp26-27).

Sensitivity analysis

When the seven physical distancing policies were considered separately (ie, without merging the two

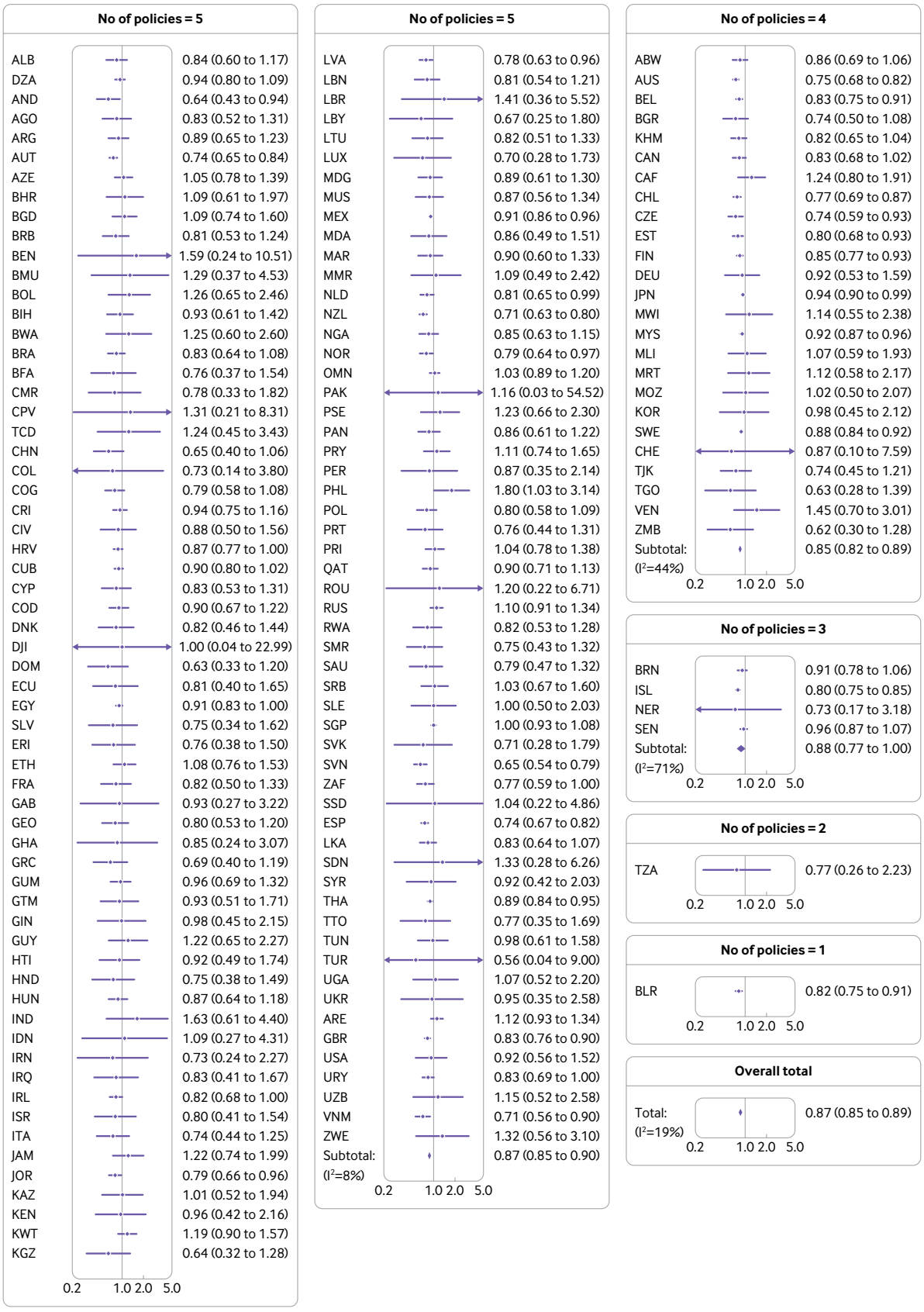

Fig 2 | Pairwise meta-analysis on the association between physical distancing interventions and change in incidence of coronavirus disease 2019. Effects are reported as incidence rate ratios (95% confidence intervals). I^2=an estimate of the percentage of total variation across the countries that is due to heterogeneity rather than chance.[26] Country codes used are based on the Alpha-3 codes by International Organization for Standardization (see appendix, pp4-5)[25]

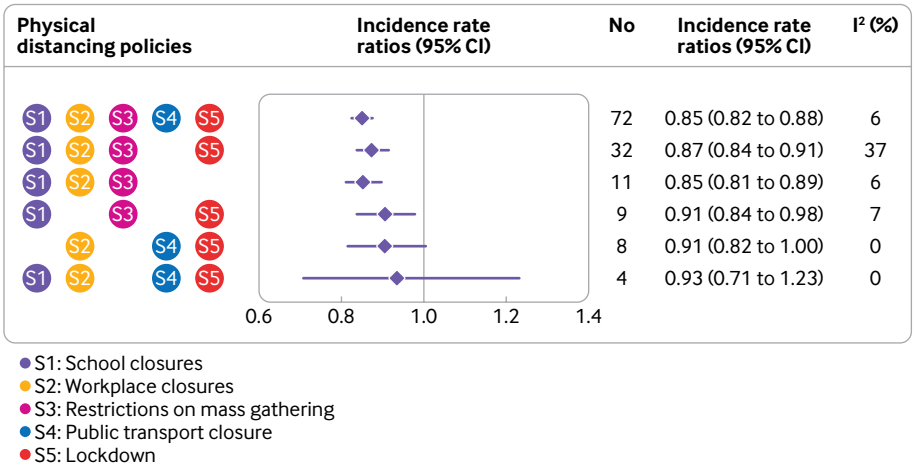

Fig 3 | Association between the combinations of physical distancing interventions and change in incidence of coronavirus disease 2019. I^2=an estimate of the percentage of total variation across the countries that is due to heterogeneity rather than chance[26]

mass gathering interventions or the two lockdown measures), the estimated effects of any physical distancing intervention were similar to those of the primary analysis (IRR 0.86, 0.85 to 0.88) (see appendix, p28). Results from the analysis excluding the seven largest countries were virtually identical to those of the primary analysis (IRR 0.87, 0.85 to 0.89) (see appendix, p29). When a five day lagged time frame was used in the sensitivity analysis, the model did not converge for seven countries (Gabon, Djibouti, India, Indonesia, Libya, Sudan, and Togo) owing to either a shorter pre-intervention follow-up time or fewer cases in the pre-intervention period. Results for the remaining 142 countries were, however, similar to those of the primary analysis (IRR 0.88, 0.87 to 0.90), as were those from the analysis using a 10 day lagged time frame for all 149 countries (IRR 0.86, 0.84 to 0.88) (see appendix, pp30-31).

Discussion

In this study, five commonly introduced physical distancing interventions in 149 countries were associated with on average a 13% reduction in the incidence of covid-19. No additional benefit was found associated with closures of public transport when a combination of school closures, workplace closures, restrictions on mass gatherings, and restrictions of population movement (ie, lockdown) was in place. A greater reduction in incidence was observed when restriction on mass gatherings was included in the intervention combination, and when lockdown was implemented earlier along with school and workplace closures. The reduction in incidence of covid-19 associated with physical distancing interventions was greater in high income countries (higher GDP per capita), those with an older population (higher proportion of population aged ≥65 years), and those with stronger preparedness for the pandemic (country health security index).

Comparison with previous research

Our finding of a beneficial effect associated with physical distancing interventions aligns with the findings from a recent epidemiological study, which reported data on the covid-19 epidemic in Wuhan, China.[8] This study found that a reduction in incidence of covid-19 was associated with a series of non-drug interventions (eg, "cordons sanitaire" or restrictions on movement, traffic restrictions, social distancing, home quarantine, centralised quarantine, and universal symptom survey). A similar study from Hubei and Guangdong in China also reported a reduction in incidence of covid-19.[17] A study from Hong Kong also reported a decrease in the transmission of SARS-CoV-2 associated with physical distancing interventions.[9] A recent study compared the incidence of covid-19 between Spain and Italy and reported a reduction in incidence of covid-19.[26] Previous studies that examined historical data on the physical distancing interventions during the 1918-19 influenza pandemic in the US reported "strong" beneficial effects from school closures, bans on public gatherings, and isolation and quarantine.[27] A more recent study on the economic consequences of the 1918-19 influenza pandemic concluded that physical distancing interventions were associated with a lower mortality.[28] This study also reported that despite adverse effects on the economy from the global pandemic, regions that took earlier and aggressive physical distancing measures grew faster economically in the post-pandemic period.[28] Other modelling studies on covid-19 also predicted a reduction in incidence of the disease associated with physical distancing interventions.[2-4] As outlined in the UK Department of Health's scientific summary on the effectiveness of policy interventions, it is difficult to compare study results because of heterogeneity in methods and approaches.[7] This report highlighted the conflicting findings on, for example, school closures and mass gatherings. Previous studies and reviews

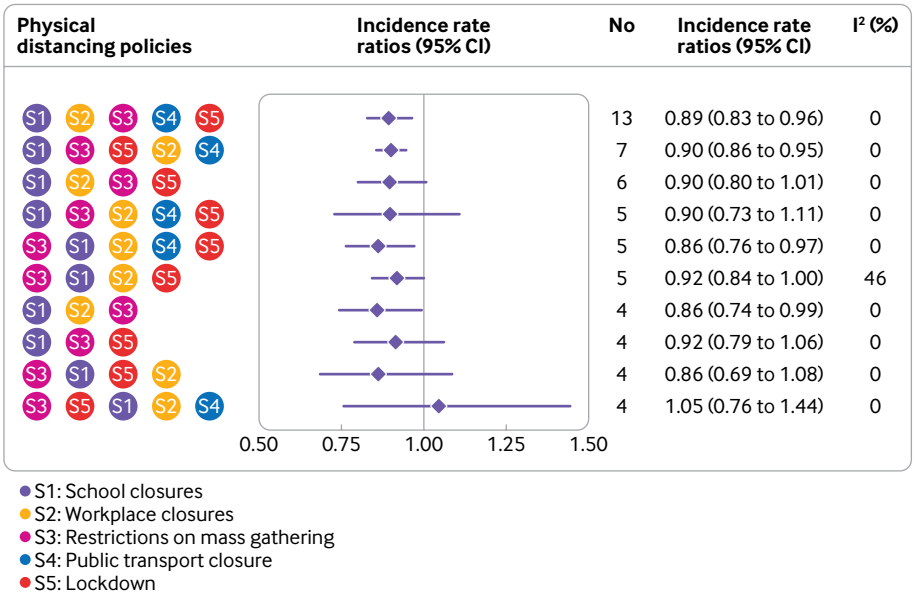

Fig 4 | Association between the sequence of physical distancing interventions and change in incidence of coronavirus disease 2019. I^2=an estimate of the percentage of total variation across the countries that is due to heterogeneity rather than chance[26]

on severe acute respiratory syndrome and Middle East respiratory syndrome also highlighted the lack of robust data on effectiveness.[6 7 29] Our findings add to this evidence base and should help to inform governmental policies on the implementation of combinations and sequences of physical distancing interventions in the future.

Strengths and limitations of this study

In this large empirical study reporting on the potential effectiveness of physical distancing policies on the incidence of covid-19, we pooled data from 149 countries, which varied in terms of economic development and political and health systems. We employed a rapid, comprehensive, and robust methodological and analytical approach to evaluate emerging data on the covid-19 pandemic, and we estimated the relative effectiveness of different policy interventions within each country. Our study answers key questions about the combination and sequence of physical distancing interventions. Closure of public transport can be problematic, especially for those working in vital services, including health, care giving, and emergency response roles. Our study suggests that, in the presence of other physical distancing measures, closure of public transport might not substantially enhance disease control. Closure of schools and workplaces and restrictions on mass gatherings leave fewer people to use public transport, and this might help to make it easier to maintain physical distancing among people working in the key service sectors. We found that intervention combinations that included restrictions on mass gatherings were consistently associated with a greater reduction in incidence of covid-19. We also found that earlier implementation of restrictions on the movement of populations (lockdown) was associated with a greater reduction in incidence of covid-19, as previously suggested by modelling studies.[2 3]

Our study does, however, have limitations. Firstly, we relied solely on the Oxford covid-19 Government Response Tracker, which tracks the measures taken by governments around the world to tackle the covid-19 pandemic.[10] The curators of this database emphasised that they took care to ensure the validity of the collected data. In all practicality, however, it is challenging to collect information on the exact date, nature, and extent of the policies by the different governments. Although our study design enabled us to conduct a comparative effectiveness analysis, it is difficult to know exact combinations and sequences of the interventions, especially when implemented within a short period. This high level dataset might obscure qualitative differences in each of the five physical distancing measures across countries. Moreover, many local and cultural factors can affect the implementation of interventions–that is, what is acceptable in one national context might not be so in another, and compliance might therefore vary widely; we did not assess compliance in this dataset. This variation might be compounded by wide differences in the ability of countries to provide additional monetary and other resources to support the implementation of interventions, although controlling for GDP in this study might have allowed for this to an extent. In many settings, a government declaration does not equate to a mandatory implementation. For example, under Japanese constitutional law, Japan's government does not have the legal authority to compel the closure of workplaces. This might also be the case in other jurisdictions.

A key limitation is that our study design did not allow us to assess the optimum time for implementation of

these physical distancing interventions; nor were we able to define the optimum time for lifting of these restrictions. Even though our data were suggestive of a greater benefit if the cancellation of public events and lockdowns are implemented earlier, along with closures of schools and workplaces, many of these estimates came from only a few countries. Our findings therefore should be interpreted with caution. In our meta-regression analysis, we found that the time between the first reported case of covid-19 and implementation of physical distancing policies was not significantly associated with the incidence of covid-19. This is contrary to anecdotal data from some countries that implemented these policies earlier (eg, South Korea) and reported success in slowing down the rate of transmission of SARS-CoV-2. Nevertheless, collated evidence from around the world (see appendix, p32) is far from confirmatory. Many countries implemented physical distancing policies earlier than others but failed to slow down the transmission of SARS-CoV-2. Overall, however, we found that earlier implementation of lockdown together with other physical distancing policies was associated with a larger reduction in the incidence of covid-19.

We did not include restrictions on international travel as this measure, although an important element of a viral containment strategy, is not strictly a physical distancing measure. Moreover, international travel restrictions of one country often affect other countries, regardless of whether those affected countries have implemented the same restrictions; this could violate the assumption of independence across the countries in the meta-analysis.

A further limitation is that, in addition to physical distancing measures, countries have implemented a wide range of other interventions that might be equally or more effective, including deployment of healthcare staff,[30] healthcare financing,[31] increased numbers of hospital beds[30] or ventilators,[32] increased and effective supply of personal protective equipment,[32] use of face coverings (including face masks) by the general population,[33-35] and mobile phone apps for contact tracing and isolation.[36 37] This is not an exhaustive list of potential ways to reduce the transmission of SARS-CoV-2.[38] We were unable to examine the deployment of such measures in this study owing to lack of valid and robust data in most of the countries. Future research will be able to examine these effects with better data availability.

We attempted to collect data on covid-19 testing rates by country, but we could only identify data for 112 countries from a variety of sources, and the validity of these data might be questionable. The outcome metric in our study was incidence, which could be influenced by testing rates. However, testing rates were potentially stable during our study period, as we restricted the analysis up to 30 days post-intervention implementation; covid-19 testing rate was not found to be a significant factor in our meta-regression analysis. Nevertheless, valid longitudinal data on covid-19 testing are yet to become available. Therefore, examining the longitudinal effect of covid-19 testing on the results reported will only be possible when robust data are available.

Ideally, we would also have examined death rates, but at this stage of the pandemic, the numbers of deaths in countries are lower, especially for those only recently experiencing the epidemic and for those that have successfully minimised the numbers of deaths. Covid-19 related deaths are also likely to be under-reported.[30 39] Future research with more complete data on incidence and mortality will help to validate these results, as well as estimate the long term effects more precisely.

Another potential limitation was our inability to examine within country heterogeneity in the implementation of these policy interventions, which is particularly relevant for large countries such as Brazil, Russia, and the US. Although not a perfect solution, we conducted a sensitivity analysis excluding the seven largest countries in our dataset, and the results of our primary analysis remained unchanged. As more data become available at smaller geographical levels, future studies should examine within country heterogeneity.

Lastly, the incidence of covid-19 is still increasing in most countries. We only assessed the short term effectiveness of physical distancing interventions.[8] Further analyses over time will be needed to influence policy decisions.[40]

Interpretation and implications for policy and practice

Despite a range of limitations in our study, the findings suggest beneficial effects of physical distancing interventions in combination, especially restrictions on mass gatherings along with school and workplace closures, allowing the maintenance of active public transport for people working in the key service sectors. Our finding of no additional benefit associated with public transport closure when other interventions are in place is likely a result of fewer people using public transport, making it more convenient to maintain physical distancing during essential travel. The sequence and timing of interventions might also be important, with earlier implementation of restrictions on mass gatherings and restrictions on movement (lockdown) showing promise. The results from this study should help inform public health policy on the effect of implementation of interventions on the incidence of covid-19. However, more empirical data will be required to help decide which interventions to lift first as the epidemic curve starts to flatten, or which interventions to implement should further waves of the covid-19 pandemic occur, as has been suggested.[41 42] As found in our analysis, a combination of interventions without restrictions on public gathering might not play a substantial role in flattening the epidemic curve.

While some forms and combinations of physical distancing policies will likely remain in place until a successful treatment or vaccine for covid-19 becomes available, the psychosocial effects of prolonged restrictions need to be properly assessed.[43 44]

Communicating these psychosocial issues with the public and patients remains a challenging task for public health, primary care, and mental healthcare providers.[43-45] Although some guidelines exist, these are not comprehensive,[45] and further research should explore the most effective ways to communicate risk and risk reduction in trusted and non-judgemental ways.

Unanswered questions and further research

Further research is needed to provide more definitive answers to remaining questions about the extent, intensity, combinations, and sequence of physical distancing interventions, as well as the need for additional interventions, in the short, medium, and long term. Further work that distinguishes physical distancing interventions better in terms of their capability to reduce transmission will help to determine their potential for risk reduction. Urgent work is needed to ensure the validity and reliability of data on covid-19 testing, incidence, mortality, and implementation and compliance with interventions. In our study we have only been able to provide a rapid and relatively crude assessment of physical distancing at a relatively early stage of the covid-19 pandemic. As the pandemic continues to evolve, it will be crucial to repeat and extend this analysis to assess the impacts of interventions in the longer term, as well as to study combinations and sequence of the lifting of physical distancing restrictions.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: NI receives salary support from the Nuffield Department of Population Health, University of Oxford; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required as data are anonymised, aggregated without any personal information, and publicly available.

Data sharing: All the data used in this study are publicly available and properly cited. However, all the data used in this study will be made publicly available on the GitHub repository (https://github.com/shabnam-shbd/COVID-19_Physical_Distancing_Policy) upon publication of the study.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We will widely disseminate the main findings to members of the public through official (press release, institutional websites, and repositories), personal, and social media.

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Web appendix: Supplementary appendix

REFERENCE 25

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

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Summary

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and is spread person-to-person through close contact. We aimed to investigate the effects of physical distance, face masks, and eye protection on virus transmission in health-care and non-health-care (eg, community) settings.

Methods We did a systematic review and meta-analysis to investigate the optimum distance for avoiding person-to-person virus transmission and to assess the use of face masks and eye protection to prevent transmission of viruses. We obtained data for SARS-CoV-2 and the betacoronaviruses that cause severe acute respiratory syndrome, and Middle East respiratory syndrome from 21 standard WHO-specific and COVID-19-specific sources. We searched these data sources from database inception to May 3, 2020, with no restriction by language, for comparative studies and for contextual factors of acceptability, feasibility, resource use, and equity. We screened records, extracted data, and assessed risk of bias in duplicate. We did frequentist and Bayesian meta-analyses and random-effects meta-regressions. We rated the certainty of evidence according to Cochrane methods and the GRADE approach. This study is registered with PROSPERO, CRD42020177047.

Findings Our search identified 172 observational studies across 16 countries and six continents, with no randomised controlled trials and 44 relevant comparative studies in health-care and non-health-care settings (n=25 697 patients). Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10 736, pooled adjusted odds ratio [aOR] 0·18, 95% CI 0·09 to 0·38; risk difference [RD] –10·2%, 95% CI –11·5 to –7·5; moderate certainty); protection was increased as distance was lengthened (change in relative risk [RR] 2·02 per m; $p_{interaction}$=0·041; moderate certainty). Face mask use could result in a large reduction in risk of infection (n=2647; aOR 0·15, 95% CI 0·07 to 0·34, RD –14·3%, –15·9 to –10·7; low certainty), with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (eg, reusable 12–16-layer cotton masks; $p_{interaction}$=0·090; posterior probability >95%, low certainty). Eye protection also was associated with less infection (n=3713; aOR 0·22, 95% CI 0·12 to 0·39, RD –10·6%, 95% CI –12·5 to –7·7; low certainty). Unadjusted studies and subgroup and sensitivity analyses showed similar findings.

Interpretation The findings of this systematic review and meta-analysis support physical distancing of 1 m or more and provide quantitative estimates for models and contact tracing to inform policy. Optimum use of face masks, respirators, and eye protection in public and health-care settings should be informed by these findings and contextual factors. Robust randomised trials are needed to better inform the evidence for these interventions, but this systematic appraisal of currently best available evidence might inform interim guidance.

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See Online for appendix

Introduction

As of May 28, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 5·85 million individuals worldwide and caused more than 359 000 deaths.[1] Emergency lockdowns have been initiated in countries across the globe, and the effect on health, wellbeing, business, and other aspects of daily life are felt throughout societies and by individuals. With no effective pharmacological interventions or vaccine available in the imminent future, reducing the rate of infection (ie, flattening the curve) is a priority, and prevention of infection is the best approach to achieve this aim.

SARS-CoV-2 spreads person-to-person through close contact and causes COVID-19. It has not been solved if

Research in context

Evidence before this study

We searched 21 databases and resources from inception to May 3, 2020, with no restriction by language, for studies of any design evaluating physical distancing, face masks, and eye protection to prevent transmission of the viruses that cause COVID-19 and related diseases (eg, severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) between infected individuals and people close to them (eg, household members, caregivers, and health-care workers). Previous related meta-analyses have focused on randomised trials and reported imprecise data for common respiratory viruses such as seasonal influenza, rather than the pandemic and epidemic betacoronaviruses causative of COVID-19 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), SARS (SARS-CoV), or MERS (MERS-CoV). Other meta-analyses have focused on interventions in the health-care setting and have not included non-health-care (eg, community) settings. Our search did not retrieve any systematic review of information on physical distancing, face masks, or eye protection to prevent transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Added value of this study

We did a systematic review of 172 observational studies in health-care and non-health-care settings across 16 countries and six continents; 44 comparative studies were included in a meta-analysis, including 25 697 patients with COVID-19, SARS, or MERS. Our findings are, to the best of our knowledge, the first to rapidly synthesise all direct information on COVID-19 and, therefore, provide the best available evidence to inform optimum use of three common and simple interventions to help reduce the rate of infection and inform non-pharmaceutical interventions, including pandemic mitigation in non-health-care settings. Physical distancing of 1 m or more was associated with a much lower risk of infection, as was use of face masks (including N95 respirators or similar and surgical or similar masks [eg, 12–16-layer cotton or gauze masks]) and eye protection (eg, goggles or face shields). Added benefits are likely with even larger physical distances (eg, 2 m or more based on modelling) and might be present with N95 or similar respirators versus medical masks or similar. Across 24 studies in health-care and non-health-care settings of contextual factors to consider when formulating recommendations, most stakeholders found these personal protection strategies acceptable, feasible, and reassuring but noted harms and contextual challenges, including frequent discomfort and facial skin breakdown, high resource use linked with the potential to decrease equity, increased difficulty communicating clearly, and perceived reduced empathy of care providers by those they were caring for.

Implications of all the available evidence

In view of inconsistent guidelines by various organisations based on limited information, our findings provide some clarification and have implications for multiple stakeholders. The risk for infection is highly dependent on distance to the individual infected and the type of face mask and eye protection worn. From a policy and public health perspective, current policies of at least 1 m physical distancing seem to be strongly associated with a large protective effect, and distances of 2 m could be more effective. These data could also facilitate harmonisation of the definition of exposed (eg, within 2 m), which has implications for contact tracing. The quantitative estimates provided here should inform disease-modelling studies, which are important for planning pandemic response efforts. Policy makers around the world should strive to promptly and adequately address equity implications for groups with currently limited access to face masks and eye protection. For health-care workers and administrators, our findings suggest that N95 respirators might be more strongly associated with protection from viral transmission than surgical masks. Both N95 and surgical masks have a stronger association with protection compared with single-layer masks. Eye protection might also add substantial protection. For the general public, evidence shows that physical distancing of more than 1 m is highly effective and that face masks are associated with protection, even in non-health-care settings, with either disposable surgical masks or reusable 12–16-layer cotton ones, although much of this evidence was on mask use within households and among contacts of cases. Eye protection is typically underconsidered and can be effective in community settings. However, no intervention, even when properly used, was associated with complete protection from infection. Other basic measures (eg, hand hygiene) are still needed in addition to physical distancing and use of face masks and eye protection.

SARS-CoV-2 might spread through aerosols from respiratory droplets; so far, air sampling has found virus RNA in some studies[2–4] but not in others.[5–8] However, finding RNA virus is not necessarily indicative of replication-competent and infection-competent (viable) virus that could be transmissible. The distance from a patient that the virus is infective, and the optimum person-to-person physical distance, is uncertain. For the currently foreseeable future (ie, until a safe and effective vaccine or treatment becomes available), COVID-19 prevention will continue to rely on non-pharmaceutical interventions, including pandemic mitigation in community settings.[9] Thus, quantitative assessment of physical distancing is relevant to inform safe interaction and care of patients with SARS-CoV-2 in both health-care and non-health-care settings. The definition of close contact or potentially exposed helps to risk stratify, contact trace, and develop guidance documents, but these definitions differ around the globe.

To contain widespread infection and to reduce morbidity and mortality among health-care workers and others in contact with potentially infected people, jurisdictions have issued conflicting advice about physical or social distancing. Use of face masks with or

without eye protection to achieve additional protection is debated in the mainstream media and by public health authorities, in particular the use of face masks for the general population;[10] moreover, optimum use of face masks in health-care settings, which have been used for decades for infection prevention, is facing challenges amid personal protective equipment (PPE) shortages.[11]

Any recommendations about social or physical distancing, and the use of face masks, should be based on the best available evidence. Evidence has been reviewed for other respiratory viral infections, mainly seasonal influenza,[12,13] but no comprehensive review is available of information on SARS-CoV-2 or related betacoronaviruses that have caused epidemics, such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). We, therefore, systematically reviewed the effect of physical distance, face masks, and eye protection on transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Methods

Search strategy and selection criteria

To inform WHO guidance documents, on March 25, 2020, we did a rapid systematic review.[14] We created a large international collaborative and we used Cochrane methods[15] and the GRADE approach.[16] We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42020177047; appendix pp 23–29). We have followed PRISMA[17] and MOOSE[18] reporting guidelines (appendix pp 30–33).

From database inception to May 3, 2020, we searched for studies of any design and in any setting that included patients with WHO-defined confirmed or probable COVID-19, SARS, or MERS, and people in close contact with them, comparing distances between people and COVID-19 infected patients of 1 m or larger with smaller distances, with or without a face mask on the patient, or with or without a face mask, eye protection, or both on the exposed individual. The aim of our systematic review was for quantitative assessment to ascertain the physical distance associated with reduced risk of acquiring infection when caring for an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. Our definition of face masks included surgical masks and N95 respirators, among others; eye protection included visors, faceshields, and goggles, among others.

We searched (up to March 26, 2020) MEDLINE (using the Ovid platform), PubMed, Embase, CINAHL (using the Ovid platform), the Cochrane Library, COVID-19 Open Research Dataset Challenge, COVID-19 Research Database (WHO), Epistemonikos (for relevant systematic reviews addressing MERS and SARS, and its COVID-19 Living Overview of the Evidence platform), EPPI Centre living systematic map of the evidence, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, relevant documents on the websites of governmental and other relevant organisations, reference lists of included papers, and relevant systematic reviews.[19,20] We handsearched (up to May 3, 2020) preprint servers (bioRxiv, medRxiv, and Social Science Research Network First Look) and coronavirus resource centres of *The Lancet*, *JAMA*, and *N Engl J Med* (appendix pp 3–5). We did not limit our search by language. We initially could not obtain three full texts for evaluation, but we obtained them through interlibrary loan or contacting a study author. We did not restrict our search to any quantitative cutoff for distance.

Data collection

We screened titles and abstracts, reviewed full texts, extracted data, and assessed risk of bias by two authors and independently, using standardised prepiloted forms (Covidence; Veritas Health Innovation, Melbourne, VIC, Australia), and we cross-checked screening results using artificial intelligence (Evidence Prime, Hamilton, ON, Canada). We resolved disagreements by consensus. We extracted data for study identifier, study design, setting, population characteristics, intervention and comparator characteristics, quantitative outcomes, source of funding

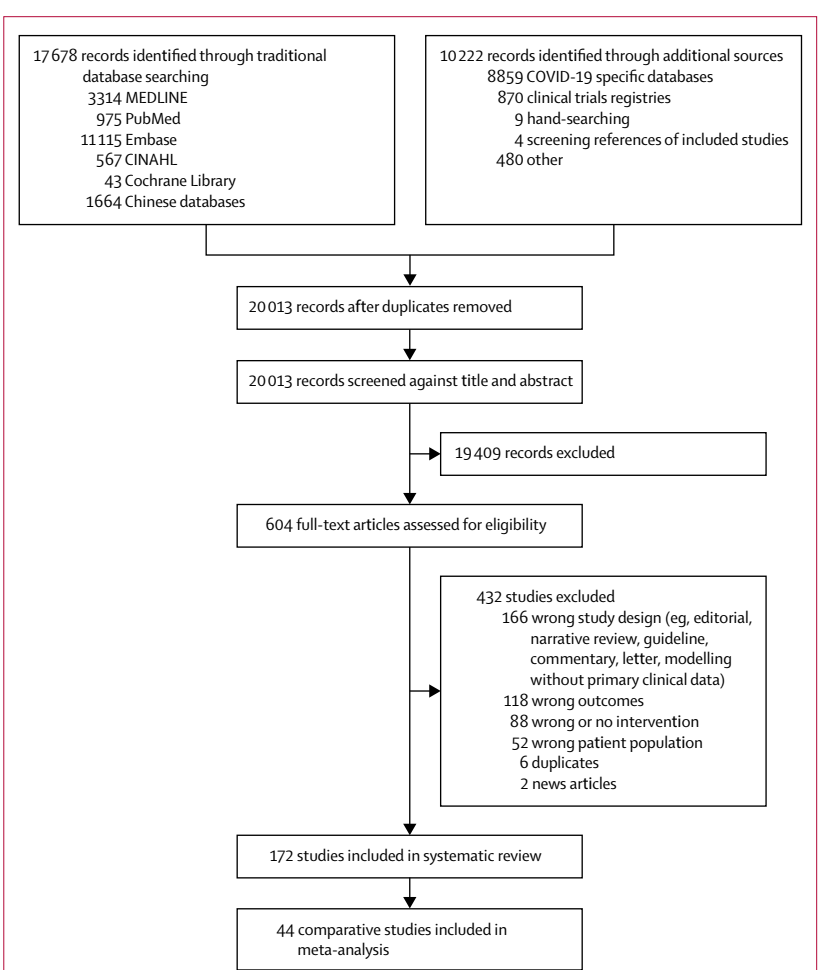

Figure 1: **Study selection**

	Population size (n)	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
Alraddadi et al (2016)[34]	283	Saudi Arabia	Health care	MERS	Confirmed	Yes	********
Arwady et al (2016)[35]	79	Saudi Arabia	Non-health care (household and family contacts)	MERS	Confirmed	No	******
Bai et al (2020)[36]	118	China	Health care	COVID-19	Confirmed	No	*****
Burke et al (2020)[37]	338	USA	Health care and non-health care (including household and community)	COVID-19	Confirmed	No	****
Caputo et al (2006)[38]	33	Canada	Health care	SARS	Confirmed	No	*****
Chen et al (2009)[39]	758	China	Health care	SARS	Confirmed	Yes	*******
Cheng et al (2020)[40]	226	China	Non-health care (household and family contacts)	COVID-19	Confirmed	No	******
Ha et al (2004)[42]	117	Vietnam	Health care	SARS	Confirmed	No	**
Hall et al (2014)[43]	48	Saudi Arabia	Health care	MERS	Confirmed	No	***
Heinzerling et al (2020)[44]	37	USA	Health care	COVID-19	Confirmed	No	****
Ho et al (2004)[45]	372	Taiwan	Health care	SARS	Confirmed	No	********
Ki et al (2019)[47]	446	South Korea	Health care	MERS	Confirmed	No	******
Kim et al (2016)[48]	9	South Korea	Health care	MERS	Confirmed	No	*****
Kim et al (2016)[49]	1169	South Korea	Health care	MERS	Confirmed	No	******
Lau et al (2004)[50]	2270	China	Non-health care (households)	SARS	Probable	Yes	******
Liu et al (2009)[51]	477	China	Health care	SARS	Confirmed	Yes	*****
Liu et al (2020)[52]	20	China	Non-health care (close contacts)	COVID-19	Confirmed	No	*******
Loeb et al (2004)[53]	43	Canada	Health care	SARS	Confirmed	No	**
Ma et al (2004)[54]	426	China	Health care	SARS	Confirmed	Yes	*********
Nishiura et al (2005)[55]	115	Vietnam	Health care	SARS	Confirmed	Yes	********
Nishiyama et al (2008)[56]	146	Vietnam	Health care	SARS	Confirmed	Yes	******
Olsen et al (2003)[57]	304	China	Non-health care (airplane)	SARS	Confirmed	No	******
Park et al (2004)[58]	110	USA	Health care	SARS	Confirmed	No	**********
Park et al (2016)[59]	80	South Korea	Health care	MERS	Confirmed and probable	No	***
Peck et al (2004)[60]	26	USA	Health care	SARS	Confirmed	No	*********
Pei et al (2006)[61]	443	China	Health care	SARS	Confirmed	No	********
Rea et al (2007)[62]	8662	Canada	Non-health care (community contacts)	SARS	Probable	No	****
Reuss et al (2014)[63]	81	Germany	Health care	MERS	Confirmed	No	*****
Reynolds et al (2006)[64]	153	Vietnam	Health care	SARS	Confirmed	No	***
Ryu et al (2019)[65]	34	South Korea	Health care	MERS	Confirmed	No	******
Scales et al (2003)[66]	69	Canada	Health care	SARS	Probable	No	**
Seto et al (2003)[67]	254	China	Health care	SARS	Confirmed	Yes	********
Teleman et al (2004)[68]	86	Singapore	Health care	SARS	Confirmed	Yes	********
Tuan et al (2007)[69]	212	Vietnam	Non-health care (household and community contacts)	SARS	Confirmed	Yes	******
Van Kerkhove et al (2019)[46]	828	Saudi Arabia	Non-health care (dormitory)	MERS	Confirmed	Yes	********
Wang et al (2020)[41]	493	China	Health care	COVID-19	Confirmed	Yes	****

(Table 1 continues on next page)

	n	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
(Continued from previous page)							
Wang et al (2020)[70]	5442	China	Health care	COVID-19	Confirmed	No	*****
Wiboonchutikul et al (2016)[71]	38	Thailand	Health care	MERS	Confirmed	No	*****
Wilder-Smith et al (2005)[72]	80	Singapore	Health care	SARS	Confirmed	No	********
Wong et al (2004)[73]	66	China	Health care	SARS	Confirmed	No	*****
Wu et al (2004)[74]	375	China	Non-health care (community)	SARS	Confirmed	Yes	********
Yin et al (2004)[75]	257	China	Health care	SARS	Confirmed	Yes	******
Yu et al (2005)[76]	74	China	Health care	SARS	Confirmed	No	*******
Yu et al (2007)[77]	124 wards	China	Health care	SARS	Confirmed	Yes	*******

Across studies, mean age was 30–60 years. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. *The Newcastle-Ottawa Scale was used for the risk of bias assessment, with more stars equalling lower risk.

Table 1: **Characteristics of included comparative studies**

and reported conflicts of interests, ethics approval, study limitations, and other important comments.

Outcomes

Outcomes of interest were risk of transmission (ie, WHO-defined confirmed or probable COVID-19, SARS, or MERS) to people in health-care or non-health-care settings by those infected; hospitalisation; intensive care unit admission; death; time to recovery; adverse effects of interventions; and contextual factors such as acceptability, feasibility, effect on equity, and resource considerations related to the interventions of interest. However, data were only available to analyse intervention effects for transmission and contextual factors. Consistent with WHO, studies generally defined confirmed cases with laboratory confirmation (with or without symptoms) and probable cases with clinical evidence of the respective infection (ie, suspected to be infected) but for whom confirmatory testing either had not yet been done for any reason or was inconclusive.

Data analysis

Our search did not identify any randomised trials of COVID-19, SARS, or MERS. We did a meta-analysis of associations by pooling risk ratios (RRs) or adjusted odds ratios (aORs) depending on availability of these data from observational studies, using DerSimonian and Laird random-effects models. We adjusted for variables including age, sex, and severity of source case; these variables were not the same across studies. Because between-study heterogeneity can be misleadingly large when quantified by I^2 during meta-analysis of observational studies,[21,22] we used GRADE guidance to assess between-study heterogeneity.[21] Throughout, we present RRs as unadjusted estimates and aORs as adjusted estimates.

We used the Newcastle-Ottawa scale to rate risk of bias for comparative non-randomised studies corresponding to every study's design (cohort or case-control).[23,24] We planned to use the Cochrane Risk of Bias tool 2.0 for randomised trials,[25] but our search did not identify any eligible randomised trials. We synthesised data in both narrative and tabular formats. We graded the certainty of evidence using the GRADE approach. We used the GRADEpro app to rate evidence and present it in GRADE evidence profiles and summary of findings tables[26,27] using standardised terms.[28,29]

For more on the **GRADEpro app** see https://www.gradepro.org

We analysed data for subgroup effects by virus type, intervention (different distances or face mask types), and setting (health care *vs* non-health care). Among the studies assessing physical distancing measures to prevent viral transmission, the intervention varied (eg, direct physical contact [0 m], 1 m, or 2 m). We, therefore, analysed the effect of distance on the size of the associations by random-effects univariate meta-regressions, using restricted maximum likelihood, and we present mean effects and 95% CIs. We calculated tests for interaction using a minimum of 10 000 Monte Carlo random permutations to avoid spurious findings.[30] We formally assessed the credibility of potential effect-modifiers using GRADE guidance.[21] We did two sensitivity analyses to test the robustness of our findings. First, we used Bayesian meta-analyses to reinterpret the included studies considering priors derived from the effect point estimate and variance from a meta-analysis of ten randomised trials evaluating face mask use versus no face mask use to prevent influenza-like illness in health-care workers.[31] Second, we used Bayesian meta-analyses to reinterpret the efficacy of N95 respirators versus medical masks on preventing influenza-like illness after seasonal viral (mostly influenza) infection.[13] For these sensitivity analyses, we used hybrid Metropolis-Hastings and Gibbs sampling, a 10 000 sample burn-in, 40 000 Markov chain Monte Carlo samples, and we tested non-informative and sceptical priors (eg, four time variance)[32,33] to inform

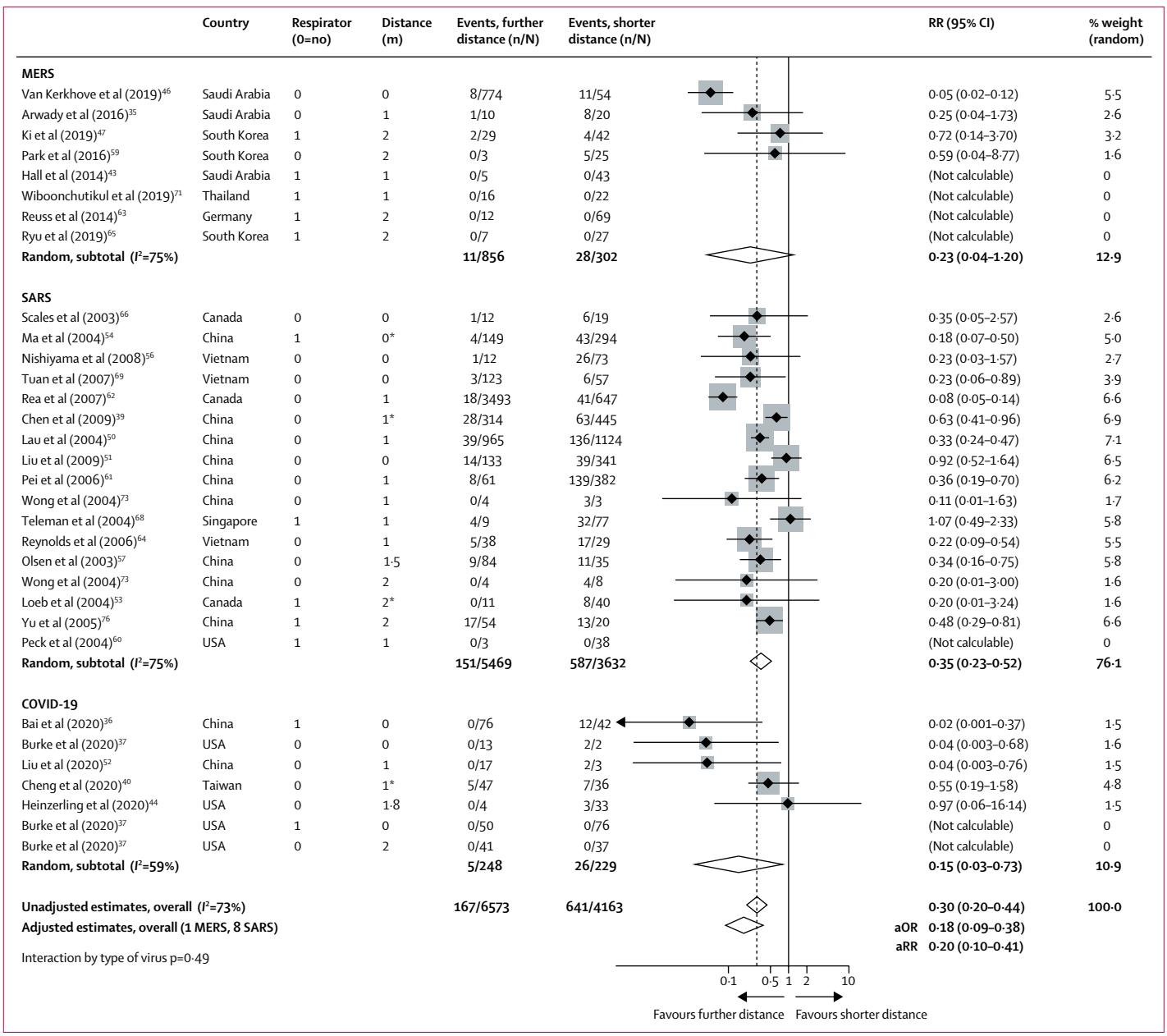

Figure 2: **Forest plot showing the association of COVID-19, SARS, or MERS exposure proximity with infection**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk. *Estimated values; sensitivity analyses excluding these values did not meaningfully alter findings.

mean estimates of effect, 95% credibility intervals (CrIs), and posterior distributions. We used non-informative hyperpriors to estimate statistical heterogeneity. Model convergence was confirmed in all cases with good mixing in visual inspection of trace plots, autocorrelation plots, histograms, and kernel density estimates in all scenarios. Parameters were blocked, leading to acceptance of approximately 50% and efficiency greater than 1% in all cases (typically about 40%). We did analyses using Stata version 14.3.

Role of the funding source

The funder contributed to defining the scope of the review but otherwise had no role in study design and data collection. Data were interpreted and the report drafted and submitted without funder input, but according to contractual agreement, the funder provided review at the time of final publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

	Studies and participants	Relative effect (95% CI)	Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission		Difference (95% CI)	Certainty*	What happens (standardised GRADE terminology)[29]
			Comparison group	Intervention group			
Physical distance ≥1 m *vs* <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736)	aOR 0·18 (0·09 to 0·38); unadjusted RR 0·30 (95% CI 0·20 to 0·44)	Shorter distance, 12·8%	Further distance, 2·6% (1·3 to 5·3)	−10·2% (−11·5 to −7·5)	Moderate†	A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2·02 times
Face mask *vs* no face mask	Ten adjusted studies (n=2647); 29 unadjusted studies (n=10 170)	aOR 0·15 (0·07 to 0·34); unadjusted RR 0·34 (95% CI 0·26 to 0·45)	No face mask, 17·4%	Face mask, 3·1% (1·5 to 6·7)	−14·3% (−15·9 to −10·7)	Low‡	Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§
Eye protection (faceshield, goggles) *vs* no eye protection	13 unadjusted studies (n=3713)	Unadjusted RR 0·34 (0·22 to 0·52)¶	No eye protection, 16·0%	Eye protection, 5·5% (3·6 to 8·5)	−10·6% (−12·5 to −7·7)	Low‖	Eye protection might result in a large reduction in virus infection

Table based on GRADE approach.[26–29] Population comprised people possibly exposed to individuals infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. Setting was any health-care or non-health-care setting. Outcomes were infection (laboratory-confirmed or probable) and contextual factors. Risk (95% CI) in intervention group is based on assumed risk in comparison group and relative effect (95% CI) of the intervention. All studies were non-randomised and evaluated using the Newcastle-Ottawa Scale; some studies had a higher risk of bias than did others but no important difference was noted in sensitivity analyses excluding studies at higher risk of bias; we did not further rate down for risk of bias. Although there was a high I^2 value (which can be exaggerated in non-randomised studies)[21] and no overlapping CIs, point estimates generally exceeded the thresholds for large effects and we did not rate down for inconsistency. We did not rate down for indirectness for the association between distance and infection because SARS-CoV-2, SARS-CoV, and MERS-CoV all belong to the same family and have each caused epidemics with sufficient similarity; there was also no convincing statistical evidence of effect-modification across viruses; some studies also used bundled interventions but the studies include only those that provide adjusted estimates. aOR=adjusted odds ratio. RR=relative risk. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. *GRADE category of evidence; high certainty (we are very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (we are moderately confident in the effect estimate; the true effect is probably close to the estimate, but it is possibly substantially different); low certainty (our confidence in the effect estimate is limited; the true effect could be substantially different from the estimate of the effect); very low certainty (we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect). †The effect is very large considering the thresholds set by GRADE, particularly at plausible levels of baseline risk, which also mitigated concerns about risk of bias; data also suggest a dose–response gradient, with associations increasing from smaller distances to 2 m and beyond, by meta-regression; we did not rate up for this domain alone but it further supports the decision to rate up in combination with the large effects. ‡The effect was very large, and the certainty of evidence could be rated up, but we made a conservative decision not to because of some inconsistency and risk of bias; hence, although the effect is qualitatively highly certain, the precise quantitative effect is low certainty. §In a subgroup analysis comparing N95 respirators with surgical or similar masks (eg, 12–16-layer cotton), the association was more pronounced in the N95 group (aOR 0·04, 95% CI 0·004–0·30) compared with other masks (0·33, 0·17–0·61; $p_{interaction}$=0·090); there was also support for effect-modification by formal analysis of subgroup credibility. ¶Two studies[54,75] provided adjusted estimates with n=295 in the eye protection group and n=406 in the group not wearing eye protection; results were similar to the unadjusted estimate (aOR 0·22, 95% CI 0·12–0·39). ‖The effect is large considering the thresholds set by GRADE assuming that ORs translate into similar magnitudes of RR estimates; this mitigates concerns about risk of bias, but we conservatively decided not to rate up for large or very large effects.

Table 2: **GRADE summary of findings**

Results

We identified 172 studies for our systematic review from 16 countries across six continents (figure 1; appendix pp 6–14, 41–47). Studies were all observational in nature; no randomised trials were identified of any interventions that directly addressed the included study populations. Of the 172 studies, 66 focused on how far a virus can travel by comparing the association of different distances on virus transmission to people (appendix pp 42–44). Of these 66 studies, five were mechanistic, assessing viral RNA, virions, or both cultured from the environment of an infected patient (appendix p 45).

44 studies were comparative[34–77] and fulfilled criteria for our meta-analysis (n=25 697; figure 1; table 1). We used these studies rather than case series and qualitative studies (appendix pp 41–47) to inform estimates of effect. 30 studies[34,37,41–45,47–51,53–56,58–61,64–70,72,74,75] focused on the association between use of various types of face masks and respirators by health-care workers, patients, or both with virus transmission. 13 studies[34,37–39,47,49,51,54,58,60,61,65,75] addressed the association of eye protection with virus transmission.

Some direct evidence was available for COVID-19 (64 studies, of which seven were comparative in design),[36,37,40,41,44,52,70] but most studies reported on SARS (n=55) or MERS (n=25; appendix pp 6–12). Of the 44 comparative studies, 40 included WHO-defined confirmed cases, one included both confirmed and probable cases, and the remaining three studies included probable cases. There was no effect-modification by case-definition (distance $p_{interaction}$=0·41; mask $p_{interaction}$=0·46; all cases for eye protection were confirmed). Most studies reported on bundled interventions, including different components of PPE and distancing, which was usually addressed by statistical adjustment. The included studies all occurred during recurrent or novel outbreak settings of COVID-19, SARS, or MERS.

Risk of bias was generally low-to-moderate after considering the observational designs (table 1), but both within studies and across studies the overall findings were similar between adjusted and unadjusted estimates. We did not detect strong evidence of publication bias in the body of evidence for any intervention (appendix pp 15–18). As we did not use case series data to inform estimates of effect of each intervention, we did not systematically rate risk of bias of these data. Therefore, we report further only those studies with comparative data.

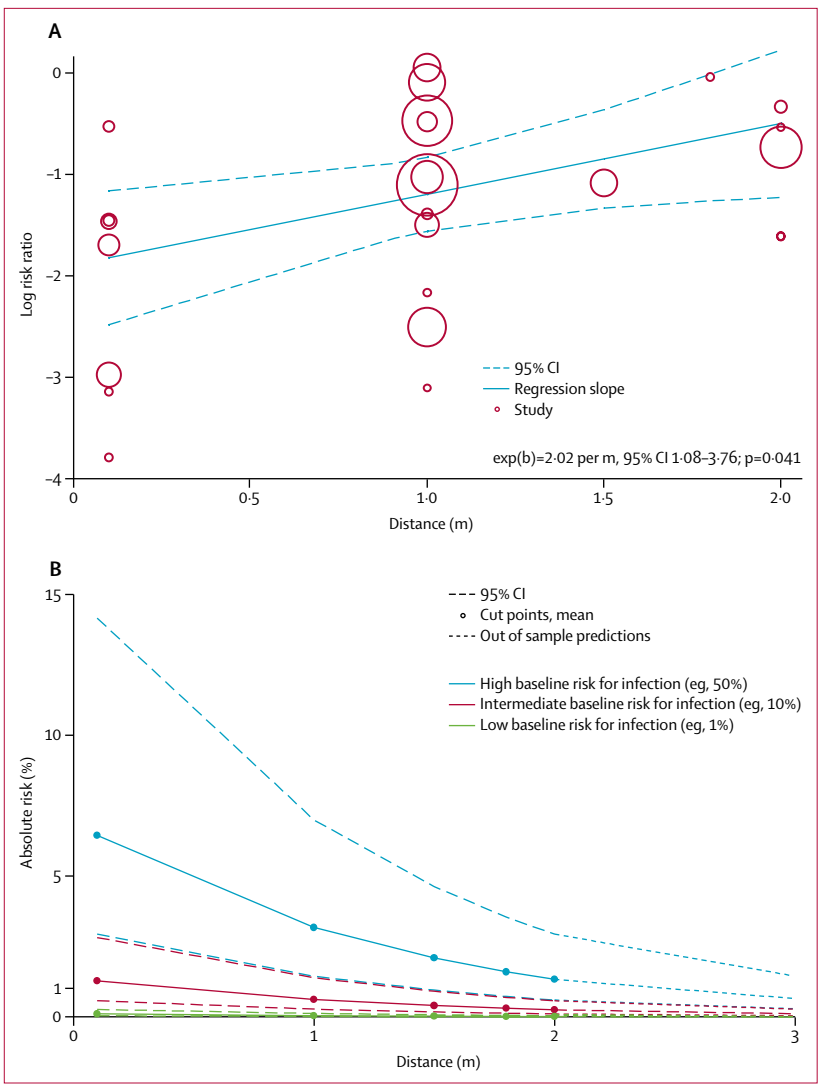

Figure 3: **Change in relative risk with increasing distance and absolute risk with increasing distance**
Meta-regression of change in relative risk with increasing distance from an infected individual (A). Absolute risk of transmission from an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV with varying baseline risk and increasing distance (B). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus.

Across 29 unadjusted and nine adjusted studies,[35–37,39,40,43,44,46,47,50–54,56,57,59–66,68,69,71,73,76] a strong association was found of proximity of the exposed individual with the risk of infection (unadjusted n=10 736, RR 0·30, 95% CI 0·20 to 0·44; adjusted n=7782, aOR 0·18, 95% CI 0·09 to 0·38; absolute risk [AR] 12·8% with shorter distance *vs* 2·6% with further distance, risk difference [RD] –10·2%, 95% CI –11·5 to –7·5; moderate certainty; figure 2; table 2; appendix p 16). Although there were six studies on COVID-19, the association was seen irrespective of causative virus ($p_{interaction}$=0·49), health-care setting versus non-health-care setting ($p_{interaction}$=0·14), and by type of face mask ($p_{interaction}$=0·95; appendix pp 17, 19). However, different studies used different distances for the intervention. By meta-regression, the strength of association was larger with increasing distance (2·02 change in RR per m, 95% CI 1·08 to 3·76; $p_{interaction}$=0·041; moderate credibility subgroup effect; figure 3A; table 2). AR values with increasing distance given different degrees of baseline risk are shown in figure 3B, with potential values at 3 m also shown.

Across 29 unadjusted studies and ten adjusted studies,[34,37,41–45,47–51,53–56,58–61,64–70,72,74,75] the use of both N95 or similar respirators or face masks (eg, disposable surgical masks or similar reusable 12–16-layer cotton masks) by those exposed to infected individuals was associated with a large reduction in risk of infection (unadjusted n=10 170, RR 0·34, 95% CI 0·26 to 0·45; adjusted studies n=2647, aOR 0·15, 95% CI 0·07 to 0·34; AR 3·1% with face mask *vs* 17·4% with no face mask, RD –14·3%, 95% CI –15·9 to –10·7; low certainty; figure 4; table 2; appendix pp 16, 18) with stronger associations in health-care settings (RR 0·30, 95% CI 0·22 to 0·41) compared with non-health-care settings (RR 0·56, 95% CI 0·40 to 0·79; $p_{interaction}$=0·049; low-to-moderate credibility for subgroup effect; figure 4; appendix p 19). When differential N95 or similar respirator use, which was more frequent in health-care settings than in non-health-care settings, was adjusted for the possibility that face masks were less effective in non-health-care settings, the subgroup effect was slightly less credible ($p_{interaction}$=0·11, adjusted for differential respirator use; figure 4). Indeed, the association with protection from infection was more pronounced with N95 or similar respirators (aOR 0·04, 95% CI 0·004 to 0·30) compared with other masks (aOR 0·33, 95% CI 0·17 to 0·61; $p_{interaction}$=0·090; moderate credibility subgroup effect; figure 5). The interaction was also seen when additionally adjusting for three studies that clearly reported aerosol-generating procedures ($p_{interaction}$=0·048; figure 5). Supportive evidence for this interaction was also seen in within-study comparisons (eg, N95 had a stronger protective association compared with surgical masks or 12–16-layer cotton masks); both N95 and surgical masks also had a stronger association with protection versus single-layer masks.[38,39,51,53,54,61,66,67,75]

We did a sensitivity analysis to test the robustness of our findings and to integrate all available information on face mask treatment effects for protection from COVID-19. We reconsidered our findings using random-effects Bayesian meta-analysis. Although non-informative priors showed similar results to frequentist approaches (aOR 0·16, 95% CrI 0·04–0·40), even using informative priors from the most recent meta-analysis on the effectiveness of masks versus no masks to prevent influenza-like illness (RR 0·93, 95% CI 0·83–1·05)[31] yielded a significant association with protection from COVID-19 (aOR 0·40, 95% CrI 0·16–0·97; posterior probability for RR <1, 98%). Minimally informing (25% influence with or without four-fold smaller mean effect size) the most recent and rigorous meta-analysis of the effectiveness of N95

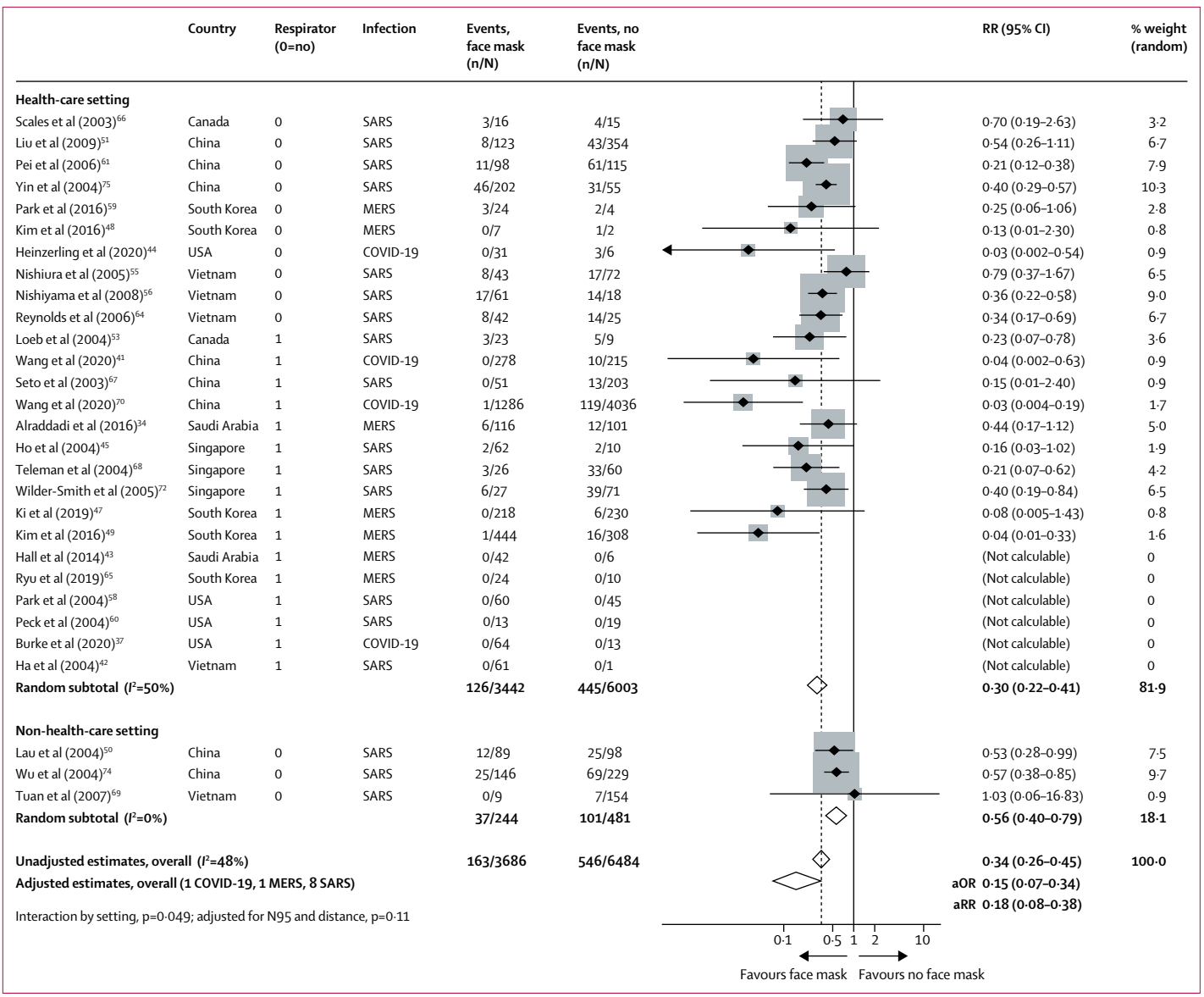

Figure 4: **Forest plot showing unadjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

respirators versus medical masks in randomised trials (OR 0·76, 95% CI 0·54–1·06)[13] with the effect-modification seen in this meta-analysis on COVID-19 (ratio of aORs 0·14, 95% CI 0·02–1·05) continued to support a stronger association of protection from COVID-19, SARS, or MERS with N95 or similar respirators versus other face masks (posterior probability for RR <1, 100% and 95%, respectively).

In 13 unadjusted studies and two adjusted studies,[34,37-39,47,49,51,54,58,60,61,65,75] eye protection was associated with lower risk of infection (unadjusted n=3713, RR 0·34, 95% CI 0·22 to 0·52; AR 5·5% with eye protection *vs* 16·0% with no eye protection, RD –10·6%, 95% CI –12·5 to –7·7; adjusted n=701, aOR 0·22, 95% CI 0·12 to 0·39; low certainty; figure 6; table 2; appendix pp 16–17).

Across 24 studies in health-care and non-health-care settings during the current pandemic of COVID-19, previous epidemics of SARS and MERS, or in general use, looking at contextual factors to consider in recommendations, most stakeholders found physical distancing and use of face masks and eye protection acceptable, feasible, and reassuring (appendix pp 20–22). However, challenges included frequent discomfort, high resource use linked with potentially decreased equity, less clear communication, and perceived reduced empathy of care providers by those they were caring for.

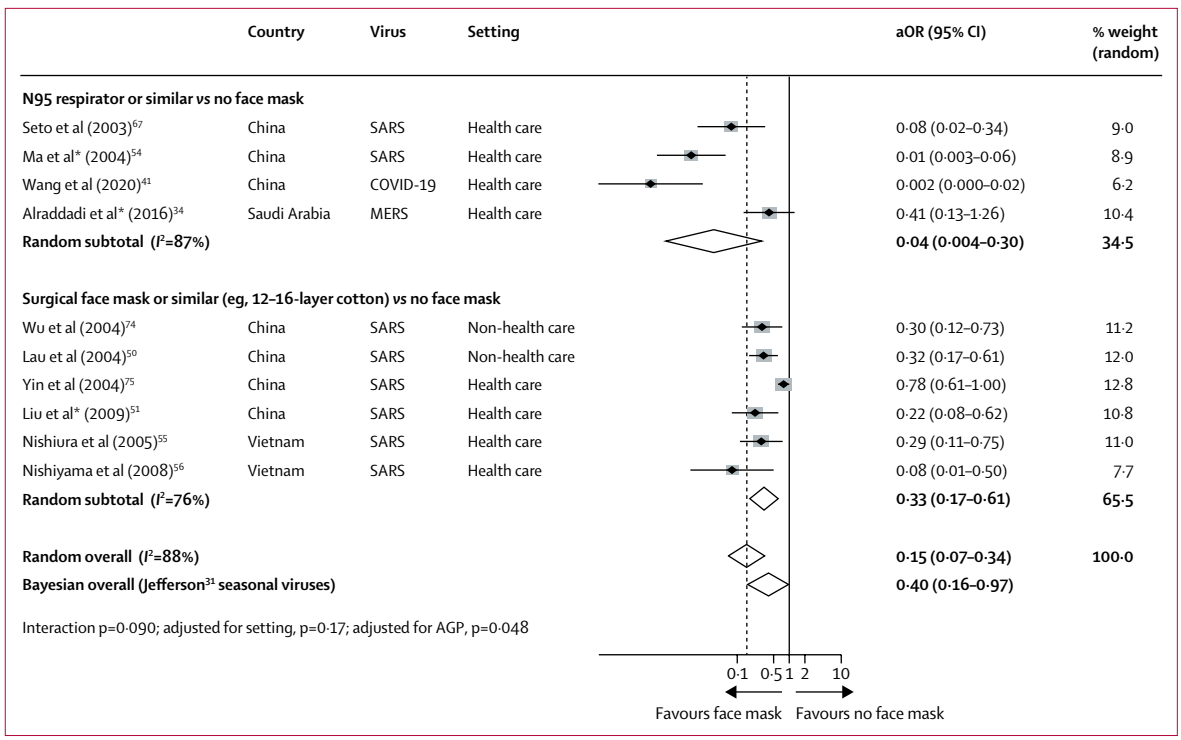

Figure 5: **Forest plot showing adjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. AGP=aerosol-generating procedures. *Studies clearly reporting AGP.

Discussion

The findings of this systematic review of 172 studies (44 comparative studies; n=25 697 patients) on COVID-19, SARS, and MERS provide the best available evidence that current policies of at least 1 m physical distancing are associated with a large reduction in infection, and distances of 2 m might be more effective. These data also suggest that wearing face masks protects people (both health-care workers and the general public) against infection by these coronaviruses, and that eye protection could confer additional benefit. However, none of these interventions afforded complete protection from infection, and their optimum role might need risk assessment and several contextual considerations. No randomised trials were identified for these interventions in COVID-19, SARS, or MERS.

Previous reviews are limited in that they either have not provided any evidence from COVID-19 or did not use direct evidence from other related emerging epidemic betacoronaviruses (eg, SARS and MERS) to inform the effects of interventions to curtail the current COVID-19 pandemic.[13,19,31,78] Previous data from randomised trials are mainly for common respiratory viruses such as seasonal influenza, with a systematic review concluding low certainty of evidence for extrapolating these findings to COVID-19.[13] Further, previous syntheses of available randomised controlled trials have not accounted for cluster effects in analyses, leading to substantial imprecision in treatment effect estimates. In between-study and within-study comparisons, we noted a larger effect of N95 or similar respirators compared with other masks. This finding is inconsistent with conclusions of a review of four randomised trials,[13] in which low certainty of evidence for no larger effect was suggested. However, in that review, the CIs were wide so a meaningful protective effect could not be excluded. We harmonised these findings with Bayesian approaches, using indirect data from randomised trials to inform posterior estimates. Despite this step, our findings continued to support the ideas not only that masks in general are associated with a large reduction in risk of infection from SARS-CoV-2, SARS-CoV, and MERS-CoV but also that N95 or similar respirators might be associated with a larger degree of protection from viral infection than disposable medical masks or reusable multilayer (12–16-layer) cotton masks. Nevertheless, in view of the limitations of these data, we did not rate the certainty of effect as high.[21] Our findings accord with those of a cluster randomised trial showing a potential benefit of continuous N95 respirator use over medical masks against seasonal viral infections.[79] Further high-quality research, including randomised trials of the optimum physical distance and the effectiveness of different types of masks in the general population and for health-care workers' protection, is urgently needed. Two trials are registered to better inform the optimum use of face masks for COVID-19 (NCT04296643 [n=576] and

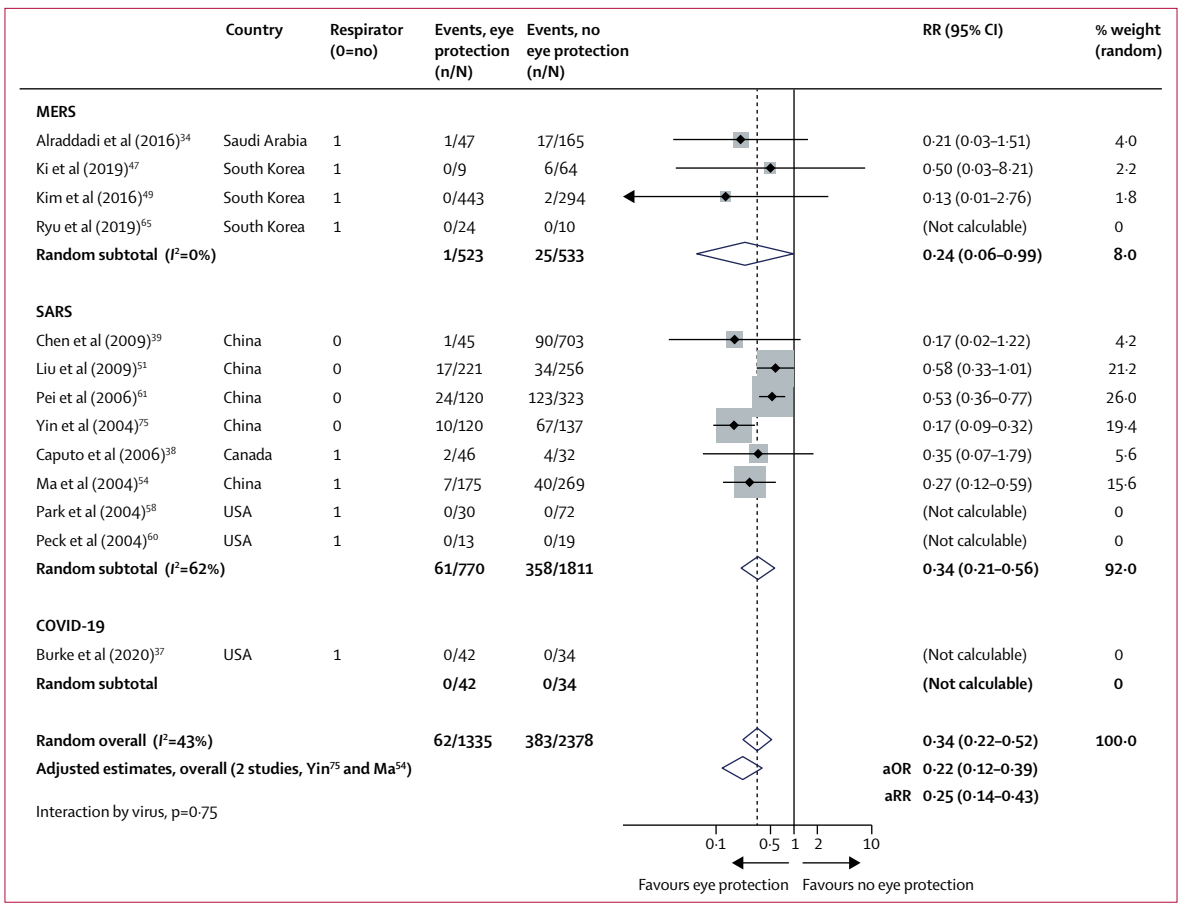

Figure 6: **Forest plot showing the association of eye protection with risk of COVID-19, SARS, or MERS transmission**
Forest plot shows unadjusted estimates. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

NCT04337541 [n=6000]). Until such data are available, our findings represent the current best estimates to inform face mask use to reduce infection from COVID-19. We recognise that there are strong, perhaps opposing, sentiments about policy making during outbreaks. In one viewpoint, the 2007 SARS Commission report stated:

> "…recognize, as an aspect of health worker safety, the precautionary principle that reasonable action to reduce risk, such as the use of a fitted N95 respirator, need not await scientific certainty".[80]

> "…if we do not learn from SARS and we do not make the government fix the problems that remain, we will pay a terrible price in the next pandemic".[81]

A counter viewpoint is that the scientific uncertainty and contextual considerations require a more nuanced approach. Although challenging, policy makers must carefully consider these two viewpoints along with our findings.

We found evidence of moderate certainty that current policies of at least 1 m physical distancing are probably associated with a large reduction in infection, and that distances of 2 m might be more effective, as implemented in some countries. We also provide estimates for 3 m. The main benefit of physical distancing measures is to prevent onward transmission and, thereby, reduce the adverse outcomes of SARS-CoV-2 infection. Hence, the results of our current review support the implementation of a policy of physical distancing of at least 1 m and, if feasible, 2 m or more. Our findings also provide robust estimates to inform models and contact tracing used to plan and strategise for pandemic response efforts at multiple levels.

The use of face masks was protective for both health-care workers and people in the community exposed to infection, with both the frequentist and Bayesian analyses lending support to face mask use irrespective of setting. Our unadjusted analyses might, at first impression, suggest use of face masks in the community setting to be less effective than in the health-care setting, but after accounting for differential N95 respirator use between health-care and non-health-care settings, we did not detect any striking differences in effectiveness of

face mask use between settings. The credibility of effect-modification across settings was, therefore, low. Wearing face masks was also acceptable and feasible. Policy makers at all levels should, therefore, strive to address equity implications for groups with currently limited access to face masks and eye protection. One concern is that face mask use en masse could divert supplies from people at highest risk for infection.[10] Health-care workers are increasingly being asked to ration and reuse PPE,[82,83] leading to calls for government-directed repurposing of manufacturing capacity to overcome mask shortages[84] and finding solutions for mask use by the general public.[84] In this respect, some of the masks studied in our review were reusable 12–16-layer cotton or gauze masks.[51,54,61,75] At the moment, although there is consensus that SARS-CoV-2 mainly spreads through large droplets and contact, debate continues about the role of aerosol,[2–8,85,86] but our meta-analysis provides evidence (albeit of low certainty) that respirators might have a stronger protective effect than surgical masks. Biological plausibility would be supported by data for aerosolised SARS-CoV-2[5–8] and preclinical data showing seasonal coronavirus RNA detection in fine aerosols during tidal breathing,[87] albeit, RNA detection does not necessarily imply replication and infection-competent virus. Nevertheless, our findings suggest it plausible that even in the absence of aerosolisation, respirators might be simply more effective than masks at preventing infection. At present, there is no data to support viable virus in the air outside of aerosol generating procedures from available hospital studies. Other factors such as super-spreading events, the subtype of health-care setting (eg, emergency room, intensive care unit, medical wards, dialysis centre), if aerosolising procedures are done, and environmental factors such as ventilation, might all affect the degree of protection afforded by personal protection strategies, but we did not identify robust data to inform these aspects.

Strengths of our review include adherence to full systematic review methods, which included artificial intelligence-supported dual screening of titles and abstracts, full-text evaluation, assessment of risk of bias, and no limitation by language. We included patients infected with SARS-CoV-2, SARS-CoV, or MERS-CoV and searched relevant data up to May 3, 2020. We followed the GRADE approach[16] to rate the certainty of evidence. Finally, we identified and appraise a large body of published work from China, from which much evidence emerged before the pandemic spread to other global regions.

The primary limitation of our study is that all studies were non-randomised, not always fully adjusted, and might suffer from recall and measurement bias (eg, direct contact in some studies might not be measuring near distance). However, unadjusted, adjusted, frequentist, and Bayesian meta-analyses all supported the main findings, and large or very large effects were recorded. Nevertheless, we are cautious not to be overly certain in the precise quantitative estimates of effects, although the qualitative effect and direction is probably of high certainty. Many studies did not provide information on precise distances, and direct contact was equated to 0 m distance; none of the eligible studies quantitatively evaluated whether distances of more than 2 m were more effective, although our meta-regression provides potential predictions for estimates of risk. Few studies assessed the effect of interventions in non-health-care settings, and they primarily evaluated mask use in households or contacts of cases, although beneficial associations were seen across settings. Furthermore, most evidence was from studies that reported on SARS and MERS (n=6674 patients with COVID-19, of 25 697 total), but data from these previous epidemics provide the most direct information for COVID-19 currently. We did not specifically assess the effect of duration of exposure on risk for transmission, although whether or not this variable was judged a risk factor considerably varied across studies, from any duration to a minimum of 1 h. Because of inconsistent reporting, information is limited about whether aerosol-generating procedures were in place in studies using respirators, and whether masks worn by infected patients might alter the effectiveness of each intervention, although the stronger association with N95 or similar respirators over other masks persisted when adjusting for studies reporting aerosol-generating medical procedures. These factors might account for some of the residual statistical heterogeneity seen for some outcomes, albeit I^2 is commonly inflated in meta-analyses of observational data,[21,22] and nevertheless the effects seen were large and probably clinically important in all adjusted studies.

Our comprehensive systematic review provides the best available information on three simple and common interventions to combat the immediate threat of COVID-19, while new evidence on pharmacological treatments, vaccines, and other personal protective strategies is being generated. Physical distancing of at least 1 m is strongly associated with protection, but distances of up to 2 m might be more effective. Although direct evidence is limited, the optimum use of face masks, in particular N95 or similar respirators in health-care settings and 12–16-layer cotton or surgical masks in the community, could depend on contextual factors; action is needed at all levels to address the paucity of better evidence. Eye protection might provide additional benefits. Globally collaborative and well conducted studies, including randomised trials, of different personal protective strategies are needed regardless of the challenges, but this systematic appraisal of currently best available evidence could be considered to inform interim guidance.

Contributors

DKC, EAA, SD, KS, SY, and HJS designed the study. SY, SD, KS, and HJS coordinated the study. SY and LH designed and ran the literature search. All authors acquired data, screened records, extracted data, and assessed risk of bias. DKC did statistical analyses. DKC and HJS wrote the report. All authors provided critical conceptual input, analysed and interpreted data, and critically revised the report.

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Declaration of interests
ML is an investigator of an ongoing clinical trial on medical masks versus N95 respirators for COVID-19 (NCT04296643). All other authors declare no competing interests.

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Two metres or one: what is the evidence for physical distancing in covid-19?

Rigid safe distancing rules are an oversimplification based on outdated science and experiences of past viruses, argue **Nicholas R Jones and colleagues**

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Physical distancing is an important part of measures to control covid-19, but exactly how far away and for how long contact is safe in different contexts is unclear. Rules that stipulate a single specific physical distance (1 or 2 metres) between individuals to reduce transmission of SARS-CoV-2, the virus causing covid-19, are based on an outdated, dichotomous notion of respiratory droplet size. This overlooks the physics of respiratory emissions, where droplets of all sizes are trapped and moved by the exhaled moist and hot turbulent gas cloud that keeps them concentrated as it carries them over metres in a few seconds.[1 2] After the cloud slows sufficiently, ventilation, specific patterns of airflow, and type of activity become important. Viral load of the emitter, duration of exposure, and susceptibility of an individual to infection are also important.

Instead of single, fixed physical distance rules, we propose graded recommendations that better reflect the multiple factors that combine to determine risk. This would provide greater protection in the highest risk settings but also greater freedom in lower risk settings, potentially enabling a return towards normality in some aspects of social and economic life.

Origins of 2 metre rule

The study of how droplets are emitted during speech or more forcefully when coughing or sneezing began in the 19th century, with scientists typically collecting samples on glass or agar plates.[3] In 1897, for example, Flugge proposed a 1-2 m safe distance based on the distance over which sampled visible droplets contained pathogens.[4] In the 1940s, visual documentation of these emissions became possible with close-up still imaging of sneezing, coughing, or talking (fig 1).[5] A study in 1948 of haemolytic streptococci spread found 65% of the 48 participants produced large droplets only, fewer than 10% of which travelled as far as 5½ feet (1.7 m).[6] However, in 10% of participants, haemolytic streptococci were collected 9½ feet (2.9 m) away. Despite limitations in the accuracy of these early study designs, especially for longer ranges, the observation of large droplets falling close to a host reinforced and further entrenched the assumed scientific basis of the 1-2 m distancing rule.[2]

Fig 1 | Short range still imaging of stages of sneezing, revealing the liquid droplets from the 1942 Jennison experiment.[5] Reproduced with permission

Yet eight of the 10 studies in a recent systematic review showed horizontal projection of respiratory droplets beyond 2 m for particles up to 60 µm.[7] In one study, droplet spread was detected over 6-8 m (fig 2).[2 8] These results suggest that SARS-CoV-2 could spread beyond 1-2 m in a concentrated packet through coughs or sneezes.[2] In recent related viral outbreaks, such as SARS-CoV-1, MERS-CoV, and Avian flu, multiple studies reported suspected spread beyond 2 m.[9 10]

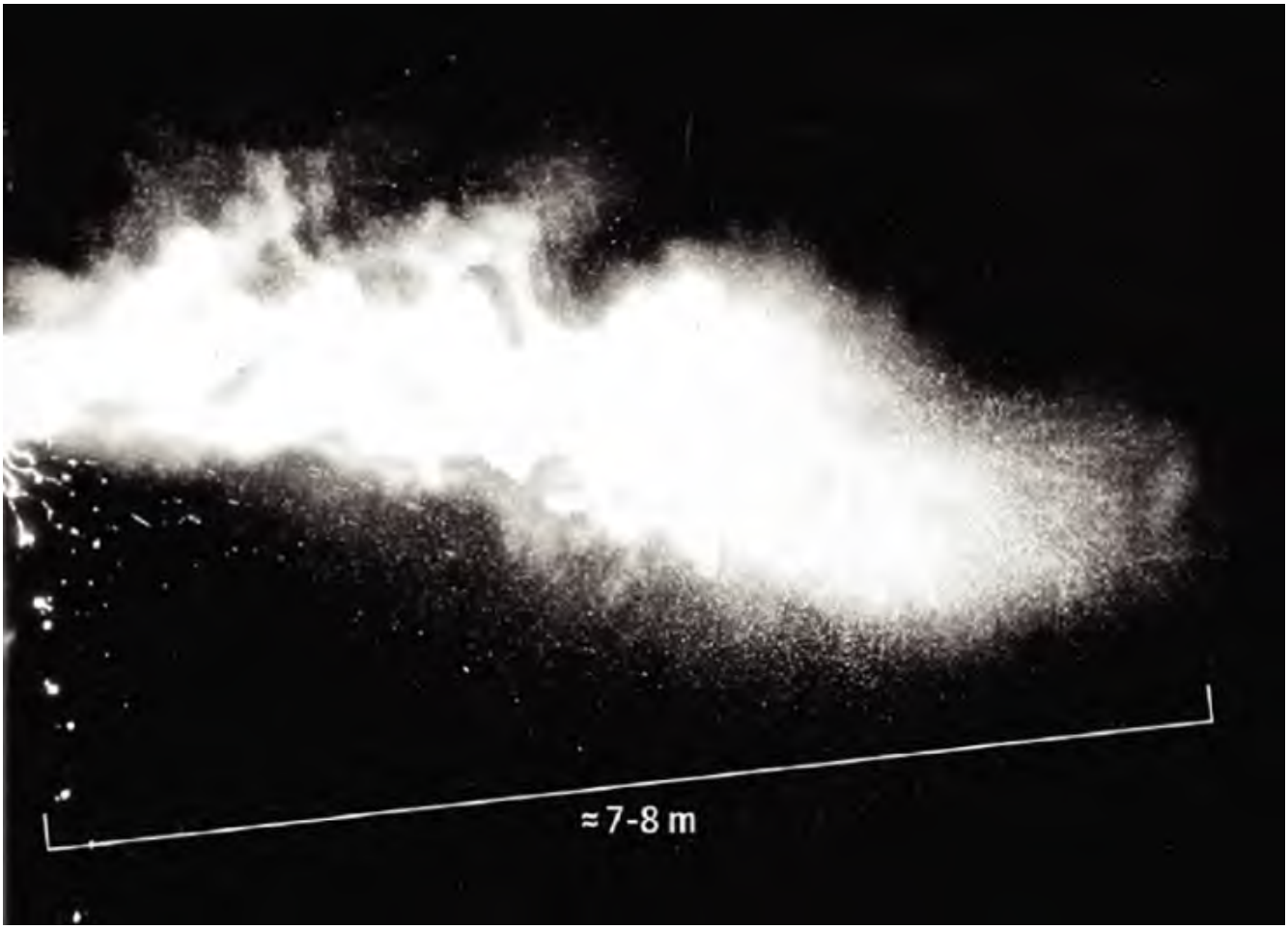

Fig 2 | Long range video imaging over 8 m of the multiphase turbulent cloud (gas cloud containing liquid droplets of all sizes) from natural human violent emission such as a sneeze, revealing a range of the cloud, and its droplet concentrated payload, of up to 7-8 m. Reproduced with permission from Bourouiba[2]

Droplet size, droplet spread

The 1-2 m rule is based on a longstanding framework which dichotomises respiratory droplets into two sizes, large and small. The size of a droplet is thought to determine how far it will travel from the infected person. According to studies by Wells, emitted large droplets fall through the air more quickly than they evaporate and land within a 1-2 metre range.[11] Small droplets (later called aerosols or airborne droplets), typically invisible to the naked eye, evaporate more quickly than they fall. Without airflow, they cannot move far, remaining in the exhaler's vicinity. With airflow they can spread along greater distances.

While conceptually useful up to a point, this dichotomy framework overlooks contemporary science about respiratory exhalations.[12] Droplets exist across a continuum of sizes. Contextual factors such as exhaled air and ambient airflow are extremely important in determining how far droplets of all sizes travel. Without exhaled airflow, the largest droplets would travel furthest (1-2 m), while the small ones would encounter high resistance (drag) and stay close to the source. When accounting for the exhaled airflow, clouds of small droplets can travel beyond 2 m in the air, and even large droplets have enhanced range.[1 2]

Airborne particle spread of SARS-CoV-2

Diseases that can be transmitted by airborne particles, such as measles and varicella, can travel much further, and in concentrated clouds, than those transmitted by large droplets, which drop from clouds more quickly. They can therefore expose others rapidly and at greater distance[2 13] and may need different public health measures, including extended physical distancing. Laboratory studies also suggest SARS-CoV-1, SARS-CoV-2, and MERS-CoV viral particles are stable in airborne samples, with SARS-CoV-2 persistent for longest (up to 16 hours).[14 15]

In a literature search for studies using air sampling techniques to detect viral particles surrounding covid-19 patients, we found nine studies in hospital and two in community settings. Seven of the hospital studies reported at least one airborne sample tested positive for SARS-CoV-2, though the proportion of positive samples across studies ranged between 2% and 64%.[16-22] Only two reported positive results in relation to distance from an infected patient (one at 2 m[18] and another at ≥4 m in the corridor[17]). Of the two hospital studies that did not find SARS-CoV-2 particles in air samples,[23 24] one collected positive swab samples from ventilation units in the patient's room, which is consistent with airborne droplet spread.[23]

Neither community study reported positive air samples, although one collected specimens up to 17 days after covid-19 carriers had left the room[25] and the other did not report time of sampling since

cleaning or sampling distance from the infected person.[26] These negative studies thus fall substantially short of proving that airborne spread does not occur.

Only two of the airborne sampling studies directly measured whether SARS-CoV-2 in the samples remained infectious, rather than just analysing for the presence of viral RNA.[18 21] No viable virus was found in either, though one found signs of viral ability to replicate.[18] Of note, no study found viable virus on surface swabs.

These studies were small, observational, and heterogeneous in terms of setting, participants, sample collection, and handling methods. They were prone to recall bias (few people can accurately recall how close they came to others when asked to remember some time later). Overall, these studies seem to support the possibility of airborne spread of SARS-CoV-2, but they do not confirm that there is a risk of disease transmission.

Force of emission, ventilation, exposure time

Breathing out, singing, coughing, and sneezing generate warm, moist, high momentum gas clouds of exhaled air containing respiratory droplets. This moves the droplets faster than typical background air ventilation flows, keeps them concentrated, and can extend their range up to 7-8 m within a few seconds.[1 2 8]

These findings from fluid dynamic studies help explain why at one choir practice in the US, a symptomatic person infected at least 32 other singers, with 20 further probable cases, despite physical distancing.[27] Other indoor case clusters have been reported within fitness gyms, boxing matches, call centres, and churches, where people might sing, pant, or talk loudly.[28-30] Interestingly, there have been few reports of outbreaks on aeroplanes,[31] which may reflect current low volume of passengers, lack of contact tracing, or relatively low risk because speaking is limited. Although publication bias is likely (events linked to outbreaks are more likely to be reported than events where no outbreak occurred), well documented stories of outbreaks demand a scientific explanation.

The heavy panting from jogging and other sports produces violent exhalations with higher momentum than tidal breathing, closer to coughs in some instances. This increases the distance reached by the droplets trapped within the exhaled cloud and supports additional distancing during vigorous exercise.[2] However, respiratory droplets tend to be more quickly diluted in well aerated outdoor settings, reducing transmission risk (a preprint from Japan reports an 18.7-fold higher risk of transmission in indoor environments than outdoors).[28]

Specific airflow patterns, and not just average ventilation and air changes, within buildings are also important in determining risk of exposure and transmission. A case report from an outbreak at a restaurant in China described 10 people within three families infected over one hour, at distances of up to 4.6 m and without direct physical contact. The pattern of transmission was consistent with the transient indoor localised ventilation airflow pattern.[32]

Few studies have examined how airflow patterns influence viral transmission; most studies report (if anything) only average indoor ventilation rates. Neglecting variation in localised air flow within a space oversimplifies and underestimates risk modelling. In homogeneous flow, patterns are known to emerge in occupied indoor spaces that depend on air conditioning, ventilation system or location, occupancy of the space, air recirculation, and filtration.

Though it is widely assumed that duration of exposure to a person with covid-19 influences transmission risk (studies of contact tracing, for example, consider thresholds of 5-15 minutes beyond which risk increases[33 34]), we are not aware of studies that quantified this variable.

Distance and transmission risk

The UK's Scientific Advisory Group for Emergencies (SAGE) estimates that the risk of SARS-CoV-2 transmission at 1 m could be 2-10 times higher than at 2 m.[35] A systematic review commissioned by the World Health Organization attempted to analyse physical distancing measures in relation to coronavirus transmission.[36] Physical distancing of <1 m was reported to result in a transmission risk of 12.8%, compared with 2.6% at distances ≥1 m, supporting physical distancing rules of 1 m or more. The review's limitations should be noted. Not all distances were explicit in the original studies; some were estimated by the review authors. Different distances were used to categorise social contact in different studies (1.8 m was considered close in one study but distant in another, for example), yet these were pooled within the same analysis. The summary relied heavily on data from the SARS-CoV-1 and MERS outbreaks and only partially accounted for environmental confounders.

More nuanced model

Environmental influences are complex and are likely to be mutually reinforcing. This is shown, for example, in meat packing plants, where outbreaks have been attributed to the combination of high levels of worker contagion, poor ventilation, cramped working conditions, background noise (which leads to shouting), and low compliance with mask wearing.[37] Similar compound risk situations might occur in other crowded, noisy, indoor environments, such as pubs or live music venues.

Physical distancing rules would be most effective if they reflected graded levels of risk. Figure 3 presents a guide to how transmission risk may vary with setting, occupancy level, contact time, and whether face coverings are worn. These estimates apply when everyone is asymptomatic. In the highest risk situations (indoor environments with poor ventilation, high levels of occupancy, prolonged contact time, and no face coverings, such as a crowded bar or night club) physical distancing beyond 2 m and minimising occupancy time should be considered. Less stringent distancing is likely to be adequate in low risk scenarios. People with symptoms (who should in any case be self-isolating) tend to have high viral load and more frequent violent respiratory exhalations.

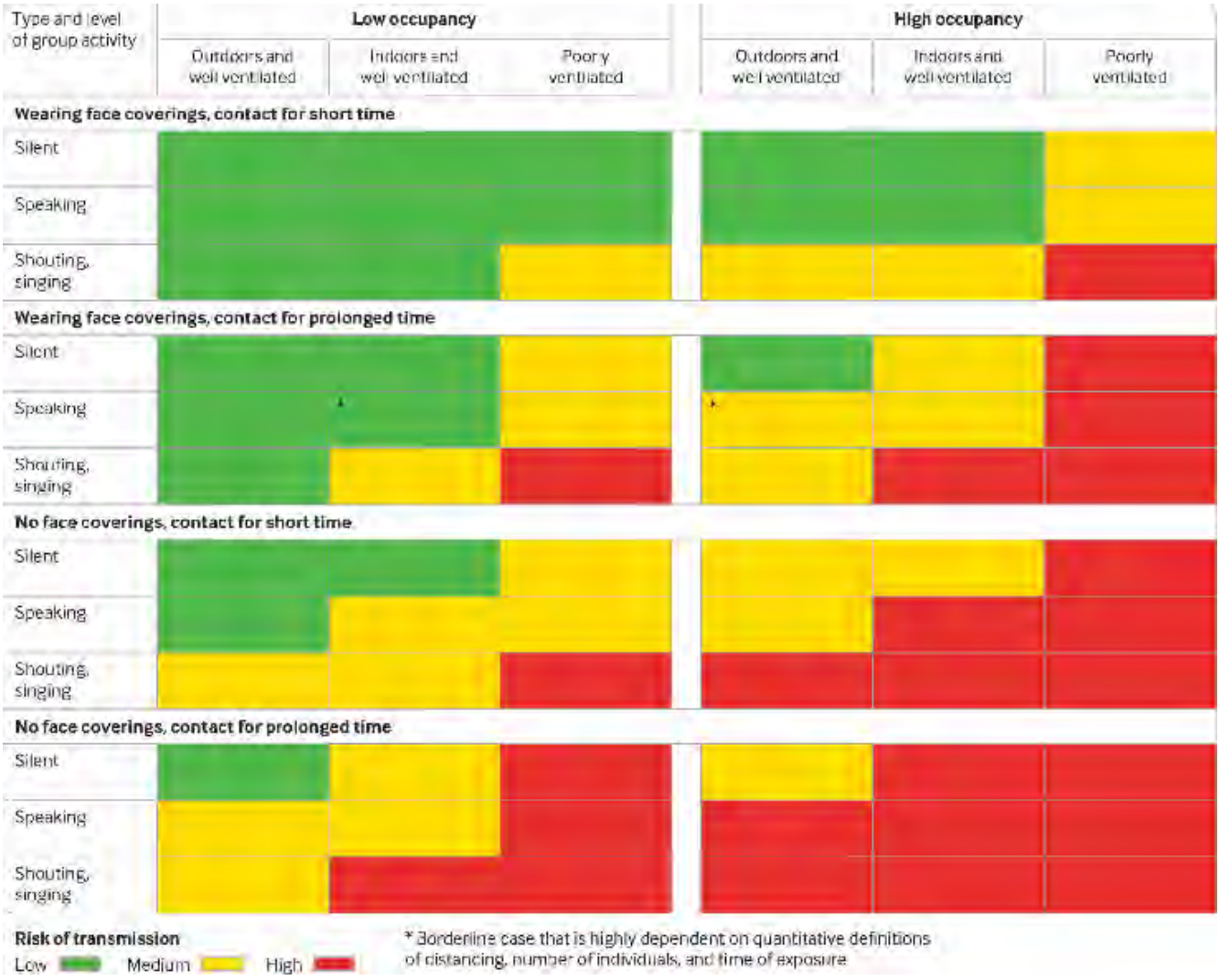

Fig 3 | Risk of SARS-CoV-2 transmission from asymptomatic people in different settings and for different occupation times, venting, and crowding levels (ignoring variation in susceptibility and viral shedding rates). Face covering refers to those for the general population and not high grade respirators. The grades are indicative of qualitative relative risk and do not represent a quantitative measure. Other factors not presented in these tables may also need to be taken into account when considering transmission risk, including viral load of an infected person and people's susceptibility to infection. Coughing or sneezing, even if these are due to irritation or allergies while asymptomatic, would exacerbate risk of exposure across an indoor space, regardless of ventilation

The levels of risk in fig 3 are relative not absolute, especially in relation to thresholds of time and occupancy, and they do not include additional factors such as individuals' susceptibility to infection, shedding level from an infected person, indoor airflow patterns, and where someone is placed in relation to the infected person. Humidity may also be important, but this is yet to be rigorously established.

Further work is needed to extend our guide to develop specific solutions to classes of indoor environments occupied at various usage levels. Urgent research is needed to examine three areas of uncertainty: the cut-off duration of exposures in relation to the indoor condition, occupancy, and level of viral shedding (5-15 minute current ad-hoc rules), which does not seem to be supported by evidence; the detailed study of airflow patterns with respect to the infected source and its competition with average venting; and the patterns and properties of respiratory emissions and droplet infectivity within them during various physical activities.

Physical distancing should be seen as only one part of a wider public health approach to containing the covid-19 pandemic. It needs to be implemented alongside combined strategies of people-air-surface-space management, including hand hygiene, cleaning, occupancy and indoor space and air managements, and appropriate protective equipment, such as masks, for the setting.

Key messages

- Current rules on safe physical distancing are based on outdated science
- Distribution of viral particles is affected by numerous factors, including air flow
- Evidence suggests SARS-CoV-2 may travel more than 2 m through activities such as coughing and shouting
- Rules on distancing should reflect the multiple factors that affect risk, including ventilation, occupancy, and exposure time

Contributors and sources: This article was adapted from a rapid review undertaken as part of the Oxford COVID-19 Evidence Service (https://www.cebm.net/covid-19/what-is-the-evidence-to-support-the-2-metre-social-distancing-rule-to-reduce-covid-19-transmission/); all authors contributed to its development and approved the final manuscript.

Patient and public involvement: Three members of the public provided feedback on the article. They strongly supported the need for an in-depth analysis of physical distancing and thought our summary figure was helpful in presenting factors that influence categories of risk. Specific feedback led to additional discussion points addressing transmission risk in complex settings such as the meat packing industry and with exercise.

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SCHOOLS FOR HEALTH

Risk Reduction Strategies for Reopening Schools

COVID-19

June, 2020

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SCHOOLS FOR HEALTH

Risk Reduction Strategies for Reopening Schools

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DISCLAIMER

This report on Risk Reduction Strategies for Reopening Schools is provided for informational and educational purposes only. It is intended to offer guidance regarding best practices regarding the general operations of buildings in an effort to reduce the risk of disease transmission, specifically novel coronavirus SARS-CoV-2 and the disease it causes, COVID-19. Adherence to any information included in this report will not ensure successful treatment in every situation, and user acknowledges that there is no "zero risk" scenario. User acknowledges that each building and situation are unique and some of the guidance contained in the report will not apply to all buildings or countries outside the United States. Furthermore, the report should not be deemed inclusive of all proper methods nor exclusive of other methods reasonably directed to obtaining the same results. The report is in no way intended to override or supersede guidance from government and health organizations, including, without limitation, the Centers for Disease Control and Prevention, the World Health Organization, the United States Government, and or any States. The information contained herein reflects the available information at the time the report was created. User recognizes that details and information are changing daily, and new information and/or the results of future studies may require revisions to the report (and the general guidance contained therein) to reflect new data. We do not warrant the accuracy or completeness of the guidance in this report and assume no responsibility for any injury or damage to persons or property arising out of or related to any use of the report or for any errors or omissions.

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EXECUTIVE SUMMARY

Schools will eventually need to reopen.

Keeping schools closed comes with massive, long-term individual and societal costs. Many children cannot effectively learn, grow, engage, socialize, be active, eat healthy food, or get support until schools reopen. Parents and caregivers cannot go back to work until children go back to school. Knowing that schools will reopen at some point, we set out to answer this question: what strategies should schools consider to reduce risk of COVID-19 transmission?

Note that a risk reduction strategy is different from a goal of achieving zero cases. There is no such thing as 'zero risk', in anything we do, and certainly not during a pandemic.

However, scientific evidence indicates that risks to students and staff can be kept low if schools adhere to strict control measures and dynamically respond to potential outbreaks.

We recognize there are immense challenges. There is no perfect plan to reopen schools safely, only 'less bad' options. There is no 'one size fits all' strategy that works for every school. Schools have limited budgets and staff. Compliance will be imperfect. Learning will be different. There will be disruption. Schools may need to reclose unexpectedly depending on local conditions. No one knows with certainty what the fall will bring in terms of this pandemic.

Despite these challenges, the enormous individual and societal costs of keeping schools closed compels us, a team focused on Healthy Buildings and exposure and risk science, to present a range of control strategies that should be considered in discussions of school reopenings:

HEALTHY CLASSROOMS: Following safe practices in classrooms

HEALTHY BUILDINGS: Breathing clean air in the school building

HEALTHY POLICIES: Building a culture of health, safety, and shared responsibility

HEALTHY SCHEDULES: Moving between rooms and locations safely

HEALTHY ACTIVITIES: Enjoying modified activities

Schools should adopt and adapt these recommendations to best fit their unique situation, depending on available personnel, resources, finances, school demographics, and building attributes. In addition, schools should frequently revisit their approach as the COVID-19 situation changes over time in each community. Although it is unlikely that any given school will be able to incorporate every recommendation, we want to emphasize that these strategies work *together* as part of a multi-layered plan to reduce exposure and limit transmission of COVID-19 in schools.

HEALTHY BUILDINGS

- Increase outdoor air ventilation
- Filter indoor air
- Supplement with portable air cleaners
- Verify ventilation and filtration performance
- Consider advanced air quality techniques
- Use plexiglass as physical barrier
- Install no-contact infrastructure
- Keep surfaces clean
- Focus on bathroom hygiene

HEALTHY CLASSROOMS

- Wear masks
- Wash hands frequently
- Maximize physical distancing to protect individuals
- Maximize group distancing to slow transmission chains
- Disinfect objects between users

HEALTHY ACTIVITIES

- Provide recess
- Modify physical education
- Reimagine music and theater classes
- Continue sports with enhanced controls
- Add structure to free time

HEALTHY SCHEDULES

- Manage transition times and locations
- Make lunchtime safer
- Rethink transportation
- Modify attendance

HEALTHY POLICIES

- Establish and reinforce a culture of health, safety, and shared responsibility
- Form a COVID-19 response team and plan
- Prioritize staying home when sick
- Promote viral testing and antibody testing
- Establish plans for when there is a case
- Support remote learning options
- De-densify school buildings
- Protect high-risk students and staff

HEALTHY CLASSROOMS

Wear masks

- Have students wear face masks as much as possible, especially when in hallways or bathrooms or in proximity to students from other classes
- Train students and staff on how to wear and care for masks
- Ensure masks meet effectiveness criteria
- Build in time throughout the day where students and staff don't have to wear masks
- Allow teachers to wear transparent face shields when teaching at the front of the room and face masks when working more closely with students

Wash hands frequently

- Wash hands immediately before: leaving home, leaving the classroom, eating, touching shared objects, touching one's face, and leaving school
- Wash hands immediately after: arriving at school, entering classroom, finishing lunch, touching shared objects, using the bathroom, coughing, sneezing, and blowing one's nose, and arriving at home
- Use hand sanitizer when washing hands is not possible

Maximize physical distancing to protect individuals

- Keep at least six feet between individuals, as much as possible, for as long as possible
- Repurpose other large, unused spaces in the school as temporary classrooms (e.g., auditorium)
- Move class outdoors, if possible, and weather permitting
- Replace hugs, handshakes, and high-fives with smiles, waves, and thumbs-ups

Maximize group distancing to slow transmission chains

- Keep class groups as distinct and separate as possible
- Limit students moving between different classrooms
- Avoid large groups and gatherings, both in and outside of school

Disinfect objects between users

- Disinfect any shared supplies between uses
- Provide disposal disinfectant wipes for individuals to use before using shared objects
- Choose lesson plans that limit student contact
- Provide students with their own separate supplies when possible

HEALTHY BUILDINGS

Increase outdoor air ventilation

- Bring in more fresh outdoor air
- Follow the decision-tree for ventilation type and corresponding strategies

Filter indoor air

- Increase the level of the air filter to MERV 13 or higher on recirculated air
- Inspect filters to make sure they are installed and fit correctly
- Check that sufficient airflow can be maintained across the filter
- Maintain and change filters based on manufacturer's recommendation

Supplement with portable air cleaners

- Supplement with air cleaning devices
- Select portable air cleaners with HEPA filters
- Size devices carefully based on the size of the room

Verify ventilation and filtration performance

- Verify through commissioning and testing
- Work with an expert to evaluate building systems, ventilation, filtration, and air cleaning
- Measure carbon dioxide (CO_2) as a proxy for ventilation

Consider advanced air quality techniques

- Attempt to maintain indoor relative humidity between 40-60%
- Consider advanced air cleaning with ultraviolet germicidal irradiation (UGVI)

Use plexiglass as physical barrier

- Install plexiglass shielding in select areas with fixed interactions (e.g., reception desk, cafeteria checkout)
- Use plexiglass shielding in the classroom if needed (e.g., around student desks, around teacher desks, between spaces at shared tables)

Install no-contact infrastructure

- Adjust use of existing infrastructure to make it touchless
- Install touchless technology for dispensers of hand soap, hand sanitizer, and paper towels

Keep surfaces clean

- Frequently clean and disinfect surfaces following directions on product labels
- Provide adequate training and personal protective equipment to protect custodial staff

Focus on bathroom hygiene

- Keep bathroom doors and windows closed and run any exhaust fans at all times
- Install lids on all toilet seats and keep the lids closed, particularly during flushing
- Stagger bathroom use

HEALTHY POLICIES

Establish and reinforce a culture of health, safety, and shared responsibility

- Provide training to teachers, staff, students, and parents/guardians prior to school opening
- Start each day with a morning message to the entire school reinforcing health messaging
- Create and display signs around the school as reminders of rules, roles, and responsibilities
- Hold weekly and monthly all-staff meetings on COVID-19 to evaluate control strategies
- Send out weekly reports and reminders to parents and students of their respective roles
- Reward good behavior

Form a COVID-19 response team and plan

- Have a person or team in charge of implementing and disseminating COVID-19 policies
- Implement contact tracing to notify class groups if they may have been exposed
- Ensure staff are aware of privacy policies regarding disclosure of COVID-19 status
- Increase staff surge capacity if possible by recruiting student teachers, substitute teachers, community volunteers, and/or recent retirees

Prioritize staying home when sick

- Ask students and school staff to stay home when not feeling well
- Request daily self-declaration that people heading into school that day are free of symptoms
- Identify a comfortable room where individuals who become ill can isolate for the rest of the school day

Promote viral testing and antibody testing

- Encourage viral testing any time someone has symptoms, even if mild
- Track testing improvements and incorporate widescale testing into future plans
- Encourage antibody testing to monitor disease progression and plan control strategies
- Provide information on where people can go for testing

Establish plans for when there is a case

- Develop a plan for what to do when a case is identified in the school
- Establish a timetable for when someone with COVID-19, and their close contacts, can return to school
- Regularly check CDC guidance for updates to their protocols and definitions

HEALTHY POLICIES

Support remote learning options

- Provide necessary supplies and support systems to continue remote education for students staying home
- Train staff on how to best facilitate remote learning
- Consider district-wide remote learning by grade, staffed by recent retirees or teachers with pre-existing conditions

De-densify school buildings

- Limit parent and visitor access
- Move parent-teacher conferences online
- Promote work-from-home for administrative duties, where possible
- Hold staff meetings via videoconferencing as much as possible

Protect high-risk students and staff

- Advocate for high-risk students and staff to have access to effective remote learning or work
- Re-assign roles if needed to allow staff members to work while staying safe
- Take extra precautions if high-risk students or staff come to school

HEALTHY SCHEDULES

Manage transition times and locations

- Stagger school arrival and departure times, class transitions, and locker access
- Set up separate entrances and exits for different groups of students when possible
- Use well-marked lines on the floor to encourage physical distancing and indicate direction of travel

Make lunchtime safer

- Use student classrooms or other school locations as temporary lunchrooms to facilitate group distancing
- Stagger lunchtimes in shared lunchrooms and clean and disinfect surfaces between groups
- Maintain physical distance between individuals eating lunch together
- Package school-provided meals in single-serving containers instead of serving food buffet-style
- Reinforce 'no sharing' of food, utensils, drinks

Rethink transportation

- Open all windows on the bus, even a little, and even in bad weather
- Reduce the number of students in each school bus to allow for physical distancing, if possible
- Modify school start times to allow students who use public transit to avoid rush hour
- Encourage walking, biking, or use of personal vehicles

Modify attendance

- Modify attendance policies to facilitate cleaning, reduce class sizes, and/or maintain group and physical distancing
- Allow for flexibility in attendance policies as situations change

HEALTHY ACTIVITIES

Provide recess

- Do not limit children's access to recess, the schoolyard, or fixed play equipment
- Wash or sanitize hands before and after recess or using high-touch equipment
- Increase supervision to limit high-risk behaviors
- Stagger recess times, or, if necessary, separate classes by schoolyard area

Modify physical education

- Hold physical education classes outdoors when possible
- Modify activities to limit the amount of shared equipment
- Choose activities that limit close contact over those with a high degree of personal interaction
- Limit use of locker rooms

Reimagine music and theater classes

- Replace higher-risk music and theater activities with safer alternatives
- Move outdoors
- Increase space between performers

Continue sports with enhanced controls

- Offer every sport if the right controls are in place
- Play outdoors as much as possible
- Limit time spent in close contact and in big groups
- Limit shared equipment, shared spaces, and the number of contacts of the team
- Modify the season schedule and restrict game attendance if feasible
- Analyze each element of practices and games to identify ways to reduce risk
- Wear masks whenever possible

Add structure to free time

- Establish occupancy limits and clear physical distancing guidelines in common spaces like a library or cafeteria
- Encourage students to remain outside when not in class
- Replace unstructured time with supervised study halls, if feasible

INTRODUCTION AND BACKGROUND

THE CHALLENGE BEFORE US

These are extraordinary times.

When the COVID-19 pandemic hit the United States in force in March 2020, every state closed its schools in response, disrupting the education of over 60 million children. Globally, 1.2 billion students, 67.7% of the global student population, were affected by school closures as of late May. Districts are now considering reopening schools due to the detrimental effects of closures on the long-term wellbeing of children and the ability of their parents or caregivers to effectively return to work.

School closures come at a big cost

School closures reduce expected student learning gains, which can have lifelong consequences and exacerbate educational and economic inequalities. The amount of learning loss due to physical school closures varies by access to remote learning, the quality of remote instruction, and the degree of student engagement. Low-income students are less likely to have access to high-quality remote learning opportunities. Greater learning loss of Black, Hispanic, and low-income students could increase the existing educational achievement gap in the United States by an estimated 15 to 20%. Beyond learning loss, COVID-19 closures will likely lead to an increase in the rate of high school drop-out. And even for students who stay in school, delaying school reopening until 2021 could lead to reductions in lifetime earnings of 1.6%, 3.3%, and 3.0% for white, Black, and Hispanic students, respectively, over a 40-year working life.

School closures may also result in negative impacts on students' current health safety. For example, a UNICEF report raised awareness that children are at greater risk of abuse, neglect, exploitation, and violence due to lockdown measures.

There is also a concern regarding impacts to physical health. Studies have found that students are increasingly sedentary the longer they are on school break and tend to experience unhealthy weight gain outside of school terms. As physical activity participation and weight status track into adulthood, there are potential lifelong health impacts of closing schools. COVID-19 school closures could increase weight gain due to reductions in access to physical education classes, outdoor spaces for physical activity, and food security for students relying on school meals.

School closures reduce expected student learning gains, which can have lifelong consequences and exacerbate educational and economic inequalities.

In addition to negative impacts on students, school closures prevent parents and caregivers – including potentially 30% of healthcare workers – from fully returning to work. Healthcare workers responsible for infection control in nursing homes, where COVID-19 risk is very high, are among the most highly affected by childcare obligations from school closures. Though school closures are intended to help slow the spread of COVID-19 to reduce the strain on healthcare, they may also serve to reduce the healthcare workforce itself.

Even if school districts decide that the societal benefits of opening schools outweigh the risks, reopening schools will not be easy. And disruption and future school closures may be necessary. There are examples internationally of schools reopening but then having to close a second time after it appeared that local COVID-19 case counts were rising. However, schools can implement concrete strategies to minimize the risk of COVID-19 outbreaks and to keep students and staff as safe and as educationally productive as possible.

Schools can make us sick, or keep us healthy

The transmission of communicable diseases can occur in school environments. Outbreaks of diseases such as chickenpox, measles, mumps, scabies, acute hemorrhagic conjunctivitis (pink eye), and norovirus in schools have all been well documented in the scientific literature. In some cases, outbreaks have occurred even in populations of school children with high vaccination rates.

There are several reasons why disease outbreaks occur in school environments. Research shows that disease outbreaks can happen when immunization against a disease is not 100% effective, when there is vaccination failure, or when there is an inadequate level of immunity in some of the students. Furthermore, the high degree of interaction of students in schools and the frequency with which children put their hands or objects in their mouths increase the transmission of disease.

Even so, historical disease outbreaks in school environments indicate that implementing adequate intervention strategies can successfully minimize COVID-19 transmission and keep students safe when reopening schools.

14 priority areas to save lives and the economy

As schools develop plans for reopening, we must all recognize that the safest way to reopen schools is to do so with COVID-19 cases under control. This requires a cohesive national response that is not yet operating across the U.S. There is a way to do this, and we must act now. With other colleagues at Harvard T.H. Chan School of Public Health, the Healthy Buildings program released a project, Covid Path Forward, that outlines 14 priority areas for saving lives and the economy. To track progress on each of the 14 Priority Areas, including Priority Area 10, which focuses on schools reopening, visit: www.CovidPathForward.com.

GUIDING PRINCIPLES

Follow the precautionary principle

Schools should err on the side of caution when it comes to health and safety. Children generally have less severe COVID-19 symptoms than adults, but they are not immune. Children can become severely ill with COVID-19, and they are capable of transmitting the virus among themselves and to family members or teachers. Older adults are at greater risk of severe COVID-19 illness. On the other hand, schools, teachers, administrators, and parents must also recognize that there is no 'zero risk'. Reopening schools will require accepting that the goal is risk and harm reduction.

Layer defenses

No one control strategy alone can limit the transmission of disease. Schools should approach reopening with a layered defense strategy, where many small interventions and strategies are combined, simultaneously. Schools should deploy an 'all in' approach that uses every control feasible.

Share responsibilities

Just as there is no single control strategy that is effective in and of itself, there is no single entity that is solely responsible for keeping everyone safe. Successfully reopening schools will require continual collaboration between administrators, staff, and teachers and ongoing cooperation among teachers, students, and parents. Everyone has a critical role to play. Getting through this pandemic will require a great deal of social trust.

Limit transmission chains

Even with the best control strategies in place, there will be cases in some schools. To limit classroom outbreaks from becoming school-wide outbreaks, schools should take steps to limit contact chains as much as possible. Within a district, school populations should not be mixed. Within a school, classes should be kept separated as much as possible. Within a classroom, kids should be physically separated as much as possible.

Be flexible

The scientific community's understanding of this virus is changing rapidly. Disease spread and timing are not fully predictable. Schools should recognize that the dynamic nature of knowledge during a global pandemic requires a flexible and adaptive approach. The strategies in this report were developed with careful attention to the most recent scientific discoveries regarding COVID-19 and its effects on and transmission among school-aged children. Our collective understanding of this virus will change, and therefore the approach schools take may change over time, too.

Ensure equity

School closures have disproportionately impacted children of lower socioeconomic status, children with disabilities, and children in other marginalized groups. The reopening of schools must be done with equity in mind. Some challenges to ensuring equity in schools during the current pandemic that should be addressed when developing plans to reopen include:

- Students and staff members may be immunocompromised;
- Students and staff members may face new mental health challenges;
- Students may have to provide childcare for siblings or work to support their families;
- Students may have learning disabilities or need accommodations that are impacted by COVID-19 control measures;
- Students may not have internet access or technology at home;
- Students and staff may have difficulty finding safe transportation to school;
- Students may rely on schools for food security;
- Students may rely on physical activity opportunities during school due to lack of neighborhood safety and/or resources to be active at home;
- Students may not have access to face masks, hand soap, or other supplies that help maintain general hygiene at home; and
- Students and staff members may vary in their understanding of COVID-19 information.

UNDERSTANDING COVID-19

How is COVID-19 transmitted?

COVID-19 is the disease caused by the SARS-CoV-2 coronavirus. Before we talk about specific reopening strategies, it is useful to recall how the COVID-19 virus spreads so we can understand when and how a specific intervention might be effective. There are three routes of transmission for COVID-19 that are supported by models and case studies of outbreaks.

Close-contact transmission can occur via droplets (> 5 μm in diameter) or aerosols (tiny droplets < 5 μm in diameter, also called droplet nuclei). Close contact transmission by droplets refers to close-range transmission of virus by sometimes-visible droplets that are coughed or sneezed by an infectious person directly onto the eyes, mouth, or nose of a nearby person. Droplet transmission can be minimized by, among other things, physical distancing and universal non-medical cloth mask-wearing. Close contact transmission by aerosols refers to transmission of virus in tiny, invisible droplets that are generated when an infectious person exhales, speaks, coughs, sneezes, or sings, and that are then inhaled by another nearby person, allowing the virus to deposit directly on the surfaces of their respiratory tract. This close contact aerosol transmission can also be minimized by, among other things, physical distancing and mask-wearing.

Long-range transmission refers to transmission of virus in aerosols, which may be generated when an infectious person exhales, speaks, sneezes, or coughs and then travel out of the immediate 6-foot vicinity of the infectious person via airflow patterns. This airborne virus can remain aloft for more than an hour indoors to infect people who are not interacting closely with the infectious person. Long-range airborne transmission can be minimized by, among other things, increasing outdoor air ventilation to dilute the concentration of airborne virus or filtering air recirculating in a room or building.

Fomite transmission refers to viral transmission via inanimate objects, like desks, tables, playground equipment, or water fountains that are contaminated with the virus. A surface could become contaminated in many ways, for example, after a person coughs directly onto an object or after they sneeze into their hand and then touch the surface. Individuals who touch the fomite while the virus remains viable, and then touch their eyes, nose, or mouth before washing their hands, could be exposed to the virus. How long the virus can be detected on fomites depends on the type of surface and the environmental conditions. Under some conditions, the COVID-19 virus can be detected up to 72 hours after deposition on hard, shiny or plastic surfaces or up to 24 hours after deposition on more porous surfaces, but the risk posed by these day(s)-later detections is much lower than the initial risk because the amount of the detectable infectious virus decreases rapidly over time. Fomite transmission of a virus can be minimized through frequent cleaning and disinfection of commonly-touched objects, through use of automatic or touchless alternatives (e.g., automatic doors), and through frequent hand washing.

What factors determine exposure?

There are three components of exposure – intensity, frequency, and duration. In general, more intense, more frequent, and/or longer duration exposures have the potential to cause more harm. In the case of COVID-19, we can reduce the risk of illness through interventions that reduce any or all of these three characteristics:

Intensity of exposure to SARS-CoV-2 may be minimized by physical distancing because the amount of SARS-CoV-2 in the environment around an infectious person is highest closest to the infectious person. Additionally, infectious people following respiratory etiquette (i.e., cover nose/mouth when coughing or sneezing) and wearing masks reduces exposure intensity to people nearby.

Frequency of exposure to SARS-CoV-2 may be minimized by reducing how often someone is in close contact with individuals outside the home who may be infectious.

Duration of exposure to SARS-CoV-2 may be minimized by spending less overall time inside in close contact with others.

What factors determine risk?

While exposure is largely a function of intensity, frequency, and duration, risk is determined by many additional factors. Most importantly, personal risk is dependent on individual susceptibility. For example, this may be a function of age, gender, pre-existing conditions, or genetics. For these reasons, two people with the same *exposure* may have very different *risk*. Discussions of risk can also be subjective, in that they depend on personal risk tolerance. Last, risk is a function of factors outside of the individual, including the local healthcare capacity, the efficacy of available treatments, and the extent of spread in the underlying community.

Two people with the same *exposure* may have very different *risk*.

What age groups are most susceptible to COVID-19?

Existing research indicates that children are less susceptible to COVID-19 than adults. Studies based on contact tracing data from Asia, PCR test results from Israel, serum antibody test results from the Netherlands, and mathematical modeling using data from six countries suggest that children are approximately half as likely as adults to become infected with COVID-19 after being in close contact with an infectious person. Older adults are more susceptible to COVID-19 than younger adults. Analysis of serum antibody data from households from the Netherlands found that 1- to 5-year-olds were 32% less likely than 18- to 45-year-olds and 51% less likely than 45+-year-olds to get COVID-19 from an infectious family member.

What are the symptoms and outcomes for kids with COVID-19?

Symptomatic children often experience many of the same symptoms as adults, including fever, cough, and fatigue, along with nasal stuffiness, rhinorrhea, sputum, diarrhea, and headache. Compared to adults, children have more upper respiratory tract involvement (including nasopharyngeal carriage) rather than lower respiratory tract involvement, and prolonged viral shedding in nasal secretions and stool.

In general, COVID-19 appears to be less severe among children than among adults. The infection fatality rate (IFR), the number of deaths per infection, is a useful metric for comparing the severity of COVID-19 infection across groups. A recent study of Geneva, Switzerland, found that individuals younger than 50 years of age had lower IFR values (ranging from 0.00032-0.0016%) compared to individuals aged 50-64 years (0.14%) and 65+ years (5.6%). Similar metrics measured in Hubei province, China, and northern Italy also found that adults with COVID-19 were more likely to die from COVID-19 than children.

In general, COVID-19 appears to be less severe among children than among adults.

While severe cases of pediatric COVID-19 are reported to be rare, some groups seem to be at elevated risk of negative outcomes. Children with comorbidities, such as pre-existing cardiac or respiratory conditions, may be at a higher risk for severe COVID-19 requiring hospitalization. Furthermore, it has recently been suggested that previously asymptomatic children may develop a hyperinflammatory syndrome with multiorgan failure. Finally, it is not yet known whether COVID-19 may have long-term negative health outcomes for children. Severe acute respiratory syndrome (SARS), another respiratory virus, was found to have negative impacts on children's aerobic capacity 15 months after they were ill. Therefore, while children comprise a small fraction of global COVID-19 cases and their symptoms are often mild, the potential for negative health outcomes in children due to transmission in schools cannot be discounted.

How long does it take for symptoms to appear?

The incubation period of a disease is defined as the time from exposure to a disease-causing agent to the time when clinical signs of a disease first appear. This period may vary between individuals and is often reported as a range. For COVID-19, the average incubation period is around 7.7 days in children and 5.4 days in adults but can range to up to 14 days.

When can someone transmit COVID-19?

It is possible for individuals to spread COVID-19 prior to experiencing any symptoms. Studies suggest that transmission of COVID-19 can occur as early as five days before onset of symptoms. For mild cases not requiring hospitalization, studies suggest that an individual is no longer able to transmit disease ten days after first experiencing symptoms (as long as they do not have a fever and have improved clinically). Severe COVID-19 cases may have a longer infectious period; one study found that the infectious period among 129 severely or critically ill hospitalized patients ranged from 0 days to 20 days after symptom onset with a median of 8 days after onset. According to the World Health Organization (WHO), two consecutive negative laboratory test results, taken at least 24 hours apart, can be used to determine the end of the infectious period.

Studies of households indicate that transmission from children to other children or to adults is much less common than transmission from adults to children or transmission between adults.

What do we know about kids spreading COVID-19?

Children's ability to transmit COVID-19 ("infectivity") is dependent on their susceptibility to infection, development of symptoms, viral load, and their risk factors for exposure and for exposing others. Contact tracing studies indicate that children were the index case (original infected person) less than 10% of the time, although further analysis accounting for asymptomatic children suggests 21% of cases could be attributed to transmission by children. Studies of households indicate that transmission from children to other children or to adults is much less common than transmission from adults to children or transmission between adults. For example, in a study in Chicago, children were responsible for 26% of secondary cases, spreading the virus both to other children and adults; in a larger study in the Netherlands, children were responsible for <5% of secondary cases and again spread the virus to other children and to adults.

One potential reason for reduced infectivity of children is their reduced susceptibility to infection, which would reduce their overall likelihood of acquiring and transmitting the virus to others.

While children can clearly transmit the virus to others and despite some evidence of prolonged nasal or fecal viral shedding in children, infectivity is reported to be lower in youth compared to adults. Preliminary models estimate that infectivity of children is 85% that of adults. In the limited available data in schools, transmission between children has also been reported to be low.

One potential reason for reduced infectivity of children is their reduced susceptibility to infection, which would reduce their overall likelihood of acquiring and transmitting the virus to others. While asymptomatic or mild cases can certainly spread COVID-19, the generally less severe symptoms in children may also reduce infectivity by not producing as many large droplets or aerosols via talking/coughing/sneezing.

Regardless of children's susceptibility to infection, symptom severity, and viral load, there are unique behavioral factors in this age group that can facilitate the spread of infectious disease, including the large number of contacts of school-aged children and the frequency with which children, particularly young children, put their hands or objects in their mouth. In the absence of further scientific knowledge about COVID-19 transmission among and by children, particularly in school settings, it is reasonable and prudent to assume that COVID-19 transmission may occur between children and from children to adults in reopened US schools.

RISK REDUCTION STRATEGIES

HEALTHY CLASSROOMS

HEALTHY BUILDINGS

HEALTHY POLICIES

HEALTHY SCHEDULES

HEALTHY ACTIVITIES

HEALTHY CLASSROOMS

In classrooms, teachers and students can prevent the spread of COVID-19 by washing their hands, maximizing physical distancing, maximizing group distancing, wearing face coverings, and avoiding shared objects. These recommendations work together to reduce the risk of exposure by close contact, long-range airborne transmission, and fomites. Each strategy complements the others to mitigate the overall risk of transmission. Schools should consider adopting a plan to incorporate these precautions when reopening and establishing a protocol for how to handle any non-compliance.

Wear masks

- Have students wear face masks as much as possible, especially when in hallways or bathrooms or in proximity to students from other classes
- Train students and staff on how to wear and care for masks
- Ensure masks meet effectiveness criteria
- Build in time throughout the day where students and staff don't have to wear masks
- Allow teachers to wear transparent face shields when teaching at the front of the room and face masks when working more closely with students

As part of a multi-layered strategy that includes physical distancing and other control measures, face masks are an effective way to mitigate transmission from individuals who are infectious, even when they do not have symptoms. When worn properly, masks limit the spread of droplets and smaller aerosols when people breathe, speak, cough, or sneeze. This is called "source control."

Schools will need to consider a wide range of social, educational, equity, and feasibility factors when deciding on a mask policy. From a safety standpoint, individuals should always wear masks as often as possible. This includes teachers, who likely speak the most and the loudest during class. If teachers have concerns about student learning and speech perception, they might consider reserving the mask for closer contact with students and instead, wearing a transparent face shield while at the front of the classroom. It's important to note that face shields are less effective at source control, especially for aerosols generated by speaking, sneezing, and coughing due to a looser fit around the face.

Young children, who may struggle to wear masks properly, might be required to at least wear masks in hallways or other non-classroom locations where physical and group distancing is more difficult to maintain. In addition, there are individuals for whom wearing a mask is not recommended or may be difficult, such as those with asthma, other breathing problems, or sensory sensitivities. For these individuals, face shields may be an acceptable alternative. Schools must decide their policy on wearing masks and any documentation, such as a medical note, necessary for alternative options. Strict mask policies would be especially important in schools that cannot adequately ensure safe physical distancing.

Schools should provide structured training to all students and staff on how to safely choose, wear, care for, clean or discard, and store their masks. For instance, an individual should wash their hands before putting on or removing the mask, only touch the mask by its straps, avoid touching the mask while it is being worn, and change masks if it becomes wet. Individuals should make sure the mask fits snugly to cover the nose bridge, mouth, and chin. Masks that fit improperly, such as leaving gaps, have been found to result in a greater than 60% decrease in filtration efficiency. Schools should consider providing the resources and/or scheduled time for students to properly wash and store their masks. Printed guidance, such as infographics from organizations like the WHO and the Centers for Disease Control and Prevention (CDC), should also be posted around the school.

Schools should provide structured training to all students and staff on how to safely choose, wear, care for, clean or discard, and store their masks.

Cloth masks may vary greatly in filtration efficiency and breathability, depending on the fabric and layering. The WHO recommends that masks be at least three layers thick, where the different layers serve to either limit the spread of droplets from the wearer's mouth or protect the mask from outside contamination and penetration. Additionally, more tightly woven materials, such as cotton fabrics with higher thread counts, are preferable, while elastic materials are not recommended due to the higher pore size and lower filtration efficiency.

Wearing a mask all day long, each and every day will be challenging and frustrating. Over time, 'mask fatigue' may set in, and compliance may drop. To limit this, classrooms can incorporate 'mask free' time during the day. For example, consider taking masks off during time spent outside when distancing can be maintained, or during quiet classroom time when there is no talking and students can stay distanced, or have half the class leave the room for activities so the remaining group can distance and take masks off. Choosing lower-risk times for breaks from masks may help ensure masks are worn during higher-risk scenarios. The risks of viral transmission during mask breaks will be lower when other interventions, such as healthy building strategies (for indoor mask breaks) and physical distancing, are in place.

Wash hands frequently

- Wash hands immediately before: leaving home, leaving the classroom, eating, touching shared objects, touching one's face, and leaving school
- Wash hands immediately after: arriving at school, entering classroom, finishing lunch, touching shared objects, using the bathroom, coughing, sneezing, and blowing one's nose, and arriving at home
- Use hand sanitizer when washing hands is not possible

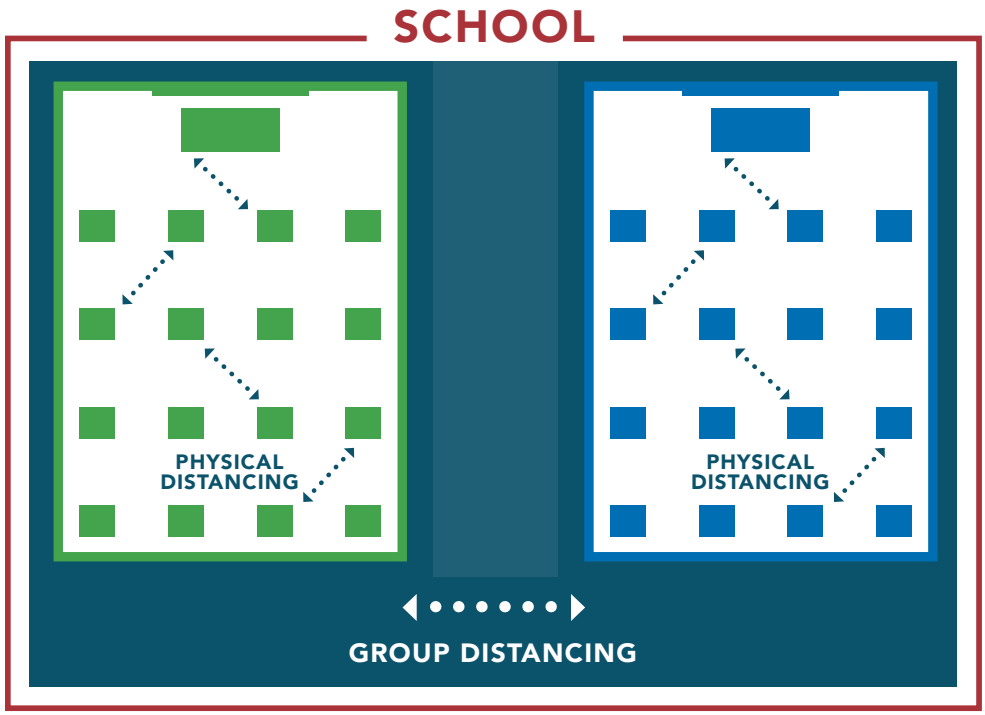
It is recommended that everyone wash their hands before and after touching any high-use items or surfaces.

Establish a plan to promote good hygiene practices across the school. Washing hands frequently with soap and water for at least 20 seconds is a simple but effective preventative precaution that addresses fomite transmission and short-range droplet transmission (in the case where infectious droplets land directly on the hand). It is recommended that everyone wash their hands before and after touching any high-use items or surfaces, both to prevent an infectious individual from contaminating a shared surface and to protect others from being infected by a contaminated surface. Everyone should also wash their hands before eating, before touching their face, after using the bathroom, and after coughing, sneezing, or blowing their nose. Handwashing should be incorporated into the school day every time students enter or leave their classrooms and during transitions between activities. Schools could consider setting up handwashing stations with soap and water in classrooms, hallways, or other rooms to help facilitate regular handwashing. If soap and water are unavailable or cannot be frequently accessed without bathroom crowding, hand sanitizer that contains at least 60% alcohol may be used, as it is also effective at inactivating SARS-CoV-2.

Maximize physical distancing to protect individuals

- Keep at least six feet between individuals, as much as possible, for as long as possible
- Repurpose other large, unused spaces in the school as temporary classrooms (e.g., auditorium)
- Move class outdoors, if possible, and weather permitting
- Replace hugs, handshakes, and high-fives with smiles, waves, and thumbs-ups

Physical distancing, separating individuals by at least six feet, lowers the probability that a person either infects someone else or becomes infected by someone else. It limits COVID-19 transmission by reducing the intensity of someone's exposure to any infectious droplets or aerosols. Physical distancing within schools could be encouraged by moving desks as far away as possible from each other, turning desks to all face the same direction, and assigning seats. If possible, large outdoor spaces, gymnasiums, cafeterias, and auditoriums could be repurposed as temporary classrooms to improve physical distancing practices for larger class sizes. If using an outdoor space, remember to consider potential effects of weather, temperature, and seasonal allergy conditions on student comfort and wellbeing. School districts may also consider moving some classes from crowded schools to schools that have extra space to promote physical distancing. Last, create a culture where acts of social solidarity that require physical contact, like hugs, handshakes, and high-fives, are replaced with new contactless signals, like smiles, waves, and giving a thumbs-up.



Maximize group distancing to slow transmission chains

- Keep class groups as distinct and separate as possible
- Limit students moving between different classrooms
- Avoid large groups and gatherings, both in and outside of school

Whereas physical distancing focuses on preventing infection transmission between classmates in the same room, group distancing aims to reduce the risk of an infection leading to a widespread outbreak in the school. For example, group distancing means that students in one class are kept separate from students in other classes, so these class groups avoid being in the same location (e.g., classroom, cafeteria, playground) at any given time. School-wide gatherings, such as assemblies in the auditorium and school field trips, should be avoided to maintain group distancing.

The strategy of keeping classes separate as much as possible may be more practical for younger students who stay within one class group rather than older grades where class groups often change. In older grades, consider making cohorts of students who take the same core courses and having elective courses be remote so that group distancing can be maintained. This may require schools to adjust class scheduling and be more prescriptive about curriculum tracks that older students can sign up for. Another strategy for specialized teachers is to have them rotate between classrooms instead of having students move between classrooms. This reduces the number of students using a particular desk, the frequency with which students touch common surfaces like door handles, the frequency of close contact interactions in hallways, and the potential exposure to aerosols in classroom air from a sick individual in the previous class.

If there is limited space for a class to practice physical distancing, students within the class could be further organized into smaller pods that stay together throughout the day, including sitting together in class and at lunch and playing together during recess. These pods within larger class groups should still be physically spread out from each other as much as possible. Other countries have found this practice helpful particularly with elementary school students for whom peer socialization is a significant part of school and complete physical distancing might be difficult to enforce.

Group distancing means that students in one class are kept separate from students in other classes, so these class groups avoid being in the same location at any given time.

Disinfect objects between users

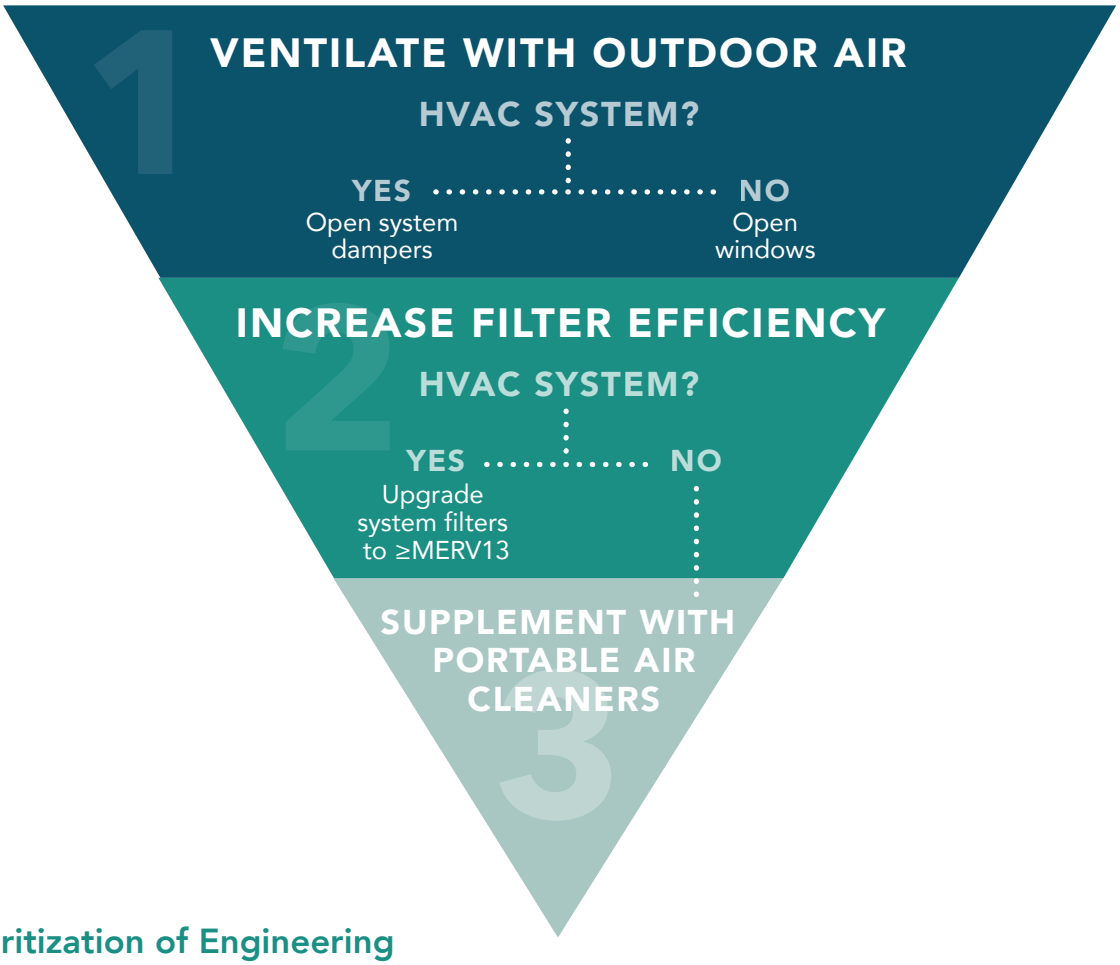
- Disinfect any shared supplies between uses
- Provide disposal disinfectant wipes for individuals to use before using shared objects
- Choose lesson plans that limit student contact
- Provide students with their own separate supplies when possible

When possible, provide each student their own supplies that they will use for all activities.

In a school setting, it will be difficult to limit sharing objects, like books, pencils, electronics, and art supplies. Schools can provide an adequate supply of disinfectant wipes in classrooms and throughout the school so individuals can disinfect objects before use. Frequent hand-washing, including before and after using shared materials, is an important control strategy that should be reinforced when objects and materials will be shared. In addition, teachers can try to select lessons and activities that do not require shared equipment or close contact. When possible, provide each student their own supplies (e.g., art supplies) that they will use for all activities. If each classroom has limited supplies, consider pooling resources and then rotating supplies between different classrooms on different days, while ensuring adherence to strict cleaning and disinfection policies.

HEALTHY BUILDINGS

Healthy building strategies that improve air quality and clean surfaces should be incorporated as part of a layered defense against COVID-19. For improving indoor air quality, we recommend prioritizing control strategies – ventilation, filtration, supplemental air cleaning – and verifying system performance regularly. For more detailed and technical guidance, we recommend reviewing the materials produced by the ASHRAE Epidemic Task Force. Schools should work with facilities managers and outside professionals to tailor these recommendations for their unique building systems.



Prioritization of Engineering Controls to Reduce Long-Range Airborne Transmission

Increase outdoor air ventilation

- Bring in more fresh outdoor air
- Follow the decision-tree for ventilation type and corresponding strategies

SARS-CoV-2 present in the coughs, sneezes, and exhaled breath of an infectious person can be transported in the air to disperse throughout a room and can remain aloft for hours. This long-range airborne virus can infect even people who haven't had close contact with the infectious person if they inhale a sufficient amount of virus. Bringing fresh outdoor air into a room can dilute and/or displace any present airborne virus, which thus reduces the probability that someone breathes enough infectious aerosol to become infected. As an ideal, holding class outdoors provides the freshest air and most effective dilution of any infectious airborne SARS-CoV-2.

As the next best solution, mechanical ventilation systems in buildings can forcibly bring outdoor air inside and then distribute that fresh air to different areas of the building. Some fraction of the indoor air is usually recirculated and mixed with the outdoor air coming in to save on cooling and heating energy costs. However, during a pandemic, when long-range airborne viral transmission can occur, air recirculation can lead to a buildup of airborne viral particles indoors and also potentially spread the virus to other areas of the building. Therefore, buildings should eliminate or minimize air recirculation (thus maximizing fresh outdoor air) to the extent possible during this period. In addition, buildings should not shut off or reduce their mechanical ventilation during before-school or after-school hours when there still may be people in the building, including students, staff, and custodians during any student programs, cleaning times, teacher class preparation, sports (e.g., if students are returning to lockers), or other activities. Finally, mechanically ventilated schools should evaluate any potential contaminant source near the outdoor air intake duct. For example, the outdoor air inlet should not be located too close to the exhaust air outlet or contaminated indoor air that is exhausted out of the building could renter (refer to local building codes on minimum required distance, generally 10 feet).

Buildings should eliminate or minimize air recirculation (thus maximizing fresh outdoor air) to the extent possible during this period.

Devices that simply recirculate the same indoor air without filtering it or replacing it with fresh air are not helpful in reducing any airborne virus present in the room.

Schools that do not have mechanical ventilation systems can increase the amount of natural ventilation via a) open windows, doors, or skylight, b) roof ventilators, c) stacks, and d) specially designed inlet or outlet openings. Opening windows can help bring in fresh outdoor air and dilute and exhaust contaminants in the indoor air. Natural ventilation through windows can be effective but is dependent on factors that drive pressure differentials between outdoors and indoors, like wind pressure and stack (or buoyancy) effects. Therefore, airflow into the building, even with open windows, is not guaranteed. To help address this, schools can consider using window fans or box fans positioned in open windows to blow fresh outdoor air into the classroom via one window and indoor air out of the classroom via another window. Note that devices that simply recirculate the same indoor air without filtering it or replacing it with fresh air are not helpful in reducing any airborne virus present in the room (including most window air conditioning units, fans used in rooms with closed windows, and fan coils and radiators).

In some cases, it is not reasonable to bring in additional outdoor air. For example, on very hot summer days or very cold winter days it may not be impossible to maintain a comfortable temperature in the classroom if the windows are open. Mechanical ventilation systems, similarly, may need to recirculate more indoor air and bring in less fresh outdoor air when extremely hot or cold outdoor air cannot be sufficiently cooled or heated before it is blown into classrooms. Other factors may also impact the ability to increase outdoor air ventilation, particularly for naturally ventilated buildings, including but not limited to, security concerns, high outdoor air pollution or pollen levels, or high outdoor noise levels. In these cases, the highest tolerable amount of outdoor air ventilation should still be used, even if students, teachers, and administrators have to adjust their clothing to be comfortable (e.g., wear a jacket indoors in the winter). In these cases where there cannot be adequate outdoor air ventilation, other strategies such as enhanced filtration and air cleaning can be used to reduce airborne SARS-CoV-2 concentrations.

Decision Tree of General Ventilation Operation Guidance for COVID-19

Building relies on natural ventilation

- Open windows
- Use window fans to promote airflow into the building

Building has mechanical ventilation system

Supply air (i.e., air being pushed into occupied rooms)

- Increase the outdoor air ventilation rate to at least the ASHRAE minimum to help dilute any airborne virus. If possible, consider increasing the outdoor air ventilation rate above the ASHRAE minimum to promote occupant health.
- Disable the demand-controlled ventilation (DCV) if present.
- Can the ratio of fresh outdoor air to recirculated air be adjusted?
  - **Yes:** Shut off or minimize airflow recirculation.
  - **No:** Increase filtration.

Exhaust & airflow between building zones

- Maintain negative pressure in locations which are possible sources of virus transmission such as bathrooms.
  - Operate exhaust fans in bathrooms at all times
  - Don't open the bathroom windows, if opening windows in bathrooms causes re-entrainment of bathroom air into other building spaces.
  - Dedicate separate local exhausts venting directly outdoors for each probable source zone, to the extent possible.

Filter indoor air

- Increase the level of the air filter to MERV 13 or higher on recirculated air
- Inspect filters to make sure they are installed and fit correctly
- Check that sufficient airflow can be maintained across the filter
- Maintain and change filters based on manufacturer's recommendation

Filtration in school buildings can help mitigate long-range airborne viral transmission by removing SARS-CoV-2 from any air that is recirculated through the building. In buildings with mechanical ventilation systems, existing filters can be upgraded to filters with efficiency ratings of at least MERV 13 or the highest MERV rating the system can handle. MERV ratings, developed by ASHRAE, indicate the percentage of particles and the sizes of particles that filters can remove from air passing through them. Filters with higher MERV ratings remove higher percentages of particles and more effectively remove small particles than filters with lower MERV ratings. Filters with MERV ratings of 13 or higher are recommended for SARS-CoV-2 by ASHRAE. Filters need to be periodically replaced and inspected to make sure they are sealed and fitted properly, with no gaps or air bypass. In some cases, if the airflow distribution system is not designed to handle a higher MERV filter, air could leak around the filter edges, compromising any benefit that might have even been gained from a lower MERV filter.

Supplement with portable air cleaners

- Supplement with air cleaning devices
- Select portable air cleaners with HEPA filters
- Size devices carefully based on the size of the room

Portable air cleaners with high-efficiency particulate air (HEPA) filters may be useful to reduce exposures to airborne droplets and aerosols emitted from infectious individuals in buildings. Portable air cleaners are typically most effective in smaller spaces, and care must be taken when choosing a device to ensure it is the correct size for the room where it will be used. One metric to consider is the clean air delivery rate (CADR). The CADR reflects both the amount of air that a unit can process per unit time and the particle removal efficiency of the filter. A helpful rule of thumb is that for every 250 square feet of space, a CADR of about 100 cfm is desirable. CADR is not the only factor to consider. Portable air cleaners vary in their ability to circulate air in the room, so not all devices with the same CADR rating are equivalent. Devices that provide better mixing of the indoor air can capture particles from more of the room's airspace and are therefore preferred. Because potential viral sources could be in various locations within a room, it may be beneficial to have several units that meet the target CADR values rather than a single larger unit. In larger spaces, industrial-sized supplemental ventilation and filtration units are available and should be considered. Furthermore, room airflow patterns and the distribution of people in the room should be considered when deciding on air cleaner placement that maximizes source control and prevents airflow from crossing people. Since air cleaners should be operated while people are present, it may be important to compare different models to find one that does not generate disruptive noise.

Verify ventilation and filtration performance

- Verify through commissioning and testing
- Work with an expert to evaluate building systems, ventilation, filtration, and air cleaning
- Measure carbon dioxide (CO_2) as a proxy for ventilation

Mechanical heating, ventilation, and air conditioning (HVAC) systems in buildings tend to get out of tune. Within several years of construction, ventilation airflows may change from how they were designed. Schools can ensure that there is adequate ventilation and filtration through a process of commissioning and testing. Commissioning is the process of checking HVAC performance to ensure that systems are operating as designed. Commissioning and testing should be performed by trained individuals and should be performed throughout the school year.

In between commissioning events, there are several ways to test whether a classroom's ventilation delivers sufficient outdoor air. In addition to working with trained experts, a school could quickly evaluate ventilation performance using carbon dioxide (CO_2) as a proxy for ventilation using low-cost indoor air quality monitors. In an unoccupied classroom, background CO_2 would be approximately equal to the concentration of CO_2 in the atmosphere: 410 ppm. When students and teachers are present in a classroom, they exhale CO_2 into classroom air at a relatively constant rate causing CO_2 to rise above the background concentration. At some point, the concentration of CO_2 reaches an equilibrium based on the amount generated indoors, and the amount diluted by ventilation. This is called 'steady-state' and can be used as a quick indicator of ventilation performance. If the measured CO_2 concentrations while students are present are mostly below 1,000 ppm, then the outdoor air ventilation is likely reaching acceptable minimums. Lower CO_2 concentrations while students are present mean there is acceptable outdoor air ventilation rates; higher CO_2 concentrations suggest other strategies for increasing outdoor air ventilation are needed.

It is important to note that CO_2 measurements are only useful when a full class of students is present; otherwise, ventilation will be overestimated. Also, while CO_2 measurements are a good indicator of overall ventilation, they will not indicate whether other air cleaning interventions are effective. For example, if a classroom is operating portable air cleaners to remove the virus from air, viruses and other pollutants will be removed even if CO_2 remains high because cleaners with HEPA filters are not designed to remove CO_2.

It is important to note that CO_2 measurements are only useful when a full class of students is present; otherwise, ventilation will be overestimated.

Consider advanced air quality techniques

- Attempt to maintain indoor relative humidity between 40-60%
- Consider advanced air cleaning with ultraviolet germicidal irradiation (UGVI)

Additional air quality controls can be considered, including maintaining higher humidity and air cleaning with ultraviolet germicidal irradiation (UVGI). Because these controls require great care in implementation, they are listed in this separate section as advanced considerations. Schools that consider these approaches should consult with outside technical experts.

People's physiological defenses against respiratory viral infection function best in mid-range humidity levels. Humidity also impacts environmental quality: dry environments are associated with higher incidence of some viral infections, such as influenza, but too much humidity can increase the presence of mites and lead to mold growth. While positive impacts of humidification on COVID-19 have not been determined, avoiding dry conditions in buildings is generally thought to be effective as a risk reduction strategy in buildings. ASHRAE suggests that maintaining relative humidity between 40% and 60% may help reduce COVID-19 infection rates. For more information on indoor relative humidity and temperature combination setpoints within this relative humidity range that are aimed at providing a healthy as well as a comfortable environment for occupants, for winter and summer operation, refer to the ASHRAE's Pandemic Task Force's reopening plan for schools and universities.

UVGI is an air cleaning technology that is sometimes used in buildings. UVGI uses low-wavelength ultraviolet light (UVC light) to destroy viruses. UVGI has been shown to be effective in disinfecting surfaces and air from bacteria and viruses such as influenza. In buildings, this technology is usually deployed as upper room UVGI to destroy airborne virus in the upper airspace of a room or as UVGI in supply air ducts to destroy airborne virus present in recirculated air. UVGI may be able to reduce exposures to airborne COVID-19. In order for UVGI to be effective, there must be sufficient contact time between the virus and the UV light; this often presents a challenge for installing an effective in-duct UVGI system. Similarly, upper room UVGI works best when the air in a room is well mixed so that airborne virus emitted by people in the lower portion of the room is lofted into the upper airspaces where it can be treated. Other potential issues with UVGI in schools include cost, maintenance, and potential health concerns of inadvertent UV exposures. In general, UVGI should be further discussed with an expert before consideration for use in a school.

Use plexiglass as physical barrier

- Install plexiglass shielding in select areas with fixed interactions (e.g., reception desk, cafeteria checkout)
- Use plexiglass shielding in the classroom if needed (e.g., around student desks, around teacher desks, between spaces at shared tables)

Schools that cannot adequately ensure physical distancing might consider installing physical barriers (e.g., plexiglass separators) in select areas. Plexiglass is a clear, solid material that acts to block transmission of large droplets between two people in close contact. Consider installing plexiglass shielding in areas where there is fixed and steady interaction, like the reception desk and cafeteria checkout. Within classrooms, plexiglass shielding may be useful for physically separating students who share tables, and as an additional barrier between the teacher and student areas of the classroom.

Install no-contact infrastructure

- Adjust use of existing infrastructure to make it touchless
- Install touchless technology for dispensers of hand soap, hand sanitizer, and paper towels

To limit fomite transmission, existing infrastructure could be replaced with contactless alternatives. For example, doors with handles could be replaced with automatic doors. If installing new infrastructure is not feasible, alternative policies could be implemented (e.g., doors could be propped open, so students do not need to touch them).

In addition to infrastructure, technology in bathrooms, classrooms, cafeterias, and other locations should be made as touchless as possible. This includes automatic dispensers of hand soap, hand sanitizer, and paper towels. Contactless hand sanitizer dispensers at the entrance inside classrooms could improve hygiene of students during transitions between activities and after touching shared objects or surfaces within classrooms. Additionally, foot pedals could be installed to replace buttons on water fountains.

Keep surfaces clean

- Frequently clean and disinfect surfaces following directions on product labels
- Provide adequate training and personal protective equipment to protect custodial staff

Shared equipment, spaces, materials, and surfaces should be cleaned and disinfected throughout the school day. Special attention could be paid to the most highly touched surfaces, such as door handles, light switches, sink handles, and any elevator buttons. In addition to cleaning by janitorial or custodial staff, provide teachers and classroom staff with disinfectant wipes to disinfect items in their classrooms between uses. The infectious virus does become inactivated over time without cleaning, but this would not be acceptable for objects regularly reused or frequently touched surfaces. The EPA has compiled a list of safe and recommended disinfectant products for use against COVID-19.

Remember, frequent hand-washing is the best defense against transmission from contaminated surfaces.

In addition, schools should ensure custodial and janitorial staff have sufficient personal protective equipment to safely clean contaminated areas, including any necessary facemasks, gloves, goggles, and gowns. They should also be trained in proper disinfection protocols and safety practices during cleaning (e.g., washing hands afterward, discarding disposable equipment, opening windows/doors to increase fresh air when possible, staying home when sick), and in best disinfection practices to prevent fomite transmission of COVID-19.

Cleaning Frequency	Examples
Daily	• Classroom desks, tables, and chairs • Shared spaces
Multiple times per day	• Door handles • Light switches • Handrails • Drinking fountains • Sink handles • Restroom surfaces • Cafeteria surfaces • Elevator buttons
Between uses	• Toys, games, art supplies, instructional materials • Keyboards, phones, printers, copy machines • Seats on bus

Focus on bathroom hygiene

- Keep bathroom doors and windows closed and run any exhaust fans at all times
- Install lids on all toilet seats and keep the lids closed, particularly during flushing
- Stagger bathroom use

SARS-CoV-2 has been found on toilets and in stool of COVID-19 hospital patients, indicating that bathrooms may be places where elevated fomite and long-range airborne transmission could occur through touching shared surfaces and breathing bioaerosols generated by toilet flushing.

Fomite transmission risk in bathrooms may be minimized by handwashing and installing touchless faucets, soap dispensers, towel dispensers, and doors. In some cases, it may be appropriate for an adult to be present to assist with or monitor handwashing in the bathroom, particularly for small children. It may also be prudent to have children wash their hands with soap and water or use hand sanitizer after they return to their classroom in a location where their teacher can monitor hand hygiene.

Fomite transmission risk in bathrooms may be minimized by handwashing and installing touchless faucets, soap dispensers, towel dispensers, and doors.

In order to prevent the spread of contaminants from bathrooms to other indoor spaces, negative pressure differentials with respect to other building zones should be maintained by running bathroom exhaust fans continuously, and keeping bathroom doors and windows closed at all times, even when not in use. Long-range airborne transmission risk in bathrooms may be further minimized by installing toilet lids, keeping lids closed when not in use, and encouraging students to close the lids before flushing.

Before re-occupying the school building after closures, schools should flush all bathroom faucets, drains, and toilets in case the water in the p-traps has evaporated. In addition, any time there is a sewer gas smell, schools should make sure to fix the plumbing.

Finally, bathrooms can be places where crowding occurs, especially when children have shared windows of time when they can use the bathroom. To enforce physical and group distancing and to minimize crowding, it may be useful to close bathrooms during transition periods and promote bathroom breaks during class time instead, to assign classrooms to use specific bathrooms or to stagger the timing of scheduled bathroom breaks by class.

HEALTHY POLICIES

How a school operates significantly impacts the safety of its students, teachers, and staff. This section outlines potential school policies to monitor and respond to potential COVID-19 cases and thus support the health of the entire school community.

Establish and reinforce a culture of health, safety, and shared responsibility

- Provide training to teachers, staff, students, and parents/guardians prior to school opening
- Start each day with a morning message to the entire school reinforcing health messaging
- Create and display signs around the school as reminders of rules, roles, and responsibilities
- Hold weekly and monthly all-staff meetings on COVID-19 to evaluate control strategies
- Send out weekly reports and reminders to parents and students of their respective roles
- Reward good behavior

Public health interventions only work when there is training and reinforcement. Schools can begin training staff, teachers, and students in the weeks leading up to the beginning of school. This can include virtual training and education sessions focused on the basics of disease transmission, new policies and procedures, and expectations regarding code of conduct. General training sessions should be supplemented with training targeted toward specific people (administrators, facilities, teachers, students, staff). A strong communications plan should be developed with daily and weekly 'all school' communications via email. Big, bold, and fun signs should be placed throughout the school to reinforce the culture of health messaging. For example, hand washing instructions could be posted in all bathrooms, physical distancing plans, and proper face mask techniques could be posted in hallways, and a COVID-19 symptom chart and contact plan could be available in the nurse's office. Administrators and teachers should begin each day with a safety message.

Public health interventions only work when there is training and reinforcement.

Form a COVID-19 response team and plan

- Have a person or team in charge of implementing and disseminating COVID-19 policies
- Implement contact tracing to notify class groups if they may have been exposed
- Ensure staff are aware of privacy policies regarding disclosure of COVID-19 status
- Increase staff surge capacity if possible by recruiting student teachers, substitute teachers, community volunteers, and/or recent retirees

Schools should have a dynamic COVID-19 plan document that they can share with students, parents/guardians, teachers, staff, and anyone else using the facilities (e.g., for election voting). As situations evolve rapidly, it may be useful to designate a person or team to act as the liaison between school administrators, teachers, students, families, and local boards of health. This team should disseminate information about new policies and programs as soon as it becomes available, including information about anything children need to carry with them (e.g., face masks) and any changes to the timing or location of classes.

Schools could consider ways to cross-train and/or recruit additional teachers and staff to form a reserve of employees that can be utilized dynamically.

The COVID-19 response team may also be responsible for gathering symptom reports and sending contact tracing notifications in collaboration with local health departments. When someone in a class is sick, contract tracing is very important to prevent a school outbreak. While Family Educational Rights and Privacy Act (FERPA) policies must be strictly adhered to, those who have been in contact with a suspected or confirmed COVID-19 case should be notified as soon as possible so they can follow quarantine procedures. Students or staff sharing classroom space with a case are assumed to be contacts, but schools may find it useful to also encourage parents and/or guardians to log additional interactions (e.g., playdates or after school activities) so they can be contacted quickly.

Additional staff members may be needed for the COVID-19 response team or due to reduced class sizes, increased requirements for supervision (e.g., during recess), and an increased number of sick days. Schools could consider ways to cross-train and/or recruit additional teachers and staff to form a reserve of employees that can be utilized dynamically. Schools may be able to increase recruiting pools by reaching out to student teachers, substitute teachers, community volunteers, and recent retirees. Care should be taken to ensure these staff are trained in school COVID-19 policies and can either work remotely or adequately maintain physical distancing at school.

Prioritize staying home when sick

- Ask students and school staff to stay home when not feeling well
- Request daily self-declaration that people heading into school that day are free of symptoms
- Identify a comfortable room where individuals who become ill can isolate for the rest of the school day

Schools should ask individuals to stay home when sick. Sick individuals staying home should face no negative consequences or unfair attendance records, and there should be a plan in place to ensure continuity in remote learning or work for sick individuals who cannot come to school in-person.

Students, school staff, and parents should be made aware of the symptoms of COVID-19. Schools should consider a daily declaration, via electronic means, that each person heading to school that day is free of symptoms. Additionally, a system should be in place for any of them to privately report symptoms, so this information can be used to make decisions about cleaning, notification of potential contacts, and/or classroom or school closures. Schools may also opt to directly screen students before school (e.g., using temperature checks and visible symptom inspections), following guidance of the CDC or other relevant organization, to ensure that students who are sick remain at home. In addition, teachers should be vigilant about the health of the students in their class and notify the school nurse or a designated administrator immediately if a child is coughing or seems to have a fever in class.

Sick individuals staying home should face no negative consequences or unfair attendance records, and there should be a plan in place to ensure continuity in remote learning or work.

If a student is found to exhibit new symptoms of illness while at school and it is not possible for them to go home immediately, the sick student could be asked to isolate in a dedicated room(s) in the school, such as the nurse's office. There should be a predetermined protocol for how to clean and disinfect any room the sick individual may have contaminated (including the isolation room). Ventilation and filtration in these isolation rooms needs to be verified. Ideally, contaminated rooms should be left empty for up to 24 hours or as long as possible before having staff clean or before allowing the room to be reoccupied. Care should be taken so as not to unnecessarily disclose student health status to other teachers or students in accordance with the Family Educational Rights and Privacy Act and Americans with Disabilities Act policies.

Promote viral testing and antibody testing

- Encourage viral testing any time someone has symptoms, even if mild
- Track testing improvements and incorporate widescale testing into future plans
- Encourage antibody testing to monitor disease progression and plan control strategies
- Provide information on where people can go for testing

Diagnostic viral testing for those with symptoms or who have come in contact with someone who has COVID-19 is a critical strategy for slowing the spread of the virus and preventing major outbreaks in schools because it can help identify those with active infections who then need to self-isolate. Schools should identify locations where students, staff, and families can be tested nearby and provide that information to everyone ahead of time. As testing capacity, speed, and accuracy improves, schools should consider more frequent testing as an approach to identify pre-symptomatic individuals.

Testing for antibodies should also be encouraged to help schools track disease progression through the community and plan control strategies. Antibody testing is a type of test to determine if someone has previously had a COVID-19 infection. Although a positive antibody test result for one individual does not guarantee immunity, current scientific evidence indicates there may be some protection, for some time. In addition, a negative antibody test does not mean that someone doesn't currently have an active infection, for which a diagnostic viral test would be needed. Regardless of antibody status, and until we have more scientific research, the same precautions should be followed by all individuals. However, at the school population level, this information may be helpful to evaluate the prevalence of past COVID-19 infections and inform future control measures.

Establish plans for when there is a case

- Develop a plan for what to do when a case is identified in the school
- Establish a timetable for when someone with COVID-19, and their close contacts, can return to school
- Regularly check CDC guidance for updates to their protocols and definitions

The CDC recommends a 2-5 day building dismissal to clean, disinfect, and contact trace in consultation with local health officials in the event there is a case in a school. This presents a massive disruption to learning, and, depending on the nature of the case and controls that are in place, schools can coordinate with local boards of health to determine if that is absolutely necessary in each instance. In addition, close contacts of the infected individual should stay at home for 14 days after their last interaction with that person.

A "close contact" is defined by the CDC as an individual who spent time closer than six feet away for at least 15 minutes with the person who had symptoms or tested positive and has not yet met the criteria for returning to school. Note that some hospitals do not consider it a 'close contact' if both people are wearing masks.

Identifying close contacts will be simplest in the case of distinct class groups that take all the same classes together; then, when an individual from the class group becomes sick, the whole class can stay home and move to remote education for 14 days after the exposure. Having the entire exposed class group stay home and transition to remote learning would also help maintain privacy for the sick individual and ensure equal educational access within the class. Isolating exposed class groups will help prevent outbreaks from occurring in the whole school. Finally, there should be a policy on when a school should entirely shut down in favor of remote education if COVID-19 appears to be spreading through the school.

Schools may find it useful to follow CDC guidance for healthcare workers when developing a school policy on when sick individuals can return to school in person. For example, if a student or staff member was suspected or confirmed to have COVID-19, they could be asked to stay at home (with remote learning or work options) until the appropriate criteria are met as described below:

If the individual has symptoms, they should stay home until:

1. At least 3 days have passed since *recovery* (resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms)
2. **AND** either:
    a. At least 10 days have passed *since symptoms first appeared*
    b. **OR** they have two negative results, spaced at least 24 hours apart, based on authorized COVID-19 diagnostic tests by a medical professional.

Otherwise, if the individual tested positive in a diagnostic COVID-19 test but does not get symptoms, they should stay home until:

1. At least 10 days have passed since the positive result in the diagnostic test (assuming no symptoms appeared during that time)
2. **OR** they have two negative results, spaced at least 24 hours apart, based on authorized COVID-19 diagnostic tests by a medical professional.

Support remote learning options

- Provide necessary supplies and support systems to continue remote education for students staying home
- Train staff on how to best facilitate remote learning
- Consider district-wide remote learning by grade, staffed by recent retirees or teachers with pre-existing conditions

There are a number of reasons that some students may need to continue remote learning as schools reopen. Students who are sick or who have family members who are sick with COVID-19 should remain at home for two weeks. Students who are immunocompromised, or have family members who are, may feel safer remaining at home. Students with behavioral or medical circumstances who may find it difficult to adjust to new policies such as no physical contact, required facemasks, or frequent handwashing may benefit from remaining at home. Older children may have to remain at home to provide childcare for younger siblings who are not in school full-time as parents return to work.

Regardless of the reason a student is learning from home, it is vital that they are provided with access to the Internet, necessary technology such as a tablet or computer, and support systems often found in schools such as guidance counselors and meals. Flexibility may be required, as some students may not have equal access to support, time, or resources to complete schoolwork at home. Schools will need to provide staff training on learning platforms that allow for equity and access to learning and that conform with students' individualized education plans and medical needs. School districts can consider creating district-wide remote learning teams for each grade level, staffed by calling up recent retirees or current teachers with pre-existing conditions so classroom teachers can focus on in-classroom learning.

De-densify school buildings

- Limit parent and visitor access
- Move parent-teacher conferences online
- Promote work-from-home for administrative duties, where possible
- Hold staff meetings via videoconferencing as much as possible

Minimizing the number of visitors in the building can help reduce the density of occupied spaces. If parents or guests need to enter the school building, they could be required to gain approval first, be briefed on school COVID-19 policies, and verify they do not have symptoms. Schools can also consider restricting visitor access to limited times when classes are in session (i.e., at times when there will not be many people in the hallways). Furthermore, any parent-teacher conferences or other planned meetings with visitors could be held online instead of at the school.

In addition, to facilitate physical and group distancing within schools and reduce everyone's risk of exposure, schools may consider classifying non-essential staff that can work remotely. Any necessary faculty or staff meetings could be held remotely through video conferencing if possible.

Protect high-risk students and staff

- Advocate for high-risk students and staff to have access to effective remote learning or work
- Re-assign roles if needed to allow staff members to work while staying safe
- Take extra precautions if high-risk students or staff come to school

Students, staff, or their family members who have pre-existing conditions making them at higher risk for a more severe case of COVID-19 may require additional considerations in order to keep them safe. It will be critical to communicate with these students, families, and staff to come up with a strategy that works best for them. In many cases, this may result in at least some degree of remote learning or teaching. In addition to the remote learning considerations above, it is important to consider the mechanisms that can allow students studying remotely to remain engaged with their teachers and classmates that are in the classroom as much as possible.

Some high-risk students who require additional safety measures may not have the same access to resources or a safe family environment for remote learning.

Some high-risk students who require additional safety measures may not have the same access to resources or a safe family environment for remote learning. In these scenarios, consider repurposing rooms within the school building as a computer lab, where high-risk students can safely complete their remote work with facilitation of a staff member. These rooms should follow all of the same protocols as classrooms and be reserved only for students who need to use them and are high-risk.

Similarly, consider allowing high-risk teachers who do not wish to work from home to work from a designated room in the school building. They may, for example, be assigned a new role (e.g., on the COVID-19 response team) or contribute to lesson planning or teaching remotely.

HEALTHY SCHEDULES

Throughout the school day, there are opportunities to reduce transmission risk. As a starting point, schools may choose to implement an attendance policy that reduces the number of students in the school at a given time. While students are in school, transition times can be limited and lunch can be modified to maintain physical and group distancing. Schools may also be able to facilitate lower-risk transportation to and from school.

Manage transition times and locations

- Stagger school arrival and departure times, class transitions, and locker access
- Set up separate entrances and exits for different groups of students when possible
- Use well-marked lines on the floor to encourage physical distancing and indicate direction of travel

School arrival, departure, and class transitions can be a high-risk time due to the potentially large number of people in close contact in school entrances, exits, and hallways. Schools may consider staggering arrival and departure times so that children in different classes are not all entering or exiting the building at the same time. Even a difference of 5-10 minutes for each class or grade level could greatly reduce the number of students in the hallway heading to the door for dismissal at one time. Students and staff should be encouraged to not loiter in entrances, exit areas, or hallways, but if waiting is necessary, lines should be clearly marked to maintain physical distancing. In small hallways or stairwells, clearly marked paths on the floor that indicate one direction of travel could be used when possible. Additionally, different doors could be used by different classes or grades to enter and exit the school to minimize crowding and to reduce the number of people touching the same doors. Other recommendations about ways to reduce the number of transition times, such as by rotating teachers (instead of students) and serving lunch in the classroom, are found in other sections of this report.

Even a difference of 5-10 minutes for each class or grade level could greatly reduce the number of students in the hallway heading to the door for dismissal at one time.

Make lunchtime safer

- Use student classrooms or other school locations as temporary lunchrooms to facilitate group distancing
- Stagger lunch times in shared lunchrooms and clean and disinfect surfaces between groups
- Maintain physical distance between individuals eating lunch together
- Package school-provided meals in single-serving containers instead of serving food buffet-style
- Reinforce 'no sharing' of food, utensils, drinks

To limit the number of contacts of students and staff and maintain group distancing, schools may serve lunch in classrooms at students' desks or in alternative lunchrooms (e.g., repurposing the gymnasium or auditorium for expanded lunch capacity).

Lunchtime brings a distinct set of challenges. Masks cannot be worn while students are eating, and many schools typically hold lunch in crowded lunchrooms. To limit the number of contacts of students and staff and maintain group distancing, schools may serve lunch in classrooms at students' desks or in alternative lunchrooms (e.g., repurposing the gymnasium or auditorium for expanded lunch capacity). If a single large lunchroom is to be used, schools may stagger lunch times, keep classrooms/cohorts together, maintain physical distance, and have all students face the same direction or be seated in a staggered pattern, so there is no face-to-face contact. It may also be helpful to clearly mark spaces where each class/cohort will sit in the shared lunchroom. Instead of students going through a line to be served school-prepared lunches, consider alternative solutions, like using single-serving containers clearly labeled with any allergens in the meal. Schools need to reinforce messaging regarding no sharing of food, utensils, and drinks.

Rethink transportation

- Open all windows on the bus, even a little, and even in bad weather
- Reduce the number of students in each school bus to allow for physical distancing, if possible
- Modify school start times to allow students who use public transit to avoid rush hour
- Encourage walking, biking, or use of personal vehicles

School policies regarding transportation to and from school will largely depend on the primary mode of transportation of students. For reducing viral transmission, the safest routes of transportation are walking, biking, or personal vehicle. There may be ways to promote use of these modes of transportation; for example, walking school bus programs for elementary schools, or the addition of more crossing guards and bike racks. Local police departments should be engaged to help with safety protocols across extended walk zones.

If students are driven to school, the school may organize drop off locations and/or times so that students can be dropped off at the door while limiting disruptions (e.g., to nearby roadways, in coordination with local police departments) and minimizing contact between students not in the same class. After school, cars can line up in the parking lot or adjacent streets, and students can meet their parent or guardian at their car. This will reduce the number of people waiting at school doors. High schools may consider designating extra parking lots or street spaces for student parking if it is anticipated that more students will be using personal vehicles.

Keep windows open on buses, and wear masks. Even opening windows a few inches can greatly increase the amount of ventilation inside the school bus. Students will need to dress appropriately while on the school bus, because windows should be cracked open even when the weather is cold outside and when it rains. Schools may also consider hiring more buses or having buses complete multiple routes so that fewer students are on each bus, although we recognize this option presents massive financial and logistical challenges. Depending on the routes and number of buses, some schools could consider designating a separate bus for each class group in order to maintain group distancing between students from different classes Assigned seating could help facilitate physical distancing, with vacant seats clearly marked. For example, one student seated per bench on both sides of the bus, skipping every other row or one student seated per bench, alternating rows on each side to create a zig-zag. Seating students starting from the back of the bus to the front could help maintain physical distancing. Consider having an additional bus aide to ensure students maintain a safe distance, as long as it's possible for the aide to also maintain appropriate physical distance.

Schools where students take public transportation can start school before or after rush hour so students are not taking crowded buses and trains. This would reduce the risk of exposure for both students and other community members on public transportation. Students should wear masks on public transportation and wash hands immediately after exiting a subway or bus.

Modify attendance

- Modify attendance policies to facilitate cleaning, reduce class sizes, and/or maintain group and physical distancing
- Allow for flexibility in attendance policies as situations change

Three attendance-based strategies to reduce transmission risk that have been proposed are staggered attendance, split attendance, and phased re-entry. Staggered attendance is when students, perhaps based on grade level or class, attend school every other day or every other week. With split attendance, half of the students in the school may attend class in the morning, and the other half may attend in the afternoon. In both strategies, when not physically attending school, students engage in remote learning. Each school could decide the best length of time between group rotations. In phased re-entry, small numbers of students are brought back to school first, such as only kindergarten students or high school seniors, then the number of students in school is increased as case numbers in the area decrease, and the school adjusts to new protocols. Schools may need to dynamically adjust their attendance policies as new cases emerge in the school or surrounding community and based on which interventions are working effectively.

Splitting attendance should be considered very carefully because it presents significant challenges for society and school operations. For example, many teachers have children of their own in other school districts. If these policies are implemented, teachers with children will not be able to report to school to teach if their child in another school has a dedicated school-from-home week.

HEALTHY ACTIVITIES

Schools are an avenue for participation in a number of activities outside of the traditional classroom environment. As much as possible, these activities should continue to be provided to students to support engagement, health, mental wellbeing, and development.

Provide recess

- Do not limit children's access to recess, the schoolyard, or fixed play equipment
- Wash or sanitize hands before and after recess or using high-touch equipment
- Increase supervision to limit high-risk behaviors
- Stagger recess times, or, if necessary, separate classes by schoolyard area

Recess, often the only opportunity to participate in unstructured free-play during the otherwise structured and sedentary school day, is beneficial to children's development of autonomy, participation in physical activity and various sensory and physical experiences, practice of social and motor skills, and attention restoration. As different areas of the schoolyard afford different levels of physical activity, types of play, and social interactions, consider the impact of new recess policies on children's ability to confer the benefits of recess. Schools can develop strategies to reduce the risk of COVID-19 transmission in order to allow for continued use of fixed equipment (play structures) and portable equipment.

One of the most important steps that can be taken is for children and teachers to wash their hands with soap and water both before and after recess. Hand sanitizer containing at least 60% alcohol can be used in situations when this is not feasible. Schools may consider having students use hand sanitizer before and after using high-touch equipment (e.g., fixed equipment or play structures). Recent research indicating that SARS-CoV-2 may be inactivated in sunlight within a relatively short time. Supervision could be increased to ensure safe practices are followed, particularly during high-risk times (start/end of recess) and in high-risk locations (enclosed or small, hard-to-see places on fixed equipment, or anywhere with high child density). Supervisors should maintain physical distance from students and continue to wear masks.

Ideally, recess times could be staggered so that children in different classes or cohorts would not interact (to maintain group distancing). If classes or cohorts must share the same recess time, entry and exit times could be staggered, or different entry and exit locations could be used for each group. If the schoolyard is large and diverse enough to provide adequate space and variety to each class (including access to all types of schoolyard locations and equipment), classes or cohorts could be provided with designated spaces on the schoolyard in which to play (if recess times cannot be staggered). These designated spaces could be rotated frequently (e.g., daily, weekly, depending on the variety available) to provide children access to a variety of schoolyard experiences.

Schools can allow use of shared portable equipment (e.g., balls, wheeled toys) as play with portable equipment promotes physical activity and allows children to practice motor and social skills. Shared equipment can be disinfected between each class/cohort, and students should wash hands after using shared equipment. Schools may also allow children to "sign out" pieces of equipment and clean each piece between uses. When possible, schools could consider how to modify games/activities to promote safe play. For example, the game "tag" could be replaced with "shadow tag," in which children step on each other's shadows instead of touching each other directly.

Modify physical education

- Hold physical education classes outdoors when possible
- Modify activities to limit the amount of shared equipment
- Choose activities that limit close contact over those with a high degree of personal interaction
- Limit use of locker rooms

Physical education aims to develop children into physically literate individuals who have the skills, fitness, and motivation necessary to participate in physical activity across the lifespan. Importantly, while both facilitate physical activity participation, recess and physical education have unique benefits and should not be substituted for one another.

When designing lesson plans, schools could choose activities that limit the amount of shared equipment (e.g., children rotate through stations and equipment is cleaned before/after each use) and contact between students (e.g., children have their own pool noodle to tag others with instead of their hands and to remember to keep distance). As some children may be less physically fit due to limited participation in activities over the previous months, schools could apply progressive overload to allow for safe, gradual increases in workload. Physical distancing, washing hands, and healthy building strategies are particularly important during indoor physical education due to increased breathing rates of students. Locker room access should be limited or staggered. Furthermore, physical education is much more than just physical activity, so schools may consider focusing on teaching the components and values of physical activity and physical fitness, as well.

Reimagine music and theater classes

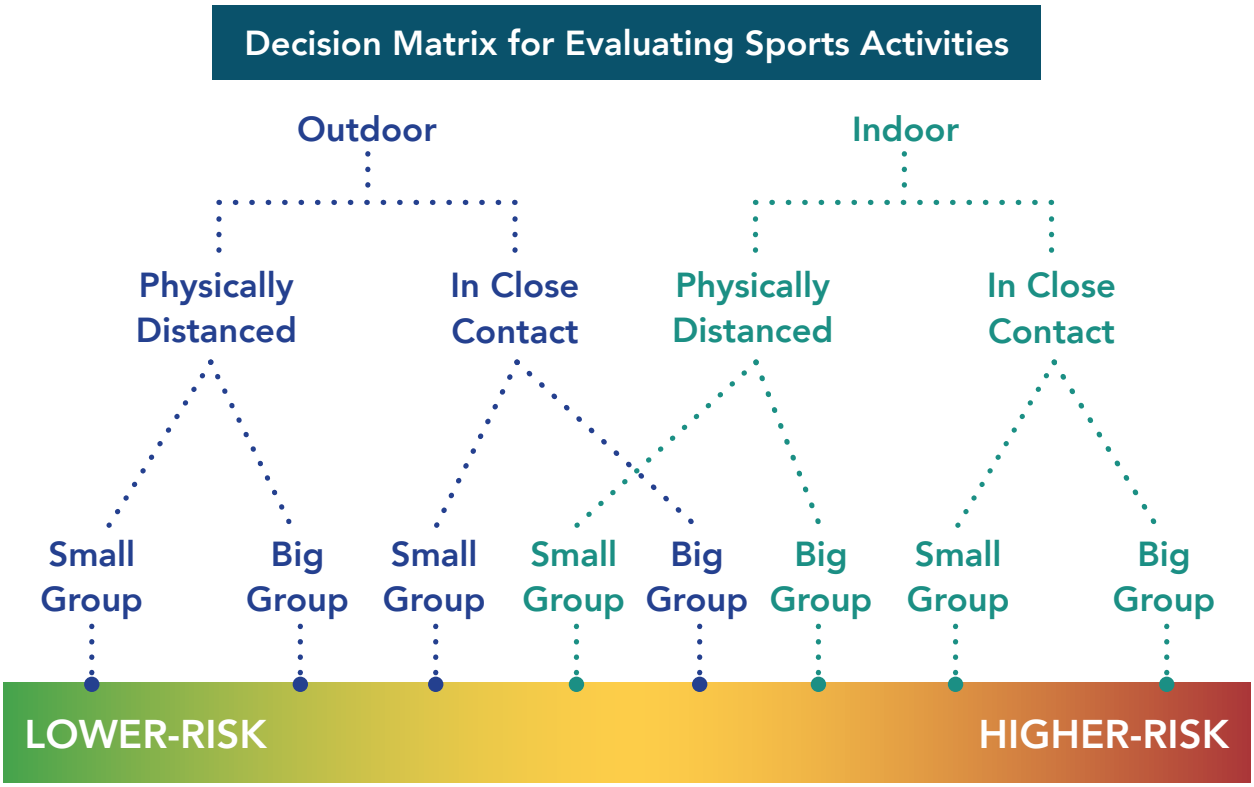
- Replace higher-risk music and theater activities with safer alternatives
- Move outdoors
- Increase space between performers

Music education is associated with numerous benefits, including higher academic scores, better memory recall, and the development of areas of the brain related to language and reasoning. Music and theater education should continue, but there are ways they can be made safer. Instruments that do not involve blowing air from the mouth, such as percussion or strings instruments, could be used instead of higher-risk woodwind instruments, which have the potential for spread of aerosols and droplets. Singing and voice projection are also higher-risk activities that carry a risk of viral transmission through aerosols and droplets. In-class instruction in these higher-risk activities can be replaced with outdoor practice (weather permitting), music theory, theater history, or vocal anatomy lessons. Another option is to continue online instruction for certain instruments, choirs, or ensembles, or practice outdoors in smaller, well-spaced groups. Additionally, all equipment, even student's personal instruments, should be cleaned routinely. Smaller music spaces such as individual practice rooms may be difficult to properly ventilate, so there should be time set aside to keep the door open and clean the room in between uses, or the rooms can be temporarily closed. In theater classes, it may be preferable to focus on rehearsing monologues, remote performances, more performances with small casts that do not require close interaction or performances that can be rehearsed outdoors.

Continue sports with enhanced controls

- Offer every sport if the right controls are in place
- Play outdoors as much as possible
- Limit time spent in close contact and in big groups
- Limit shared equipment, shared spaces, and the number of contacts of the team
- Modify the season schedule and restrict game attendance if feasible
- Analyze each element of practices and games to identify ways to reduce risk
- Wear masks whenever possible

Sport participation offers students a number of psychological and physical benefits and drives physical activity both in childhood and later in adulthood. The risk of transmission for each sport will depend on a number of factors, so decisions regarding specific sports will need to be nuanced. All sports carry some risk of transmission, and that risk varies by the activity. For example, some sports may be a higher risk during competition but can be a lower risk during practice and drills. But even for sports with lower overall risk, there can be periods of higher risk times during practice or in the locker room. The overall risk is not necessarily about the sport, per se, but about the activities taking place within each sport. The flow chart provided in this section may help decision-makers identify the overall risk level of sports activities across three factors: location, distancing, and group size.



Outdoor sports may be less risky than indoor sports, so hold as many practices and games outdoors as possible. Individuals being in close contact increases risk of transmission, so strategies to limit close contact of players should be employed. For example, limit full gameplay to competitions and focus practices on other elements of skill development. Also, consider limiting the number of competitions in a season overall or hold within-team or within-school competitions. To the extent possible, teams should avoid competing with teams that are not local or not part of their conference or league. If big groups are present during the sport, implement strategies to de-densify (e.g., alternate work out days/times for different parts of the team) and maintain physical distancing as much as possible. Teams may also consider ways to shorten the duration of time spent indoors for a particular practice or competition when feasible.

Regardless of overall risk level, there are some strategies that can be implemented in all sports to reduce risk of transmission. An overarching goal is to limit shared spaces, shared equipment, and close contact. This means not using locker rooms or staggering locker room use, limiting shared equipment (which should be cleaned and disinfected frequently), and avoiding team huddles and high fives. In-person meetings (e.g., team meetings) should take place remotely, outdoors, or in spaces where physical distancing can be maintained. Workouts, practices, and drills could be completed individually or in small cohorts to maintain physical distancing and so that equipment can be cleaned between uses. A certain number of practices per week could also be dedicated to at-home workouts.

Consider limiting the number of competitions in a season overall or hold within-team or within-school competitions. To the extent possible, teams should avoid competing with teams that are not local or not part of their conference or league.

The number of people in direct contact with the team and/or staff can be reduced by eliminating or limiting the number of attendees and other non-essential personnel at sporting events. Physical distance between spectators should be maintained, and schools should clearly mark six feet distances in lines, hallways, and/or seating. Spectators, if allowed at all, should wear masks and be asked to bring signs and applaud the players instead of yelling and cheering; playing music on a loudspeaker at certain times during the event may help improve energy without the cheering.

To limit risk during practices and competitions, players, coaches, and attendees should wear face masks whenever possible. While coaches and referees may wear face masks at all times, athletes may wear masks on the sidelines/bench, in locker rooms, and/or during gameplay, depending on the sport. To ensure anyone wearing masks stays hydrated, they should be encouraged to take mask-free water breaks, while physically distanced from others and while following safe mask removal techniques (e.g. only touching the mask from its straps). Team members could have a spare in case the mask gets too sweaty. In addition, athletes should not wear masks during periods of extreme heat or if they have asthma or other breathing problems. Finally, coaches are recommended to analyze every element of practices and games to identify ways to reduce risk, such as using hand or electronic whistles instead of whistles that touch the mouth, and to consider sport-specific strategies (e.g., not switching which side of the court/field each team plays on after halftime, using “kick-ins” instead of ‘throw-ins” in soccer, plexiglass shields instead of cages for hockey).

Add structure to free time

- Establish occupancy limits and clear physical distancing guidelines in common spaces like a library or cafeteria
- Encourage students to remain outside when not in class
- Replace unstructured time with supervised study halls, if feasible

Children in older grades often have more freedom than younger children. Although breaks from classes are important, safety precautions need to be maintained. When possible, schools could have students spend free blocks outside where there is more fresh air, and physical distancing is easier. If inside, schools may consider assigning student classes to specific common spaces (to preserve group distancing), putting limits on the number of students allowed in each space, and creating clear rules and demarcations on how to maintain physical distance. To limit unsupervised time further, schools may consider entirely replacing free blocks with supervised study halls.

When possible, schools could have students spend free blocks outside where there is more fresh air, and physical distancing is easier.

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UPDATED

COVID-19: Guidance for School Reopening

JULY 29, 2020

SickKids®

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Holland Bloorview Kids Rehabilitation Hospital

Kingston Health Sciences Centre
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London Health Sciences Centre

McMaster Children's Hospital

UNITY HEALTH TORONTO

Preamble

The main objective of this document is to advocate for the safe return of children and youth to school by emphasizing the importance of school reopening for broader child health, balanced against the potential and important risks of coronavirus disease 2019 (COVID-19).

This living document is meant to provide information to policy-makers by highlighting paediatric-specific considerations based on our collective experience with children and their families/caregivers. The first version of the document was created by a core group of health-care workers at The Hospital for Sick Children (SickKids) and Unity Health Toronto, including those with expertise in paediatrics, infectious diseases, infection prevention and control, school health, psychiatry and mental health.[1] In this updated version, refinements have been made with contributions and endorsements from other Ontario paediatric hospitals (CHEO, Holland Bloorview Kids Rehabilitation Hospital, Kingston Health Sciences Centre, Children's Hospital at London Health Sciences Centre, McMaster Children's Hospital and Unity Health Toronto), epidemiologists, public health physicians, and a volunteer advisory group of teachers and parents. It was also reviewed by physicians from adult infectious diseases.

Given that educators of elementary and secondary school students are best positioned to appreciate the operational and logistical considerations in adapting school and class routines to incorporate new health and safety protocols, the following is not intended as an exhaustive school guidance document or implementation strategy. The safe return to school is the primary responsibility of the Ministry of Education and should include input from several key stakeholders including the Chief Medical Officer of Health, Ministry of Health, Ministry of Labour, public health authorities, teachers, principals, other school-related authorities, parents and children.

It is essential to note that keeping schools open safely will be facilitated by low case burden and community transmission of SARS-CoV-2 and, therefore, it is imperative that interventions to reduce disease prevalence and community transmission be maintained.

The recommendations in this document were drafted and accepted based on consensus of the authors. Areas of disagreement are highlighted. Where evidence exists, it was summarized and used to form the basis of recommendations. However, several statements are made based on expert opinion with the rationale provided and evidence gaps highlighted. We acknowledge the existence of various support documents from other jurisdictions, including but not limited to those referenced herein.[2-4]

It is important to note that the recommendations reflect the epidemiology of Severe Acute Respiratory Syndrome-coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19, in Ontario as of July 27, 2020 and may evolve as the epidemiology of SARS-CoV-2 changes and as new evidence emerges. It is essential to note that keeping schools open safely will be facilitated by low case burden and community transmission of SARS-CoV-2 and, therefore, it is imperative that interventions to reduce disease prevalence and community transmission be maintained.

As a society and individuals, we all have a significant role in remaining vigilant and adhering to public health recommendations to keep community transmission as low as possible. As academic clinicians and scientists, we are also committed to the conduct of rigorous academic research that will help generate evidence where there may be gaps, which is of critical importance.

The ability of the public school system to effectively carry out its mission will depend in part on the resources made available to the schools. Personnel considerations include the potential need for trained screeners at school entry, health-care providers working with the schools (e.g. telephone or virtual support, on-site support), additional custodian and cleaning staff, and an expanded number of teachers, guidance counsellors, social workers, psychologists and support teachers. The adaptation of the curricula to permit expanded outdoor education and the development of distance learning options will also presumably require resources. Adequate supplies of personal protective equipment (PPE), hand hygiene supplies (soap and hand sanitizer) and environmental cleaning materials will be needed as well. Addressing structural deficiencies, such as large class sizes, small classrooms and poor ventilation, must be part of any plan to reopen schools.

Lastly, it is imperative that there are rigorous testing and contact tracing strategies in place, with clear roles and responsibilities outlined between schools and public health authorities around case, contact and outbreak management to help mitigate the impact in the event of students or teachers/school staff becoming sick at school and/or testing positive for SARS-CoV-2.

Introduction

In considering the reopening and maintaining the safe opening of schools during the current phase of the COVID-19 pandemic in Ontario, it is critical to balance the risk of direct infection and transmission of SARS-CoV-2 in children and youth, school staff and the community, with the harms of school closure on children's physical health, developmental health, mental health and learning. While school closures were reasonable as part of the early pandemic response, current evidence and experience support the concept that children and youth can return to school in a manner that maximizes their health and minimizes risks from a public health perspective.[5-8] The American Academy of Pediatrics,[9] the Canadian Paediatric Society[10] and The European Academy of Pediatrics[11] have issued statements emphasizing the importance of children and youth returning to school. We also believe education to be absolutely critical for the development of children and youth, a human right and a *sine qua* non for the future well-being of our society.

Maximizing Children's Health

Multiple reports from around the world indicate that children and youth account for less than 5-10% of SARS-CoV-2 symptomatic infections.[12-14] In Canada, of 114,597 COVID-19 cases reported as of July 27, 2020, 8,747 (7.5%) were in individuals aged 0-19 years.[15] While this may, at least in part, be related to testing strategies and test performance in children and youth as well as early school closure, there is some data to suggest children, particularly those under 10 years of age, may be less susceptible to SARS-CoV-2 infection and potentially less likely to transmit the virus to others.[16-21] There is also strong evidence that the majority of children and youth who become infected with SARS-CoV-2 are either asymptomatic or have only mild symptoms, such as cough, fever and sore throat.[12, 13, 22-24] Severe acute disease requiring intensive care admission has been described in a small minority of paediatric cases, particularly among those with certain underlying medical conditions, but the clinical

course is much less severe than in adults, and deaths are extremely rare.[13, 14, 25, 26] However, it is important to emphasize that children (especially children with complex medical conditions) have largely been isolated, so it is possible that these data may change over time as children attend school and are interacting more with peers and adults. The recently described multisystem inflammatory syndrome in children (MIS-C) is a serious condition, potentially attributable to SARS-CoV-2 infection, for which ongoing surveillance is required; current data suggests MIS-C is rare, potentially treatable with immune modulatory therapies and associated with a low mortality rate of 0-2%.[27-32]

Thus, the primary impetus for reopening schools is to optimize the overall health and welfare of children and youth, rather than solely to facilitate parent/caregiver return to work or reopening of the economy.

The community-based public health measures (e.g. provincial lockdown, school closures, stay-at-home orders, self-isolation) implemented to mitigate COVID-19 and "flatten the curve" have significant adverse health and welfare consequences for children and youth.[33] Though unintended, some of these consequences include decreased vaccination coverage,[34] delayed diagnosis and care for non-COVID-19 related medical conditions,[33, 35-37] and adverse impact on their social development and mental health.[38-41] Increased rates of depression and anxiety have already been observed; increased rates of substance use and addiction, and suicidal behaviour are believed to have occurred. A recent survey by Children's Mental Health Ontario found one in three Ontario parents reported their child's mental health has deteriorated from being home from school and more than half of the parents noticed behavioural changes in their child.[42] These ranged from drastic changes in mood, behaviour and personality, to difficulty sleeping and more. Those with pre-existing mental health issues have been hit particularly hard. Several organizations, including the American Psychological Association (APA) and World Health Organization (WHO), have highlighted concerns about the potential impact of lockdown on family discord, and family violence including intimate partner violence, and child/youth maltreatment.[43, 44] Risk factors that may contribute to the increased risk of child/youth maltreatment in this context include the heightened rates of parental/caregiver unemployment, family financial stress, parental mental illness, including increased substance use and lack of social supports. Furthermore, current school closures mean that supervision of at-risk children/youth is reduced as is the identification by teachers and other school personnel of children/youth experiencing maltreatment.[45] Thus, the primary impetus for reopening schools is to optimize the overall health and welfare of children and youth, rather than solely to facilitate parent/caregiver return to work or reopening of the economy.

As mentioned, it is critical to balance the risk of direct infection and transmission of SARS-CoV-2 in children and youth, school staff and the community with the harms of school closure, which is impacting children and youth's physical health, developmental health, mental health and learning. Based on the evidence available at the present time and the current epidemiology, it is our view that the adverse impacts of school closure on children and youth significantly outweigh the current benefit of keeping schools closed in order to reduce the risk of COVID-19 in children, youth, school staff and the community at large.

Public Health Implications of Return to School

While the concerns around infection and infectious complications in children and youth appear to be relatively small, it is important to consider the potential role they play in SARS-CoV-2 transmission and disease propagation particularly with respect to teachers, other school staff and families. Children and youth are considered to be efficient transmitters of influenza and other respiratory virus infections and this was one of the rationales for school closures early in the COVID-19 pandemic. However, data from multiple countries suggest that children under 10 years of age are probably less likely to transmit SARS-CoV-2 than older children or adults,[6, 16, 17, 46-48] although the significance and magnitude of that difference remains uncertain. In addition, there are emerging data suggesting that children 10 years and older may transmit SARS-CoV-2 at rates similar to those of adults.[20]

Studies focusing on SARS-CoV-2 transmission in the school setting are limited. However, there is some evidence to suggest that schools do not appear to have played a significant role in propagating SARS-CoV-2 transmission.[5-8] Even when cases have been identified in schools, contact tracing and testing have not identified a large number of secondary cases in most circumstances.[5, 6, 49, 50] Furthermore, several countries have reopened schools without demonstrating a significant increase in cases when community rates have been low.[5, 6, 49-52] Vigilance is nevertheless warranted given the emerging data on transmission from teenagers noted above,[20] reports of school-based outbreaks (e.g. Israel[53] and Chile[54]) and the high seroprevalence rate observed in a high school in a heavily impacted area in France.[55] Regarding the post-return to school outbreak that occurred in Israel, it is noteworthy that both index cases had attended school despite pre-existing mild symptoms, class sizes were large (35-38 students) and crowded, and a heat wave necessitated continuous air conditioning and discontinuation of mask use.[53] Furthermore, of those with confirmed infection, 57% of children/youth and 24% of teachers had no symptoms, symptoms were mild in those who developed symptoms, and no hospitalizations related to the outbreak were reported.

Despite the overall reassuring, albeit limited, evidence cited above, it is imperative that ongoing surveillance and research be conducted on the role of children and youth who are asymptomatic and symptomatic in propagating SARS-CoV-2 transmission once schools are reopened. It needs to be recognized that it will not be possible to remove all risk of infection and disease now that SARS-CoV-2 is well-established in many communities. Mitigation of risk, while easing restrictions, will be needed for the foreseeable future. The mitigation strategies implemented for school reopening have varied from country to country,[56] in part depending on local epidemiology. While outbreaks have been reported in schools in some countries (e.g. Israel[53] and Chile[54]), the risk mitigation strategies appear to have been largely successful in the majority of other countries when community transmission is low.[5, 6, 49-52]

Minimizing Individual and Public Health Risks

Return to school has generally been associated with an increase in cases of community-associated seasonal respiratory viral infections. As a result, it is anticipated

that there may be an increase in cases of COVID-19 and other seasonal respiratory viral infections with similar symptoms upon the resumption of school and appropriate measures should be proactively put in place to mitigate the effects of such an increase. It will be critical to monitor the impact of school reopening on SARS-CoV-2 transmission and thresholds should be identified that would trigger re-evaluation of mitigation strategies as well as the school model. However, given the significant adverse health and social implication of school closure on children, youth and families, and the likelihood that other social factors/clusters (e.g. other congregate settings and large social gatherings) will be the primary drivers of case increases, school closure should be a last-resort intervention; public health measures should prioritize closure of all other non-essential congregate settings prior to school closures. To prevent premature school closing, robust public health interventions, including readily available rapid-turnaround testing and contact tracing, should be prioritized and pre-specified thresholds for implementing more intensive mitigation strategies should be developed. It will be important to thoroughly investigate outbreaks to determine their causes and, specifically, to investigate the role of children and youth versus adults in order to better understand SARS-CoV-2 spread dynamics in general and to be able to improve mitigation strategies.

Public health measures should prioritize closure of all other non-essential congregate settings prior to school closures.

School Delivery

The Ontario Ministry of Education has released guidance around the return to school and identified several options for education delivery, including remote, hybrid/adapted and daily in-person.[57] Potential advantages and disadvantages of various school models are summarized in Appendix 1. In our view, given the current epidemiology, a daily school model is best as it allows for consistency, stability and equity regardless of the region in which children and youth live. Though full-time remote learning would diminish the likelihood of SARS-CoV-2 transmission, it almost certainly would be insufficient to meet the needs of Ontario children and youth. A hybrid/adapted model would also likely be inferior (especially in elementary school) to a daily school model in terms of educational outcomes, would be problematic for working parents and caregivers, and it may not lead to reduced risk of SARS-CoV-2 spread because of the potential need for families to find care on off days (e.g. many families may engage grandparents or high-school students as babysitters or combine resources with other families). Irrespective of the chosen model, educators should prepare for transition from one model to another depending on local SARS-CoV-2 epidemiology. For example, temporary transition to hybrid or full-time distance learning may be needed if a large-scale school-based outbreak were to occur.

Our recommendation from an overall health perspective is that children and youth return to a daily school model with risk mitigation strategies in place.

Emerging evidence indicates that the social and economic burden of COVID-19 disproportionately impacts racialized communities and those with less wealth.[58] This is likely related to a variety of factors, including more crowded living spaces, reduced access to health care, PPE or testing, and, for some, frontline work with increased exposure risk.[58] Distance learning further disadvantages children and youth living in higher-burden COVID-19 areas where socioeconomic and language barriers limit access to quality online learning. The effect on these children's and youth's education has already been substantial and further delays of return-to-school will almost certainly compound educational disparities.

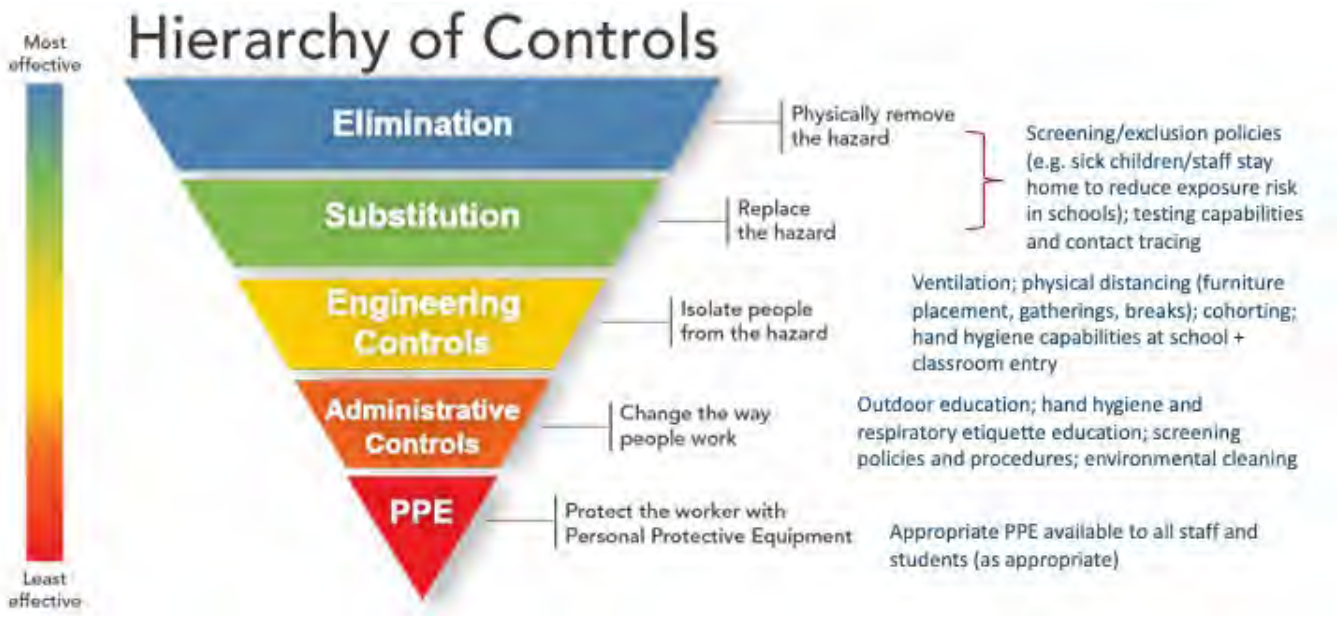
Our recommendation from an overall health perspective is that children and youth return to a daily school model with risk mitigation strategies in place. Educators must be consulted to provide input on each model from a learning impact lens. It is important to acknowledge that there is not one specific measure that will prevent infections from occurring in schools, but rather a bundle of infection prevention and control measures that need to be put into

place to help reduce infection risks (Figure 1, Hierarchy of controls; adapted from CDC, available at: https://www.cdc.gov/niosh/topics/hierarchy/default.html).[59] Equity of resources and management/auditing of these risk mitigation strategies will be critical, and policy makers must ensure that an ethical framework with transparent rationale is provided to the public to ensure buy-in and trust in the decisions made.

At the same time, it is important that the new normal in school is designed to optimize learning and social development, while ensuring that the health and safety of teachers and school staff remain a top priority. With this in mind, the following sections of the document summarize the considerations for school reopening based on the available evidence, as well as expert opinion, organized into the categories that follow. Where appropriate, recommendations have been provided for elementary school (Grade K-5), middle school (Grades 6-8) and high school (Grades 9-12) classes/students.

1. Screening to prevent symptomatic individuals from entering the school
2. Hand hygiene
3. Physical distancing
4. Non-medical and medical face masks for students
5. Cohorting
6. Environmental cleaning
7. Ventilation
8. Mitigation of risk for students at higher risk for severe disease
9. Special considerations for children and youth with medical, physical, developmental and/or behavioural complexities
10. Mental health awareness and support for all children
11. Protection of teachers and school staff
12. Protection of at-risk persons or families
13. Management of suspected and confirmed SARS-CoV-2/COVID-19 cases and their contacts
14. Communicating about COVID-19 to children, youth and parents/caregivers
15. Opportunities to improve evidence-based decision making
16. Additional considerations

Figure 1. Hierarchy of Controls (Adapted from CDC)[59]



1. Screening to prevent symptomatic individuals from entering the school

In order to prevent the spread of SARS-CoV-2 infection, students, teachers and other employees who have signs/symptoms of COVID-19 (according to Ministry of Health and local public health guidance) must stay home and decisions about testing and return to school should be guided by provincial public health guidance. In addition, return to school decisions for those who have had an exposure to SARS-CoV-2 should be in accordance with local public health recommendations.

Guidance Statement(s):

- It is essential that strict screening and exclusion policies are in place for students and employees who are symptomatic or have been exposed to SARS-CoV-2 and directed to self-isolate by public health.
- Teachers and principals should be provided with information on symptoms of COVID-19 in children[60] so that appropriate action can be taken if children develop symptoms during the day.
- Screening students for signs and symptoms of SARS-CoV-2 infection could occur prior to arrival at school, on site (i.e. at the school) or a combination.
    - Daily screening on site provides reassurance that the screening has been completed, however, it could result in increased lines (resulting in crowding and mixing between children, youth and parents/caregivers) and is likely not practical without significant staggering of start times. It is also not reasonable to expect teachers or other school staff to perform routine screening in addition to their regular work tasks.
    - We would strongly recommend that parents and caregivers be empowered to play an active role in daily screening of their children and youth prior to them leaving for school. A standard checklist should be provided for parents/caregivers/older students for this purpose (language and literacy considerations will be important). Parents/caregivers may require access/support from a health-care provider and/or local public health unit when they are unsure. This is especially the case for children and youth with underlying medical conditions and chronic symptoms.
    - Provision of an attestation of completion of the daily screening (either virtual, such as a cell phone app, or paper for those unable to do so virtually) would add extra assurance, but consideration should be given to ensure that the process is not onerous such that it disadvantages groups with limited technological supports.
    - Parents/caregivers should be educated around the importance of providing truthful information both for their child and others' safety. This has been the approach taken by public health for other communicable disease.
- If screening students as they enter the school is selected as a strategy, additional staff and infrastructure resources would be required and appropriate training provided to them to effectively complete the task.
- On-site temperature measurement or pulse oximeter checks are not recommended because fever and hypoxia are not consistent symptoms in children and youth (present in only a minority of cases)[61] and would result in lines and delayed school entry, and has not been shown to be an effective screening strategy to date.
- Employers and the government play a critical role in supporting parents/caregivers who need to stay at home with their child because their child is sick or in isolation due to SARS-CoV-2 infection or exposure. This support is essential to reduce the burden on parents/caregivers and reduce the likelihood parents/caregivers will need to send their child/youth to school with symptoms (e.g. paid sick days available for workers).
- Virtual learning or other forms of structured learning should be put in place for children and youth who are required to stay home because they are sick or in isolation due to SARS-CoV-2 infection or exposure, or if parents/caregivers choose to keep their child/youth home from school. It will be important to continue to work to identify options for students who have limited internet availability or other barriers to online learning.

2. Hand hygiene

SARS-CoV-2 and other respiratory viruses are primarily spread by respiratory droplet transmission and should be the focus of preventative measures. As a result, and because virus shedding may occur prior to symptom onset or in the absence of symptoms, routine, frequent and proper hand hygiene (soap and water or hand sanitizer) is critical to limit transmission.[62] Proper hand hygiene is one of the most

effective strategies to prevent the spread of most respiratory viruses, including SARS-CoV-2, alongside respiratory etiquette, particularly during the pre-symptomatic phase of illness.

Guidance Statement(s):

- Children and youth should be taught how to clean their hands properly (with developmentally and age-appropriate material)[63] and taught to try and avoid touching their face, eyes, nose and mouth as much as possible. This should be done in a non-judgmental and positive manner.
- Respiratory etiquette; children and youth who have symptoms of a respiratory tract infection must stay home and should be reminded to sneeze or cough into a tissue followed by hand hygiene, or their elbow/sleeve if no tissue is available.
- There should be age-appropriate signage placed throughout the school to remind children and youth to perform proper hand hygiene.
- Students and staff should perform hand hygiene upon entering and before exiting the building, after using the washroom, before and after eating, and before and after playtime with shared equipment/toys. In addition, a regular schedule for hand hygiene, above and beyond what is usually recommended, is advised. Possible options would be to have regularly-scheduled hand hygiene breaks based on a pre-specified schedule. For practical reasons and to avoid excess traffic in the hallways, the preferred strategy for these extra hand hygiene breaks would be hand sanitizer unless sinks are readily available in the classroom.
- If masks are worn, students and staff should be instructed to perform hand hygiene before putting on and after touching or removing their mask.
- Access to hand hygiene facilities (hand sanitizer dispensers and sinks/soap) is critical with consideration for ensuring accessibility for those with disabilities or other accommodation needs (See Section 9 for additional considerations). Hand sanitizer (60-90% USP grade alcohol, not technical grade alcohol) should be available in all classrooms. Safety precautions to avoid toxic exposure (e.g. ingestion) from hand sanitizers should be in place.
- Adequate resources and a replenishment process need to be in place to ensure supplies are available to perform hand hygiene frequently. Liquid soap and hand sanitizer will need to be replenished and tissues available for drying. No-touch waste receptacles should be available for disposal of materials.

3. Physical distancing

The objective of physical distancing is to reduce the likelihood of contact that may lead to transmission and has been a widely used strategy during the pandemic.[64] In the school setting, several control measures can be put in place to encourage physical distancing, especially when prolonged exposure is expected (e.g. in the classroom). However, while physical distancing and its role in the prevention of infection transmission should be discussed with students of all ages, it is likely not practical to enforce strict physical distancing in elementary school children, especially during periods of play. Cohorting (discussed in Item #5) is an additional strategy that can be used to facilitate close interactions, while minimizing the number of potential exposures. Interaction, such as playing and socializing, is central to child development and should not be discouraged.

Current distancing recommendations in Canada and the United States are 2 metres and 6 feet, respectively. However, it is recognized that a 1 metre (or approximately 3 feet) separation also provides protection[64] and may approach the benefits of 2 metres (approximately 6 feet) in the school setting where children should be asymptomatic,[9] and especially for younger children as they are likely less efficient transmitters of SARS-CoV-2.[6, 16, 17, 46, 47] In middle and high school students, physical distancing is an important strategy, especially during periods of prolonged exposure indoors (e.g. the classroom), and they are more likely able to adhere to distancing recommendations. We emphasize that distancing is not an all-or-nothing proposition and optimizing distancing in as many indoor school settings as possible will likely diminish SARS-CoV-2 transmission substantially.

It is also acknowledged that transmission of the virus will likely be attenuated in outdoor settings and outdoor play and learning have many benefits for children and youth. School boards and educators should therefore incorporate outdoor learning activities into the curriculum.

Guidance Statement(s):

Education:

- The role of physical distancing to prevent infection transmission should be discussed with elementary, middle and high school students.
- All students should be informed about how physical distancing has been implemented in the school (e.g. desks separated, expected behaviours) and the expected practices in the school environment.
- Physical distancing will likely be difficult to strictly enforce in elementary school children, but developmentally and age-appropriate education can emphasize the importance of hand hygiene, avoiding body fluid exposure, avoiding putting toys in their mouth good respiratory etiquette and avoiding close contact especially for long periods of time (e.g. touching, hugging, hand holding).

Classrooms

- When students are in the classroom, efforts should be made to arrange the classroom furniture to leave as much space as possible between students,[65] with seats facing the same direction, where possible.
  - For elementary and middle school students, a 1 metre (3 foot) separation between desks in the classroom may be a reasonable balance to achieve beneficial effect from distancing and to practically accommodate children in the classroom. For desks that are configured in a manner that makes this impractical, a 1 metre separation between students can be considered. However, further data on age-related transmission risks may help to refine this recommendation.
  - For high school students, a separation of 2 metres between students is preferred given the transmission risk may be higher in this age group.
- Smaller class sizes should be a priority strategy as it will aid in physical distancing and reduce potential spread from any index case. Several jurisdictions have reopened schools with maximum class sizes ranging from 10-15.[56] However, there is limited evidence on which to base a pre-specified class size. Decisions should take into account the available classroom space in addition to the number of exposures that would occur should a student or staff test positive.
- Where needed, the use of non-traditional spaces should be explored to accommodate smaller classes in order to allow daily school attendance. This may necessitate additional teacher/educational resources.
- Educators should be asked to assess and incorporate outdoor learning opportunities as weather permits. This will likely require specific programming and resources to optimize learning activities.

Large gatherings/assembly

- Large gatherings/assemblies should be cancelled for the immediate future. Any gathering size should be in accordance with local public health guidance.
- Choir practices/performances and band practices/performances involving wind instruments may pose a higher risk of transmission.[66, 67] As such, it is recommended that these be cancelled for the immediate future. When the situation allows, special consideration should be given to safely resuming such activities (depending on local epidemiology and performance venue).
- When and if band practices/performances involving wind instruments resume, ideally instruments should not be shared between students. If sharing is required due to limited supply of instruments, it is essential that the instruments be thoroughly cleaned and disinfected between use.

Lunch and recess breaks

- Stagger break and lunch times (or have lunch in classrooms) to reduce larger crowds in cafeteria settings and keep groups of students together (see cohorting below).
- Hand hygiene should be performed prior to and after lunch breaks, with easy access to hand sanitizer.
- If weather permits, lunch and nutrition breaks should be held outside.
- Shorter lunch breaks with more frequent nutrition breaks may help reduce the length of less supervised interactions.

Outdoor and other activities

- During outdoor activities, such as recess, physical distancing should not be strictly enforced especially in elementary school children. A cohorting strategy (see Section #5) is preferred.
- All students should perform hand hygiene before and after sports activities/outdoor play/playground use.
- Sports and physical education classes should be encouraged and continue with risk mitigation strategies in place. It is advisable to delay restarting close contact sports (e.g. wrestling, rugby, football), as well as indoor team sports (e.g. basketball). When the situation allows (e.g. based on local epidemiology), special consideration should be given to their safe restart. We note that physical education classes will be much easier to have outside on a regular basis than other pedagogic activities.
- Hand hygiene is critical prior to and after all sports or physical activities.
- Sports equipment (e.g. balls, hockey sticks etc.) should be cleaned at the conclusion of the activity.
- Sharing of personal sports equipment should not occur.
- Schools should endeavour to offer as many of their usual clubs and activities as possible. Most clubs and activities, with the exception of choir/band, should involve less crowding than regular classes, and so should be feasible inside or outside.

4. Non-medical and medical face masks for students

The use of non-medical cloth masks/face coverings (NMMs) in the school setting is a complex and nuanced issue. Unfortunately, current evidence does not provide clarity on the optimal approach and needs to consider the broad range of student ages and developmental levels, the varying ability to practice physical distancing indoors, as well as the dynamic level of risk associated with community spread at any particular time and within specific communities. Based on current public health guidance recommending or mandating the use of NMMs in indoor public settings, we are currently recommending the use of masks for high school students (with consideration for middle school students) whenever physical distancing cannot be maintained (provided there is no contra-indication for developmental, medical or mental health reasons). It is important to try to find periods in the day where NMMs can be safely removed. However, given that there has been considerable disagreement among the authors around this issue, it will be critical to assess the use of masks on an ongoing basis throughout the school year and adjust accordingly based on the development of further evidence, changes and epidemiology. The following paragraphs highlight some of the important complexities of using masks in children, in particular as it relates to elementary school students.

The benefit of NMMs and medical masks is that they may reduce transmission from individuals who are shedding the virus, as they may help to prevent the respiratory droplets from the wearer from coming into contact with others.[68] While NMM use has been recommended and/or mandated for use by public health authorities in Ontario in indoor spaces,[69] it is important to note that their use is recommended primarily for source control (i.e. preventing infectious particles from spreading from the wearer), not as PPE. In children and youth, there are limited data on the effectiveness of NMM use for source control, but there remains a theoretical benefit especially for older children and youth. However, in order to be effective, NMMs would need to be worn correctly, which for many otherwise healthy children and youth will be difficult to do for a full school day; even more significant barriers exist for children and youth with underlying medical, developmental and mental health conditions.

In some countries, particularly in Asia where masking culture is more ingrained and longstanding, children have worn NMMs upon return to school. However, several European countries have had children successfully return to school without NMMs.[6] Evidence specific to children and youth on NMMs is lacking.

Until there is definitive evidence, decisions around NMM use in schools should take into consideration the benefit from source control (which may vary by age) balanced with the negative consequences/risks (e.g. increased facial touching, false sense of safety) of NMM use. As noted above, the practicality of wearing a NMM for prolonged periods of time is an important consideration. Other factors to consider include availability of other risk mitigation strategies, local epidemiology and community public health directives. Finally, given this uncertainty, we feel that the perspective of educators on the front lines has to be taken into account when deciding on policy and implementation considerations relating to masking. Preferences in this regard might well vary across jurisdictions in relation to local epidemiology and perceived risks.

There was not full agreement among contributors on the need and role of NMM use in children in different circumstances. The guidance statements below reflect the consensus (preferred) recommendation and the percentages indicate the level of agreement among the contributing paediatric care providers (n=36).

Consensus Guidance Statement(s):

- The use of NMMs in the school setting should be driven by local epidemiology with age-specific considerations (agree 94%, neutral 3%, disagree 3%).
- When transmission in the community is low, the use of NMMs throughout the entire school day should not be mandatory for elementary, middle or high school students returning to school. But, NMM use should always be respected if a student chooses to wear one. Safe masking practices (e.g. proper wearing/storage/removal) should be reinforced with educational materials provided to parents, students and teachers (agree 78%, neutral 11%, disagree 11%).
- Given the current epidemiology, the use of NMMs is not recommended for elementary school students (agree 61%). A significant minority supported the use of NMMs when physical distancing was not possible (agree 33%).
- Given the current epidemiology, the use of NMMs is recommended for middle school students whenever physical distancing cannot be maintained, provided there is no contra-indication for developmental, medical or mental health reasons (agree 64%). A minority supported the mandatory use of NMMs at all times (agree 8%).
- Given the current epidemiology, the use of NMMs is recommended for high school students whenever physical distancing cannot be maintained, provided there is no contra-indication for developmental, medical or mental health reasons (agree 61%). A minority supported the mandatory use of NMMs at all times (agree 22%).
- As it is difficult to wear a NMM for a prolonged period of time, efforts should be made to ensure distancing in the classroom such that NMMs do not need to be worn constantly (see physical distancing section) (agree 92%, neutral 8%). Otherwise, it is important to try to find periods in the day where NMMs can be safely removed.
- In the setting of high or rising community transmission or school outbreaks (as directed by public health), the role of NMM use should be reassessed.
- Any recommendation or requirement to wear NMMs needs to address issues around equitable access to masks
- School-aged children and youth who are not able to remove their NMM without assistance should not wear a NMM due to safety concerns.[69] NMMs should also not be worn by children or youth who cannot tolerate a NMM due to cognitive, sensory or mental health issues.
- Rationale should be provided to children and youth to reconcile any differences in guidance between school and other indoor spaces (if public health mandates exist in their region). This could be accomplished by discussing the other safety measures in place (e.g. screening, hand hygiene, physical distancing, cohorting) that are being used to protect students and teacher/staff.
- Face shields as a mitigation strategy are not routinely recommended for elementary school students (agree 86%), middle school students (agree 89%) and high school children (agree 80%). But face shield use should be respected if a student chooses to wear one with or without a NMM.

The following points were considered in developing this guidance:

- Public mask wearing is likely beneficial as source control when worn by persons shedding infectious SARS-CoV-2 virus when physical distancing is not possible in public spaces (e.g. public transit, grocery store).[68]
- There is a lack of evidence that wearing a NMM prevents SARS-CoV-2 transmission in children and youth, though it remains likely, especially for older children and youth. The

benefit for younger children may not be significant both because their baseline infection and transmission risk is probably lower and because of a higher likelihood of improper NMM use.

- It is recognized that high school-aged students and to lesser extent middle school-aged children may be able to wear NMMs for a longer period of time than younger children without close monitoring.
- Children and youth's social development hinges upon their interactions, facial expressions and body language. Though important for all age groups, this is particularly so for younger children.
- If worn incorrectly (e.g. touched frequently, not covering mouth and nose, removed and placed back without hand hygiene), NMMs could lead to increased risk of infection.
- It is impractical to expect most children and youth to wear a NMM properly for the duration of the school day. Elementary school-aged children, in particular, would need assistance to follow appropriate procedures for putting on and taking off the NMM (e.g. during meal times, snack times). In addition, during these times when the NMM is removed, the NMM would need to be stored appropriately to prevent infection spread.
- While teaching and training children and youth on appropriate NMM use may overcome some of the limitations of NMM use, studies have shown that it is difficult for health-care workers to wear a mask for prolonged periods in the hospital setting and it is therefore anticipated that it would be difficult for children as well.
- The NMM may not be tolerated by certain populations with underlying conditions (e.g. asthma, allergies, neurodevelopmental disorders, mental health challenges) and especially during warm/humid weather conditions.
- The addition of NMMs may increase anxiety, interfere with the therapeutic learning environment, and increase inattention or distraction in children and youth, particularly for those who may already struggle with attention, such as those with attention deficit hyperactivity disorder (ADHD) or other developmental disorders.
- Children and youth with expressive communication difficulties (including those with articulation problems, neurologic issues), those who are learning the primary Canadian language of instruction (English or French) as a second language, and many others may be disproportionately adversely affected by having to wear a NMM at school.

- The benefit of NMMs may be attenuated by the repeated and prolonged interactions at school. Children attend school for a significant portion of their waking hours and, as such, interactions are more similar to their home environment compared to brief community interactions where NMMs are recommended.
- It is likely that NMMs will be disposed of improperly throughout the school and potentially lead to increased risk by children playing with them. It is acknowledged that while fomite spread is not the predominant mode of transmission,[70] it likely contributes to transmission given evidence demonstrating presence of SARS-CoV-2 in the vicinity of infected individuals and the fact that fomite transmission does occur with other respiratory viruses, including human coronaviruses.[71]
- It will be very difficult for teachers and/or school administrators to enforce mandatory masking both in elementary and secondary schools.
- Patients have been required to wear a mask at numerous paediatric health-care facilities. In this context, mandatory masking is typically for a brief and well-defined period of time, when children and youth can be closely monitored by their parents and hospital staff to ensure appropriate mask use. This is also intended to prevent transmission to a population with significant medical comorbidities and/or immune compromise. Similarly, some jurisdictions have mandated that persons over 2 years wear masks in indoor spaces. Again, this is a time-limited scenario where they can be monitored by their parents/caregivers and should be differentiated from the school setting. Furthermore, the school setting is different from most settings where indoor masking is mandated where large numbers of strangers interact (e.g. shopping malls), physical distancing is difficult and contact tracing is not possible.
- Face shields have been suggested by some as an alternative to face masks as they may block aerosolized droplets. This supports its current use as a component of PPE, but there is currently no evidence that face shields alone are effective as source control.[72]

5. Cohorting

The purpose of cohorting is to limit the mixing of students and staff so that if a child/youth or employee develops infection, the number of exposures would be reduced. It also allows for more timely case and contact follow-up. For example, a single class in Grade 1 could represent a cohort and they should avoid close mixing with individuals from other classes/grades in confined indoor spaces. Cohorting is likely most beneficial in elementary school children where physical distancing is less practical. For high school students, the need to take different classes may make strict cohorting difficult and, as a result, physical distancing should be emphasized. We recognize that this poses a significant infrastructure challenge for many schools. The benefits of cohorting will be attenuated in many, such as those who require bus transport to school and those who require after-school care; such children could potentially be present in several cohorts (e.g. class cohort, bus cohort, after-school cohort).

Guidance Statement(s):

- To the extent possible, cohorting classes could be considered for the younger age groups and for children and youth with medical and/or behaviour complexities (see Section 9), so that students stay mostly with the same class group and there is less mixing between classes and years. This applies to both indoor as well as selected prolonged outdoor activities with close physical interactions.
- Student well-being and mental health should be prioritized, however, such that class or program switching should not be denied on the basis of cohorting.
- Cohorting and mixing should take into consideration the number of children/youth that would be exposed should a student or staff test positive for SARS-CoV-2 with the goal of minimizing the number of contacts.

6. Environmental cleaning

SARS-CoV-2 has been detected on a variety or surfaces[73] and survival depends on the type of surface. It is possible that infection can be transmitted via fomites by touching contaminated surfaces and then touching mucous membranes (i.e. mouth, nose, eyes).[74] While fomite transmission is not the predominant mode of transmission,[70] environmental cleaning and disinfection are important to reduce the risk of transmission of SARS-CoV-2 and other infections in schools.

Guidance Statement(s):

- A regular cleaning schedule, using Health Canada-approved disinfectants,[75] should be used with emphasis on high-touch surfaces and washrooms.
- Efforts should be made to reduce the need to touch objects/doors (no-touch waste containers, prop doors open).
- Policies to ensure there is "no sharing" of food, water bottles or cutlery should be enforced as a priority.
- The importance of hand hygiene to children after contact with any high-touch surface (such as door handles) should be reinforced.
- When possible, toys and class equipment that can be cleaned and disinfected by staff and/or students (as appropriate) should be used.
- School closures during school hours for the purpose of more intensive cleaning may carry more harm (in the form of missed instruction time) than benefit.

7. Ventilation

It is expected that environmental conditions and airflow influence the transmissibility of SARS-CoV-2. Adequately ventilated classroom environments (e.g. open windows with air flow, improved airflow through ventilation systems and reduction in recirculated air) are expected to be associated with less likelihood of transmission compared with poorly ventilated settings.

Guidance Statement(s):

- Attention should be paid to improving classroom ventilation (e.g. optimizing ventilation system maintenance and increasing the proportion of outside air brought in through these systems) in consultation with experts in physical plant design and modification.
- The use of outdoors or environments with improved ventilation should be encouraged (e.g. keeping windows open, weather permitting).

8. Mitigation of risk for students at higher risk for severe disease

Some children may be at higher risk of adverse outcome from COVID-19 due to underlying medical conditions, such as immunocompromised states or chronic medical conditions, including cardiac and lung disorders and neuromuscular disorders.[26, 76, 77] Children and youth who have medically complex conditions, particularly those with medical technological supports associated with developmental disabilities and/or genetic differences, are also in a potentially higher risk category.[26] At the present time, there is no convincing evidence to suggest the level of medical risk to these children and youth from SARS-CoV-2 is different from other respiratory viruses. As a result, given the unintended consequences associated with not attending school, attending school is recommended for the majority of these children and youth (see Section 9 for more details pertaining specifically to medically and behaviourally complex children and youth). Nevertheless, we recognize that the data pertaining to this group of children and youth is limited as they have likely been following isolation rules even more stringently than healthy children and, therefore, it is essential that ongoing monitoring take place so that adjustment of the school model and preventive interventions can be made according to emerging evidence.

Guidance Statement(s):

- The majority of children and youth with underlying medical conditions should be able to safely attend school provided that the appropriate enhanced safety measures are in place. However, it is recommended that parents/caregivers discuss this with the child's health-care providers so that they can make an informed decision based on individual circumstances. This is particularly relevant for children with newly diagnosed illnesses requiring the first-time use of new or augmented immunosuppression.
- In the event that such children/youth have a documented exposure to SARS-CoV-2, in addition to involvement of the local public health unit, it is recommended that the child's/youth's parent/caregiver(s) contact the child's/youth's health-care provider for further management if they have concerns.

9. Special considerations for children and youth with medical, physical, developmental and/or behavioural complexities

Return to school will present unique challenges to children and youth with medical, developmental and/or behavioural complexities and their families. This includes children

requiring intensive supports for activities of daily living and/or medical conditions, such as feeding, toileting or breathing supports. Many of these families have had a prolonged period of time in home isolation compounded by a lack of respite and/or homecare supports. In particular, the challenges for families and children/youth with neurodevelopmental disorders, such as autism spectrum disorder, caused by cessation of school during the pandemic have been identified.[78] Transitioning medically and behaviourally complex children and youth back to school requires specific focus and should be prioritized as many of these children/youth and families have been disproportionately impacted by the pandemic response and are already in crisis mode.[79] Consultation with their parents and families to better understand their individual circumstances and needs is recommended.

Children and youth with medical, physical, developmental and/or behavioural complexities often have educational assistants (EAs) and nursing support in the school environment who may assist children/youth with toileting, suctioning, cough assist and G-tube feeds. These individuals require additional consideration with regards to measures to help mitigate their personal infection risk and infection transmission to others.

Guidance Statement(s):

- Parents/caregivers may consider scheduling appointment(s) with their health-care provider(s) for a return to school consultation(s) if the they think their child's/youth's complexities and medical status warrant this.
- Parents/caregivers and school staff should liaise to accommodate a more individualized return to school to ensure smoother transitions. Equitable access to school is essential.
- Children and youth with neurodevelopmental disorders/behavioural challenges should be allowed modified transition back to school. Optimally, this would involve the option to visit the school prior to general school opening. Difficulties with transitioning back to school should not be used to exclude children and youth from school and any delayed transition plans need weekly reassessment.
- Behaviour/ASD school board teams need to be involved in transition planning prior to school re-entry for children and youth who are likely to have significant challenges. More resources may need to be devoted to these teams due to increased demand.
- In cases where therapists (both internal and external to the school board) are supporting a child/family, active communication between the school, parents and therapist are encouraged to develop transition plans.
- Ensure that those families who choose not to send their child/youth to school receive remote learning opportunities and do not lose access to in-home supports, including home care and respite supports.
- Ensure that students continue to receive access to therapy and nursing services while in the school. Maximize continuity among those providing services and/or use virtual care for service provision, to decrease exposures. If in-school rehabilitation supports are delayed, accommodations should be made to ensure that their rehabilitation needs are being met either at home or in person at their local children's treatment centre.
- Provide environmental (e.g. smaller class size) and classroom supports (e.g. teacher aides) for those children and youth who may need assistance with hygiene measures.
- Guidelines for children and youth with complex respiratory needs, including ventilation/tracheostomy, are currently being developed by respiratory medicine specialists and the team from Holland Bloorview Kids Rehabilitation Hospital in consultation with public health.
- Policies and procedures should be in place for the cleaning of specialized equipment.
- EAs and nursing staff who support activities of daily living and cannot physically distance require appropriate PPE. Ideally, EAs should be assigned to a single classroom (if appropriate) and every effort should be made to minimize sharing of EAs between classrooms.
- The additional resource requirements to facilitate safe return to school should not be a barrier to return to in-person education for children and youth with medical, developmental and/or behavioural complexities.

10. Mental health awareness and support for all students

A proactive approach to school reopening is important in order to minimize the adverse mental health impact on children/youth.[33] Where foreseeable, schools and school boards should make every effort to address known sources of distress and extend flexibility within existing administrative processes.

For example, many children and youth enrolled in transition years (Grades 6, 8, 12) during the 2019-2020 school year were required to make decisions regarding special education programs, school registration, or other specific educational programming in the absence of usual sources of information, including school visits or meetings. Every effort should be made to allow program flexibility in this regard during the first months of the school year, in the event that children/youth and parents realize they have made an incorrect program or school choice. It can be anticipated that rigidity would likely lead to increased stress, anxiety, depression and school refusal that could be otherwise avoided.

Similarly, children and youth can be anticipated to return to school at different academic levels even within a classroom. It will be critical to provide opportunities for early identification of learning needs and academic support to ensure that children and youth neither become overwhelmed nor bored in the school setting, as these are frequent antecedents to school refusal and mental health problems.

It can be anticipated that some children and youth may experience increased stress and anxiety related to the COVID-19 pandemic or to the implementation of risk mitigation strategies in their school environment.[39, 80] In addition, children and youth may have pre-existing mental health conditions, such as anxiety, depression, ADHD and substance abuse, which may have been exacerbated by lockdown measures, including school closures, and may experience symptom escalation on return to school. Educators should have adequate guidance and information about possible signs of mental health struggles and parents and educators should be encouraged to engage with their associated school-based health centre where available or encourage families to seek support from the child's/youth's physician.

Guidance Statement(s):

- Flexibility in program and/or school enrolment should be provided for children and youth who have transitioned to a new program or school for the 2020-2021 school year. Students who are particularly anxious about attending a new school should be offered the opportunity to visit the school in the week prior to the first day of school.
- Increased and timely in-school educational support should be provided to students and classroom teachers to enable early identification and remediation of learning gaps that some students will have incurred during the school closures.
- Teachers should be vigilant to potential child maltreatment situations given current concerns regarding possible elevated risk of child maltreatment that may have been undetected during the period of school closures.
- Children and youth with mental health concerns may or may not require graduated transition back to school; where required, active communication between the school, parent, youth and therapist should be undertaken on a regular basis to ensure continued progress toward full-time return to school.
- Accessible mental health support services adapted for diverse groups and at-risk populations should be provided, ideally in collaboration with educators, mental health professionals, and paediatricians.

11. Protection of teachers and school staff

Although this document is focused on school-aged children and youth, we believe the safety of school staff is paramount, with the goal of having teachers and school staff, at a minimum, as safe in the classroom as they would be in other community or work environments. We recognize the tremendous challenge that teachers face from a personal, health perspective, as well as from an operational lens. Risk mitigation for teachers and other school staff should take into account situations where close contact and possible body fluid exposure (i.e. saliva, respiratory secretions) may occur. We have provided several considerations, but detailed recommendations are beyond the scope of this document.

Guidance Statement(s):

- Physical distancing of school staff from children/youth and other staff should be emphasized. Teachers should maintain a distance of 2 metres (~6 feet) from students and other staff as much as possible, recognizing that distancing will not be feasible in classrooms with the youngest children.
- Staff lounges and common areas should be restructured (as needed) to ensure physical distancing, and staff should be reminded of the importance of distancing from other staff. Whenever physical distancing cannot be maintained, whether in the classroom or other parts of the school building, we recommend the wearing a face mask/covering.
- Facial expression is a critical part of communication, particularly for younger children, children for whom English/French is a second language, and children with certain underlying conditions such as hearing impairment or speech delay. Facial expression is also critical to teacher-student connection, which is an important factor in teacher effectiveness. This should be taken into consideration when developing NMM and PPE strategies for teachers.
- Depending on community infection rates, if close prolonged contact with others cannot be avoided, the use of personal PPE is recommended with input from experts in occupational health and safety and the Ministry of Labour. However, if used in the classroom, the teacher should explain the rationale to the children/youth in a developmentally appropriate manner.
- It is acknowledged that some teachers and other school staff may choose to regularly wear NMMs or other PPE. This is a personal choice and should not be discouraged.
- Staff may need to use enhanced PPE, including medical masks, face shields, gowns and gloves, in specific situations (e.g. the child who becomes ill at school and needs close physical attention). Such PPE should be readily available together with the training and policies/procedures to deal with this situation. Having designated staff trained in PPE use may facilitate preparedness and comfort among staff.
- Policies and procedures need to be developed in consultation with individuals with occupational health and safety expertise for **all** staff, in particular staff workers that have increased risk of severe outcomes/complications from COVID-19 (e.g. high-risk immunocompromised persons, such as those post-organ transplant, advanced age).
- To the extent possible, consideration should be given to assigning supply teachers to one school for as long a period of time as possible in order to minimize exposures both for their own safety and for the safety of other teachers and students. A minimum two-week interval between assignments would help reduce the risk of infection transmission from one school to another if there is a need for supply teachers to change schools.

12. Protection of at-risk persons or families

With regards to children and youth's home environment, it would be appropriate to consider the risk posed by potentially infected children/youth and school staff to household members (e.g. children, siblings, parents, grandparents, roommates). The risk posed by SARS-CoV-2 likely varies in relation to socioeconomic status, household overcrowding and the presence of other children/youth and adults at increased risk of severe COVID-19 at home.

Guidance Statement(s):

- A separate document is being prepared by SickKids in collaboration with others to provide guidance to families on how to mitigate risks in the home environment, especially where there is a sibling, parent or older adult with underlying conditions that put them at increased risk for more severe disease reside in the same home.

13. Management of suspected and confirmed SARS-CoV-2/COVID-19 cases and their contacts

It is anticipated that there will be cases of symptomatic and asymptomatic SARS-CoV-2 infection identified at schools and it is important that public health authorities and schools be prepared to respond to cases involving both students and staff. This includes the need for readily available testing and contact tracing, which is critical for the timely detection and avoidance of outbreaks. Parents and caregivers need to be empowered by their employers to be able to take paid sick days and/or work remotely if their children/youth are not able to attend school. We recognize that neither laypeople nor health-care providers will be able to reliably distinguish between COVID-19 and other respiratory viral illnesses on a clinical basis (i.e. without a diagnostic test).

Parents and caregivers need to be empowered by their employers to be able to take paid sick days and/or work remotely if their children/youth are not able to attend school.

Guidance Statement(s):

- Staff, families and children/youth should be aware of the symptoms and signs associated with COVID-19. Individuals with symptoms or signs consistent with COVID-19 must stay home. Staff and students who develop symptoms or signs consistent with COVID-19 while at school must be sent home with exposures to others minimized during this process.
- Special awareness is required for those with medical conditions, such as asthma, allergic rhinitis and conjunctivitis, as the symptoms associated with flares may overlap with SARS-CoV-2 infectious symptoms. Every effort should be made by parents/caregivers in conjunction with the health-care team to maximize the control of these underlying conditions. In the event of an acute flare, depending on extent, children/youth may need to have nasopharyngeal testing for SARS-CoV-2.
- A process should be in place for the management of symptomatic staff and students who are at school. This process should be clearly documented, prior to the reopening of schools, between local public health authorities and the school boards.
    - This should include separation from other students and staff, masking of the affected person if tolerated, use of PPE for other school staff if close interaction with the affected individual is required, cleaning surfaces the individual has been in contact with and, in the case of symptomatic students, contacting caregivers for pick up as soon as possible.
- There should be clear protocols for management of staff and students who are exposed to a confirmed SARS-CoV-2/COVID-19 case.
- All staff and students who develop signs or symptoms consistent with COVID-19 should undergo testing for SARS-CoV-2 in accordance with public health recommendations. There should be clear testing recommendations by local public health units with information about where testing can be completed.
- Schools should carefully document attendance of students, staff and visitors and ensure up-to-date contact information to facilitate public health management should a case be identified in the school. Schools should have a rapid method to contact students/families with information.
- Rapid involvement of public health for any confirmed SARS-CoV-2/COVID-19 cases in the school setting is essential in order to perform timely contact tracing and followup. There should be clear testing recommendations for contacts with information about where testing can be completed.
- There needs to be clear guidance from public health for return to school for those who test negative, test positive, and for those who do not get tested.
- Educational materials targeted to school staff, children/youth and parents should be developed for those who are exposed, which are culturally sensitive and clearly delineate subsequent management.
- Consideration must be given as to how to maintain confidentiality of confirmed SARS-CoV-2/COVID-19 cases within the school. Strategies should be put in place to manage potential issues when students return (e.g. stigma, bullying).

14. Communicating about COVID-19 to children, youth and parents/caregivers

It is acknowledged that clear, age and developmental stage-appropriate communication about COVID-19 and what to expect when children and youth return to school should occur in advance of school reopening. In addition, it will be important that regular updates be provided to children and their parents/caregivers throughout the school year.

Guidance Statement(s):

- Parents/caregivers, children/youth and the community at large should be educated that SARS-CoV-2 is likely to persist and circulate like other respiratory viruses in the future. It is unlikely that herd immunity will be achieved in Ontario (by vaccination or natural infection) in the near term, and so the operationalization of school in the context of COVID-19 will likely be an issue for a prolonged period.
- Parents/caregivers should be made aware that SARS-CoV-2 causes mild disease in the majority of children,

youth and young adults. The best overall strategy for these cohorts and the population at large, taking into account the massive secondary adverse health and well-being implication of the lockdown, is to return to school with enhanced safety measures in place.

- Parents/caregivers and children/youth and the community at large should be provided with up-to-date information on local COVID-19 epidemiology and other emerging evidence pertaining to COVID-19. It is felt that provision of such information will aid in reducing anxiety in parents/caregivers and children/youth.
- Ensuring up-to-date childhood immunizations, as well as annual influenza vaccination, should be promoted as a strategy to reduce the circulation of a common infectious agent circulating in fall/winter and thus limit, where possible, other preventable infections.

15. Opportunities to improve evidence-based decision making

Decisions about reopening schools in the safest way possible for students, families, teachers and other school staff are of unprecedented complexity especially given the existing gaps of evidence-based data relating to SARS-CoV-2 transmission and effectiveness of mitigation strategies in children. As schools begin to reopen over the coming months, this represents an opportunity to conduct rigorous research that will help close the knowledge gap and will therefore continue to improve and inform decision-making during the school year. Priority areas of research include but are not limited to the following:

- Understanding optimal surveillance strategies for schools in areas of low and higher community transmission. Considerations include evaluating the use of non-testing-based data (e.g. absenteeism, screening) and testing-based strategies for students and teachers (including serology and PCR testing) for surveillance.
- Utility of innovative technologies for screening and contact tracing in the school setting (e.g. cellphone technologies).
- Assessing the effectiveness and consequences of risk mitigation strategies such as masking, face shields, physical distancing (1 metre versus 2 metre distance) and cohorting, on learning, health and mental health outcomes for children of different ages in schools within the context of existing school infrastructures.
- Investigation of school outbreaks to determine their causes and, specifically, to investigate the role of children and youth compared to staff/adults in order to better understand SARS-CoV-2 spread dynamics in general and to be able to improve mitigation strategies in the school setting.
- In order to facilitate the development of testing-based surveillance and monitoring strategies for SARS-CoV-2, there are various areas of research that require attention:

- The evaluation of point-of-care testing strategies, and contact tracing strategies for surveillance and management of potential outbreaks in schools.
- Development of new testing methodologies that are more comfortable, feasible, with rapid return compared to nasopharyngeal swabs. Experience from our academic hospitals has shown that children who require frequent nasal swabbing develop anxiety for the testing, which in many cases has led to test refusal. Examples for alternative sampling could include, anterior nare (front of the nose) nasal testing, buccal swab testing, saliva sampling, as well as swabs of the throat/oral cavity. Additionally, testing is being evaluated by some groups in an attempt to detect the urinary excretion of SARS-CoV-2.

16. Additional considerations

It is recognized that there are other school support staff, in addition to teachers, who may have significant exposure to students and other staff. Guidance for their safe return to work should be developed in collaboration with occupational health and safety and public health groups. In particular, bus drivers and transportation to school is an important consideration that will need detailed recommendations, including bus scheduling options, addressing bus capacity, and other safe operational considerations.

Guidance for parents/caregivers and children/youth on alternative travel options should be developed. One potential concern is that more parents/caregivers will drive their children/youth to school, either because of reduced school bus capacity (related to public health measures for buses) or because they feel it is safer, which could increase traffic congestion and risk of pedestrian injury. Strategies to accommodate such a scenario could include enhanced safety supervision and education, and expanding drop-off and pick-up locations near the school. For children and youth who do not live far from school, walking or cycling/scootering should be encouraged, weather permitting. Expanded facilities for storage of bicycles and scooters may be needed.

Summary

This document is intended to provide guidance for a safe return to school and highlight the harms caused by prolonged school closure. It should not be viewed as a comprehensive guide to the precise mechanics of school reopening. As discussed, the risks of severe illness from SARS-CoV-2 infection in children, which appears to relatively small, need to be balanced with the harms of school closure and the public health risks of disease transmission. Current evidence suggests that young children are less likely than teenagers or adults to transmit SARS-CoV-2 and, with few exceptions, school reopening with various implementations of infection prevention and control measures has been successful and not usually associated with outbreaks when community transmission is low. On balance, therefore, given the current epidemiology in Ontario, it is recommended that children and youth return to school and that the messaging around this clearly articulates the rationale for the recommendations outlined in this document in order to help reduce the fear and anxiety in parents and children/youth. It will also be critical to ensure that safety and wellness of teachers and school staff is prioritized.

In our view, a daily school model is best as it allows for consistency, stability and equity regardless of the region in which children live. An important factor to consider in this respect is emerging evidence indicating inequalities in the social and economic burden of COVID-19, which may further disadvantage children/youth living in areas with higher infection burden where educational inequality and barriers to online learning may be more pronounced.[58] Therefore, return to school and implementation prioritization decisions should be based on the principle of equity for all children and youth. The public school system is uniquely positioned to address some of the inequities that disproportionately impact Black, Indigenous, People of Colour and other disadvantaged groups in Ontario. In addition, we appreciate that the living conditions for children/youth vary across socioeconomic groups and, therefore, recommend that further work be done to develop guidance and identify supports needed for situations where children/youth reside within the same home as individuals with underlying conditions that put them at increased risk of more severe disease. Finally, it is important to note that these recommendations reflect the evidence available at the present time and are likely to evolve as new evidence emerges and as information is gathered from other jurisdictions that have reopened schools already.

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Appendix 1: Potential Advantages and Disadvantages of School Reopening Models ¥

FULL-TIME IN-PERSON SCHOOL WITH BASIC RISK MITIGATION §		
CATEGORY	**POTENTIAL ADVANTAGES**	**POTENTIAL DISADVANTAGES**
Educational environment	• Most comprehensive and holistic educational environment option for all children, especially those with developmental delays or special educational needs • Maximizes learning potential for all children, including those from families with limited financial, intellectual, or time resources to support schooling children at home • Maximizes teachers' ability to identify children with special needs, including those with cognitive delays or behavioural challenges and the ability to implement individual education plans (IEPs) • Maximizes teachers' ability to recognize mental health issues or social concerns for children including neglect or maltreatment	• A substantial proportion of parents may choose not to let their children return to school because of fear of SARS-CoV-2, which would likely put their children at a disadvantage (with respect to learning, social interaction) • Teachers and other school staff may not feel adequately protected with this approach
Social environment	• Maximizes social development (socialization with peers and teachers); this will likely be of particular importance to children with certain underlying conditions, such as autism spectrum disorder • For young children in particular, face-to-face interaction is likely to enhance learning, including non-verbal communication skills, empathy and emotional regulation • Enhances daily routines for children and youth, which can support healthy eating, physical activity, and sleep	• Bullying may be increased (e.g. those who want to wear masks may be bullied)
Health impacts	• Reduced risk of anxiety, depression and other mental health disorders related to not being with peers, teachers, and due to home isolation • Reduced impact on mental health and well-being in children with and without underlying mental health disorders related to not being with peers or teachers • Potentially increase physical activity through light exercise, such as walking, and moderate/vigorous activity with resumption of gym class and recess periods • Maximizes opportunity for children to participate in school-based extracurricular activities • Maximizes opportunities for school-based developmental supports (occupational therapy, physiotherapy, speech and language support) • Maintaining up-to-date school-based vaccination rates • Enable school breakfast programs to restart, nutritional programs in schools for families who may not be able to provide healthy meals/snacks	• Potential risk of SARS-CoV-2 infection in school-aged children and school staff, including those with underlying co-morbidities and other risk factors • Potential risk of SARS-CoV-2 infection for other children and adults living in the home (including those at higher risk; e.g. grandparents) if a child or teacher/school staff becomes infected at school • Risk of outbreaks in school leading to disruption of school setup • Children with underlying allergies/chronic cough disorders (e.g. asthma) may be disadvantaged by being inappropriately barred from school attendance due to "symptoms" • Potential increased risk of anxiety or fear related to possibility of SARS-CoV-2 infection • Potentially less impact on school-based SARS-CoV-2 spread than more aggressive strategies outlined below • Potentially less impact on school-based spread of other respiratory viruses (e.g. influenza, respiratory syncytial virus) and some vaccine-preventable diseases (e.g. chickenpox, Streptococcus pneumoniae) especially in populations with reduced vaccination rates • Potential toxic exposure of children to cleaning agents
Family and societal impacts	• Minimizes risk of caregiver unemployment, loss of family income and subsequent impacts on health • Maximizes parental/work productivity potential	• A substantial proportion of parents may choose to keep their children at home because of fear of infection • Teachers and other school staff may not feel adequately protected with this approach • Increased overall financial cost to schools and increased garbage volume on the school grounds related to personal protective equipment requirements • Children who do get sick will need to stay home, which could temporarily impact parent/caregiver ability to work

FULL TIME IN-PERSON SCHOOL WITH RISK MITIGATION INCLUDING MANDATORY PERSONAL PROTECTIVE EQUIPMENT †		
CATEGORY	**POTENTIAL ADVANTAGES**	**POTENTIAL DISADVANTAGES**
Educational environment	• Maximizes teachers' ability to identify those with special needs, including children with cognitive delays or behavioural challenges and the ability to implement individual education plans (IEPs) • Maximizes teachers' ability to recognize mental health issues or child abuse signs • Enhances learning potential for children from under-served communities • Reduces risk of adverse impacts on children from families with limited financial, intellectual, or time resources to support in-home child schooling • Teachers may feel more protected and therefore better able to carry out their teaching tasks	• A proportion of parents may choose not to let their children return to school because of fear of SARS-CoV-2, which may put their children at a disadvantage (with respect to learning, social interaction) • Use of mitigation strategies may be distracting (uncomfortable etc.) for both teachers, other school staff and children, limiting the benefit of the school environment • Loss of opportunity for children to learn from facial expression and non-verbal cues if masking routinely used; this may be particularly problematic for those with developmental delays, special needs, hearing impairments and those for whom English is a second language • The need to use mitigation strategies and enforcement of these strategies may increase fear/anxiety for some children and potentially have long-term psychological impacts
Social environment	• Social development supported by being present with peers and teachers with some limited precautions • Enhances daily routines for children and youth, which is important to support healthy eating, physical activity and sleep	• For young children in particular, use of mitigation interventions may to an extent adversely impact interaction and learning, particularly non-verbal communication skills • For children in transition (new to a school), masking may impair their ability to make new friends and connect with new teachers
Health impacts	• Potentially reduced risk of anxiety, depression and other mental health disorders compared with online school • Potentially reduced impact on symptoms in children with underlying mental health disorders compared with online school • Potentially increased physical activity through resumption of gym class and recess periods • Some opportunity for children to participate in school-based extracurricular activities • Some opportunities for school-based developmental supports (occupational therapy, physiotherapy, speech and language support) • May (with some restrictions) enable school breakfast programs to re-start, nutritional programs in schools for families who may not be able to provide healthy meals/snacks • Maintaining up-to-date school- based vaccination rates • Potential reduction in school-based spread of SARS-CoV-2 • Potential reduction in school-based spread of other respiratory viruses (e.g. influenza, respiratory syncytial virus) and some vaccine-preventable diseases (e.g. *Streptococcus pneumoniae*) especially in populations with reduced vaccination rates	• Mitigation interventions may not be reasonable or feasible for many children, especially those who are younger or with underlying conditions • Improper use/application of mitigation interventions could increase the risk of SARS-CoV-2 infection in school age children and school staff infections, including those with underlying conditions • Improper use/application of mitigation interventions could potentially increase risk of SARS-CoV-2 infection for other children and adults living in the home (including those at higher risk; e.g. elderly grandparents) • Improper use/application of mitigation interventions could potentially increase risk of outbreaks in school leading to disruption of school setup • Wearing certain personal protective equipment (i.e. masks) may interfere with physical activity, such as during recess, gym class, and extracurricular sports • Children with underlying allergies/chronic cough disorders (e.g. asthma) may be disadvantaged by being inappropriately barred from school attendance due to "symptoms" • May increase anxiety, feelings of social anxiety for some children, and difficulties with peer or teacher interactions among children with social skills deficits/problems reading social cues (e.g. ADHD) • Potential toxic exposure of children to cleaning agents
Family and societal impacts	• Minimizes risk of caregiver unemployment, loss of family income and subsequent impacts on health • Maximizes parental/work productivity potential	• Children who do get sick will need to stay home, which could temporarily impact parent/caregiver ability to work • Increased overall financial cost and garbage volume on the school grounds related to personal protective equipment requirements

HYBRID SCHOOLING APPROACH (ALTERNATING WEEKS OR DAYS AT SCHOOL AND VIRTUAL) WITH RISK MITIGATION OPTIONS AS ABOVE		
CATEGORY	**POTENTIAL ADVANTAGES**	**POTENTIAL DISADVANTAGES**
Educational environment	• Reduced class size more manageable for teachers • Intermediate ability of teachers to identify special needs, implement IEPs, recognize delays/school challenges • Intermediate ability of teachers to identify and recognize mental health issues or child abuse signs	• Reduced in-class time likely to adversely impact overall learning, disruptive schedule • Concomitant online classes may complicate schools' ability to cover full curriculum equitably • Intermediate ability to identify special needs, implement IEPs, recognize delays/school challenges • Intermediate ability to recognize mental health issues or child abuse signs • May pose a challenge for teachers in measuring learner engagement • Children from low resource settings and rural locations with poor Internet connectivity may fall behind due to lack of access to technology (software/hardware, connectability) • Inequity/disadvantage for families with no financial, intellectual, protected space or time resources to support online learning • Reduced opportunities for special education support (e.g. education assistant) for children with existing learning needs
Social environment	• Some socializing in the school environment is better than none	• May heighten fear/anxiety for some children given the frequent changes to schedules, coping with two worlds (social and mental health impacts of this), increased absenteeism • Difficult for all children, most particularly for younger children and those with underlying conditions (e.g. anxiety, autism spectrum disorders etc.) where a routine structure is best • Challenging for children new to a school (e.g. Grades 6, 9) or new to a community as time in school may be too limited or fragmented to consolidate new connections
Health impacts	• May reduce risk of SARS-CoV-2 infection for school-aged children and school staff • May reduce risk of SARS-CoV-2 infection for other children and adults living in the home (including those at higher risk; e.g. grandparents) • May, with some restrictions, enable school breakfast programs to restart, nutritional programs in schools for families who may not be able to provide healthy meals/snacks • Potential reduction in school-based spread of SARS-CoV-2 due to enhanced social distancing, including less physical school attendance • Potential reduction in school-based spread of other respiratory viruses (e.g. influenza, respiratory syncytial virus) and some vaccine-preventable diseases (e.g. chickenpox, *Streptococcus pneumoniae*) in populations with reduced vaccination rates	• Increase risk of anxiety, depression and other mental health disorders • Worsening of symptoms in children with underlying mental health disorders • Increased screen time during "off school" times • Potential risk of online bullying • Decreased physical activity • Children with underlying allergies/chronic cough disorders (e.g. asthma) may be disadvantaged by being inappropriately barred from school attendance due to "symptoms" • Risk of SARS-CoV-2 transmission from mixing of cohorts if parents hire middle school or high school students to care for their children so they can continue to work • Some children may be left unsupervised at home placing them at risk for accidental and non-accidental injury • Risk of child abuse may increase (e.g. may tip the balance in parents at risk of abusive behaviour)
Family and societal impacts	• May increase opportunities for parent-child bonding and promote meaningful interaction on off-days from school	• Likely very disruptive to caregiver employment; may predispose to loss of family income; this is likely to disproportionately impact the most economically vulnerable groups (e.g. single-parent households) • Very disruptive to parental/work productivity potential

FULL-TIME ONLINE SCHOOL		
CATEGORY	**POTENTIAL ADVANTAGES**	**POTENTIAL DISADVANTAGES**
Educational environment	• Beneficial for the minority of children who cannot attend school because they are sick or in isolation due to SARS-CoV-2 infection or exposure, or if parents/caregivers choose to keep their child home from school • Potentially reduced risk of SARS-CoV-2 infection for teachers, which would be beneficial particularly for those at increased risk of severe disease • Teacher cohort capacity likely to be maximized	• Reduction in overall achievement for students, especially those who lack self-regulation or who lack adequate supervision in the home • Teachers may not be adequately trained/prepared for online learning management systems and online curriculum delivery • Reduced ability to identify special needs, implement IEPs, recognize delays/ school challenges • Reduced ability to recognize mental health issues or child abuse signs • Children from low resource settings and rural locations with poor Internet connectivity may fall behind due to lack of access to technology (software/hardware, connectability) • Inequity/disadvantage for families with no financial, intellectual, protected space or time resources to support online learning • Reduced opportunities for special education support (e.g. education assistant) for children with existing learning needs • No opportunities for school-based developmental supports (occupational therapy, physiotherapy, speech and language support) • Home environment may not be conducive to learning because the space is small and shared by many people resulting in multiple distractions • May be difficult for students with poor self-regulation
Social environment	• Generally not advantageous; some ability for students to communicate with each other using the chat function of certain learning management systems (i.e. Brightspace)	• Decreased socialization with peers; reduction in social skill development; this is likely to be particularly harmful to those with special needs (e.g. autism spectrum disorders) • Difficult for all children, most particularly for younger children and those with underlying conditions (e.g. anxiety, autism spectrum disorders etc.) where a routine structure is best • Decreased face-to-face interaction leading to reduced pickup of facial expression and social cues
Health impacts	• Eliminates risk of school-based SARS-CoV-2 infection for both school age children and school staff • Reduced SARS-CoV-2 infection risk for other children and adults living in the home (including those at higher risk; e.g. grandparents) due to children/school staff having less risk of exposure • Potential reduction in spread of other respiratory viruses (e.g. influenza, respiratory syncytial virus) and some vaccine-preventable diseases (e.g. chickenpox, Streptococcus pneumoniae) in populations with reduced vaccination rates	• Increase risk of anxiety, depression and other mental health disorders • Worsening of symptoms in children with underlying mental health disorders • Increased screen time • Increased risk of online bullying • May expose some children (e.g. teenagers) to potentially dangerous online activity (e.g. watching adult videos, gambling) • Decreased physical activity • Delayed receipt of routine childhood immunizations • Risk of SARS-CoV-2 transmission from mixing of cohorts if parents hire middle school or high school students or other outside the home caregivers to care for their children so they can continue to work • Some children may be left unsupervised at home placing them at risk for accidental and non-accidental injury • Risk of child abuse may increase (e.g. may tip the balance in parents at risk of abusive behaviour)
Family and societal impacts	• For some families the increased contact between parents and children may be beneficial	• Adverse impact on caregiver employment and family income • Dramatic reduction in parental/work productivity; many parents will not be able to work • No respite for parents (particularly for those with children of high needs, such as those who are medically complex)

¥ The purpose of this table is to provide general perspectives on potential advantages and disadvantages of the predominant school reopening models currently being contemplated. Some portions are more applicable to kindergarten and elementary school-aged children than older children.

§ Full-time school with basic risk mitigation = limited physical distancing measures, optional- only masking for school staff and students (on an age-appropriate basis and with provision of materials by the school board so as not to disadvantage those with limited resources), hand hygiene protocols, cleaning protocols and outbreak management protocols.

† Full-time school with risk mitigation = robust physical distancing, mandatory masking for school staff and students, hand hygiene protocols, cleaning protocols and outbreak management protocols.

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Bidirectional impact of imperfect mask use on reproduction number of COVID-19: A next generation matrix approach☆

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ABSTRACT

The use of masks as a means of reducing transmission of COVID-19 outside healthcare settings has proved controversial. Masks are thought to have two modes of effect: they prevent infection with COVID-19 in wearers; and prevent transmission by individuals with subclinical infection. We used a simple next-generation matrix approach to estimate the conditions under which masks would reduce the reproduction number of COVID-19 under a threshold of 1. Our model takes into account the possibility of assortative mixing, where mask users interact preferentially with other mask users. We make 3 key observations:
1. Masks, even with suboptimal efficacy in both prevention of acquisition and transmission of infection, could substantially decrease the reproduction number for COVID-19 if widely used.
2. Widespread masking may be sufficient to suppress epidemics where R has been brought close to 1 via other measures (e.g., distancing).
3. "Assortment" within populations (the tendency for interactions between masked individuals to be more likely than interactions between masked and unmasked individuals) would rapidly erode the impact of masks. As such, mask uptake needs to be fairly universal to have an effect.
This simple model suggests that widespread uptake of masking could be determinative in suppressing COVID-19 epidemics in regions with R(t) at or near 1.

Background

The use of masks as a means of reducing transmission of COVID-19 outside healthcare settings has proved controversial. Available evidence suggests that masks and other face coverings reduce both transmission and acquisition of droplet-borne respiratory viruses in healthcare settings (Chu et al., 2020; Leung et al., 2020; Offeddu et al., 2017) but evidence outside healthcare is limited. Ecological evidence suggests that countries where mask use is widespread have controlled COVID-19 epidemics more rapidly (Kai, Goldstein, Morgunov, Nangalia, & Rotkirch, 2004), and models suggest that even imperfect

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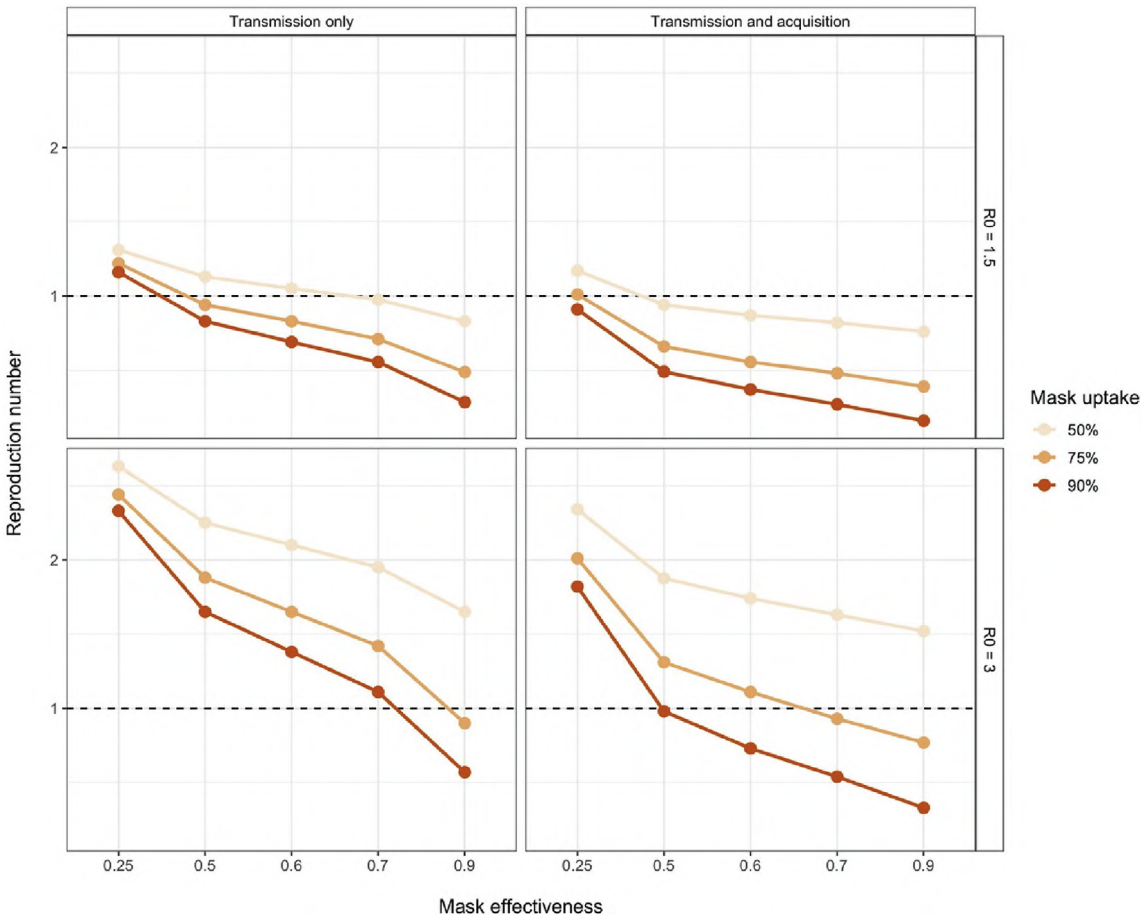

Fig. 1. Effect of Mask Uptake and Effectiveness on Reproduction Number of COVID-19
Effective reproduction number (R) is plotted on the Y-axis and increasing mask effectiveness is plotted on the X-axis in both figures. Curves represent 50% (light), 75% (medium) or 90% (dark) uptake of masks in the population. Top panels represent a scenario with baseline R = 1.5; and masks reducing transmission only (left), or both transmission and acquisition of infection with equal effectiveness (right). Bottom panels are identical, but use a baseline R = 3.

use of masks and other face coverings could be a potent disease control intervention, due to the bidirectional effects of masks on disease transmission (Eikenberry et al., 2020).

Objective

To use a simple, "next generation matrix" approach to explore the impact of masks on epidemic reproduction numbers under varying assumptions around effectiveness, uptake, and population mixing patterns.

Methods and findings

We can represent mask use in a population using a simple mixing approach whereby the "force of infection" (rate of infection of susceptibles) in masked (λ_m) and unmasked (λ_u) individuals is:

$$\begin{pmatrix} \lambda_m \\ \lambda_u \end{pmatrix} = \begin{pmatrix} \beta_{mm} & \beta_{um} \\ \beta_{mu} & \beta_{uu} \end{pmatrix} \begin{pmatrix} I_m \\ I_u \end{pmatrix}$$

Here I_m and I_u represent prevalent infections among masked and unmasked individuals. Each β_{ij} represents the product of contact rate and transmission probability from an infectious individual with mask use status i, acting on a susceptible person with mask use status j. Population mixing may be random, but assortativity is also possible, in which case masked individuals would interact predominantly with other masked individuals, and vice versa. Assortativity would manifest as zeroes in the

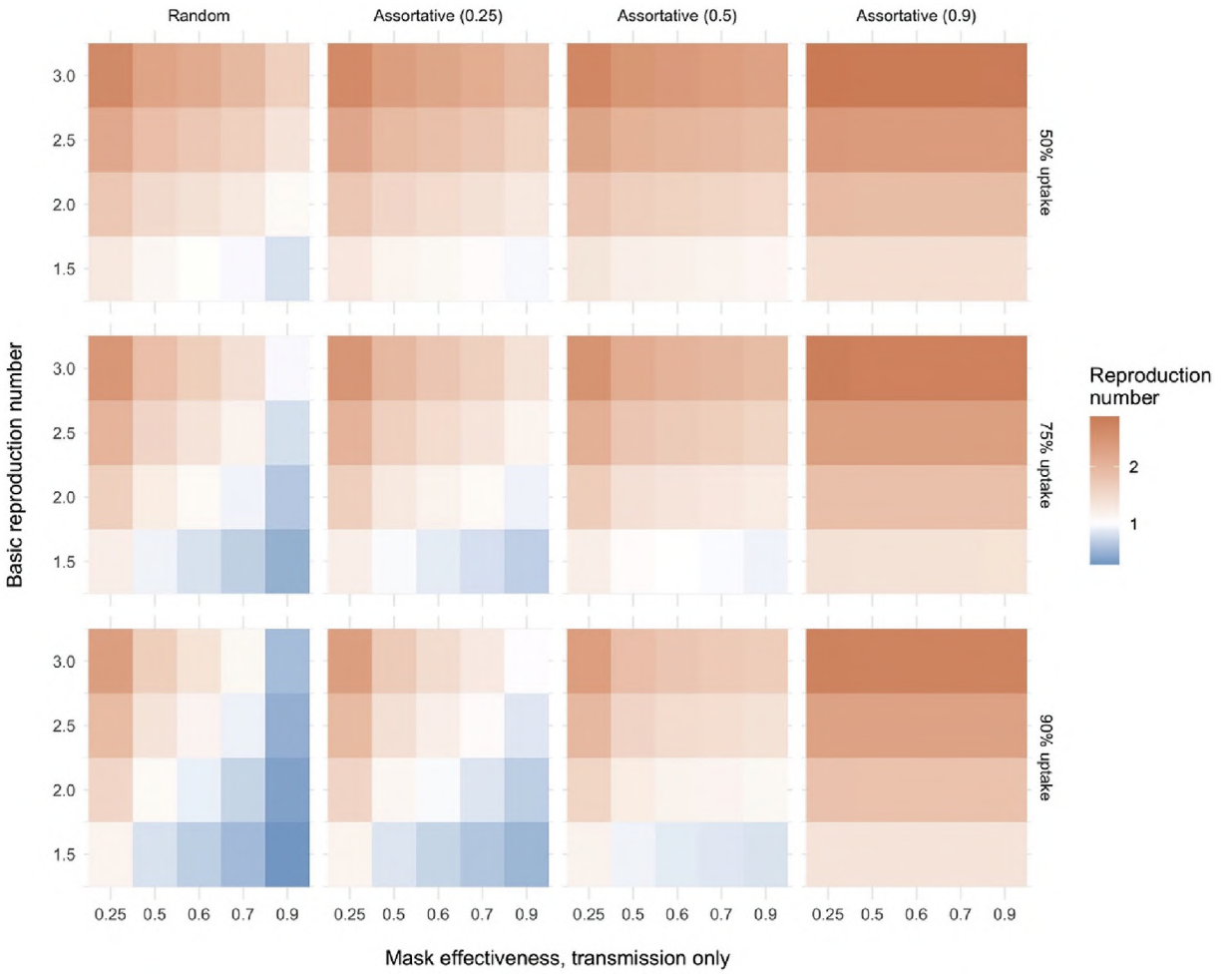

Fig. 2. Diminished Effect of Masks on Reproduction Number of COVID-19 with Assortative Mixing.
Baseline effective reproduction number (R) is plotted on the Y-axis and increasing mask effectiveness is plotted on the X-axis, across four different scenarios with respect to assortativity. Left handed panels show random mixing, while the three right hand panels show progressive increases in assortativity (coefficients of 0.25, 0.5 and 0.9, based on the approach of Garnett and Anderson (Garnett & Anderson, 1996)). The effective reproduction number, R, in each scenario is represented by color coding, with red areas signifying $R > 1$, white signifying $R = 1$, and blue areas signifying $R < 1$. It can be seen that R falls below 1 more easily with random mixing than with assortative mixing; when assortativity is extreme (far right panel), R cannot be brought below 1, even when R_0 is low, mask use is widespread, and masks are highly efficacious. Note that simulations in this figure consider only reduction of transmission risk, and assume that masks do not prevent acquisition of infection.

anti-diagonal of the matrix (Garnett & Anderson, 1996). This simple model is available as a Microsoft Excel spreadsheet at: https://figshare.com/articles/Next_Generation_Matrix_Approach_to_Mask_Use_for_COVID-19/12279266. Reproduction numbers (the number of new cases created by prevalent cases) can be estimated as the largest non-negative eigenvalue of the next-generation matrix:

$$\begin{pmatrix} R_{mm} & R_{um} \\ R_{mu} & R_{uu} \end{pmatrix} = \begin{pmatrix} \beta_{mm} N_m D_m & \beta_{um} N_m D_u \\ \beta_{mu} N_u D_m & \beta_{uu} N_u D_u \end{pmatrix}$$

Here N is population size and D is duration of infectivity; contact numbers and disease duration are equivalent for masked and unmasked individuals such that differences in β_{ij} relate entirely to the effectiveness of mask use for transmission (E_T) and for prevention of acquisition of infection (E_A). For example, β_{mm} would be estimated as $\beta_{mm} \cdot (1 - E_T) \cdot (1 - E_A)$. Using this simple model, we see that widespread adoption of partially effective masks can reduce R from a high baseline value (e.g., 3) to below 1, provided mask use is widespread and masks impact both transmission and acquisition of infection (Fig. 1, bottom panels). If R is closer to 1 (e.g., 1.5) as may be the case following social distancing, limited mask uptake with effects limited entirely to reduced transmission may be sufficient to drive R to values below 1 (Fig. 1, top panels).

Assortative mixing diminishes the impact of masking (Fig. 2), concentrating the epidemic in non-masked segments of the population. Assortativity is modeled using the approach of Garnett and Anderson (Garnett & Anderson, 1996), by adding an assortativity constant (η) to the matrix; values of η closer to 0 approximate random mixing while values closer to 1 represent extreme assortativity.

Discussion

Recommendations for the public use of masks and other face coverings for prevention of COVID-19 transmission have proven surprisingly contentious in high-resource countries. The reasons for this are likely varied and include concerns about diminished mask supply for healthcare workers and false reassurance for masked individuals with diminution of social distancing. Nonetheless, as we demonstrate here, even modest mask effectiveness for reduction of transmission of COVID-19 could have important effects on epidemic dynamics, especially given that pre-symptomatic transmission of disease is an important feature of COVID-19 epidemiology, and may account for over 40% of all transmission events (He et al., 2020). Even a partial reduction of this burden of transmission may be sufficient to drive reproduction numbers below 1, especially when they have been brought close to 1 by other non-pharmaceutical epidemic control measures such as aggressive physical distancing. While we used a slightly different mathematical approach, our findings are consistent with those published by Eikenberry et al. (Eikenberry et al., 2020), and provide a degree of cross-validation of those findings. We also show here that the benefit of masks may be diminished via assortative mixing patterns, if mask-users predominantly contact other mask users. As such, the impact of masks and other face coverings in reducing COVID-19 transmission is likely to be greatest if attention is paid to ensuring availability for disadvantaged populations.

Our analysis has several limitations, including the model's simplicity and the lack of precise estimates for mask effectiveness in the context of COVID-19. However, it should be noted that our model is likely conservative; a recent systematic review suggested, based on the best available evidence, that face masks reduce the risk of acquisition of viral infection by 85% (95% CI 66–93%) (Chu et al., 2020); as we note here, the impact of masking is markedly enhanced if both acquisition and transmission are reduced. In a health emergency like the current pandemic, decisions may need to be made on the basis of best available information, even if that information is imperfect. In the absence of evidence of harms done by masking, and with even preliminary evidence that they could influence epidemic growth, we suggest that their more widespread use be considered by jurisdictions which have not yet advocated this intervention.

Declaration of competing interest

The research was supported by a grant to DNF from the Canadians Institutes for Health Research (2019 COVID-19 rapid researching funding OV4-170360). None of the authors has any conflict of interest to declare.

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REFERENCE 30

Regulatory considerations on the classification of non-medical masks or face coverings: Notice to industry

Date published: July 24, 2020

This notice explains under which circumstances non-medical masks or face coverings would be subject to the regulatory framework for medical devices during the COVID-19 pandemic.

On this page

About non-medical masks or face coverings

Non-medical masks or face coverings may help reduce the spread of respiratory droplets from the user to others or to the surroundings.

Non-medical masks or face coverings are generally made of fabric and come in a range of shapes and styles. Most often, they are sewn masks and secured with ties or straps around the head or behind the ears. They may be made in a factory, by a home-based small business or hand-made by people for self use or donation to others.

Since May 20, 2020, Canadians have been advised to wear face coverings when in the community. The Federal-Provincial-Territorial (FPT) Special Advisory Committee on COVID and the Public Health Agency of Canada (PHAC) recommended that people wear **face coverings** when:

- it is not possible to consistently maintain a 2-metre distance from others, particularly in crowded public settings
- the local epidemiology and rate of community transmission warrant it

Many public health authorities are now requiring the wearing of non-medical masks or face coverings in public settings considered to pose increased risk of COVID-19 transmission. At this time, it is understood that face coverings do not provide a complete barrier to virus-sized particles produced by the wearer when speaking, laughing, singing, coughing or sneezing. While it has not been proven that they protect the wearer from exposure to the infectious respiratory droplets of others, it is reasonable to believe that some protection may be provided. The level of protection depends on the materials and methods used, and most importantly, how it fits.

Wearing face coverings are an additional personal practice, along with proper hand washing and physical distancing. Covering one's mouth and nose help reduce the spread of respiratory droplets.

For more information on face coverings and their limitations, please refer to non-medical masks and face coverings.

Regulatory considerations

In the context of the COVID-19 pandemic, face coverings with medical claims or representations are considered medical devices and are regulated as such.

This approach allows for greater regulatory oversight of face coverings used for medical purposes. It also eases the way for Canadians to access non-medical face coverings that can help reduce the spread of respiratory droplets. Furthermore, this approach will provide Canadians with information about the degree of protection they may expect from a non-medical mask or face covering. This will allow them to select a product based on their individual risk profile. For example, people who are at risk of more severe disease if infected with COVID-19 may wish to use a mask with an established higher level of protection.

Face coverings regulated as medical devices (medical masks)

Face coverings that make medical claims or representations to reduce the risk of or prevent the user from contracting COVID-19 are **medical masks**. They are regulated as Class I medical devices.

Some medical claims or representations include the following statements:

- to protect the user from contracting COVID-19
- for anti-viral or anti-bacterial protection (for example, contains a drug or biologic)
- for use as a medical mask
- to provide liquid barrier protection
- designed as a respiratory protective device (for example, used for particulate filtration)
- for use in high-risk aerosol generating medical procedures

Medical masks may be authorized for sale or import into Canada through the following regulatory pathways:

- interim order authorization to import and sell medical devices related to COVID-19
- expedited review and issuance of Medical Device Establishment Licences related to COVID-19
- exceptional importation and sale of certain non-compliant medical devices related to COVID-19

For details on the authorization pathways, please refer to COVID-19 medical masks and respirators.

All medical masks, including face coverings regulated as medical devices, must meet specific international standards for Class I medical devices, such as ASTM F2100. These standards include requirements for bacterial filtration effectiveness, and may include specifications for particle filtration efficiency, flammability and fluid resistance.

Labelling for medical masks must contain:

- clear statements on their intended use (for instance, the purpose for which the device is manufactured, sold or represented) **and**
- specific performance specifications for their proper use (for example, filtration efficiency and fluid resistance)

Medical masks must come with bilingual labelling, either on the packaging or with the device itself.

Non-medical masks or face coverings

Some face coverings are not regulated as medical devices. These are masks that do **not** make medical claims or indicate they will reduce or prevent the user from contracting a disease. Non-medical claims include the following statements:

- Face coverings can play an important role in situations where physical distancing is not possible or is unpredictable.
- When worn properly, a person wearing a non-medical mask or face covering may reduce the spread of their respiratory droplets.
- These non-medical masks or face coverings have not been tested to meet any standards. Although encouraged, wearing a non-medical mask or face covering is not a substitute for physical distancing and hand washing.

A number of reference documents outline the preferred material, design and best practices for wearing face coverings. These include:

- AFNOR Spec – Barrier masks V1.0 by the French Standardization Association
- Community face coverings – Guide to minimum requirements, methods of testing and use (CWA 17553:2020) by the European Committee for Standardization

These documents are different from the standards that apply to medical masks, as face coverings may not protect the user from external respiratory droplets. As well, the filtration capability of a face covering depends on factors such as design, seams, material, layering and shape.

Health Canada has not set out or endorsed any standards for face coverings at this time. We are actively monitoring the development of standards for face coverings and may revise our position when new information becomes available.

Related links

- About medical devices
- COVID-19 medical masks and respirators
- Non-medical masks and face coverings
- Advice on the use of masks in the context of COVID-19 (World Health Organization)

REFERENCE 31

ASTM Standardization News

Standards for Medical Face Masks and Protective Clothing

BY TIM SPRINKLE

Healthcare workers wear face masks to prevent germs from their noses and mouths from passing to the patient as well as to protect themselves from infection. The scrubs and gowns they wear serve similar purposes, protecting healthcare workers as well as patients from the accidental transmission of disease, as do the drapes that are used during surgery.

In recent weeks, the topic of protective clothing has become very much mainstream, with these products entering broader use outside of hospitals and healthcare facilities in response to COVID-19. Face masks, gowns, and other articles of protective clothing are in high demand as people seek to avoid spreading or contracting the novel coronavirus.

All of these products fall under the purview of ASTM International's committee on personal protective clothing and equipment (**F23**) and its subcommittee on biological (**F23.40**). The biological subcommittee develops and maintains standards that are meant to protect healthcare workers or the healthcare environment from biological hazards that can cause infection.

READ MORE: Full List of ASTM International Standards Made Available at No Charge

Sarah Smit, chair of the biological subcommittee, recently identified the most important standards for protective personal equipment (PPE), listed below. These standards are among many that ASTM International has made available at no charge in order to support manufacturers, test labs, health care professionals, and the general public as they respond to the global COVID-19 public health emergency.

1. Specification for performance of materials used in medical face masks (F2100)

According to Smit, medical face mask material performance is based on testing for bacterial filtration efficiency (**F2101**), differential pressure (EN 14683), sub-micron particulate filtration efficiency (**F2299**), resistance to penetration by synthetic blood (**F1862**), and flammability (16 CFR Part 1610). The intended use for medical face masks is to protect the wearer from splashes or sprays during healthcare procedures, as well as keeping large splashes and sprays from the wearer from reaching the environment.

Personal protective equipment has played a key role in the response to COVID-19.

2. Test Method for Evaluating the Bacterial Filtration Efficiency (BFE) of Medical Face Mask Materials, Using a Biological Aerosol of Staphylococcus aureus (F2101)

This standard is important for evaluating the ability of a mask to keep aerosol droplets – caused by talking, coughing, and sneezing – away from the wearer's mouth and nose. It will also show the mask's ability to prevent aerosols from the wearer's mouth from reaching the environment. The bacteria used is *Staphylococcus aureus*, which is attached to liquid droplets with sizes ranging from 0.65–9 microns and above with 3 microns as the mean particle size. A filtration efficiency is then reported: This is the ratio of the amount of bacterial aerosols challenging the mask versus the amount that was able to penetrate the mask.

3. Test method for determining the initial efficiency of materials used in medical face masks to penetration by particulates using latex spheres (F2299/F2299M)

A standard that has received a great deal of attention in worldwide media recently, this test measures the sub-micron particulate filtration efficiency, and is required for medical face masks in case healthcare procedures generate small particles. Per FDA guidance, the particle size is 0.1 microns and the particles are non-neutralized for medical face masks.

4. Test method for resistance of medical face masks to penetration by synthetic blood (horizontal projection of fixed volume at a known velocity) (F1862/F1862M)

This standard applies specifically to the synthetic blood penetration testing that's designed to mimic the real-world situations in which the masks are used, according to Smith. In this case, the test is designed to determine whether or not the mask would effectively protect a surgeon from blood spatter. Medical face masks are intended to resist liquid penetration based on a number of different factors, including the surface tension and viscosity of the fluids themselves, as well as the structure and relative hydrophilicity or hydrophobicity of the materials and the design of the mask itself. F1862 sets the standard for this type of testing as well as for the creation of the synthetic blood used in the test.

5. Test method for resistance of materials used in protective clothing to penetration by blood-borne pathogens using Phi-X174 bacteriophage penetration as a test system (F1671/F1671M)

As we are seeing with the the COVID-19 outbreak, viruses can be very resilient, and extensive precautions must be taken to protect medical professionals and patients from potential transmission in a hospital setting. According to Smit, this test is used to determine penetration in protective clothing using a very small virus, the Phi-X174 bacteriophage. This test is particularly sensitive, detecting viral penetration using a biological assay technique where visual penetration may not occur, and is usually performed on surgical gowns. Note: F1670 is similar standard that uses synthetic blood for testing and is a visual penetration test. It is usually performed on drapes.

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INDUSTRY SECTORS:

Medical

REFERENCE 32

When to Wear Gloves

When Gloves Are and Aren't Needed

Updated July 16, 2020

Print

For the general public, wearing gloves is not necessary in most situations, like running errands. CDC recommends wearing gloves when you are cleaning or caring for someone who is sick.

Practice everyday preventive actions like keeping social distance (at least 6 feet) from others, washing your hands with soap and water for 20 seconds (or using a hand sanitizer with at least 60% alcohol), and wearing a mask when you have to go out in public.

When to use gloves

When cleaning
When you are routinely cleaning and disinfecting your home.

Use gloves when cleaning and disinfecting or providing care to someone who is sick

- Follow precautions listed on the disinfectant product label, which may include-
  - Wearing gloves (reusable or disposable)
  - Having good ventilation by turning on a fan or opening a window to get fresh air into the room you're cleaning
- Wash your hands after you have removed the gloves.

When caring for someone who is sick
If you are providing care to someone who is sick at home or in another non-healthcare setting

- Use disposable gloves when cleaning and disinfecting the area around the person who is sick or other surfaces that may be frequently touched in the home.
- Use disposable gloves when touching or having contact with blood, stool, or body fluids, such as saliva, mucus, vomit, and urine.
- After using disposable gloves, throw them out in a lined trash can. Do not disinfect or reuse the gloves.
- Wash your hands after you have removed the gloves.

When gloves aren't needed

- Wearing gloves outside of these instances (for example, when using a shopping cart or using an ATM) will not necessarily protect you from getting COVID-19 and may still lead to the spread of germs.
- The best way to protect yourself from germs when running errands and after going out is to regularly wash your hands with soap and water for 20 seconds or use hand sanitizer with at least 60% alcohol.

Protect yourself in other ways

COVID-19 is a respiratory virus and is mainly spread through droplets created when a person who is infected coughs, sneezes, or talks.

Protect yourself by keeping at least 6 feet from others

You can protect yourself by

- Keeping social distance (at least 6 feet) from others
- Washing your hands with soap and water for 20 seconds (or using a hand sanitizer with at least 60% alcohol) at key times
- Practicing everyday preventive actions

Gloves in the workplace

Guidelines and recommendations for glove use in healthcare and work settings will differ from recommendations for the general public.

Last Updated July 16, 2020
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REFERENCE 33

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Emergency Forum

THE OCULAR MANIFESTATIONS AND TRANSMISSION OF COVID-19: RECOMMENDATIONS FOR PREVENTION

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☐ **Abstract—Background: Coronavirus disease-2019 (COVID-19), caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been linked to ocular signs and symptoms in several case reports. Research has demonstrated that SARS-CoV-2 is spread primarily through close contact via respiratory droplets, but there is the possibility for ocular transmission, with the conjunctiva as a conduit as well as a source of infection. Discussion: Ocular manifestations of SARS-CoV-2 include follicular conjunctivitis, and have been repeatedly noted as an initial or subsequent symptom of COVID-19-positive patients. Particularly in patients with ocular manifestations, there is evidence that the virus may present in tears, based on the detection of SARS-CoV-2 in conjunctival swab samples via reverse transcription polymerase chain reaction. The virus may therefore be transmittable from the ocular surface to a new host via contact with the ocular mucosa, tears, or subsequent fomites. Conclusions: All health care professionals should ask patients about ocular symptoms consistent with SARS-CoV-2, and use eye protection such as goggles or face shields as part of the standard personal protective equipment for high-risk patients in addition to wearing of masks by both the patient and provider, and should consider tears to be potentially infectious.** © **2020 Elsevier Inc. All rights reserved.**

☐ **Keywords—COVID-19; SARS-CoV-2; conjunctivitis; ocular transmission; ophthalmic precautions**

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an enveloped RNA virus of the betacoronavirus family of zoonotic origin, with phylogenetic similarity to other strains, such as the SARS-CoV responsible for the pandemic of 2003 (1). There are no studies to date demonstrating ocular transmission of SARS-CoV-2, despite evidence of ocular signs, including follicular conjunctivitis, in coronavirus disease-2019 (COVID-19) patients. Although primary transmission of COVID-19 appears to be via large respiratory droplets, the eyes may serve as a source of infection as well as an entryway for transmission (2).

OCULAR TROPISM

Belser and colleagues previously described an anatomical theory for ocular transmission of respiratory disease via the nasolacrimal system (3). They suggested that the ocular mucosal immune system, composed of the conjunctiva, cornea, lacrimal glands, and lacrimal drainage system, clears fluid from the eye and transports it to the inferior meatus of the nose. Therefore, if a respiratory droplet is deposited on the surface of the eye, the virus-containing fluid can then enter the respiratory system

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through the nose, gaining access to the lungs. Respiratory syncytial virus (RSV) is one respiratory illness that has been demonstrated to be primarily spread through the eyes and nose. The eyes, in addition to the nose and upper respiratory system, are home to various receptors that have been linked to viral binding in RSV infection. Therefore, the eyes are a portal of entry for RSV, and the use of eye protection has been demonstrated to reduce the nosocomial spread of RSV (3).

Additional data supporting this theory includes the presence of a viral load in the tear fluid of patients with a variety of respiratory illnesses. This theory has been studied in animal models including mice, ferrets, rabbits, and cotton rats. The viruses tested in these species included adenoviruses and influenza viruses, and the animal models used intrastromal inoculation or dropwise inoculation onto the cornea. After inoculation, viral loads were detected in tear samples from all animals. These animals were also found to have clinical signs of respiratory viral infection comparable with traditional intranasal inoculation (3). Similar studies have also demonstrated ocular manifestations of feline coronaviruses. In a study of feline CoV-positive cats, 90% had antigen detected in the conjunctiva after testing conjunctival swabs, suggesting ocular tissues and tears could be infectious (4). Human studies assessing ocular transmission of coronaviruses are needed to confirm these theories from animal models.

SEVERE ACUTE RESPIRATORY SYNDROME 2003

Given that SARS-CoV and SARS-CoV-2 are from the same family of coronaviruses and share phylogenetic similarity, it seems likely that findings from the SARS epidemic of 2003 may be demonstrated with COVID-19. SARS-CoV was found to have a primary mode of transmission through direct or indirect contact of infectious droplets with mucous membranes including the eyes, nose, or mouth (5). A study of health care workers infected by contact with intubated patients with confirmed SARS demonstrated a statistically significant relationship (p-value = 0.001) between infection and eye protection. Health care workers who did not properly wear goggles or other eye protection had higher rates of infection compared with those who did, yielding an odds ratio of 7.34 (6). This study provided evidence that ocular transmission of respiratory illness may occur without eye protection, particularly in health care settings, and highlights that the conjunctiva could have been a portal for entry for SARS-CoV.

Furthermore, a 2003 case series first reported the detection of SARS-CoV in tears after reverse transcription polymerase chain reaction (RT-PCR) analysis. In this study of 36 patients with probable SARS, 3 patients were found to have tear samples positive for SARS-CoV via conjunctival swab (7). The samples were collected at one time point for each patient no more than 9 days after onset of fever. This study highlighted the second possibility demonstrating the ocular transmission of SARS: that the tears are direct sources of infectious material. Given there is a viral load in tears, it is possible that contact with the eye and subsequent fomites can lead to inoculation of the virus in other persons much in the way demonstrated by respiratory droplets. The authors from this study recommended against the use of reusable eye equipment such as applanation tonometers and urged the use of goggles in addition to masks, gowns, and gloves for personal protective equipment (PPE).

OCULAR COVID-19 STUDIES

There are currently few peer-reviewed studies demonstrating ocular manifestations of SARS-CoV-2; most studies published to date originate from China and consist of small case series. A study of 38 COVID-19-positive patients in Hubei Province, China demonstrated that 12 patients reported ocular symptoms and 2 had positive conjunctival swabs (8). Signs included conjunctival hyperemia, chemosis, epiphora, or increased ocular secretions. The roughly one-third of patients who were found to have ocular signs were noted to have more severe manifestations of COVID-19 in general.

Other smaller studies have confirmed that SARS-CoV-2 is shed in tears, albeit with a low incidence. A study at Wuhan University identified 67 laboratory-confirmed or suspected COVID-19-positive patients. Of these patients, 3 had positive RT-PCR results from conjunctival swab but no ocular symptoms (9). One patient reported conjunctivitis as his first symptom but had a subsequent negative conjunctival swab. Another single-center cross-sectional study at Tongji Hospital in Shanghai, China demonstrated similar results. Of 72 patients with laboratory-confirmed COVID-19, 2 patients reported conjunctivitis and of the 2, only one tested positive via RT-PCR from conjunctival swab (10). A prospective interventional study was also performed at Zhejiang University. The protocol called for two tear and conjunctival collections per patient at intervals of 2 to 3 days, which were tested via RT-PCR. Of 30 patients enrolled, only one patient had conjunctivitis and he was the sole patient with positive conjunctival swab (11).

A case report from Shenzhen, China highlighted a patient presenting with bilateral ocular redness, foreign body sensation, and tearing without blurred vision on day 13 after developing systemic COVID-19 symptoms (12). The patient then had a slit lamp examination that showed bilateral moderate conjunctival injection, watery

discharge, inferior palpebral conjunctival follicles, and tender palpable preauricular lymph nodes consistent with acute viral conjunctivitis. RT-PCR results from conjunctival swab on days 13, 14, and 17 were positive for SARS-CoV-2 but were found to be in lower concentration than respiratory specimens. The patient was treated with ribavirin eye drops and had resolution of ocular symptoms by day 19 of illness.

Similarly, a case report from the National Institute for Infectious Diseases in Rome, Italy confirmed ocular symptoms and SARS-CoV-2-positive RT-PCR conjunctival samples in a COVID-19 positive patient (13). This patient had bilateral conjunctivitis as part of her initial presentation in addition to cough, sore throat, and coryza. Ocular swabs were collected starting on day 3 of hospital admission and were continued with almost daily frequency until day 27. The conjunctivitis was noted to resolve at day 20 and the patient continued to have daily viral SARS-CoV-2 RNA detection in ocular samples until day 21. Furthermore, this patient had a subsequent positive ocular swab on day 27, which was days after SARS-CoV-2 was undetectable by a nasopharyngeal swab. This suggests that tears can be a potential source of infection early on in the disease course and that the conjunctiva may sustain viral replication for an extended period of time.

DISCUSSION

Although the reported incidence of both ocular symptoms and positive conjunctival swabs for SARS-CoV-2 has been fairly low to date, it is important to note that conjunctival swabs from these small case series may have had insufficient tear material to detect the virus in the samples, thus accounting for the low incidence of positive swabs. However, a paucity of evidence is not enough to rule out the possibility of ocular transmission. Suspected COVID-19 patients could also have experienced ocular symptoms that are being underreported. To increase the accuracy of ocular data collection in patients presenting with COVID-19 symptoms, we recommend including questions for the eye portion of the review of systems. Suspected COVID-19 patients should be asked about eye redness, itching, and discharge when a full review of systems is sought by the emergency physician. Emergency physicians should also include COVID-19 in their differential diagnosis for patients presenting with conjunctivitis or isolated ocular signs given the various aforementioned case reports demonstrating conjunctivitis as a first symptom of the disease.

In addition, we recommend informing patients of the possibility of ocular transmission of SARS-CoV-2. This includes informing patients that there has been anecdotal demonstration of COVID-19 seropositivity with isolated ocular symptoms and signs. Regardless of whether they have ocular signs, patients should be instructed to avoid touching the eyes, nose, and mouth to prevent viral spread. They should be advised to discontinue contact lens use if conjunctivitis is diagnosed. In addition, the American Academy of Ophthalmology (AAO) has recently published an article asking all contact lens wearers to consider switching to glasses during this outbreak (14). They urge that reducing contact lens use will reduce the amount of times the patient touches the eye and can provide a physical barrier between respiratory droplets and ocular mucosa to limit ocular transmission of SARS-CoV-2.

For the ophthalmic examination in particular, universal precautions should be followed, including standard infection prevention strategies as well as new approaches geared toward COVID-19, as outlined by the AAO (15). Disposable equipment such as tonometer tips should be used wherever possible, and ophthalmic examination should be performed in a limited number of rooms by a limited number of people. Equipment, including slit lamps, should be thoroughly wiped down with disinfectant wipes, as should all other surfaces in the patient room. Extra caution should be taken during ophthalmic examinations due to the close proximity of the provider's and patient's faces. For this reason, the AAO has recommended the use of N95 masks for ophthalmologists or other physicians providing ophthalmic care to patients potentially infected with SARS-CoV-2 (15). Given the shortage of PPE, if an N95 mask is not available, a surgical face mask should still be worn by both parties. If the patient's presentation constitutes a slit lamp examination, breath shields should be installed on all slit lamps, and the patient should be instructed to refrain from speaking during the examination. The use of a direct ophthalmoscope should also be limited in the emergency department (ED) setting.

CONCLUSION

SARS-CoV-2 is primarily spread through respiratory droplets, though aerosolized transmission is important as well. The eye may represent a source of transmission through infected tears as well as a window for infection via respiratory droplets or aerosolized particles contacting the conjunctiva. Moving forward, all EDs, hospitals, and physician offices should follow precautions to limit potential ocular transmission of COVID-19 (16). This is especially important as the number of patients presenting to the ED with ocular complaints is likely to rise given the temporary closure of comprehensive ophthalmologists' and optometrists' offices due to the pandemic. The mitigation strategies outlined above for preventing ocular transmission of COVID-19 go beyond the standard

infection prevention protocols currently used in ophthalmology practices and would be recommended for emergency physicians taking care of any eye patients.

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REFERENCE 34

Model-based projections for COVID-19 outbreak size and student-days lost to closure in Ontario childcare centers and primary schools

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ABSTRACT

There is a pressing need for evidence-based scrutiny of plans to re-open childcare during the COVID-19 pandemic. Here we developed an agent-based model of SARS-CoV-2 transmission within a childcare center and households. Scenarios varied the student-to-educator ratio (15:2, 8:2, 7:3), and family clustering (siblings together vs. random assignment). We also evaluated a primary school setting (30:1, 15:1 and 8:1) including cohorts that alternate weekly. In the childcare scenarios, grouping siblings significantly reduced outbreak size and student-days lost. We identify an intensification cascade specific to classroom outbreaks of respiratory viruses with presymptomatic infection. In both childcare and primary school settings, each doubling of class size from 8 to 15 to 30 more than doubled the outbreak size and student-days lost, by factors of 2-5, respectively 2.5-4.5, depending on the scenario. Proposals for childcare and primary school reopening could be enhanced for safety by switching to lower ratios and sibling groupings.

Introduction

As nations around the world grapple with the psychosocial, civic, and economic ramifications of social distancing guidelines, the critical need for widely-available Early Childhood Education (or colloquially, "childcare") services have, once again, reached the top of policy agendas[1,2]. Whether arguments are centered on human capital (i.e., "children benefit from high-quality, licensed educational environments, and have the right to access such care") or the economy (i.e., "parents need childcare in order to work, and the economy needs workers to thrive"), the conclusion is largely the same: childcare centers are re-opening, at least in some capacity, and this is taking place before a vaccine or herd immunity can mitigate potential spread of SARS-CoV-2 (the virus that causes COVID-19). Outbreaks of COVID-19 in emergency childcare centers and schools have already been observed[3], causing great concern as governments struggle to balance "flattening the curve" and preventing second waves with other pandemic-related sequelae, such as the mental well-being of children and families, access to education and economic disruption.

Governments and childcare providers are tirelessly planning the operations of centers, with great efforts to follow public health guidelines for reducing SARS-CoV-2 contagion[4]. However, these guidelines, which will result in significantly altered operational configurations of childcare centers and substantial cost increases, have yet to be rigorously examined. Moreover, discussions of childcare are presently eclipsed by general discussion of "school" reopening[5]. That being said, for many parents, the viability of the school-day emerges from before and after school programming that ensures adequate coverage throughout parents' work schedules. Yet, reopening plans often fail to mention the critical interplay between school and childcare, even though many childcare centers operate within local schools[6]. Consequently, a model that comprehensively examines the multifaceted considerations surrounding childcare operations may help inform policy and planning. As such, the purpose of the present investigation is to develop an agent-based model that explores and elucidates the multiple interacting factors that could impact potential SARS-CoV-2 spread in school-based childcare centers.

In Ontario, Canada (the authors' jurisdiction), childcare centers were permitted to reopen on June 12, 2020, provided centers limit groupings (e.g., classrooms) to a maximum of 10 individuals (educators and children, inclusive)[7]. Additionally, all centers had to come up with a plan for daily screening of incoming persons, thorough cleaning of rooms before and during operations, removal of toys that pose risk of spreading germs, allowing only essential visitors, physical distancing at pick-up and drop-off, and a contingency plan for responding should anyone be exposed to the virus (e.g., closing a classroom or center for a period of time). Further school-specific recommendations have been recently outlined by The Toronto Hospital for Sick Children[6], which

include specific guidelines for screening, hand hygiene, physical distancing, cleaning, ventilation, and masking. While this influential report has become the guiding framework for school reopening in Ontario, there remains no discussion of childcare operations in relation to SARS-CoV-2 spread. Guidelines for primary schools call for either full re-opening, with up to 30 students per classroom attending every day, or with cohorts of 15 students attending in alternate weeks.

Simulation models of infectious disease spread have been widely applied during the COVID-19 pandemic, as in previous pandemics[8,9]. Modelling is used to determine how quickly the pathogen can spread[10], how easily it may be contained[11], and the relative effectiveness of different containment strategies[12,13]. Sensitivity analysis is crucial to assess whether model predictions are robust to uncertainties in data[14], which is particularly important during a pandemic caused by a novel emerging pathogen like SARS-CoV-2. Agent-based models are particularly well-suited to situations where a highly granular description of the population is desirable and where random effects (stochasticity) is important. Such models have been previously applied in both pandemic and non-pandemic situations[15–17], and is our choice of modelling methodology in the present work focusing on SARS-CoV-2 transmission in schools and households. Our objective was to use our agent-based model to project the impact of student-to-educator (or in the case of childcare centres, child-to-educator) ratios and sibling grouping strategies on outbreaks of COVID-19 and student-days lost to classroom closure in a hypothetical childcare center and primary school.

Below, the modelling approach, results, and interpretation of the present modelling exercise are described. In the following Methods section, the rationale and parameterization of the model are specified in detail. In the Results section, the performance of the model under different assumptions is showcased. We start with analyzing the childcare center setting and end with the primary school setting. Lastly, the discussion will provide a review and interpretation of this study, including any limitations and future suggestions for research.

Model Overview

A detailed description of the model structure, assumptions and parameterization appears in the Methods section. We developed an agent-based model of SARS-CoV-2 transmission in a population structured into households and classrooms, as might represent a childcare setting or a small primary school (Figure 1A). Individuals were categorized into either child or adult, and contacts between these groups were parameterized based on contact matrices estimated for the Canadian setting. Household sizes were determined from Canadian demographic data. Classroom sizes and student-educator ratios were determined according to the scenario being studied. For the childcare setting we analyzed student-educator ratios of 8:2 and 7:3, giving a maximum class size of 10 representative of the smaller enrollment at schools. We also analyzed a student-educator ratio 15:2, giving a total class size of 17. Along with class size, we also consider class composition. Individuals may spread the infection to their household members each day, so effective contacts and interaction in the classroom may result in qualitatively different spreading patterns. As such, children in this model can be assigned to classrooms either randomly (*RA*) or by grouping siblings (or otherwise cohabiting students) together (*ST*) in an attempt to reduce SARS-CoV-2 transmission. For the primary school setting, we considered student-educator ratios of 8:1, 15:1, and 30:1, all with the random allocation. For the 8:1 and 15:1 ratios we also considered scenarios where cohorts of 8 or 15 students attending the same classroom but in alternating weeks. These scenarios were labelled 8(A):1 and 15(A):1. In the primary school setting, we considered the higher student-educator ratio 30:1 as an example of larger class size. Some plans considered in reopening Ontario educational institutions divides this larger class size into two alternating cohorts of 15 students each with a single shared educator; we call this scenario 15(A):1. Rotation occurs each week, so that one cohort engages with online material while the other receives face-to-face instruction for 5 days, after which the cohorts exchange roles. The student-educator ratios 8:1 and 8(A):1 were also included for comparison to smaller class sizes. For primary schools we considered only the RA allocation.

SARS-CoV-2 could be transmitted in households, classrooms or in common areas of the school, all of which were treated as homogeneously mixing on account of evidence for aerosolized routes of transmission[18]. Individuals were also subject to a constant background risk of infection from other sources, such as shopping centers. Figure 1B shows the progression of the illness experienced by each individual in the model. In each day, susceptible (S) individuals exposed to the disease via community spread or interaction with infectious individuals (those with disease statuses P, A and I) become exposed (E), while previously exposed agents become presymptomatic (P) with probability δ. Presymptomatic agents develop an infection in each day with probability δ, where they can either become symptomatically infected (I) with probability η or asymptomatically infected (A) with probability $1-\eta$. If a symptomatic individuals appears in a classroom, that classroom is closed for 14 days (in the case of alternating cohorts for primary schools, we assumed both cohorts are closed). Other classrooms in the same school may remain open. Asymptomatic students and educators return at the end of this period while symptomatic students and educators remain at home and symptomatic educators are replaced by substitutes.

Children are less affected by the SARS-CoV-2 virus than adults, and account for a smaller proportion of COVID-19 cases[19]. However, the role of children in SARS-CoV-2 transmission is still debated, and existing epidemiological evidence is limited by lack of empirical studies in school settings, which have been closed for much of 2020. Other studies show that children shed a similar amount of virus to adults[20]. To account for this ambiguity, we used contact matrices drawn from populations

under 'business as usual' circumstances as a proxy of what contact rates would look like under a full reopening of schools and workplaces[21], but but we considered both a high transmission rate scenario and a low transmission rate scenario. The low transmission rate scenario represented either reduced transmission rates in children, and/or highly effective infection control through consistent use of high-effectiveness masks, social distancing, and disinfection protocols (see Methods section for details). In total the permutations on student-educator ratios, transmission rate assumptions, siblings versus non-sibling groupings, and alternating cohorts yielded 22 scenarios (Table 1).

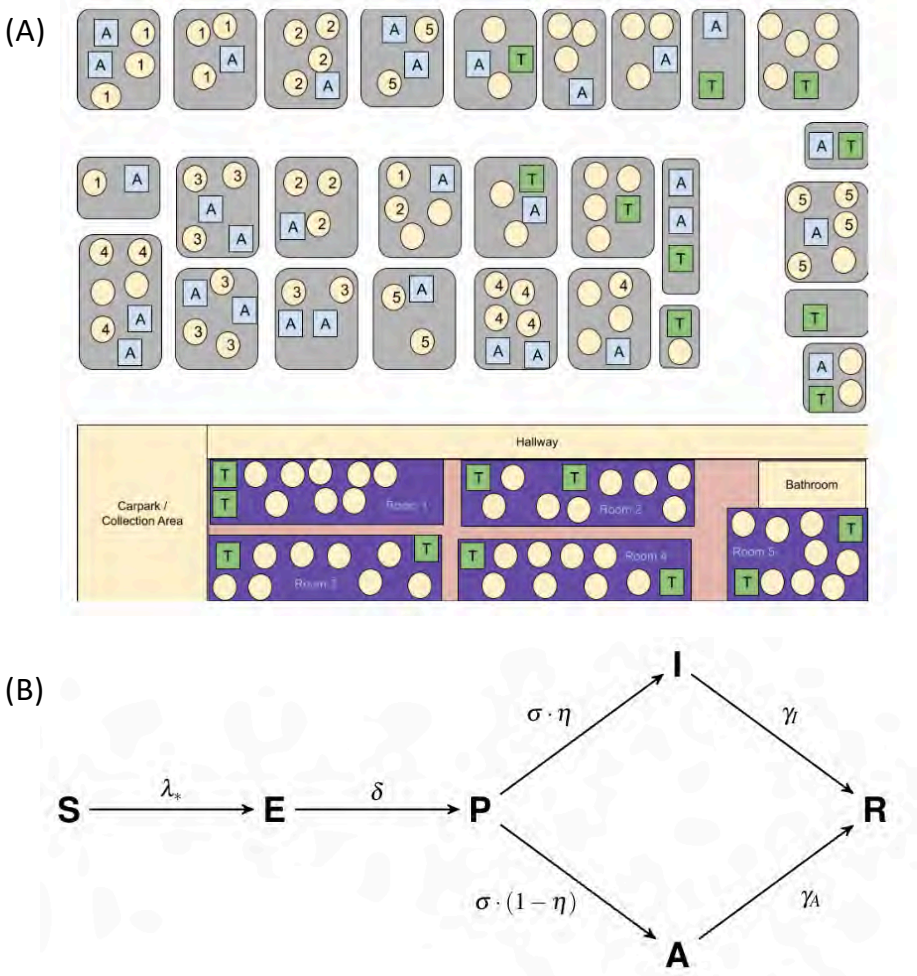

Figure 1. (A) Schematic representation of model population. 'A' represents adult, 'T' represents educator, and circles represent children. Grey rectangles represent houses and the school is represented at the bottom of the figure. Numbers exemplify possible assignments of children in households to classrooms. (B) Diagram showing the SEPAIR infection progression for each agent in the simulation (see Methods for definitions of parameters).

Results

Initial stages of the outbreak

The time evolution of the outbreaks are illustrated in Fig. 2, which shows the proportion of actively infected school attendees (both children and educators) per day in twelve childcare center scenarios. Many of the scenarios tend to produce a well-defined outbreak curve close to the start of the simulation, even with classroom closure protocols in place. However, the outbreaks are more strongly household-driven for the 7:3 and 8:2 ratios than the 15:2 ratio; this is apparent in the weekly waves superimposed on the overall epidemic curve more strongly in the 15:2 scenarios, on account of the impact of weekends. The 15:2 ratio also tends to generate earlier, more intense outbreaks, while 7:3 and 8:2 scenarios produce fewer infections that are more sporadically distributed throughout the simulated time horizon. In the case of high transmission, the maximum mean level of exposure (E) is 4.97% in the 15:2 RA configuration 18 days into the the simulation, on average, with peak 3.03% presymptomatic (P)

Childcare center		
High transmission	15:2 student to educator ratio	siblings togethern (ST)
		random allocation (RA)
	8:2 student to educator ratio	siblings together
		random allocation
	7:3 student to educator ratio	siblings together
		random allocation
Low transmission	15:2 student to educator ratio	siblings together
		random allocation
	8:2 student to educator ratio	siblings together
		random allocation
	7:3 student to educator ratio	siblings together
		random allocation
Primary school		
High transmission	8:1 student to educator ratio	random allocation
	8:1 student to educator ratio, alternating cohorts	random allocation
	15:1 student to educator ratio	random allocation
	15:1 student to educator ratio, alternating cohorts	random allocation
	30:1 student to educator ratio	random allocation
Low transmission	8:1 student to educator ratio	random allocation
	8:1 student to educator ratio, alternating cohorts	random allocation
	15:1 student to educator ratio	random allocation
	15:1 student to educator ratio, alternating cohorts	random allocation
	30:1 student to educator ratio	random allocation

Table 1. 22 Scenarios evaluated based on different assumptions about transmission probabilities, educator-student ratios, and student allocation.

Figure 2. Time series of the proportions of exposed (E), presymptomatic (P), asymptomatic (A) and infected (I) individuals in the simulation for each scenario. The ensemble means are represented by solid lines, while the respected shaded ribbons show one standard deviation of the results.

and 1.64% asymptomatic (A) attendees at days 12 and 19 respectively. Meanwhile, peak mean exposure in scenario 7:3 ST occurs on day 2, with 1.9% attendees exposed to the disease, with presymptomatic cases never exceeding that of the start of any simulation.

Supplementary Tab. S1 summarizes the information from the figures, showing the days until the 30-day peak of each proportion of active infections in the center. Here we can see that active infections peak far earlier with the ST allocation

than with the RA allocation for both high ($\alpha = 0.75$) and low ($\alpha = 0.25$) transmission rates in most cases, and have either equal or smaller peaks for most maximum proportions corresponding to the RA allocation independent of student-educator ratio. In the case of high transmission, peak proportions decrease with the number of students per class in half of the tested scenarios (statuses P and I with RA allocation, and status E). In the low transmission case, there is a reversal in trend, with peak proportions increasing with decreasing number of exposed (E) and presymptomatic (P) students per class. There is no obvious relationship between peak days for infected (I) and asymptomatic (A) individuals in the high transmission case, neither for asymptomatic (A) individuals in the low transmission case.

The basic reproduction number R_0 is the average number of secondary infections produced by a single infected person in an otherwise susceptible population[22]. When there is pre-existing immunity, as we suppose here, we study the effective reproduction number R_e - the average number of secondary infections produced by a single infected person in a population with some pre-existing immunity. Supplementary Fig. S1A shows the estimated R_e and mean population size (school plus all associated households) over the course of each simulation, computed by tracking the number of secondary infections produced by a single primary case. The R_e values measured from the simulation range from 1.5 to 3 on average, depending on the scenario. These R_e values are generally lower than the typical range of R_0 values between 2 to 3 reported in the literature[23]. This is the expected relationship, not only because of pre-existing immunity, but also because the R_e values in our simulation capture transmission only in schools and workplaces, while the R_0 values in the literature are measured for SARS-CoV-2 transmission in all settings, including workplaces and other sources of community spread.

There is little correlation between mean population size (Supplementary Fig. S1A, line), number of households (not shown) and the corresponding R_e estimate (Supplementary Fig. S1A, bars), leaving only the number of children per classroom responsible for the gross increasing trend in R_e in both high ($\alpha = 0.75$) and low ($\alpha = 0.25$) transmission scenarios. Equation 3 shows that child-child contact within the classroom occurs at least 2 times more often than any other type of contact; given that the majority of the attendees of the school are children, we can expect R_e to depend on the number of children enrolled in the school.

This is further demonstrated by the bar charts of Supplementary Fig. S1B, which show the distribution of times between the primary infection case and the first secondary infection. The scenarios with the highest ratio of children to educators (15:2) show the quickest start of the outbreak in both high and low transmission cases, with RA having the highest proportion of trials where the first secondary infection occurred within a single day in the high transmission case. In comparison, scenario 7:3 RA showed the slowest average initial spread in the high transmission case, while the low transmission case sees low rates for both 8:2 and 7:3. Configuration ST (except for ratio 7:3) frequently results in faster secondary spread over the first two days (even in the first 2 weeks).

Outbreak duration

Each individual simulation end when all classes are at full capacity and there are no active infections in the population–aside from community infection, this marks the momentary halt of SARS-CoV-2 spread. From this, we get a description of the duration of the first outbreak. (There could well be a second outbreak sparked by some community infection among individuals who remain susceptible at the end of the first outbreak). Box plots in Fig. 3 show that the 15:2 ratio in both RA and ST allocations gives a median outbreak duration at least as large as all other scenarios (for both low and high transmission cases). Another general observation is that classroom allocation (RA vs. ST) doesn't change the distribution of outbreak duration for student-educator ratios 8:2 and 7:3 as drastically as it does for 15:2, whereas ST allocation results in lower median duration (24 vs 43 for RA allocation) and significantly lower maximum duration for the 15:2 ratio (61 vs. 88 for RA allocation without outliers) in the high transmission case.

This is mirrored in the low transmission case as well. A possible explanation lies in the number of students per classroom. The child-child contact rate (Eqn. 3) is far higher than any other contact rate, implying that the classroom is the site of greatest infection spread (demonstrated in Fig. 4A). ST allocation differs from RA allocation in its containment of disease transfer from the classroom to a comparatively limited number of households. This effect (the difference between ST and RA) is amplified with the addition of each new student to the classroom, so that while the difference between 7:3 and 8:2 may be small (only 1 student added), the effect becomes far exaggerated when the student number is effectively doubled (15 students vs. 7 or 8).

The evolution of the numbers of susceptible (S) and recovered/removed (R) school attendees provides additional information on the course of the outbreak, since they represent the terminal states of the infection process in each individual by the end of the outbreak. Supplementary Fig. S1C shows the proportion of susceptible and recovered current school attendees (who have not been sent home due to classroom outbreaks). As with all results so far, the 15:2 RA scenario most efficiently facilitates disease spread through the school in both high and low transmission cases, with the proportion of recovered attendees (R) overtaking the number of never-infected attendees (status S) on day 34 in the case of high transmission ($\alpha = 0.75$). Performance between 8:2 and 7:3 with ST allocation is similar for both transmission rates, though all scenarios show smaller variation over trials featuring lower infection transmission. As shown in Fig. 3, scenario 15:2 RA gave the longest average simulation time in the

Figure 3. Box plots depicting the distribution of simulation durations for each scenario. Taken together with the stopping criteria of the simulations and measures of aggregate, these describe the duration of the outbreak. Red dots represent the arithmetic mean of the data.

high transmission scenario; this is also reflected in Supplementary Fig. 2, where the longest outbreak lasted 134 days.

Outbreak size and classroom closure

Figure 4A shows the mean number of infections in each location in all scenarios, as well as the total number of infections in each scenario (the 'outbreak size'). As expected, many more infections occur in the high transmission scenario ($\alpha = 0.75$), and the error bars of the plot show greater standard deviation of the results than in the low transmission ($\alpha = 0.25$) scenario. But for each location and regardless of the transmission rate scenario, the number of infections increases rapidly with the number of children in the classroom in each room allocation. The 15:2 ratio is universally the worst allocation across all possible scenarios. However, the difference between the outbreak size in different scenarios decreases as the transmissibility of the virus drops (so to speak, the gap been between the 15:2 RA and 15:2 ST scenarios decreases as α decreases, and so with other student-educator ratios). When the transmission rate is high, the relatively larger variety (by household) and prevalence of child-child interactions has a multiplicative effect on the number of effective transmissions in the classroom. Lower transmissibility thereby decreases the classroom infection rates relative to the household transmission rates.

The numbers of student-days forfeited due to classroom closure are given in Fig. 4B, according to scenario. (The number of student-days forfeited is the number of days of closure times the number of students who would otherwise have been able to continue attending.) In all scenarios, the 15:2 student-educator ratio is quantitatively the worst strategy examined by almost an order of magnitude, resulting in the highest possible number of student-days forfeited. RA allocation shows worse performance than ST in all scenarios. Both the low ($\alpha = 0.25$) and high ($\alpha = 0.75$) transmissibility scenarios favour the 7:3 student-educator ratio and ST allocation, with a lower number of student-days forfeited. The poor performance of 15:2 ratio occurs because it suffers from a multiplicative effect: larger class sizes are more likely to be the origin of outbreak, and when the outbreak starts, more children are affected when the classroom is shut down. Moreover, since it's possible for a student or educator to be infected during a 14-day closure, not all attendees necessarily return to class upon reopening; sick educators are replaced with substitutes. As such, these class closures results in otherwise healthy students missing potentially additional school days beyond the 14-day closure period. The 15:2 strategy suffers particularly from this effect, since transmission is facilitated when more students are in a classroom.

Naturally, a high incidence of COVID-19 cases will result in multiple room closures; one way to see this is to look at the number and duration of room closures, both shown in Fig. S1D. In all scenarios, schools spent (on average) more days with one closed classroom than any other number. We can also observe a difference in RA and ST allocations for the 7:3 ratio: with both high and low transmission rate ($\alpha = 0.25$ and $\alpha = 0.75$ respectively), RA allocation results in a higher number of class closures.

Primary school settings

The primary school setting shows the same cascade of intensifying outbreaks and rapidly mounting student-days of closure as class sizes increase (Fig. 5). This effect occurs in both childcare centres and primary schools because firstly, in a larger classroom it is more likely that a student tests positive for COVID-19. Secondly, when the classroom closes as a result, more students are affected by the closure. Thirdly, because COVID-19 is characterized by presymptomatic infection and aerosol dispersal, there is more infection in larger classrooms before the closure is enacted. Introducing more children into the

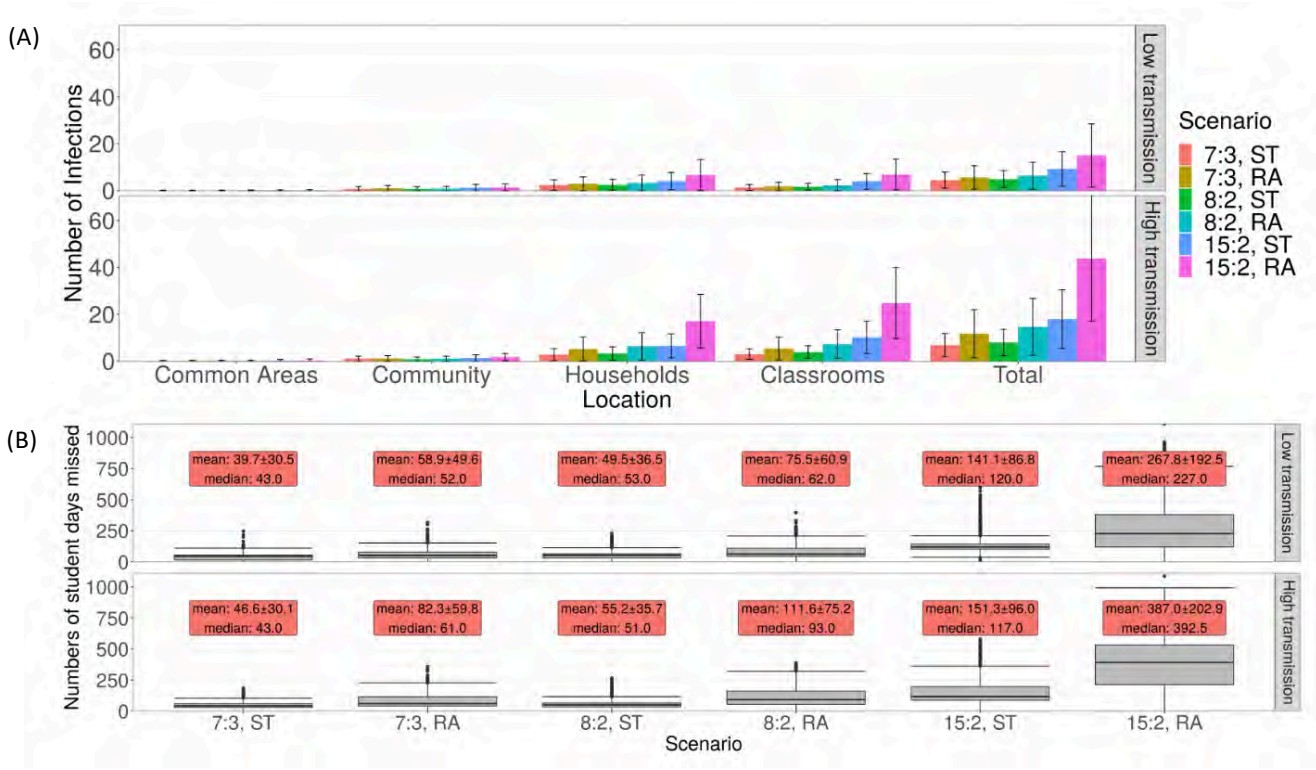

Figure 4. COVID-19 outbreak size and student-days lost to closure in the childcare setting. (A) the mean number of infections occurring among all school attendees in each location over time for each scenario. The height of each bar gives the ensemble mean and its standard deviation is represented by error bars. (B) Box plots showing the number of student days forfeited over the course of the simulation due to class closure upon the detection of an outbreak. Red text boxes show the mean and standard deviation of closure.

classroom increases the effective reproductive ratio (R_e) for both low and high rates of transmission while cohorting/alternation has little effect (Supplementary Fig. S2A), and similar strategies (that is, differing by only 1 student or educator per class, or by alternation) give similar reproductive ratios R_e (compare to Supplementary Fig. S1A).

There is little difference between numbers of forfeited student days between the similar scenarios 8:1 and 8(A):1, as well as as 15:1 and 15(A):1 (Fig. 5B). Since the shutdown of a classroom affects both cohorts, there will be very little difference in virus spread between scenarios allotting the same number of students per classroom. This effect is also seen in Supplementary Fig. 5A. Comparison of Fig. 4A and Fig. 5A show similar distributions of outbreak size for all student-teacher ratios, signifying that cohorting does not significantly change the results of structured interactions featured in the model. The true benefit of cohorting arises in the consideration of class sizes, given the desire for contact time with all enrolled students. Comparison of Fig. 4B and Fig. 5B shows that the similar scenarios 15:2 RA, 15:1 RA and 15(A):1 RA all result in a comparable number of forfeited student-days in both low and high transmission scenarios, as do the scenarios 8:2 RA, 8:1 RA and 8(A):1 RA.

Higher student-educator ratios facilitate faster disease spread through the school than smaller ones (Supplementary Fig. S2B). One major difference is the weekly fluctuation of the infection status curves visible in the cohorted scenarios 8(A):1 and 15(A):1. These fluctuations correspond to the rotation of the student cohorts through the school term. Transitions between majority susceptible and recovered regimes is delayed (high transmission) or prevented (low transmission) by cohorting; we see that alternating strategies result in better aggregate infection outcomes, even when classroom capacity is held constant. Scenario 15(A):1 also results in shorter mean and median outbreak lengths in the entire population in both low and high transmission cases (Supplementary Fig. S2C).

Sensitivity Analysis

We conducted a sensitivity analysis on β^H, β^C, λ and R_{init} (see Supplementary Appendix for details). We found that variation in rates of household and classroom interaction and infection (β^H and β^C) and the number of individuals initially recovered (R_{init}) greatly impact SARS-CoV-2 transmission, but did not change the relative performances of the 22 scenarios. The greatest influence on outcomes remain the scheme of allocation of students to classrooms (RA or ST), the number of students per class

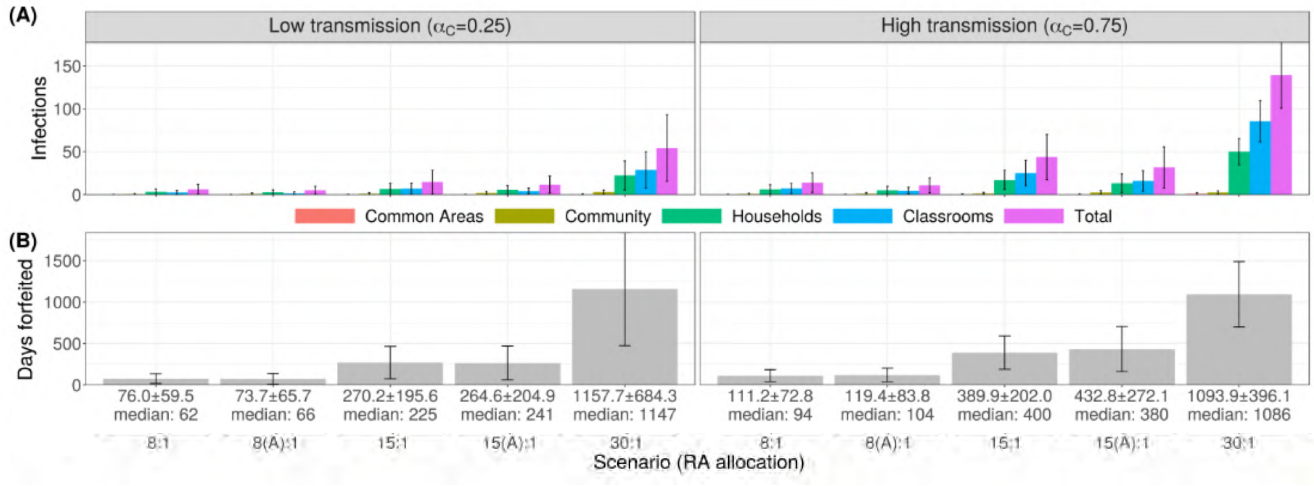

Figure 5. COVID-19 outbreak size and student-days lost to closure in the childcare setting. (A) Bar charts showing the mean number of infections occurring in each location over the time of the simulation, (B) Bar charts showing the number of student days forfeited due to classroom closures sparked by disease outbreak. Error bars represent one standard deviation of the corresponding data.

(15, 8 or 7), and whether the transmission rate in the classrooms is low or high (α_C). Other important factors include classroom closure upon identification of a symptomatic case and the interaction patterns of asymptomatic infected individuals in the household upon classroom closure (i.e. whether they continue to interact in close contact, as would be necessary for younger children, or whether children are old enough to effectively self-isolate). Our baseline assumption was to assume asymptomatic infected individuals who are sent home due to closure of a classroom are able to self-isolate. This assumption is conservative, since inability to self-isolate under these circumstances would result in higher projected outbreak sizes.

Discussion

We developed and simulated an agent-based model of SARS-CoV-2 transmission in childcare center and primary school settings for the purposes of informing reopening policies. The model was configured to capture SARS-CoV-2 transmission in a local school building, since many childcare centers operate across several classrooms within schools. These services are an essential bridge for many parents who are unable to drop-off or pick-up children around school hours due to work. Our findings suggest that variability in class size (i.e., number of children in a class) and class composition (i.e., sibling groupings versus random assignment) influence the nature of SARS-CoV-2 transmission within the childcare context. Specifically, a 7:3 student-to-educator ratio that utilized sibling groupings yielded the lowest rates of transmission, while a 15:2 ratio consistently performed far worse. Findings for the primary school ratios show a similar acceleration of negative impacts with increasing class size. Findings from our simulations are sobering, as educators in the province lobbied for a 15 student cap on classrooms in Summer 2020. Our study suggests that classes of this size pose a tangible risk for COVID-19 outbreaks, and that lower ratios would better offset infection and school closures. While school reopening guidelines[6], public health agencies[24], and public petitions[25] have called for smaller class sizes, governments appear to be following some recommendations in reopening plans while ignoring others.

This accelerating effect of increasing classroom sizes occurs because of three factors working in concert. Firstly, a larger class means that a student is more likely to test positive for COVID-19 at some point. Secondly, when a larger class is closed as a result, it affects more students. Third, presymptomatic transmission and higher densities of students ensure that more children become infected before classroom closure is enacted, resulting in larger outbreak sizes due to more cases both before the closure, and after the closure as the infection continues to spread in households. This particular mechanism is specific to institutional outbreaks for infectious diseases with pre-symptomatic transmission worsened by aerosol transmission routes[18].

Policies related to childcare and traditional school reopening have not been well integrated[26]. In Ontario, childcare classrooms were capped at a maximum of 10 occupants, overall (hence the 8:2 and 7:3 ratios in the present study)[7]. Conversely, procedures for traditional "school" classrooms have been given the go-ahead for 15 children (hence the 15:2 ratio). While allowable class sizes will differ somewhat as a function of child age and jurisdiction, it seems likely that early childhood and elementary school classes may actually surpass these numbers in Ontario. Our findings demonstrate that the 15:2 ratio represents a significantly higher risk, not only for SARS-CoV-2 spread, but for school closures. In one scenario (15:2 random

assignment), the modeled outbreak lasted for 105 days. Given that childcare and schools are often operating within the same physical location, this policy discrepancy is questionable. Based on our simulations, a lower ratio (7:3) is indicated. Moreover, it appears that this configuration could be enhanced through the utilization of sibling groupings.

An examination of student days missed due to classroom closure further elucidates the favorability of smaller class size and sibling grouping as a preventative measure. In this analysis, the worst configuration was the 15:2 random assignment ratio. Again, this was observed in both high transmission and low transmission environments. In the most unfavorable scenario (15:2 RA), there were cumulatively 387 and 267 student days forfeited in high versus low transmission settings, respectively. Conversely, in the best scenario (7:3, siblings together), there were only 47 and 40 student days forfeited. Thus, our simulations suggest that the lower ratios and sibling groupings offer a safeguard against high disruptive classroom closures[27,28]. Given this, a proactive and preventative approach that builds in realistic levels of reduced class time would be better than a reactive strategy that yields unpredictable closure events due to outbreaks.

Several policy and procedural recommendations have emerged from this modeling exercise. First, it is recommended that childcare and school settings, alike, consider lowering student-to-educator ratios. Commensurate with the present findings, a 7:3 ratio (10 individuals per class including both children and adults) outperforms a 15:2 ratio on key metrics. Second, there also appears to be benefit associated with sibling groupings. Thus, a siblings together configuration should be considered. Third, the majority of transmission occurred in the classroom. As such, it is important for reopening plans to consider social distancing and hygiene procedures within classrooms - a recommendation that may only be feasible with fewer children in the classroom. It is unlikely that classrooms with 15 or more children will afford children with the necessary space to socially distance. Finally, in the primary school settings, significant benefits accrue for 15(A):1 relative to the 30:1 student-educator ratio, and thus decision-makers should reconsider the conventional model of putting 30 students in classrooms every day in favour of cohorts of 15 students alternating weekly.

Finally, the present study has a number of limitations that should be considered. While it is becoming increasingly clear that COVID-19 risk varies as a function of social determinants of health (e.g., socioeconomic status, race, ethnicity, immigration status, neighborhood risk), along with opportunities for social distancing[29], the present study did not take these considerations into account. Future simulation studies might consider how these social determinants intersect with childcare and school configurations. Additionally, this study was primarily concerned with SARS-CoV-2 infection and student days lost. That being said, there are many important outcomes to consider in relation to children's developmental health in the pandemic. Longitudinal studies considering children's learning and mental health outcomes in relation to new childcare and school configurations are strongly indicated[30].

Materials and Methods

Population Structure

There are N households in the population, and a single educational institution (either a school or a school, dependent on scenarios to be introduced later) with M rooms and a maximum capacity dependent on the scenario being tested. Effective contacts between individuals occur within each household, as well as rooms and common areas (entrances, bathrooms, hallways, etc.) of the institution. All groups of individuals (households and rooms) in the model are assumed to be well-mixed.

Each individual (agent) in the model is assigned an age, household, room in the childcare facility and an epidemiological status. Age is categorical, so that every individual is either considered a child (C) or an adult (A). Epidemiological status is divided into stages in the progression of the disease; agents can either be susceptible (S), exposed to the disease (E), presymptomatic (an initial asymptomatic infections period P), symptomatically infected (I), asymptomatically infected (A) or removed/recovered (R), as shown in Fig. 1B.

In the model, some children in the poFpulation are enrolled as students in the institution and assigned a classroom based on assumed scenarios of classroom occupancy while some adults are assigned educator/caretaker roles in these classroom (again dependent on the occupancy scenario being tested). Allocations are made such that there is only one educator per household and that children do not attend the same institution as a educator in the household (if there is one), and *vice versa*.

Interaction and Disease Progression

The basic unit of time of the model is a single day, over which each attendee (of the institution) spends time at both home and at the institution. The first interactions of each day are established within each household, where all members of the household interact with each other. An asymptomatically infectious individual of age i will transmit the disease to a susceptible housemate with the age j with probability $\beta^H_{i,j}$, while symptomatically infectious members will self-isolate (not interact with housemates) for a period of 14 days.

The second set of interpersonal interactions occur within the institution. Individuals (both students and educators) in each room interact with each other, where an infectious individual of age i transmits the disease to some susceptible individual of age j with probability $\beta^C_{i,j}$. To signify common areas within the building (such as hallways, bathrooms and entrances), each

individual will then interact with every other individual in the institution. There, an infectious individual of age j will infect a susceptible individual of age i with probability $\beta^O_{i,j}$.

To simulate community transmission (for example, public transport, coffee shops and other sources of infection not explicitly modelled here), each susceptible attendee is infected with probability λ_S. Susceptible individuals not attending the institution in some capacity are infected at rate λ_N, where $\lambda_N > \lambda_S$ to compensate for those consistent effective interactions outside of the institution that are neglected by the model (such as workplace interactions among essential workers and members of the public).

Figure 1B shows the progression of the illness experienced by each individual in the model. In each day, susceptible (S) individuals exposed to the disease via community spread or interaction with infectious individuals (those with disease statuses P, A and I) become exposed (E), while previously exposed agents become presymptomatic (P) with probability δ. Presymptomatic agents develop an infection in each day with probability δ, where they can either become symptomatically infected (I) with probability η or asymptomatically infected (A) with probability $1-\eta$.

The capacity of the sole educational institution in the model is divided evenly between 5 rooms, with class size and student-educator ratio governed by one of three basic scenarios: seven students and three educators per room ($7:3$), eight students and two educators per room ($8:2$), and fifteen students and two educators per room ($15:2$). Classroom allocations for children can be either randomised or grouped by household (siblings are put in the same class).

Symptomatically infected agents (I) are removed from the simulation after 1 day (status R) with probability γ_I, upon which they self-isolate for 14 days, and therefore no longer pose a risk to susceptible individuals. Asymptomatically infected agents (A) remain infectious but are presumed able to maintain regular effective contact with other individuals in the population due to their lack of noticeable symptoms; they recover during this period (status R) with probability γ_A. Disease statuses are updated at the end of each day, after which the cycles of interaction and infection reoccur the next day.

The actions of symptomatic (status I) agents depend on age and role. Individuals that become symptomatic maintain a regular schedule for 1 day following initial infection (including effective interaction within the institution, if attending), after which they serve a mandatory 14-day isolation period at home during which they interaction with no one (including other members of their household). On the second day after the individual's development of symptoms, their infection is considered a disease outbreak centerd in their assigned room, triggering the closure of that room for 14 days. All individuals assigned to that room are sent home, where they self-isolate for 14 days due to presumed exposure to the disease. Symptomatically infected children are not replaced, and simply return to their assigned classroom upon recovery. At the time of classroom reopening, any symptomatic educator is replaced by a substitute for the duration of their recovery, upon which they reprise their previous role in the institution; the selection of a substitute is made under previous constraints on educator selection (one educator per household. with no one chosen from households hosting any children currently enrolled in the institution).

Parameterization

The parameter values are given in Supplementary Tab. S2. The sizes of households in the simulation was determined from 2016 Statistics Canada census data on the distribution of family sizes[31]. We note that Statistics Canada data only report family sizes of 1, 2 or 3 children: the relative proportions for 3+ children were obtained by assuming that 65% of families of 3+ children had 3 children, 25% had 4 children, 10% had 5 children, and none had more than 5 children. Each educator was assumed to be a member of a household that did not have children attending the school. Again using census data, we assumed that 36% of educators live in homes with no children, where an individual lives alone with probability 0.282, while households hosting 3, 4, 5, 6, and seven adults occur with probability 0.345, 0.152, 0.138, 0.055, 0.021 and 0.009 respectively. Others live with ≥ 1 children in households following the size and composition distribution depending on the number of adults in the household. For single-parent households, a household with a single child occurs with probability 0.169, and households with 2, 3, 4 and 5 children occur with probabilities 0.079, 0.019, 0.007 and 0.003 respectively. With two-parent households, those probabilities become 0.284, 0.307, 0.086, 0.033 and 0.012.

The age-specific transmission rates in households are given by the matrix:

$$\begin{bmatrix} \beta^H_{1,1} & \beta^H_{1,2} \\ \beta^H_{2,1} & \beta^H_{2,2} \end{bmatrix} \equiv \beta^H \begin{bmatrix} c^H_{1,1} & c^H_{1,2} \\ c^H_{2,1} & c^H_{2,2} \end{bmatrix}, \tag{1}$$

where $c^H_{i,j}$ gives the number of contacts per day reported between individuals of ages i and j estimated from data[21] and the baseline transmission rate β^H is calibrated. To estimate $c^H_{i,j}$ from the data in Ref.[21], we used the non-physical contacts of age class 0-9 years and 25-44 years of age with themselves and one another in Canadian households. Based on a meta-analysis, the secondary attack rate of SARS-CoV-2 appears to be approximately 15% on average in both Asian and Western households[32]. Hence, we calibrated β^H such that a given susceptible person had a 15% chance of being infected by a single infected person in their own household over the duration of their infection averaged across all scenarios tested (App.). As such, age specific

transmission is given by the matrix

$$\beta^H \cdot \begin{bmatrix} 0.5378 & 0.3916 \\ 0.3632 & 0.3335 \end{bmatrix}. \tag{2}$$

To determine λ_S we used case notification data from Ontario during lockdown, when schools, workplaces, and schools were closed[33]. During this period, Ontario reported approximately 200 cases per day. The Ontario population size is 14.6 million, so this corresponds to a daily infection probability of 1.37×10^{-5} per person. However, cases are under-ascertained by a significant factor in many countries[34]–we assumed an under-ascertainment factor of 8.45, meaning there are actually 8.45 times more cases than reported in Ontario, giving rise to $\lambda_S = 1.16 \times 10^{-4}$ per day; λ_N was set to $2 \cdot \lambda_S$.

The age-specific transmission rates in the school rooms is given by the matrix

$$\begin{bmatrix} \beta^C_{1,1} & \beta^C_{1,2} \\ \beta^C_{2,1} & \beta^C_{2,2} \end{bmatrix} \equiv \beta^C \begin{bmatrix} c^C_{1,1} & c^C_{1,2} \\ c^C_{2,1} & c^C_{2,2} \end{bmatrix} \equiv \beta^C \begin{bmatrix} 1.2356 & 0.0588 \\ 0.1176 & 0.0451 \end{bmatrix}, \tag{3}$$

where $c^C_{i,j}$ is the number of contacts per day reported between age i and j estimated from data[21]. To estimate $c^C_{i,j}$ from the data in Ref.[21], we used the non-physical contacts of age class 0-9 years and 20-54 years of age, with themselves and one another, in Canadian schools. Epidemiological data on secondary attack rates in childcare settings are rare, since schools and schools were closed early in the outbreak in most areas. We note that contacts in families are qualitatively similar in nature and duration to contacts in schools with small group sizes, although we contacts are generally more dispersed among the larger groups in rooms, than among the smaller groups in households. On the other hand, rooms may represent equally favourable conditions for aerosol transmission, as opposed to close contact. Hence, we assumed that $\beta^C = \alpha_C \beta^H$, with a baseline value of $\alpha_C = 0.75$ based on more dispersed contacts expected in the larger room group, although we varied this assumption in sensitivity analysis.

To determine β^O we assumed that $\beta^O = \alpha_O \beta^C$ where $\alpha_O \ll 1$ to account for the fact that students spend less time in common areas than in their rooms. To estimate α_O, we note that β^O is the probability that a given infected person transmits the infection to a given susceptible person. If students and staff have a probability p per hour of visiting a common area, then their chance of meeting a given other student/staff in the same area in that area is p^2. We assumed that $p = 0.05$ and thus $\alpha_O = 0.0025$. The age-specific contact matrix for β^O was the same as that used for β^C (Eqn. 3).

Model Initialisation

Upon population generation, each agent is initially susceptible (S). Individuals are assigned to households as described in the Parameterisation section, and children are assigned to rooms either randomly or by household. We assume that parents in households with more than one child will decide to enroll their children in the same institution for convenience with probability $\xi = 80\%$, so that each additional child in multi-child households will have probability $1 - \xi$ of not being assigned to the institution being modelled.

Households hosting educators are generated separately. As in the Parameterisation section, we assume that 36% of educators live in adult-only houses, while the other educators live in houses with children, both household sizes following the distributions outlined in the Parameterization section. The number of educator households is twice that required to fully supply the school due to the replacement process for symptomatic educators outlined in the Disease Progression section.

Initially, a proportion of all susceptible agents R_{init} is marked as removed/recovered (R) to account for immunity caused by previous infection moving through the population. A single randomly chosen school attendee is chosen as a primary case and is made presymptomatic (P) to introduce a source of infection to the model. All simulations are run until there are no more potentially infectious (E, P, I, A) individuals left in the population and the institution is at full capacity. All results were averaged over 2000 trials.

Estimating β^H

Agents in the simulation were divided into two classes: "children" (ages $0-9$) and "adults" (ages $25-44$). Available data on contact rates[21] was stratified into age categories of width 5 years starting at age 0 ($0-5$. $5-9$, $10-14$, etc.). The mean number of contacts per day $c^H_{i,j}$ for each class we considered (shown in Eq. 2) was estimated by taking the mean of the contact rates of all age classes fitting within our presumed age ranges for children and adults.

For β^H calibration, we created populations by generating a sufficient number of households to fill the institution in each of the three tested scenarios; $15:2$, $8:2$ and $7:3$. In each household, a single randomly chosen individual was infected (each member with equal probability) by assigning them a presymptomatic disease status P; all other members were marked as susceptible (disease status S). In each day of the simulation, each member of each household was allowed to interact with the infected member, becoming exposed to the disease with probability given in Eqn. 2. Upon exposure, they were assigned disease status E. At the beginning of each subsequent day, presymptomatic individuals proceeded to infected statuses I and A,

and infected agents were allowed to recover as dictated by Fig. 1B and Supplementary Tab. S2. This cycle of interaction and recovery within each household was allowed to continue until all infected individuals were recovered from illness.

We did not allow exposed agents (status E) to progress to an infectious stage (I or A) since we were interested in finding out how many infections within the household would result *from a single infected household member*, as opposed to added secondary infections in later days. At the end of each trial, the specific probability of infection (π_n) in each household H_n was calculated by dividing the number of exposed agents in the household (E_n) by the size of the household $|H_n|$ less 1 (accounting for the member initially infected). Single occupant households ($|H_n| = 1$) were excluded from the calculation. The total probability of infection π was then taken as the mean of all π_n, so that

$$\pi = \frac{1}{D}\sum_n \pi_n = \frac{1}{D}\sum_{|H_n|\geq 2} \frac{E_n}{|H_n| - 1}, \tag{4}$$

where D represents the total number of multiple occupancy households in the simulation. This modified disease simulation was run for 2000 trials each of different prospective values of β^H ranging from 0 to 0.21. The means of all corresponding final estimates of the infection rate were taken per value of β^H, and the value corresponding to a infection rate of 15% was interpolated.

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Supplementary Appendix

Sensitivity Analysis: varying α_0 and B_H

The parameter β^H represents the rate of interaction in the household, and thereby regulates the spread of the disease. For each value of α_0, increasing the rate of interaction in the home β^H increases the number of infections produces for both RA (Supplementary Fig. S3) and ST (Supplementary Fig. S4) allocation. In most scenarios (7:3 RA being one of the exceptions), varying α_0 (for constant β^H) produces a small increase in the number of infections produced throughout the simulation. The rate of increase also depends on the number of children in the classroom; for the scenario 31:1 RA, increasing β^H from 0.0545 to its baseline value 0.109 almost triples the number of total infections.subsection*Sensitivity Analysis - Varying α_0 and R_{init}

The parameter R_{init} refers to the proportion of individuals we presume are recovered from some previous period of infection spread, while α_0 is responsible for the rate of infection in common areas relative to the infection rate in the classroom. All other parameters are set to the baseline values given in Supplementary Tab. S2. These parameters were varied together by 50% in either direction. In Supplementary Figs. S5 and S6, increasing values of R_{init} lower both the means and standard deviations of the total number of infections for each value of α_0. Also, for each value of R_{init}, the total number of infections produced increases with α_0 . This shows opposing interaction between increasing common area infection and increasing initial recovery rate; one increases infection and the other lowers it (respectively).

Sensitivity Analysis - Varying α_0 and λ_i

From Tab. S2, parameter λ_i varies the amount of community infection in the model (infection due to other sources not modelled, such as public transport); be reminded that we assumed that the rate of community infection is effectively twice the baseline value for those individuals in the model not attending the school.

For each value of α_0 in Supplementary Fig. S8, the total number of infections produced in the simulation increases with λ in each scenario with random allocation (RA), and also with grouping by household (ST, Supplementary Fig. S7). For each λ, there is no consistent relationship between the numbers of infections and the value of α_0. This result is intuitive; though the effect is not pronounced, increasing the rate of community infection increases the total number of infections in each tested scenario.

Supplementary Figures and Tables

			Peak Time			**Maximum** $(\times 10^{-4})$		
α_C	**Status**	**Allocation**	**15:2**	**8:2**	**7:3**	**15:2**	**8:2**	**7:3**
0.75	**P**	**RA**	12	0	0	304	200	200
		ST	4	0	0	193	200	199
	E	**RA**	18	3	3	497	252	204
		ST	3	3	2	336	227	195
	I	**RA**	12	2	2	49	37	35
		ST	4	2	2	30	34	37
	A	**RA**	19	5	5	165	198	111
		ST	5	5	4	82	113	103
α_C	**Status**	**Allocation**	**15:2**	**8:2**	**7:3**	**15:2**	**8:2**	**7:3**
0.25	**P**	**RA**	0	0	0	118	200	200
		ST	0	0	0	118	200	201
	E	**RA**	4	3	5	96	113	128
		ST	2	2	3	96	105	117
	I	**RA**	2	2	2	19	27	21
		ST	2	2	2	19	30	21
	A	**RA**	5	4	5	69	111	100
		ST	5	5	5	62	102	102

Table S1. Times at which the mean proportions of presymptomatic (P), exposed (E), symptomatically infected (I) and asymptomatically infected (A) school attendees peak during the first 30 days of simulation with secondary spread with respect to each of the scenarios tested, and the corresponding peak number of cases.

Parameter	Meaning	Baseline Value	Source
η	probability of symptomatic infection	0.6 (adults)	TBD
		0.4 (children)	TBD
δ	transition probability, $E \to P$	0.5/day	[35,36]
σ	transition probability, $P \to I,A$	0.5/day	[35,36]
γ_I	transition probability, $I \to R$	1.0/day	[35,36]
γ_A	transition probability, $A \to R$	0.25/day	[35,36]
c_{ij}^H	household contact matrix	...	[21]
β^H	transmission probability in households	0.109	[32], calibrated
c_{ij}^C	room contact matrix	...	[21]
β^C	transmission probability in classrooms	$\beta^C = \alpha_C \beta^H$, $\alpha_C = 0.75$	[32], assumption
β_{ij}^O	transmission probability in common areas	$\beta^O = \alpha_O \beta^C$, $\alpha_O = 0.0025$	[21,32], assumption
λ_i	infection rate due to other sources	1.16×10^{-4}/day	[33], estimated
R_{init}	initial proportion with immunity	0.1	assumption
ξ	probability of sibling attending same center	0.8	assumption
o	proportion of childless educators	0.36	[31], assumption
	household size distributions		[31]

Table S2. Parameter definitions, baseline values and literature sources.

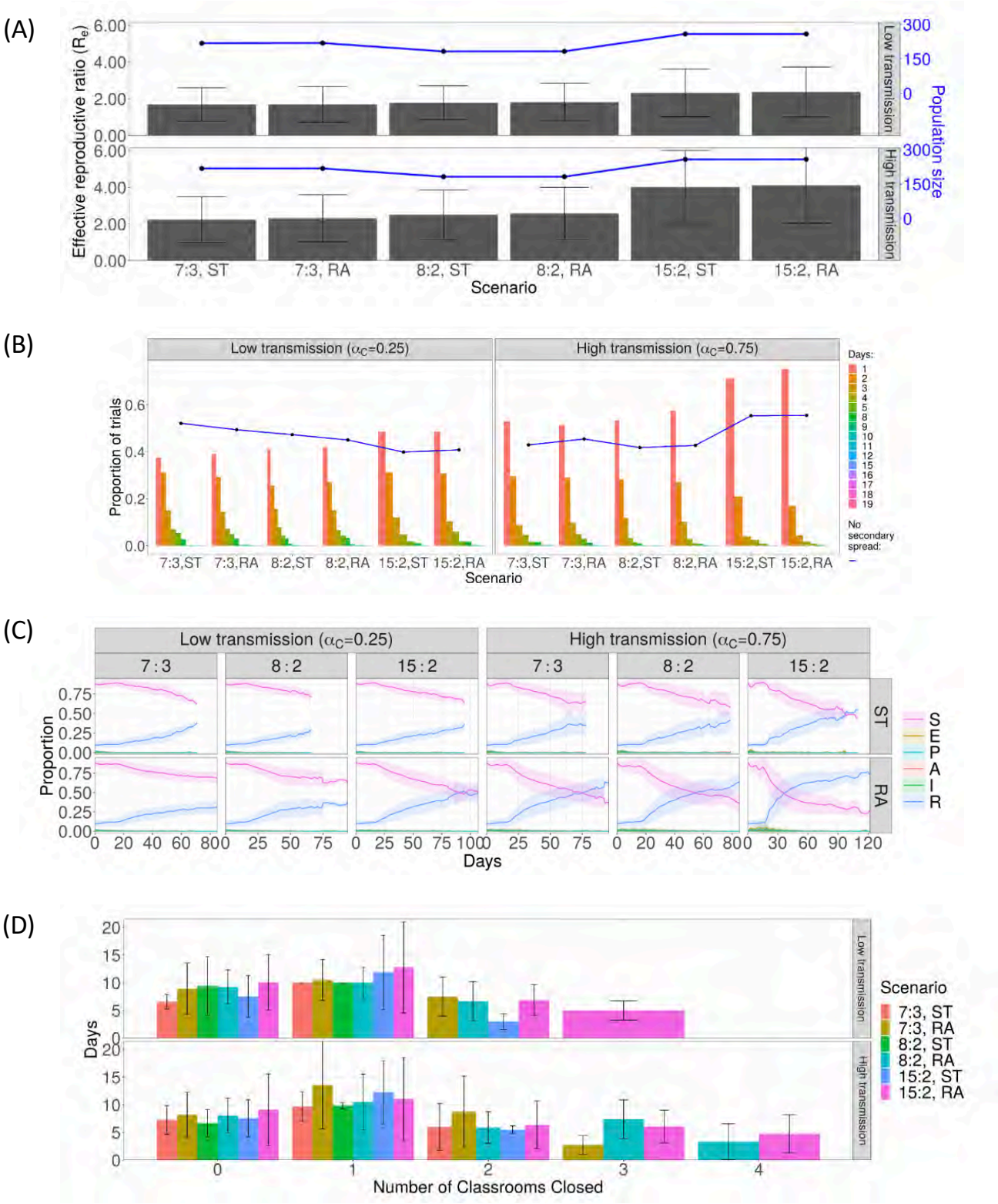

Figure S1. (fig:Combined2) Supplementary Results for Childcare Setting. (A) Bar chart showing the effective reproduction number R_e in the entire population (with error bars denoting one standard deviation), with a line plot showing the mean population size. Both low and high transmission scenarios are shown. (B) Diagram showing the proportion of trials without secondary spread (curve), and the time taken to produce the first secondary infection (bar chart), both sorted by scenario. (C) Time series detailing the trends in the mean proportions of current school attendees in each stage of disease progression. Shaded ribbons around each curve show one standard deviation of the averaged time series. Only trials showing secondary spread were included in the ensemble means shown. (D) Bar chart showing the number of days for which some number of rooms in the school were closed due to disease outbreak. Scenarios are represented by different colours; the height of each bar gives the relevant ensemble mean with its standard deviation represented by error bars.

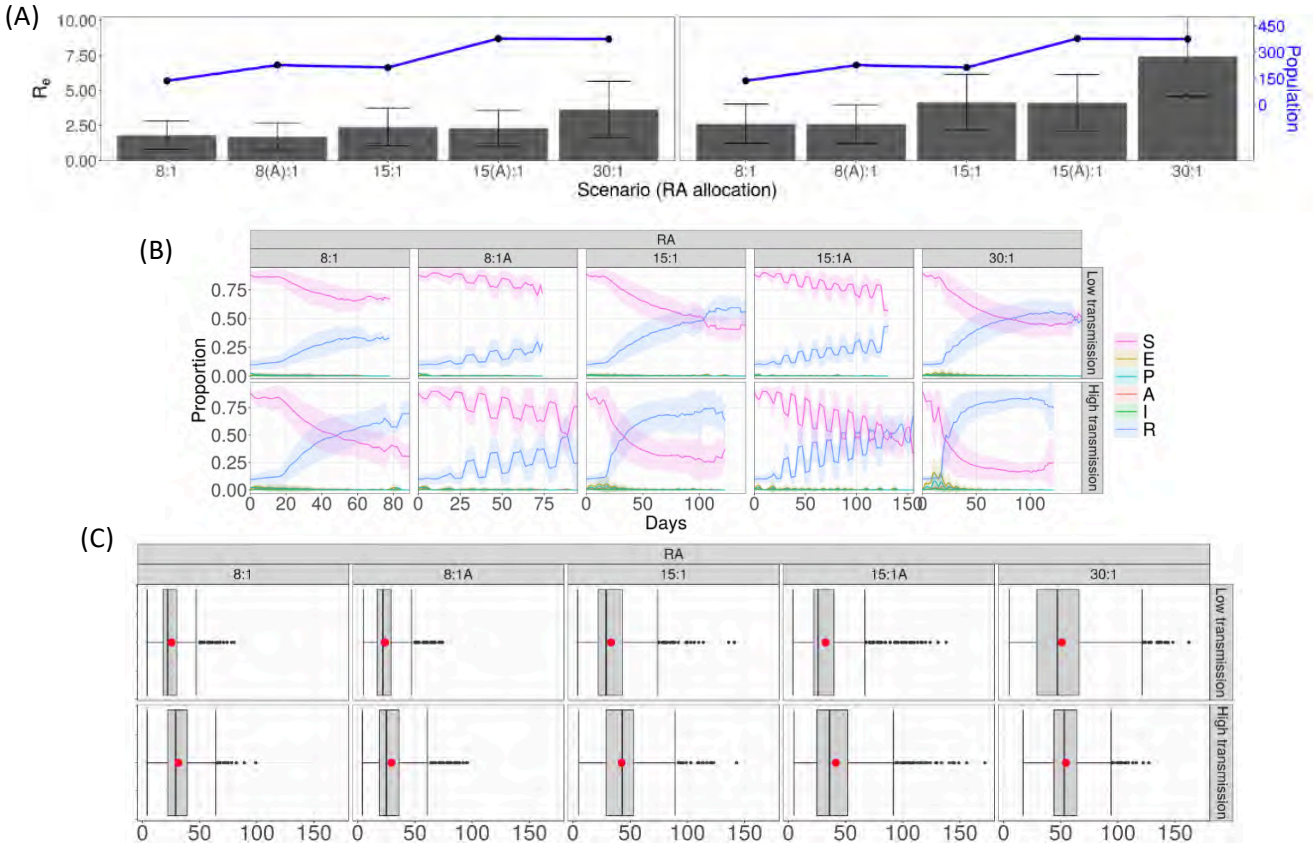

Figure S2. (fig:Combined1) Supplementary results for the primary school scenario. (A) Bar chart showing the effective reproduction number R_e in the entire population (with error bars denoting one standard deviation), with a line plot showing the mean population size. Both low and high transmission scenarios are shown. (B) Time series showing the trends in the mean proportions of current school attendees in each stage of disease progression. Shaded ribbons around each curve show one standard deviation of the averaged time series. Only trials showing secondary disease spread were included in the ensemble means shown. (C) Box plots depicting the distribution of simulation durations for each scenario, describing the length of the outbreak. Red dots represent the arithmetic mean of the data.

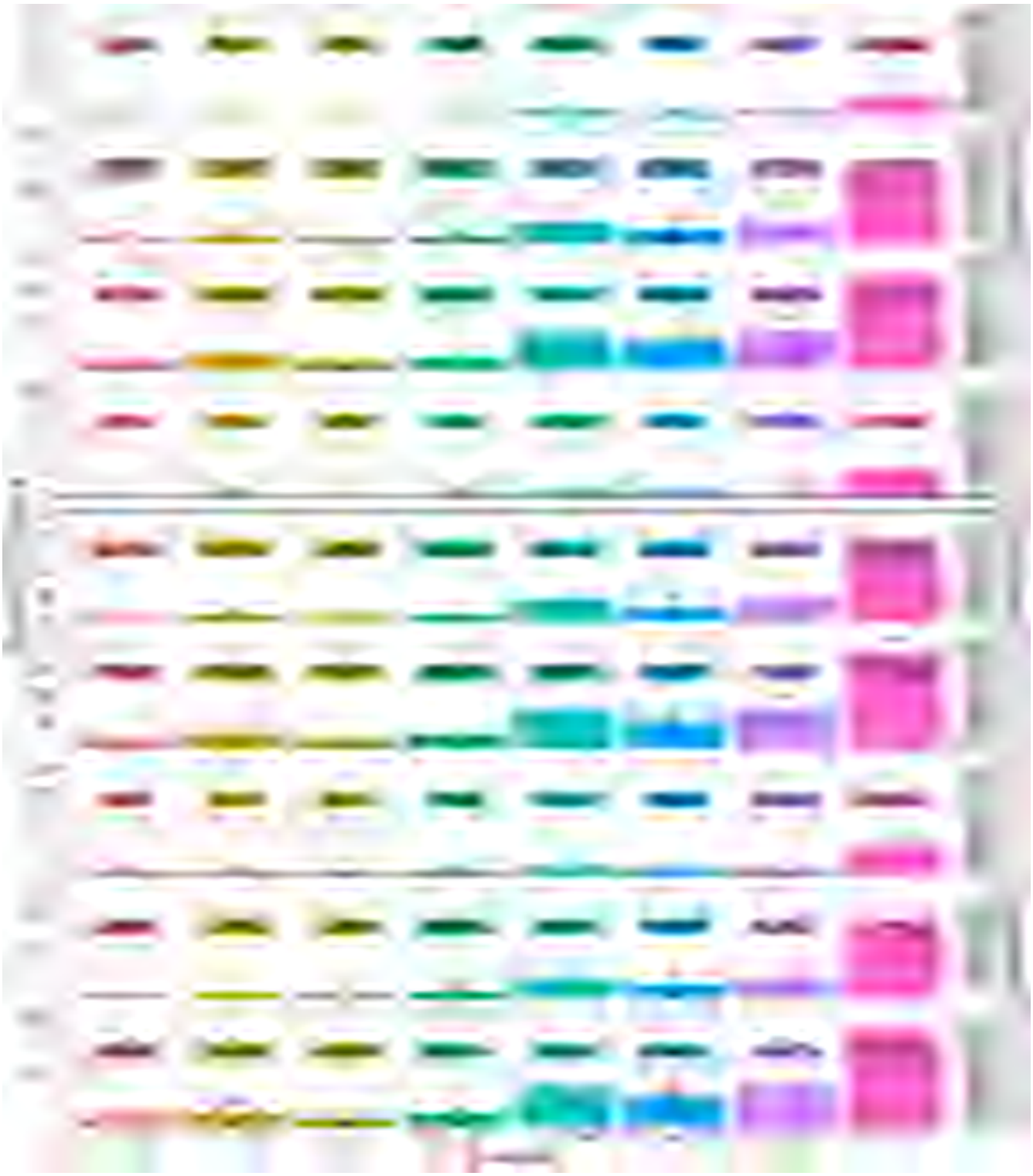

Figure S3. Results of varying the parameters β^H and α_0 by (50% each) on the total number of produced infections for RA allocation. Error bars denote a single standard deviation of the data used, and boxed text shows the corresponding mean and standard deviation.

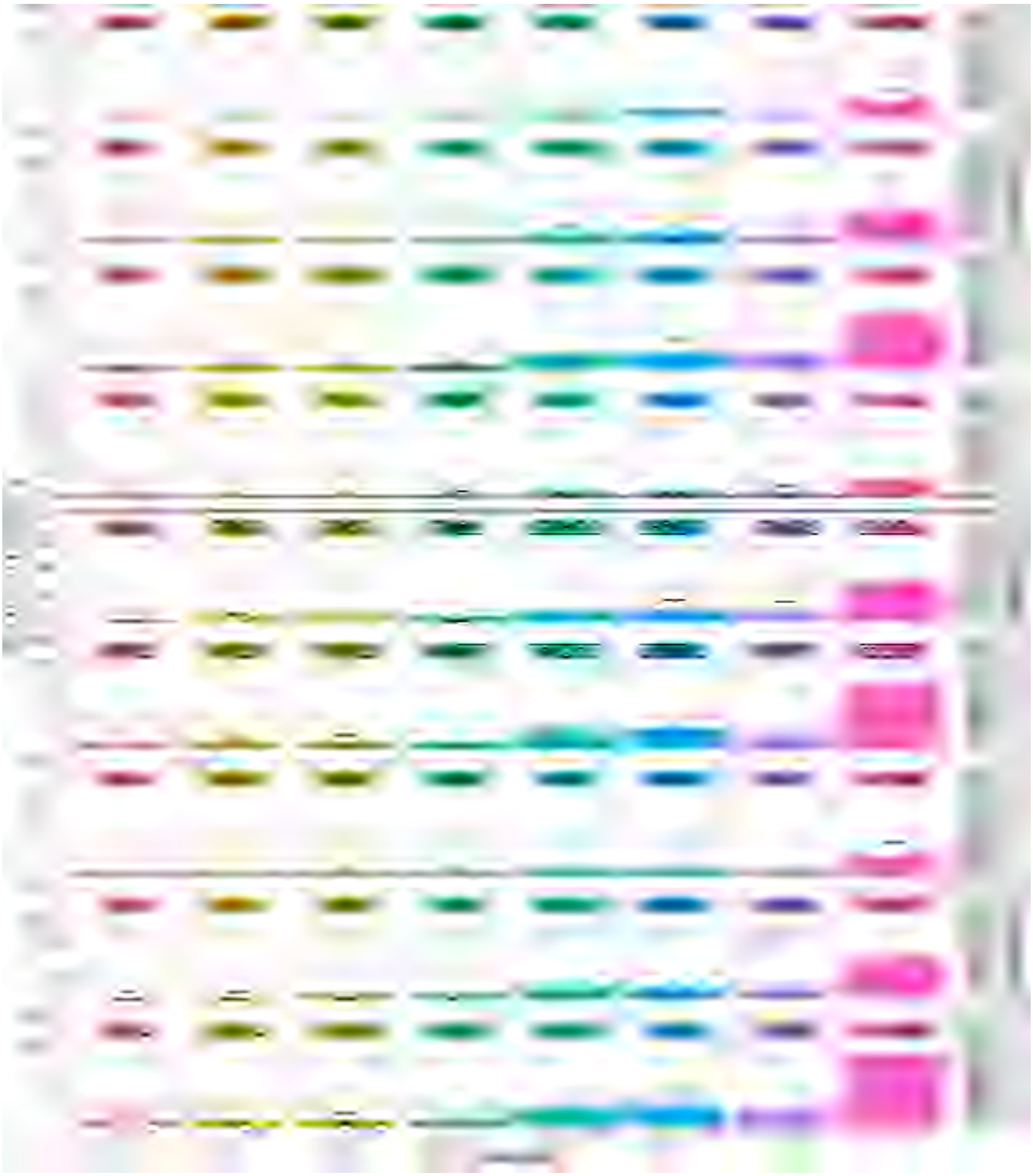

Figure S4. Results of varying the parameters β^H and α_0 by (50% each) on the total number of produced infections for ST allocation. Error bars denote a single standard deviation of the data used, and boxed text shows the corresponding mean and standard deviation.

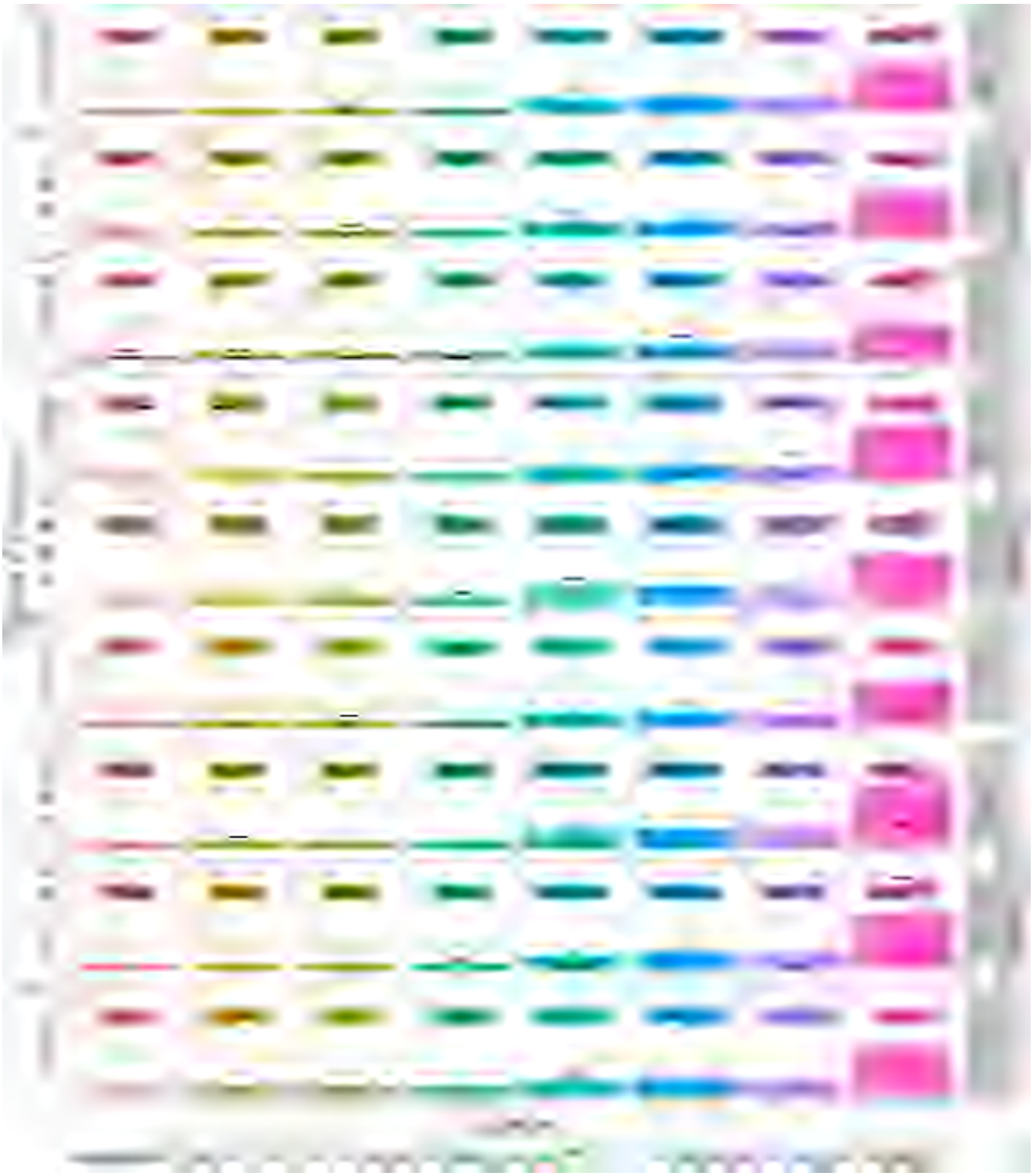

Figure S5. Results of varying the parameters R_{init} and α_0 by (50% each) on the total number of infections for ST allocation. Text in boxes denotes the mean and standard deviation of the data corresponding to the parameters and error bars denote a single standard deviation of the data used.

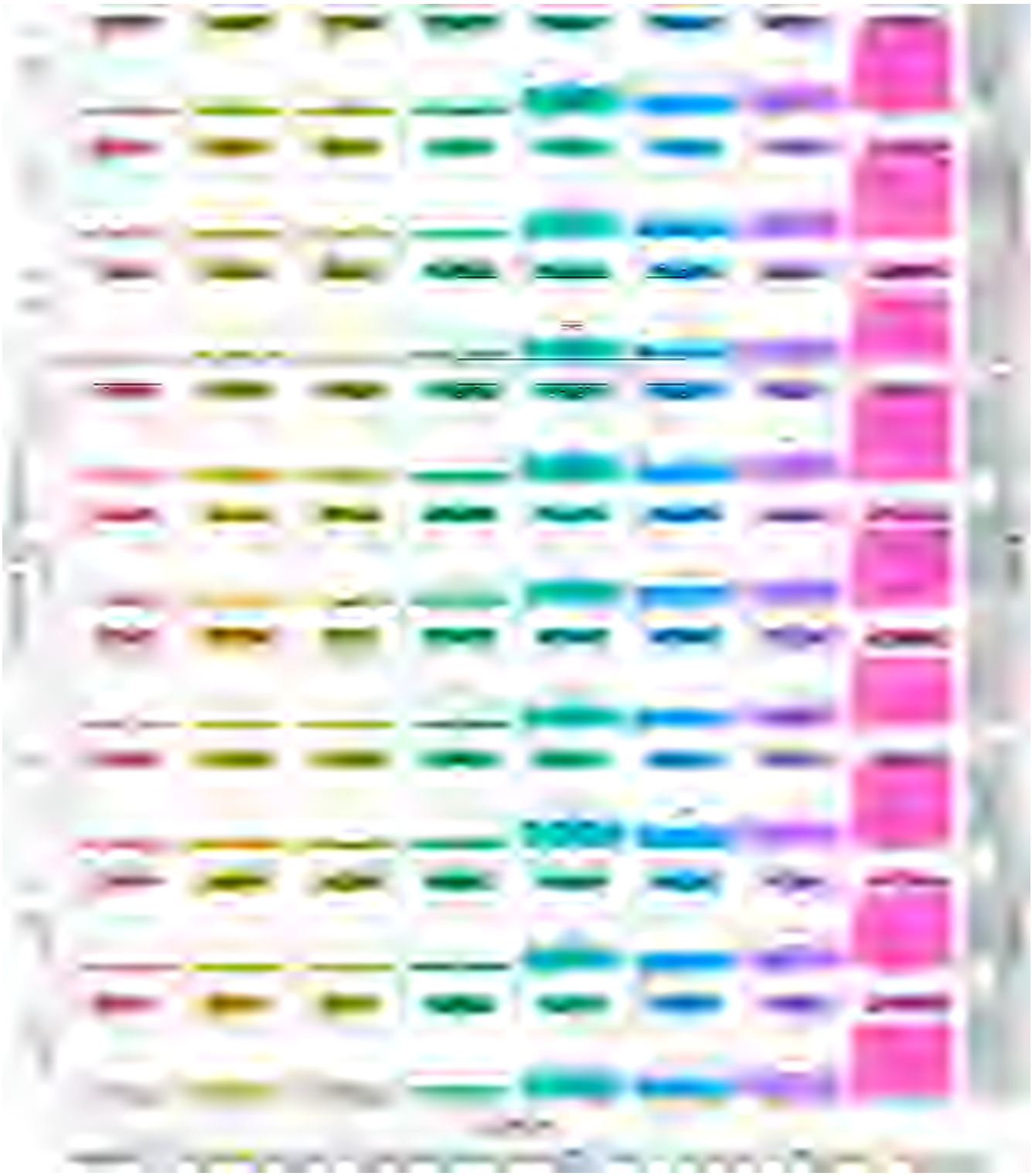

Figure S6. Results of varying the parameters R_{init} and α_0 by (50% each) on the total number of infections for RA allocation. Text in boxes denotes the mean and standard deviation of the data corresponding to the parameters and error bars denote a single standard deviation of the data used.

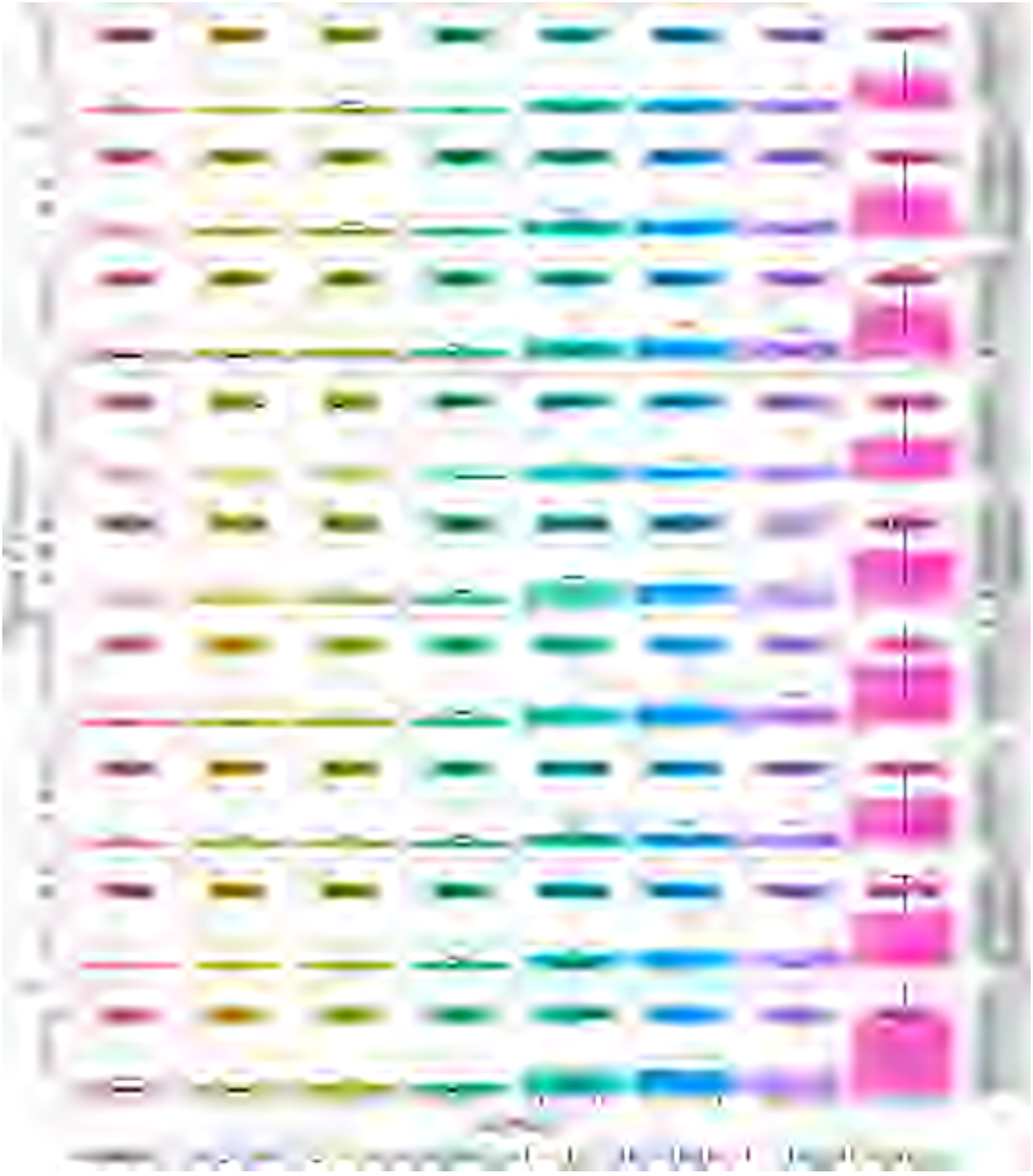

Figure S7. Results of varying the parameters λ_i and α_0 by (50% each) on the total number of infections for ST allocation. Text in boxes denotes the mean and standard deviation of the data corresponding to the parameters and error bars denote a single standard deviation of the data used.

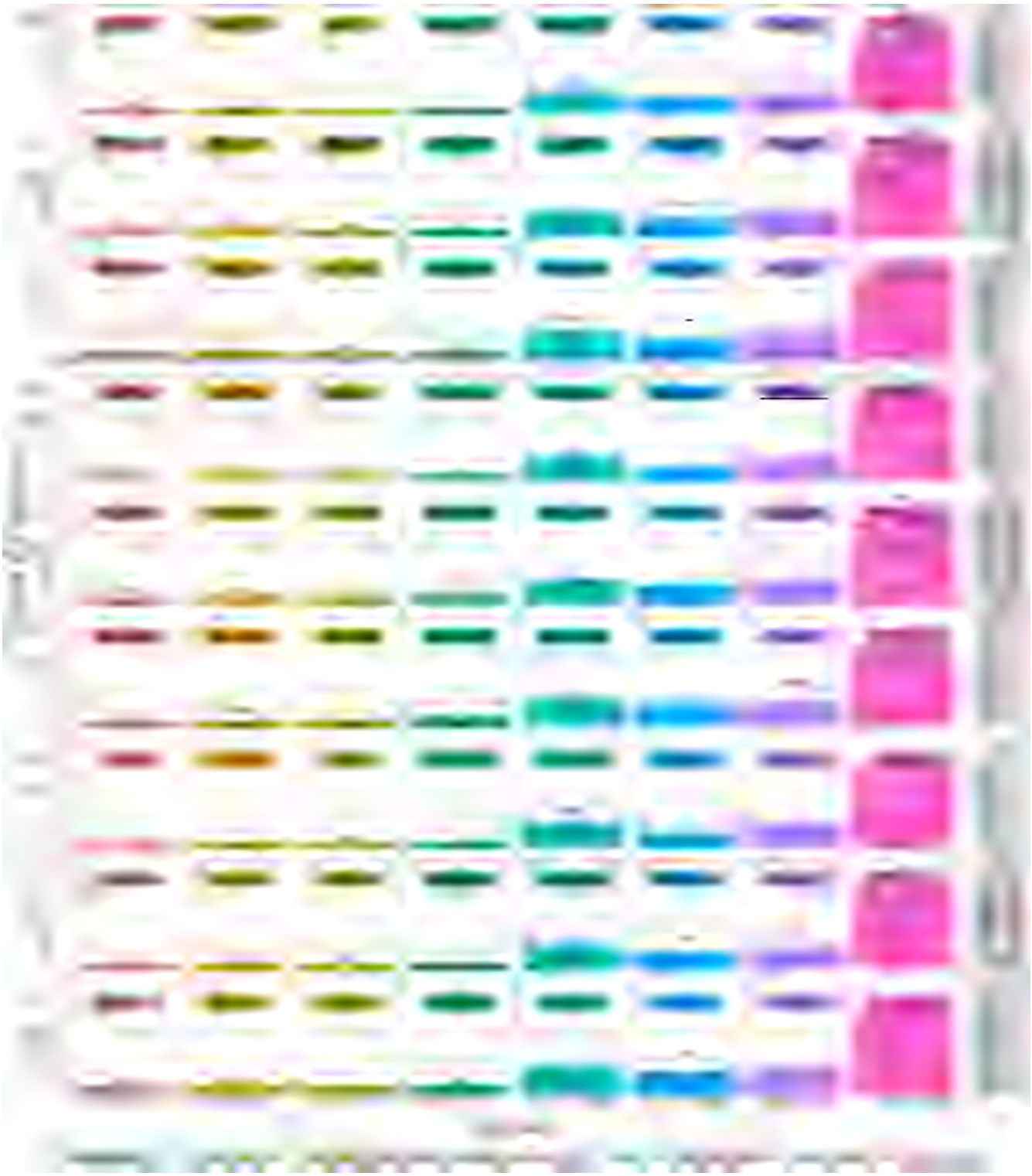

Figure S8. Results of varying the parameters λ_i and α_0 by (50% each) on the total number of infections for ST allocation. Text in boxes denotes the mean and standard deviation of the data corresponding to the parameters and error bars denote a single standard deviation of the data used.

REFERENCE 35

Study updates

September 14, 2020

Researchers and teachers provide initial observations from school simulation study

Researchers and clinicians from The Hospital for Sick Children (SickKids) led a study on August 19 and 20, 2020, looking at the effects of physical distancing, masking, hand hygiene and other health and safety measures for students and teachers returning to school during the COVID-19 pandemic. While formal results are not yet available, the researchers and teachers involved in the study have compiled preliminary observations and key learnings from their experiences running simulated school days.

“Management of the COVID-19 pandemic has been very complex and filled with tremendous anxiety. As health-care providers and parents, we can empathize with the teachers, school staff, school boards and the education sector as a whole, who are now facing a great deal of uncertainty,” says Dr. Michelle Science, Co-Principal Investigator of the study and Staff Physician in the Division of Infectious Diseases

at SickKids. “As the school year progresses, sharing key learnings and best practices from simulations or real-world experiences could help enhance everyone’s safety measures. Having the flexibility to adjust these safety measures will strengthen our collective response to COVID-19.”

The simulation included over 190 students and 15 teachers from both public and independent schools. Students of all ages attended the simulations, which included in-classroom learning, lunch, recess and parent/caregiver pick-up and drop-off. All students were required to submit a paper screening tool asking about COVID-19 symptoms at the start of each school day.

The researchers and teachers discussed their initial observations and shared their key learnings with school boards and public health authorities to inform back-to-school planning.

“As the return to school has already started, teachers across the province are likely learning, or have already learned, the same observations we made,” says Dr. Clyde Matava, Co-Principal Investigator of the study, Staff Anesthesiologist and Associate Chief of Perioperative Services, Department of Anesthesia and Pain Medicine, SickKids. “We hope the wide release of these initial findings will foster conversations between stakeholders to share invaluable knowledge about school safety that can only be gleaned from real-world settings.”

The study team is analyzing data and planning a peer reviewed publication in the near future. The initial observations below have not been published in a peer-reviewed journal and are meant to serve as helpful considerations for schools and school boards.

Observations

Observations

Teacher involvement

Teachers played a critical role in the set-up and design of the school days. Their intimate knowledge of classrooms and procedures, combined with their active involvement in the planning process, allowed for smooth and creative implementation of the health and safety measures.

Classroom set-up

The classrooms used during the simulation resembled a typical public school classroom (i.e. 32 feet by 24 feet). With these room sizes, it was not possible to maintain a two-metre distance between students and accommodate more than 12-15 students in the class even with the desks against all four walls.

- There was crowding at entry points even with staggered class starts and fewer students than at most public and private schools.
- The entry process took longer than expected. This involved collection and inspection of a paper screening tool, staggered entry by classes, hand hygiene, and application of a liquid indicator that was part of the study procedure.
- Having a designated staff member (e.g. supervisory duty teacher at an entry point) to indicate to teaching staff when their class could proceed with entry helped for smoother transitions that provided sufficient distancing.

- Students were unsure of what to do with their masks during recess (for example, masks secured around wrists became soiled). Several children in the younger grades needed new masks provided throughout the school day.

- Several parents wanted to check in with the teacher at the beginning and end of the school day and were often not wearing masks because of the outdoor pick up. As a result, it was difficult for teachers to maintain distance while supervising the children and support a conversation with parents.
- On-site staff congregated in shared spaces like workrooms and offices.

Considerations

* Classroom set-up:
    - Remove any non-student related furniture
    - Utilize all available space (including desks against walls and at the back of the class)
    - If class sizes are not reduced, alternative classroom set-ups should be explored to promote physical distancing (e.g. small cohorted groups within classes)

- Staggering of start dates will facilitate reduced crowding as students adapt to new entry processes.
- Ongoing staggering of start times will likely be required at most schools to avoid crowding on entry, especially in the presence of an active screening strategy.
- A process is needed for late students who miss entry with their cohorts.
- All available doors should be used for entry and exit to reduce crowding.
- Routine on-site screening at entry points will require additional time and is likely not feasible without multiple screeners.
- A clear process should be developed for mask storage during recess and communicated to staff, families, and students. Our group recommends;
    - Store masks in a labelled, clean and dry bag that can be kept on the student during breaks (e.g. in their pocket or fanny pack)
    - Unprotected mask storage (e.g. lanyards or wearing as “wristlet”) may lead to soiling and the need for mask changes.
    - If lanyards are used, ensure there is a safety release / breakaway mechanism (to reduce strangulation risk) and they should ideally be removed on the playground.
- A process for teacher communication with parents/caregivers should be developed and communicated in advance of school to limit non-essential in-person discussions which may lead to crowding and

delayed school dismissal.

* Staff involved in the direct supervision of students should be encouraged to minimize their time (outside school hours) inside the school building, especially in shared spaces like staffrooms and department workrooms.
* For staff members not directly involved in the physical supervision of students, consideration should be given to working off-site to avoid unnecessary congregating with other staff.

REFERENCE 36

Screening K-12 Students for Symptoms of COVID-19: Limitations and Considerations

Updated July 23, 2020

This document provides guidance to K-12 schools on COVID-19 symptom screening as part of a school reopening process. The guidance detailed here is intended only for **students in K-12** school settings. The number of reported children with SARS-CoV-2 (the virus that causes COVID-19) infection who experience symptoms, the types of symptoms they experience, and the severity of those symptoms differs from adults. Additionally, the consequences of excluding students from essential educational and developmental experiences differ from excluding individuals from other settings. Therefore, the considerations described here are different than those for other settings and populations. For guidance related to screening of teachers and staff, please refer to CDC's Interim Guidance for Businesses and Employers Responding to Coronavirus Disease 2019 and the "Prevent Transmission Among Employees" section of CDC's Resuming Business Toolkit .

We learn more about COVID-19 every day, and as more information becomes available, CDC will continue to update and share information. As our knowledge and understanding of COVID-19 evolves, this guidance may change. **However, based on the best available evidence at this time:**

- **CDC does not currently recommend universal symptom screenings (screening all students grades K-12) be conducted by schools.**
- **Parents or caregivers should be strongly encouraged to monitor their children for signs of infectious illness every day.**
- **Students who are sick should not attend school in-person.**

COVID-19 is a newly identified disease caused by the virus, SARS-CoV-2. Scientists are still learning about how it spreads, how it impacts children, and what role children may play in its spread. Limited data about COVID-19 in children suggest that children are less likely to get COVID-19 than adults, and if they do contract COVID-19, they generally have less serious illness than adults. While uncommon, deaths and rare illness such as multisystem inflammatory syndrome in children (MIS-C) may still occur.

People with COVID-19 have had a wide range of reported symptoms – ranging from mild symptoms to severe illness. Symptoms may appear **2-14 days after exposure to** SARS-CoV-2. Symptoms can include:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches

- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

This list does not include all possible symptoms and children and youth with SARS-CoV-2 infection may experience any, all, or none of these symptoms. (See Symptoms of Coronavirus for more information).

Given the wide range of symptoms and the fact that some people with SARS-CoV-2 infection (the virus that causes COVID-19) are asymptomatic, there are limitations to symptom screening conducted by schools for the identification of COVID-19.

Limitations of Symptom Screenings as Part of a School Reopening Strategy

- **Symptom screenings will fail to identify some students who have SARS-CoV-2 infection**. Symptom screenings are not helpful in identifying individuals with SARS-CoV-2 infection who are asymptomatic or pre-symptomatic (they have not developed signs or symptoms yet but will later). Others may have symptoms that are so mild, they may not notice them. In fact, children are more likely than adults to be asymptomatic or to have only mild symptoms. [1], [2], [3] The exact percentage of children with SARS-COV-2 infection who are asymptomatic is still unknown, but recent large studies have suggested around 16% of children with SARS-CoV-2 infection do not develop symptoms. [4] This means that even when schools have symptom screenings in place, some students with SARS-CoV-2 infection, who can potentially transmit the virus to others, will not be identified.

- **Symptom screenings will identify only that a person may have an illness, not that the illness is COVID-19.** Many of the symptoms of COVID-19 are also common in other childhood illnesses like the common cold, the flu, or seasonal allergies. The table below illustrates some of the overlap between the symptoms of COVID-19 and other common illnesses.

Table. Many symptoms of COVID-19 are also present in common illnesses

Symptoms of COVID-19	Strep Throat	Common Cold	Flu	Asthma	Seasonal Allergies
Fever or chills	X		X		
Cough		X	X	X	X
Sore throat	X	X	X		X
Shortness of breath or difficulty breathing				X	

Fatigue		X	X	X	X
Nausea or Vomiting	X		X		
Diarrhea	X		X		
Congestion or Runny Nose		X	X		X
Muscle or body aches	X	X	X		

Note: The table above does not include all COVID-19 symptoms

Available for Download

The overlap between COVID-19 symptoms with other common illnesses means that many people with symptoms of COVID-19 may actually be ill with something else. This is even more likely in young children, who typically have multiple viral illnesses each year. For example, it is common for young children to have up to eight respiratory illnesses or "colds" every year.[1]Although COVID-19 and illnesses like colds or the flu have similar symptoms, they are different disease processes.

Some studies have tried to identify which symptoms may best predict whether an individual has COVID-19, although these studies have primarily focused on those over 18-years-old.[6], [7], [8], [9] In children, fever has been the most frequently reported symptom. However, fever is common in many other illnesses, and temperatures can be taken improperly and falsely interpreted as fever. Additionally, there is no symptom or set of symptoms that only occurs in children diagnosed with COVID-19.

Additionally, students with chronic conditions like asthma or allergies may have symptoms like cough or nasal congestion without having any infection at all. As a result, symptom screenings have the potential to exclude some students from school repeatedly even though they do not have COVID-19 or any contagious illness. This in turn may worsen disparities in students who already miss school frequently because of chronic medical conditions.

Students who are sick with contagious illnesses should not attend school, but most illnesses do not require the same level or length of isolation that COVID-19 does. Excluding students from school for longer than what is called for in existing school policies (e.g., fever free without medication for 24-hours) based on COVID-19 symptoms alone risks repeated, long-term unnecessary student absence.

Symptom screenings alone are inadequate to reduce SARS-CoV-2 transmission because of the limitations mentioned. Even when symptom screenings are implemented, other mitigation strategies (such as promoting healthy behaviors, maintaining healthy environments, maintaining healthy operations, and preparing for when someone gets sick) are still needed to help protect students, teachers, and staff from COVID-19.

The exact level of effectiveness of symptom screening in schools is not known at this time. While screening may reduce some SARS-COV-2 transmission in schools, transmission may still occur because of asymptomatic, pre-symptomatic, and mildly symptomatic students. Additionally, because symptom screenings will likely identify individuals who have symptoms that are unrelated to COVID-19 and, at times, unrelated to any infectious illness, students may be inappropriately excluded from school, which may cause unintended harm. It is because of these limitations that CDC does not currently recommend that universal symptom screenings be conducted at schools.

Considerations If Symptom Screenings Are Used in School Settings

For schools that choose to implement on-site symptom screenings, CDC offers the following considerations:

- Consider the scientific evidence outlined above and weigh the risks and benefits to students, staff, and the larger community.
- Consider how school policies regarding symptom screenings can balance the resources required and feasibility of implementation and the risk of transmission in schools.
- Consider ways to reduce the likelihood of excluding students who do not have COVID-19 from essential instructional and critical developmental experiences.
- Before sharing personally identifiable information on students concerning COVID-19, consider Federal, state, and local requirements, including provisions in the Family Educational Rights and Privacy Act (FERPA).

Some of the factors schools may weigh include:

Feasibility

- If symptom screenings are implemented by the school, are there enough staff who are sufficiently trained in screening procedures as well as in putting on and taking off personal protective equipment (PPE)?
- How will results of screening be verified (e.g., temperatures taken improperly can lead a falsely elevated temperature to be interpreted as a fever)?
- Is proper equipment (e.g., thermometers, PPE) available in sufficient quantities?
- How will proper cleaning of the screening area and equipment be ensured?
- Will processes be in place to ensure screeners and students maintain safe distance during screening?
- If symptom screenings are conducted by parents, guardians, or caregivers, will results be reported and verified?
- Will processes be used to follow-up if parents, guardians, or caregivers do not report screening results?
- What training for teachers and other school personnel will be provided regarding how to have conversations with parents about conducting home symptom screening? What protections will be included for staff who are more susceptible to COVID-19?

Harm mitigation

- What strategies are needed to reduce the harms to students and their families when students are excluded from school, such as students who rely on school meals or impact on parental ability to work, when screenings falsely identify their chronic symptoms as symptoms of COVID-19?
- How will students with chronic conditions or special health care needs be accommodated to minimize the risk of symptom screenings falsely identifying chronic symptoms as symptoms of COVID-19?
- How will stigma be reduced for students who are identified as having symptoms of COVID-19, regardless of whether they actually have COVID-19?
- What is the emotional impact of daily screenings on young children and how can fear of new mitigation protocols, such as adults wearing personal protective equipment (PPE), be reduced?
- How will ill students be afforded the opportunity to make up any missed classwork without penalty to reduce mental or physical anxieties about missed academic opportunities when screening falsely identifies their

chronic symptoms as symptoms of COVID-19?

Level of community transmission in the area where the school is located

- If there is minimal COVID-19 transmission in the community, symptom screenings will be more likely to identify people with symptoms who have something other than COVID-19. Symptom screening in this scenario will be more likely to identify other things, not SARS-CoV-2/COVID-19, including certain chronic symptoms, some of which may not require staying home.
- When there is more community transmission, the likelihood that individuals with symptoms actually have COVID-19 is higher. Therefore, symptom screenings may be more helpful when COVID-19 transmission in the community is high.

Recommendations of local public health authorities

- Regardless of above factors, schools should ensure that their policies follow the recommendations of local public health officials and are consistent with Federal, state, and local laws, including FERPA.
- Schools that chose to conduct symptoms screening should contact their local health departments with questions regarding practices and implementation.

Uses of symptom screening

Schools should also understand what symptoms screening does and does not do. When implemented, the purpose of symptom screening is to identify individuals who may have COVID-19 and exclude those individuals from a setting to reduce the risk of transmission to others. Symptom screening **does not** assess whether it is safe for an individual student to attend school or whether a student has an increased risk for severe illness if they develop COVID-19. Symptom screenings also do not provide enough information to diagnose someone with COVID-19.

There is not a single symptom that is uniquely predictive of a COVID-19 diagnosis. A COVID-19 viral test is needed to confirm if someone has a current infection. Schools may already have illness management criteria in place for school admittance; this is an opportunity to review that criteria and consider recommending stricter adherence to their existing illness management criteria.

Although CDC does not currently recommend conducting universal symptom screening at school, students should not attend school when they are sick. Home symptom screenings rely on students and their parents, guardians, or caregivers initially identifying when the student may have signs and symptoms of illness and to take action (such as staying home). This process can also be followed by school staff by monitoring children for overt symptoms of any infectious illness that may develop during the school day and helping the student and family take needed actions.

It is essential for schools to reinforce to students, parents or caregivers, and staff **the importance of students staying home when sick** until at least 24 hours after they no longer have a fever (temperature of 100.4 or higher) or signs of a fever (chills, feeling very warm, flushed appearance, or sweating) without the use of fever-reducing medicine (e.g., Tylenol). Policies that encourage and support staying home when sick will help prevent the transmission of SARS-CoV-2 (and other illnesses including flu) and help keep schools open.

Symptom screening at home can be helpful to determine if a student:

1. currently has an infectious illness that could impair their ability to learn, or
2. is at risk of transmitting an infectious illness to other students or to school staff.

What content should schools include in a home screening process for parents or caregivers?

Schools that elect to encourage parents, guardians, or caregivers to conduct daily home screenings should ask parents to report their answers on two topics: **Symptoms** and **Close Contact/Potential Exposure** (see below). Parents, guardians, and caregivers can self-report the answers to these questions through existing school health portals or school communication platforms in the morning before the student leaves for school. Schools can use the template below to share with parents and aid in daily reporting.

Daily Home Screening for Students

Parents: Please complete this short check each morning and report your child's information [INSERT YOUR SCHOOL REPORTING INSTRUCTIONS] in the morning before your child leaves for school.

Daily Home Screening for Students [1 page]

SECTION 1: Symptoms

If your child has any of the following symptoms, that indicates a possible illness that may decrease the student's ability to learn and also put them at risk for spreading illness to others. Please check your child for these symptoms:

- ☐ Temperature 100.4 degrees Fahrenheit or higher when taken by mouth
- ☐ Sore throat
- ☐ **New** uncontrolled cough that causes difficulty breathing (for students with chronic allergic/asthmatic cough, a change in their cough from baseline)
- ☐ Diarrhea, vomiting, or abdominal pain
- ☐ New onset of severe headache, especially with a fever

SECTION 2: Close Contact/Potential Exposure

- ☐ Had close contact (within 6 feet of an infected person for at least 15 minutes) with a person with confirmed COVID-19
- ☐ Traveled to or lived in an area where the local, Tribal, territorial, or state health department is reporting large numbers of COVID-19 cases as described in the Community Mitigation Framework
- ☐ Live in areas of high community transmission (as described in the Community Mitigation Framework) while the school remains open

Return-to-School Policies

If the student/parent/caregiver answers YES to any question in Section 1 but NO to any questions in Section 2, the student would be excused from school in accordance with existing school illness management policy (e.g., until symptom-free for 24 hours without fever reducing medications).

If the student or parent or caregiver answers YES to any question in Section 1 and YES to any question in Section 2, the student should be referred for evaluation by their healthcare provider and possible testing. CDC strongly encourages local health departments to work with local school systems to develop a strategy to refer symptomatic individuals to an appropriate healthcare provider or testing site. State, Tribal, territorial, and local health officials and/or healthcare providers will determine when viral testing for SARS-CoV-2 is appropriate. Schools should not require testing results as a part of return to school policies. Students who have received a negative test result should be allowed to return to school once their symptoms have otherwise improved in accordance with existing school illness management policies.

Students diagnosed with COVID-19 or who answer YES to any question in Section 1 and YES to any question in Section 2 without negative test results should stay home, isolate themselves from others, monitor their health, and follow directions from their state or local health department. Students and their families should be advised that the local health department may contact the family for contact tracing. If contacted, families should notify the contract tracer that the student attended school.

Students diagnosed with COVID-19 or who answer YES to any component of Section 1 AND YES to any component of Section 2 without negative test results should be permitted to return to school should be in line with current CDC recommendations in "When Can I Be Around Others". A negative test or doctor's note should **not** be required for return. Questions regarding return to school should be jointly decided in consultation with parents or caregivers, school personnel, and the student's healthcare provider.

Students who are excluded from school should be afforded the opportunity, as soon as feasible when they are well enough to participate in classwork, to make up any missed classwork without penalty in order to reduce mental or physical anxieties about missed academic opportunities.

School Isolation Protocols

Some students may develop symptoms of infectious illness while at school. Schools should take action to isolate students who develop these symptoms from other students and staff.

- Students with any of the symptoms in Section 1 should follow their school's current illness management policy to minimize transmission to others, to optimize learning opportunities, and to allow for these symptoms to resolve (at least 24 hours without fever reducing medications or in accordance with existing school illness policy).

- Students who develop any of the symptoms in Section 1 while at school should be placed in an isolation area separate from staff and other students:
    - School staff (e.g., workers, teacher aides, school health staff) who interact with a student who becomes ill while at school should use Standard and Transmission-Based Precautions when caring for sick people.
    - Students who are sick should go home or to a healthcare facility depending on how severe their symptoms are, and follow CDC guidance for caring for oneself and others who are sick.

- Students identified at school who develop any of the symptoms in Section 1 AND answer YES to any of the questions in Section 2 should be placed in an isolation area separate from staff and other students (e.g., a nurse's office) and then sent home or to a healthcare facility if symptoms indicate a need for further evaluation:
    - If a school needs to call an ambulance or bring a student to the hospital, they should first alert the healthcare staff that the student may have been exposed to someone with COVID-19.
    - After the student is placed in an isolation area, school staff who work in the isolation area should follow CDC's Considerations for Cleaning and Disinfecting your Building or Facility.
    - **Note:** In developing plans for placing students with symptoms in an isolation area, schools should be mindful of appropriate safeguards to ensure that students are isolated in a non-threatening manner, within the line of

sight of adults, and for very short periods of time.

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ORIGINAL PAPER

WILEY

How should our testing behaviour change with time in children in current COVID-19 pandemic?

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Abstract

Backgrounds: More paediatric-confirmed cases have been reported with the global pandemic of COVID-19. This study aims to summarize the key points and supply suggestions on screening paediatric COVID-19 patients more appropriately.

Materials and Methods: We retrospectively included paediatric patients who have accepted SARS-CoV-2 RT-PCR testing in Children's Hospital of Chongqing Medical University (30 January 2020 to 13 February 2020) and compared them with paediatric-confirmed COVID-19 cases. Besides, a review was carried out by analysing all current literature about laboratory-confirmed paediatric cases with COVID-19.

Results: There were 46 suspected cases included in the descriptive study. The results of SARS-CoV-2 RT-PCR testing were all negative. Compared with paediatric-confirmed cases, the incidence of epidemic history was lower in suspected cases ($P < .001$). The rate of fever ($P < .001$), cough ($P < .001$), headache or dizziness ($P < .001$), vomiting ($P < .001$) and abdominal discomfort or distention ($P = .01$) were more observed in the included suspected children. There were more children having decreased WBC count in the confirmed group. In the literature review, twenty-nine studies were obtained with 488 paediatric COVID-19 cases. 88.6% of them had epidemiological history. Cough and fever were the most common symptoms. Compared with older patients, the incidence of fever, respiratory symptoms, lethargy and headache or dizziness was lower, while gastrointestinal symptoms were reported more.

Conclusions: Children with a history of close contact with confirmed cases, manifested as cough and fever should be paid more attention to after excluding infection of other common pathogens. Atypical symptoms should not be over-emphasized in screening paediatric COVID-19. More studies are needed for guiding efficient recognition in paediatric COVID-19.

KEYWORDS

COVID-19, paediatric, SARS-CoV-2, suspected cases

Yin Zhang and Jilei Lin contributed equally to this work.

1 | INTRODUCTION

In December 2019, a series of pneumonia cases with coronavirus disease 2019 (COVID-19) occurred in Wuhan, Hubei Province, China.[1-3] This study aims to share clinical experience in screening paediatric cases suspected with COVID-19 in a Chinese children's hospital. Besides, we will discuss the differences in epidemiological, clinical, laboratory and radiological characteristics between adults and children in the COVID-19 pandemic by reviewing the current literature reporting laboratory-confirmed paediatric cases with COVID-19. We hope to improve the measures of screening paediatric suspected cases to avoid missed diagnosis and save medical sources in the current COVID-19 pandemic.

2 | METHODS

2.1 | A descriptive analysis

Reporting of the descriptive analysis in this study conforms to broad EQUATOR guidelines.[4]

2.1.1 | Data source

We included paediatric patients who have accepted SARS-CoV-2 RT-PCR testing in Children's Hospital of Chongqing Medical University, China from 30 January 2020 to 13 February 2020 and retrospectively collected the clinical data.

2.1.2 | Study population

The inclusion criteria were as follows: (a) under 18 years old, and (b) having accepted SARS-CoV-2 RT-PCR testing for nasal and pharyngeal swab or anal swab specimens. Children were excluded if they met any of the following criteria: (a) not having accepted SARS-CoV-2 RT-PCR testing, (b) the clinical data were not obtained or seriously absent.

2.1.3 | Criteria for paediatric suspected cases

Included suspected paediatric patients should meet the criteria for paediatric suspected cases according to 'Diagnosis and Treatment Protocol for pediatric COVID-19(the 2nd Revised Version)' carried out by experts on COVID-19 in Children's Hospital of Chongqing Medical University, China[5] or recognized with high risk of infected with SARS-CoV-2 by experts.

2.1.4 | Data collection

The demographic characteristics, clinical symptoms, signs, laboratory findings and radiologic assessments were extracted from electronic medical records. Demographic characteristics included gender, age and epidemiological history; clinical symptoms included cough, fever, runny nose, stuffy nose, sore throat, nausea, vomiting, diarrhoea, abdominal discomfort or distension and headache/dizziness; signs included moist rales and wheezing; Laboratory findings included WBC count, the ratio of lymphocyte (L%) and CRP. Radiologic assessments included chest X-ray and/or computed tomography scan (CT).

2.2 | Literature review

2.2.1 | Literature search strategy

A comprehensive search for case or case series studies on paediatric confirmed cases was conducted using the following databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CKNI), CQ VIP Database, Wanfang Data from 1 January 2019 to 25th March 2020, without any restriction. Search strategies as (COVID 19 OR coronavirus disease 2019 OR 2019 novel coronavirus OR 2019-nCoV OR Wuhan coronavirus OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2) AND (infants OR neonates OR newborns OR toddlers OR child OR children OR adolescents OR paediatric) were used. The corresponding Chinese key terms were used in Chinese databases. We reviewed the reference lists of articles for other studies to supplement our search.

2.2.2 | Study selection and data extraction

The inclusion criteria of studies: (a) included children were under 18 years old, and (b) included children were laboratory-confirmed COVID-19 cases and the SARS-CoV-2 RT-PCR testing was positive for nasal and pharyngeal swab or anal swab specimens. The exclusion criteria were as follows: (a) unpublished studies or (b) duplicate studies. Data including epidemiological history, clinical symptoms, laboratory findings and radiologic assessments were extracted.

2.3 | Statistical analysis

Categorical variables were summarized as counts (n) and percentages (%). In comparison of clinical features between paediatric suspected and confirmed cases, proportions for

categorical variables were compared using Chi-square tests or Fisher's exact tests as appropriate. Children's age was described using medians and interquartile ranges (IQR) because the data were not normally distributed. A *P* value less than .05 was considered statistically significant, and all tests were two-tailed. All statistical analyses were performed using SPSS 25.0.

3 | RESULTS

3.1 | The descriptive analysis

3.1.1 | Characteristics of included suspected cases

According to the inclusion criteria, there were 46 children included in this study. The results of SARS-CoV-2 RT-PCR testing were all negative in the included children. The age of the 46 included children (19 girls and 27 boys) ranged from 1 day to 14 years old. There were 23 children having a history of epidemiology (50%). Thirty-four children had fever (73.9%); 34 children had cough (73.9%); 12 children had runny nose (26.1%); nine children had vomiting (19.6%); four children had diarrhoea (8.7%); four children had headache or dizziness (8.7%); four children had stuffy nose (8.7%); and three children had abdominal discomfort or distention (6.5%). Clinical signs were mild in most cases. The WBC count was lower than normal in 4 children (8.7%) and normal in 34 children (73.9%). The lymphocyte ratio was decreased in 21 children (45.7%) and normal in 20 children (43.5%). CRP was increased in 15 children (32.6%). COVID-like pneumonia signs were obtained in radiologic assessments in 32 children (69.6%). Cloudy opacity was observed in 47.8% of all suspected cases. The descriptive data of the included cases are presented in Table 1.

TABLE 1 The clinical features of paediatric suspected and confirmed COVID-19 patients

	Suspected cases	Confirmed cases	
	n = 46	n = 488	*P*
Demographic characteristics			
Gender (boy/girl)	27/19	287/201	.99
Age (months)	37 (11-90)	—	—
Epidemiological history (%)	23 (50%)	410/463 (88.6%)	<.001
Clinical symptoms (%)			
Cough	34 (73.9%)	221/488 (45.3%)	<.001
Fever	34 (73.9%)	220/488 (45.1%)	<.001
Runny nose	12 (26.1%)	74/488 (15.2%)	.054
Stuffy nose	4 (8.7%)	66/488 (13.5%)	.354
Headache or dizziness	4 (8.7%)	4/488 (0.8%)	.003
Vomiting	9 (19.6%)	25/488 (5.1%)	<.001
Diarrhoea	4 (8.7%)	32/488 (6.6%)	.806
Abdominal discomfort or distention	3 (6.5%)	3/488 (0.6%)	.01
Clinical signs (%)			
Moist rales	4 (8.7%)	—	—
Wheezing	3 (6.5%)	—	—
Laboratory findings			
WBC			
Decreased	4 (8.7%)	53/270 (19.6%)	.075
Normal	34 (73.9%)	196/270 (72.6%)	.852
Increased	8 (17.4%)	21/270 (7.8%)	.07
L%			
Decreased	21 (45.7%)	13/34 (38.2%)	.507
Normal	20 (43.5%)	14/34 (41.2%)	.837
Increased	5 (10.9%)	7/34 (20.6%)	.229
Increased CRP	15 (32.6%)	37/101 (36.6%)	.636
Radiological assessments			
Pneumonia signs (%)	32 (69.6%)	355/452 (78.5%)	.164
Cloudy opacity (%)	22 (47.8%)	—	—
Patchy shadow (%)	8 (17.4%)	—	—
Ground-glass opacity (%)	2 (4.3%)	—	—
Nodular shadow (%)	3 (6.5%)	—	—

3.2 | Literature review

A rapid secondary analysis and review were conducted to analyse the characteristics of paediatric COVID-19 cases based on current literature. Consequently, a total of 29 studies were obtained.[6-34] A total of 488 paediatric cases with COVID-19 were included. We re-analysed the data on epidemiological history, clinical symptoms, laboratory findings and radiologic assessments. The analysis showed 88.6% of the paediatric cases had epidemiological history. There were 24.2% of paediatric COVID-19 patients having no symptoms. Cough and fever were the top two symptoms and consisted of 45.3% and 45.1% in included paediatric cases, respectively, which is similar to a descriptive study with a total of 171 paediatric cases.[17] In laboratory findings, paediatric confirmed cases often have decreased or normal level of WBC count (19.6%, 72.6%, respectively) and lymphocyte ratio (38.2%, 41.2%, respectively). Abnormal CRP was observed in 36.6%

of cases; 78.5% radiologic assessments were abnormal with pneumonia signs.

To compare the data with paediatric confirmed cases, a single-arm meta-analysis including COVID-19 patients with no restriction of age was also included.[35] In the comparison, the incidence of fever and cough is much lower than that of older patients. Furthermore, the incidence of exploration, dyspnoea, lethargy and headache/dizziness was lower, while gastrointestinal symptoms (nausea, vomiting and diarrhoea) were reported more in paediatric confirmed cases. Less abnormalities in WBC count, the ratio of lymphocyte and CRP were recorded in paediatric cases with COVID-19. The detailed information is shown in Table 2 and Table S1.

3.3 | Comparing paediatric suspected cases with confirmed cases

We compared the clinical features between the included paediatric suspected cases and paediatric confirmed cases. The incidence of epidemic history was lower in suspected cases than that in confirmed cases ($P < .001$). The rate of fever ($P < .001$), cough ($P < .001$), headache or dizziness ($P = .003$), vomiting ($P < .001$) and abdominal discomfort or distention ($P = .01$) was more observed in the included suspected children. The WBC count was normal in the majority of both suspected and confirmed cases, while there were more children having decreased WBC count in the confirmed group. The comparison is shown in Table 1.

4 | DISCUSSION

In this study, we conducted a review summarizing the clinical features of paediatric confirmed COVID-19 patients and compared them with adult COVID-19 patients. In rapidly reviewing literature reporting confirmed cases with COVID-19, the results showed that the incidence of fever and cough was lower in paediatric cases than that in older infected ones although these symptoms still occupied vital positions of all. However, gastrointestinal symptoms (nausea, vomiting and diarrhoea) were reported more in paediatric confirmed cases.

To share experience and give suggestions on screening paediatric suspected cases more appropriately, this study also collected clinical information of paediatric suspected cases in a children's hospital and analysed the features of them. After the outbreak of COVID-19 in China, a team with experts dedicating to respiratory, infectious disease, critical care and radiology in Children's Hospital of Chongqing Medical University was established. With paediatric cases with COVID-19 emerging, the criteria of paediatric suspected cases were promulgated by the expert group. The criteria were based on the recent evidence and emphasized that paediatric cases often present mild manifestations and atypical symptoms should be attached importance to. Consultations would be held in time for those who are likely to be infected with SARS-CoV-2, and then the RT-PCR testing was decided to conduct or not. Although the included paediatric suspected cases all had negative SARS-CoV-2 RT-PCR testing results, we may learn lessons in the screening process by comparing clinical features of the paediatric suspected cases with confirmed cases. In the literature review, most confirmed cases had a definite history of epidemiology and had close contact with family members who were infected with SARS-CoV-2. However, only a half of the included suspected cases had

TABLE 2 The clinical features of confirmed paediatric and adult cases in literature review

	Paediatric cases	Adult cases
	n = 488 (%)	n = 1995 (%)
Epidemiological history (%)	88.6	—
Clinical symptoms		
Cough (%)	45.3	68.60
Fever (%)	45.1	88.50
Asymptomatic (%)	24.2	—
Exploration (%)	2.3	28.20
Dyspnoea (%)	0.4	21.90
Runny nose (%)	15.2	—
Stuffy nose (%)	13.5	—
Sore throat (%)	18.6	—
Lethargy (%)	4.3	35.80
Headache or dizziness (%)	0.8	12.10
Nausea (%)	1.6	3.90
Vomiting (%)	5.1	
Diarrhoea (%)	6.6	4.80
Abdominal discomfort or distention (%)	0.6	—
Laboratory findings		
WBC		
Decreased	19.6	29.40
Normal	72.6	—
Increased	7.8	—
L%		
Decreased	38.2	64.50
Normal	41.2	—
Increased	20.6	—
Increased CRP	36.6	44.30
Radiologic assessments		
Pneumonia signs(%)	78.5	—

possible epidemic history, and none of them reported close contact with confirmed COVID-19 cases. Therefore, the history of contact with confirmed cases provided by caregivers is vitally important in the screening process. We suggest parents and clinicians keep following the trends of COVID-19 pandemic with the global outbreak of COVID-19.

In the global COVID-19 pandemic, we have to focus more on clinical symptoms in view that more unclear information about the epidemic history would be obtained. To our knowledge, fever and cough are important hints in COVID-19, no matter in adults or children. The evidence may remind clinicians to pay attention to fever and cough, but in order to avoid the wrong judgement, we still suggest clinicians to exclude the infection of other pathogens which were more common in the peak time of respiratory tract infection. Current evidence indicated that paediatric confirmed cases would present more abnormal gastrointestinal symptoms than adults; however, some patients only present gastrointestinal symptoms but were treated wrongly as suspected cases. Clinicians should notice that rare cases start with only gastrointestinal symptoms in previous reports and no research confirmed that atypical symptoms such as abnormal gastrointestinal symptoms, headache or dizziness were in close relationship with COVID-19. Besides, the difference in WBC count between suspected and confirmed cases indicated that decreased or normal WBC count is more valuable for screening paediatric COVID-19, although increased WBC count should not be the reason to rule out the infection.

The highlight of this study should be noted. First, we summarized the key points and supplied suggestions on screening paediatric COVID-19 more appropriately by comparing suspected cases who had negative SARS-CoV-2 RT-PCR testing results and laboratory-confirmed cases. Second, this study conducted a literature review, analysing the clinical features of paediatric confirmed COVID-19 cases and comparing them with adult patients.

However, there are limitations in this study. Firstly, there was no direct evidence to conclude the characteristics of paediatric COVID-19 because no one was confirmed with COVID-19 in this study. Besides, the sample size was too small, more large-scaled studies are needed urgently to provide more reliable evidence for protecting children in current COVID-19 pandemic.

5 | CONCLUSIONS

Nausea, vomiting and diarrhoea are more observed in paediatric COVID-19 patients than older ones. However, cough and fever were the most common symptoms in paediatric confirmed cases with COVID-19. Children with a history of close contact with confirmed cases, manifested as cough and fever should still be paid more attention to after excluding infection of other common pathogens. Atypical symptoms such as abnormal gastrointestinal symptoms, headache or dizziness should not be over-emphasized in screening paediatric COVID-19. More studies should be carried out to support efficient recognition in children in current COVID-19 pandemic.

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CONFLICT OF INTEREST

There is no conflict of interest among all authors in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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REFERENCE 38

Rapid communication

A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020

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On 13 March 2020, Israel's government declared closure of all schools. Schools fully reopened on 17 May 2020. Ten days later, a major outbreak of coronavirus disease (COVID-19) occurred in a high school. The first case was registered on 26 May, the second on 27 May. They were not epidemiologically linked. Testing of the complete school community revealed 153 students (attack rate: 13.2%) and 25 staff members (attack rate: 16.6%) who were COVID-19 positive.

As part of the coronavirus disease (COVID-19) pandemic containment measures, Israel's government declared complete closure of all educational facilities on 13 March 2020. Limited schools reopening (kindergartens, grades 1–3 and 11–12) only in small groups was approved on 3 May 2020. Subsequently, all school classes reopened on 17 May 2020, with requirement for daily health reports, hygiene, facemasks, social distancing and minimal interaction between classes. Ten days later, the first major COVID-19 school outbreak in Israel emerged in a high school. The first case was registered on 26 May and the second on 27 May. The two cases were not epidemiologically linked. Testing of the complete school community revealed 153 students (attack rate: 13.2%) and 25 staff members (attack rate: 16.6%) who were COVID-19 positive. Overall, some 260 persons were infected (students, staff members, relatives and friends). In this report, we aim to describe the investigation and epidemiological characteristics of the school's outbreak.

Outbreak description and epidemiological investigation

School 1 is a regional public school; students arrive from suburbs and neighbourhoods, by public or school bus. It contains 1,190 students aged 12–18 years (grades 7–12) and 162 staff members. The school reopened after 2 months' closure on Monday, 18 May 2020. Students returned to their previous classrooms and received instructions on preventive procedures. On 19–21 May (Tuesday to Thursday), an extreme heatwave occurred. Hence, the Ministry of Health exempted schoolchildren from facemasks for these 3 days.

The first COVID-19 case (Student A) was notified on 26 May 2020. The source of infection was unknown. Close contacts from household (n = 4), students (n = 50) and teachers (n = 14) were instructed to self-isolate. The second case (Student B) was notified on 27 May 2020. According to the epidemiological investigation, both students attended school during the days of 19–21 May and reported mild symptoms (anosmia, ageusia, fever and headache). They were from different grades and were not epidemiologically linked.

With the emergence of two unrelated cases within 2 days, the district health office declared an 'outbreak status' including school closure, isolation instructions and testing of the school community. During that long weekend (a Jewish holiday, 28–30 May 2020), mass COVID-19 testing was conducted as a joint effort of the school leadership and community, the four Health Funds, Magen David Adom (national emergency services organisation), the local municipality and the district health office.

Ten teachers and 26 students who had not attended school since reopening were excluded. Most of the remaining school community was tested, 151 of 152 staff members and 1,161 of 1,164 students. Overall, 153 students and 25 staff members were confirmed as COVID-19-positive. The data from the epidemiological investigation are shown in the Table. The COVID-19 rates differed between groups. Male cases were slightly overrepresented. The rate of cases reporting symptoms, upon meticulous questioning, was 43%

Table

Epidemiological investigation data, COVID-19 outbreak, Israel, May 2020 (n = 1,316[a])

Group	Number of persons	Number tested	Males		Confirmed cases		Males, of confirmed cases		Median age in years (cases)	Symptoms	
			n	%	n	Rate (%)	n	%		n	%
7th grade	197	197	106	53.8	40	20.3	25	62.5	13	19	47.5
8th grade	197	197	102	51.8	34	17.3	19	55.9	14	15	44.1
9th grade	187	187	94	50.3	61	32.6	32	52.5	15	30	49.2
10th grade	200	200	110	55.0	9	4.5	6	66.7	16	2	22.2
11th grade	195	194	98	50.5	6	3.1	3	50.0	17	0	0
12th grade	188	186	87	46.8	3	1.6	1	33.3	18	0	0
All students	1,164	1,161	597	51.4	153	13.2	86	56.2	15	66	43.1
Staff	152	151	51	33.8	25	16.6	9	36.0	40	19	76

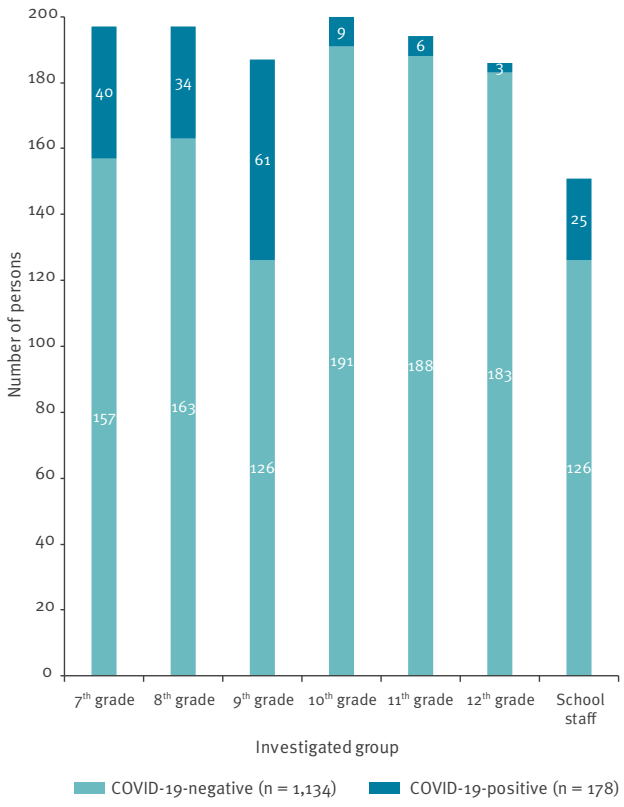
COVID-19: coronavirus disease.

[a] Overall 1,312 members of the school community were tested: 1,161 students and 151 staff.

(66/153) among students and 76% (19/25) among staff. The leading symptoms reported were cough, headache, fever, sore throat and myalgia. One emergency room visit was recorded and no hospitalisations.

Figure 1

Results of COVID-19 testing, school outbreak, Jerusalem, May 2020 (n = 1,312)



COVID-19: coronavirus disease.

COVID-19 rates were higher in junior grades (7–9) than in high grades (10–12) (Figure 1). The peak rates were observed in the 9th grade (20 cases in one class and 13 cases in two other classes) and the 7th grade (14 cases in one class). Of the cases in teachers, four taught all these four classes, two taught three of the four classes and one taught two of these four classes.

An environmental school inspection reported crowded classes: 35–38 students per class, class area 39–49 m², allowing 1.1–1.3 m² per student (below the 1.5 m² standard). Distancing among students and between students and teachers was not possible. Furthermore, during the extreme heatwave, air-conditioning functioned continuously in all classes. The air-conditioning system was separate for each class. The junior grades (7–9) and the high grades (10–12) are situated in one large building, yet in separate wings, and share the schoolyard and public spaces. According to the school schedule, students study 6 days (Sunday to Friday) for 38–40 h weekly (6.3–6.7 h daily on average). Daily travel time to school depends on distance and traffic conditions and lasts 20–45 min. Most students also participate in extracurricular activities such as sports teams or dance classes for an average of 2–4 h per week.

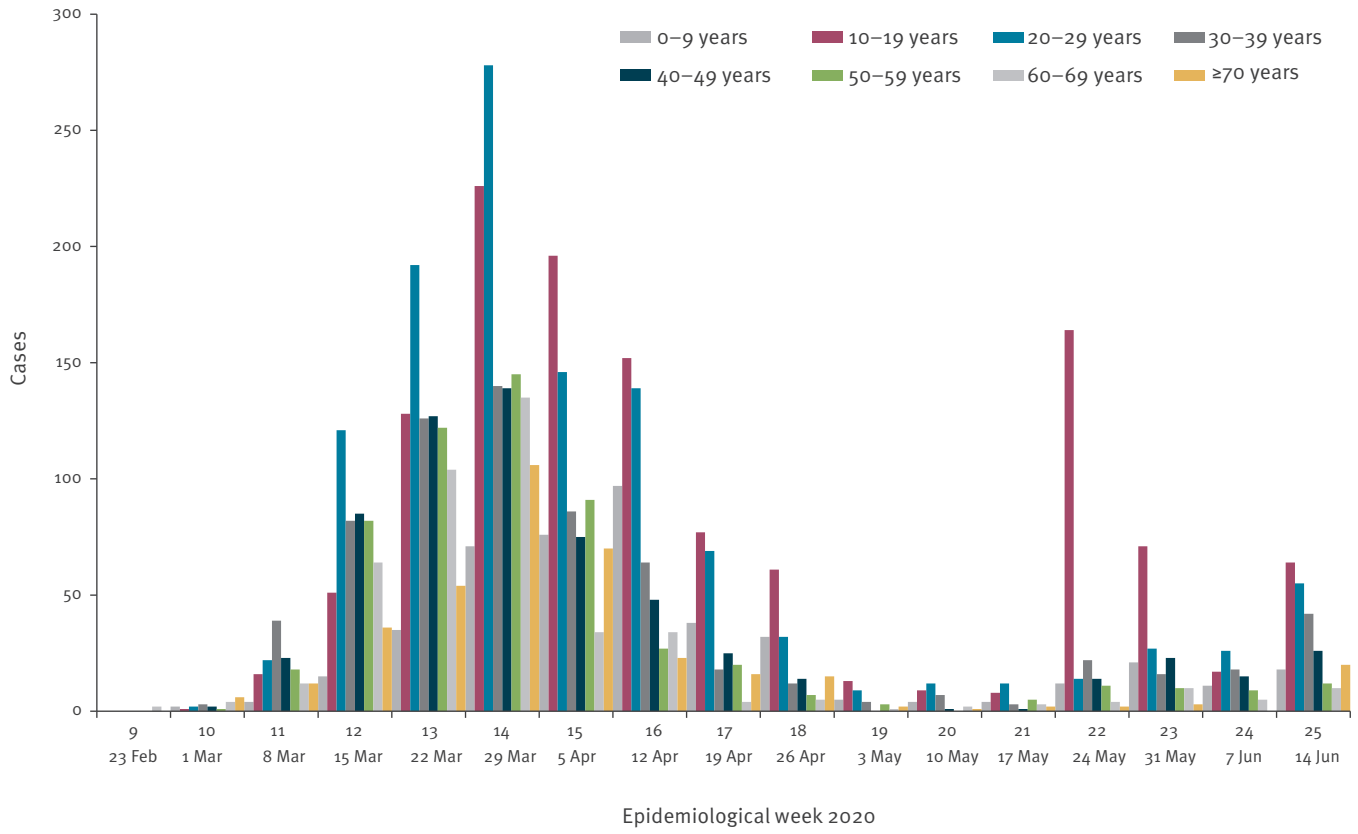
As at 30 June 2020, 100 of 153 (65.4%) students and 16 of 25 (64%) staff members have recovered (with two negative PCR results). Evaluating the recovery period revealed that 60% of asymptomatic cases recovered within 25 days vs only 37% of symptomatic cases.

Cases outside the first affected school

By mid-June 2020, 87 additional confirmed COVID-19 cases had occurred among close contacts of the first school's cases. These included siblings attending

Figure 2

COVID-19 cases, Jerusalem, February–June 2020 (n = 5,519)



COVID-19: coronavirus disease.

other schools, friends and participants in sports and dancing afternoon classes, students' parents and family members of school staff.

COVID-19 cases age distribution in the Jerusalem district

The large school outbreak led us to evaluate the age distribution of COVID-19 cases before and after schools' reopening. From week 9 to week 25 in 2020, 5,519 confirmed COVID-19 cases were reported in the Jerusalem district. As schools reopened on 17 May 2020, the evaluation point selected was 1 week later, on 24 May 2020 (week 22). The evaluation showed that before 24 May 2020, the proportion of the 10–19 years-olds (representing schoolchildren), was 19.8% (938/4,747) of cases in weeks 9–21, increasing to 40.9% (316/772) after 24 May 2020, in weeks 22–25 (Figure 2).

From week 9 to week 24 in 2020, 18,448 confirmed COVID-19 cases were reported nationally, 5,184 cases in the Jerusalem district and 13,264 cases in all the other districts in Israel, excluding Jerusalem. The age pyramid of confirmed COVID-19 cases in the Jerusalem district vs nationally (excluding Jerusalem) showed a prominence of the 10–19 years-olds in Jerusalem, 22.6% vs. 13.9% in all the other districts (Figure 3).

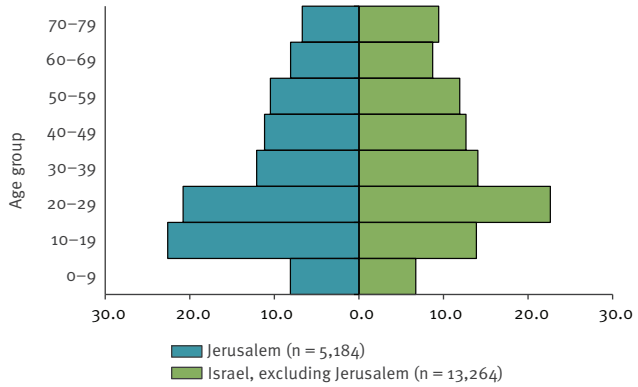
Discussion

On 27 January 2020, Israel's health minister declared COVID-19 infection a notifiable disease requiring immediate reporting. By 21 June 2020, some 20,778 confirmed COVID-19 cases had been reported with 306 fatalities [1]. Israel's population is 9.1 million (median age: 30 years) [2]. Like other countries, Israel implemented diverse containment measures including quarantine. Nationally, there are 1.7 million schoolchildren, 830,000 kindergarten children and 170,000 teachers and staff [3]. Full closure of educational facilities occurred on 13 March 2020. Elsewhere, 107 countries had implemented national school closures by 18 March 2020 [4].

COVID-19 cases are defined clinically (fever›38 °C, cough, respiratory illness etc.) and epidemiologically. Laboratory confirmation requires detection of SARS-CoV-2 nucleic acid by PCR in nasopharyngeal swabs. The district health offices perform epidemiological investigations and contact tracing and issue isolation instructions and guidance to healthcare, educational and other facilities. The Health Funds, via community clinics, follow patients, refer to hospital if necessary and provide counselling to patients and families. The Jerusalem health office serves 1.25 million residents

Figure 3

Age distribution of COVID-19 cases, Israel, May 2020 (n = 18,448)



COVID-19: coronavirus disease.

(median age: 23.5 years), characterised by moderate to low socioeconomic status and large households [5].

The high school outbreak in Jerusalem displayed mass COVID-19 transmission upon school reopening. The circumstances promoting infection spread involved return of teenage students to their regular classes after a 2-month closure (on 18 May) and an extreme heatwave (on 19 May) with temperatures rising to 40 °C and above [6] that involved exemption from facemasks and continuous air-conditioning. Classes in the first affected school had more than 30 students. Israel's secondary school classes are crowded (average: 29 students in public schools) compared with the Organisation for Economic Cooperation and Development (OECD) average (23 students) [7]. COVID-19 in a school necessitates a prompt response. Classmates and teachers should be considered close contacts (particularly in crowded classes), as should students in groups mixing several classes, extra-curricular activities and school buses. Temporary school closure is prudent (especially in large regional schools) pending investigation results.

Most student cases presented with mild symptoms or were asymptomatic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents is considered mild compared with adults. A review of 18 studies (1,065 hospitalised paediatric patients) presented overall good prognosis for that age group [8]. A Chinese study of 171 paediatric cases infected with SARS-CoV-2 reported main signs of fever, cough and pharyngitis, 16% were asymptomatic [9]. In a European multicentre study (582 children), COVID-19 was usually mild, a small fraction developed severe disease and mortality was rare [10]. In a study in New York State, Kawasaki-like disease and myocarditis have been linked to COVID-19 infection, with the condition termed multisystem inflammatory syndrome (MIS-C) in children [11]. French paediatric surveillance data also support linkage between SARS-CoV-2 infection and MIS-C [12].

The role of children and adolescents in COVID-19 spread is equivocal; epidemiological data imply insignificance of children in transmission [13]. School closure is a public health tool in influenza pandemic preparedness plans, based on high infectiousness and susceptibility in schoolchildren and high contact rates [14]. School reopening policy after the COVID-19 lockdown varies considerably between nations and therefore requires ongoing assessment [13].

Conclusions and recommendations

COVID-19 prevention in schools involves studying in small groups and minimising student mixing in activities and transportation. Teachers and parents should lead by wearing facemasks, hand hygiene, keeping physical distance etc. School attendance should be avoided at any sign of illness. Learning from home may also reduce the need for class attendance. Outdoors classes should also be considered. COVID-19 prevention encompasses avoiding the 'three Cs': closed spaces with poor ventilation, crowded places and close-contact settings [15]. The European Centre for Disease Prevention and Control's report on air-conditioning and ventilation systems and COVID-19 recommends increasing air exchange rate and outdoor air use and decreasing air recirculation, aiming to reduce spread in indoor spaces [16]. Finally, appropriate planning of COVID-19 prevention for the next school year is essential.

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Conflict of interest

None declared.

Authors' contributions

Chen Stein-Zamir, Nitza Abramson and Hanna Shoob collected data, performed the investigation and data analysis and wrote the manuscript. Erez Libal, Menachem Bitan, Tanya Cardash, Refael Cayam and Ian Miskin performed the patients' follow-up, provided data and reviewed the manuscript.

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Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases

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Abbreviations: BE, Belgium; DE, Germany; FI, Finland; GB, Great Britain; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland

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ABSTRACT

Background

Mathematical modelling of infectious diseases transmitted by the respiratory or close-contact route (e.g., pandemic influenza) is increasingly being used to determine the impact of possible interventions. Although mixing patterns are known to be crucial determinants for model outcome, researchers often rely on a priori contact assumptions with little or no empirical basis. We conducted a population-based prospective survey of mixing patterns in eight European countries using a common paper-diary methodology.

Methods and Findings

7,290 participants recorded characteristics of 97,904 contacts with different individuals during one day, including age, sex, location, duration, frequency, and occurrence of physical contact. We found that mixing patterns and contact characteristics were remarkably similar across different European countries. Contact patterns were highly assortative with age: schoolchildren and young adults in particular tended to mix with people of the same age. Contacts lasting at least one hour or occurring on a daily basis mostly involved physical contact, while short duration and infrequent contacts tended to be nonphysical. Contacts at home, school, or leisure were more likely to be physical than contacts at the workplace or while travelling. Preliminary modelling indicates that 5- to 19-year-olds are expected to suffer the highest incidence during the initial epidemic phase of an emerging infection transmitted through social contacts measured here when the population is completely susceptible.

Conclusions

To our knowledge, our study provides the first large-scale quantitative approach to contact patterns relevant for infections transmitted by the respiratory or close-contact route, and the results should lead to improved parameterisation of mathematical models used to design control strategies.

The Editors' Summary of this article follows the references.

Introduction

Preparing for outbreaks of directly transmitted pathogens such as pandemic influenza [1–3] and SARS [4–9], and controlling endemic diseases such as tuberculosis and meningococcal diseases, are major public health priorities. Both can be achieved by nonpharmaceutical interventions such as school closure, travel restrictions, and contact tracing, or by health-care interventions such as vaccination and use of antiviral or antibiotic agents [2,10–13]. Mathematical models of infectious disease transmission within and between population groups can help to predict the impact of such interventions and inform planning and decision making. Contact rates between individuals are often critical determinants of model outcomes [14]. However, few empirical studies have been conducted to determine the patterns of contact between and within groups and in different social settings.

In comparison to HIV and sexually transmitted diseases [15–17] and drug/needle sharing networks [18], where a number of large-scale empirical studies have been conducted on contact patterns, relatively little effort has been devoted to infections spread by respiratory droplets or close contact. Instead, the contact structure for these infections has been assumed to follow a predetermined pattern governed by a small number of parameters that are then estimated using seroepidemiological data [19,20]. A small number of studies have attempted to directly quantify such contact patterns, but they were conducted in small or nonrepresentative populations [14,21–25]. Hence, it is unclear to what extent the results can be generalized to an overall population and across different geographical areas. To address this lack of empirical knowledge, we present here results from, to our knowledge the first, large-scale, prospectively collected, population-based survey of epidemiologically relevant social contact patterns. The study was conducted in eight different European countries using a common paper diary approach and covering all age groups. We use these data to assess how an emerging infection could spread in a wholly susceptible population if it were transmitted by the social contacts measured here.

Methods

Survey Methodology

Information on social contacts was obtained using cross-sectional surveys conducted by different commercial companies or public health institutes in Belgium (BE), Germany (DE), Finland (FI), Great Britain (GB), Italy (IT), Luxembourg (LU), The Netherlands (NL), and Poland (PL). The recruitment and data collection were organised at the country level according to a common agreed quota sampling methodology and diary design. The surveys were conducted between May 2005 and September 2006 with the oral informed consent of participants and approval of national institutional review boards following a small pilot study to test feasibility of the diary design and recruitment [26].

Survey participants were recruited in such a way as to be broadly representative of the whole population in terms of geographical spread, age, and sex. In BE, IT, and LU, survey participants were recruited by random digit dialling using land line telephones; in GB, DE, and PL survey participants were recruited through a face-to-face interview; survey participants in NL and FI were recruited via population registers and linked to a larger national sero-epidemiology survey in NL. Children and adolescents were deliberately oversampled, because of their important role in the spread of infectious agents. For more details on the survey methodology in the various countries, see Table S1.

Briefly, only one person in each household was asked to participate in the study. Paper diaries were either sent by mail or given face to face to participants. Participants were coached by telephone or in person on how to fill in the diary.

Diaries recorded basic sociodemographic information about the participant, including employment status, level of completed education, household composition, age, and sex. Participants were assigned a random day of the week to record every person they had contact with between 5 A.M. and 5 A.M. the following morning. Participants were instructed to record contacted individuals only once in the diary. A contact was defined as either skin-to-skin contact such as a kiss or handshake (a physical contact), or a two-way conversation with three or more words in the physical presence of another person but no skin-to-skin contact (a nonphysical contact). Participants were also asked to provide information about the age and sex of each contact person. If the age of a contact person was not known precisely, participants were asked to provide an estimate of the age range (the midpoint was used for data analysis). For each contact, participants were asked to record location (home, work, school, leisure, transport, or other), the total duration of time spent together (less than 5 min, 5–15 min, 15 min to 1 h, 1–4 h, or 4 h or more) as well as the frequency of usual contacts with this individual (daily or almost daily, about once or twice a week, about once or twice a month, less than once a month, or for the first time).

Diaries were translated into local languages (see Text S1 for the diary used in GB) and are available on request in the following languages: Dutch, English, French, Finnish, German, Italian, Polish, Portuguese, and Swedish. Diaries for young children were filled in by a parent or guardian on their behalf. Older children who obtained parental consent were given diaries with simplified language to fill in on their own (see Table S1 for more details).

Data Analysis

Main effects of covariates (age, sex, household size, and country) on numbers of contacts were assessed using multiple censored negative binomial regression [27]. The data were right censored at 29 contacts for all countries because of a limited number of possible diary entries in some countries. Additionally, a sensitivity analysis was performed to assess the effects of different handling of professional contacts between the countries.

The log-likelihood function ll for the censored negative binomial was

$$ll = \sum_{i=1}^{n} w_i(\delta_i \log(P(Y = y_i|\mathbf{X}_i)) + (1-\delta_i)\log(1 - \sum_{j=0}^{28} P(Y = j|\mathbf{X}_i))),$$

where w_i is the weight of observation i, $\delta_i = \begin{cases} 1 \text{ if } y_i < 29 \\ 0 \text{ if } y_i \geq 29 \end{cases}$ is an indicator variable for censoring, y_i is the number of observed

contacts, $\mathbf{X}_i$ is the vector of explanatory variables, and P is the probability function of the negative binomial distribution:

$$P(Y = y_i|\mathbf{X}_i) = \frac{\Gamma(y_i + 1/\alpha)}{\Gamma(y_i + 1)\Gamma(1/\alpha)} \left(\frac{1}{1 + \alpha\mu}\right)^{1/\alpha} \left(\frac{\alpha\mu}{1 + \alpha\mu}\right)^{y_i},$$

where $\mu = \exp(\mathbf{X}_i\beta)$; β is the vector of coefficients and α is the overdispersion parameter.

Sampling weights—the inverse of the probability that an observation is included because of the sampling design—were calculated for each country separately, based on official age and household size data of the year 2000 census round data published by Eurostat (http://epp.eurostat.ec.europa.eu/) (see Table S2) and used to correctly estimate population-related quantities. Overall statistics should be considered indicative of general trends and levels, but specific statistical representativity for the whole of Europe is not claimed, since participating countries, although geographically and socially diverse, are not a representative or random selection at the European level.

Association Rule Analysis

Mining association rules is a tool for discovering patterns between variables in large databases [28]. Let X,Y denote disjoint nonempty items in the contact survey, such as daily frequency, duration of more than 4 h, and physical contact. Association rules are rules of the form $X \rightarrow Y$ that measure how likely the event Y is, given X. In this context X is called antecedent while Y is called consequent. Rules are typically extended to include more items in the antecedent but are restricted to include only one item in the consequent. The length of the rule is defined as the total number of items in both antecedent and consequent.

Selecting interesting rules from the set of all possible rules is based on various measures of significance and interest. The best-known are support, confidence, and lift. The support of an association rule $X \rightarrow Y$ is defined as the relative frequency of $X \cap Y$. Finding rules with high support can be seen as a simplification of the learning problem called "mode finding" or "bump hunting." The confidence of a rule is the conditional probability $P(Y|X)$ indicating what percentage of times the rule holds and thus measuring the association between $\{X,X^c\}$ and $\{Y,Y^c\}$. Using both constraints, the set of rules can further be filtered by the lift, which is defined as the ratio of the relative frequency of $X \cap Y$ and the product of relative frequencies of X and Y. The lift can be interpreted as the ratio of the rule's observed support to the support expected under independence. Greater lift values indicate stronger associations. Additionally, a Chi-square test for the rule-corresponding two-by-two table consisting of cells $X \cap Y$, $X^c \cap Y$, $X \cap Y^c$, $X^c \cap Y^c$, where ^{c} refers to the complementing set of items, can be used to test statistical significance of the association. Whenever the Chi-square distribution seemed inappropriate due to small sample size, a Fisher exact test was used. For a more extensive overview of applying association rules on contact data see [29].

Contact Surface Smoothing

Contact surface smoothing was performed by applying a negative binomial model on the aggregated number of contacts (both physical and nonphysical) over 5 y age bands for both responders and contacts using a tensor product spline as a smooth interaction term [30,31].

Epidemiological Modelling: Simulating the Initial Phase of an Epidemic

We explore the age-specific incidence of infection during the initial phase of an epidemic of an emerging infectious disease agent that spreads in a completely susceptible population. We focus on the generic features of epidemic spread along the transmission route that is specified by physical and nonphysical contacts as defined here. We partition the population into 5 y age bands, and we group all individuals aged 70 y and older together. This process results in 15 age classes. We denote the number of at-risk contacts of an individual in age class j with individuals in age class i by k_{ij}. We take k_{ij} as proportional to the observed number of contacts (both physical and nonphysical) that a respondent in age band j makes with other individuals in age band i. The matrix with elements k_{ij} is known in infectious disease epidemiology as the next generation matrix $\mathbf{K}$ [32]. The next generation matrix can be used to calculate the distribution of numbers of new cases in each generation of infection from any arbitrary initial number of introduced infections. For example, when infection is introduced by one single 65-y-old infected individual into a completely susceptible population, we can denote the number of initial cases in generation 0 by the vector $\mathbf{x}_0 = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0)^T$. The expected numbers of new cases in the ith generation are denoted by the vector $\mathbf{x}_i$, and this vector is calculated by applying the next generation matrix $\mathbf{K}$ i times to the initial numbers of individuals $\mathbf{x}_0$, that is, $\mathbf{x}_i = \mathbf{K}^i\,\mathbf{x}_0$. For large i, the vector $\mathbf{x}_i$ will be proportional to the leading eigenvector of $\mathbf{K}$. We find that, in practice, the distribution of new cases is stable after five generations; that is, the distribution no longer depends on the precise age of the initial case. The incidence of new infections per age band is obtained by dividing the expected number of new cases per age class by the number of individuals in each age class. To facilitate comparison among countries, we normalized the distribution of incidence over age classes such that for each country the age-specific incidences sum to one.

Results

Description of Sample

A total of 7,290 diaries covering all contacts made by respondents during a full day were collected in eight countries ranging from 267 in NL to 1,328 in DE (see Table 1). 37.6% of participants in our survey were under 20 y of age, 12.4% of participants were over 60 y of age, and the medians were 28 y in BE (the lowest) to 33 y in DE (the highest). Returns of diaries by female participants showed a slight excess in all countries (ranging from 50.8% in FI to 55.7% in DE). In all countries except DE, single-person households were underrepresented in our sample (Table S2). This can be partially explained by the fact that children and adolescents were deliberately oversampled, and they are more likely to live in larger households.

Overall, 35.3% of the participants were in full-time education, 32.6% employed, 11% retired, 6.1% homemakers, 3.6% unemployed or seeking employment, whereas 8.6% recorded "other," and 2.8% failed to record their occupation. The proportion employed or in full-time education was fairly consistent across the eight countries; the other categories differed somewhat between countries.

Table 1. Number of Recorded Contacts per Participant per Day by Different Characteristics and Relative Number of Contacts from the Weighted Multiple Censored Negative Binomial Regression Model

Category	Covariate	Number of Participants	Mean (Standard Deviation) of Number of Reported Contacts	Relative Number of Reported Contacts (95% Confidence Interval)[a]
Age of participant, y	0–4	660	10.21 (7.65)	1.00
	5–9	661	14.81 (10.09)	1.42 (1.28–1.55)
	10–14	713	18.22 (12.27)	1.73 (1.57–1.90)
	15–19	685	17.58 (12.03)	1.68 (1.52–1.84)
	20–29	879	13.57 (10.60)	1.45 (1.33–1.57)
	30–39	815	14.14 (10.15)	1.45 (1.34–1.57)
	40–49	908	13.83 (10.86)	1.38 (1.27–1.50)
	50–59	906	12.30 (10.23)	1.31 (1.20–1.42)
	60–69	728	9.21 (7.96)	1.06 (0.96–1.16)
	70+	270	6.89 (5.83)	0.81 (0.73–0.88)
	Missing value	65	9.63 (9.05)	0.91 (0.66–1.17)
Sex of participant	Female	3,808	13.39 (10.57)	1.00
	Male	3429	13.51 (10.67)	0.99 (0.96–1.02)
	Missing value	53	10.92 (8.60)	1.57 (1.09–2.05)
Household size	1	749	8.87 (8.27)	1.00
	2	1,645	10.65 (9.14)	1.17 (1.11–1.24)
	3	1,683	12.87 (10.26)	1.20 (1.13–1.27)
	4	2,041	15.84 (11.17)	1.36 (1.28–1.44)
	5	814	16.47 (11.21)	1.46 (1.35–1.56)
	6+	358	17.69 (10.98)	1.56 (1.43–1.70)
Day of the week	Sunday	862	10.10 (8.76)	1.00
	Monday	1,032	13.32 (10.31)	1.33 (1.24–1.41)
	Tuesday	1,116	14.17 (10.83)	1.39 (1.31–1.48)
	Wednesday	1,017	14.58 (11.14)	1.38 (1.29–1.47)
	Thursday	1,069	14.70 (11.23)	1.41 (1.32–1.50)
	Friday	1,122	14.72 (11.25)	1.43 (1.34–1.52)
	Saturday	936	11.63 (9.11)	1.20 (1.12–1.28)
	Missing value	136	12.48 (10.66)	1.24 (1.08–1.40)
Country[b]	BE	750	11.84 (9.85)	1.00
	DE	1,341	7.95 (6.26)	0.70 (0.65–0.74)
	FI	1,006	11.06 (7.89)	0.94 (0.88–1.00)
	GB	1,012	11.74 (7.67)	0.99 (0.92–1.05)
	IT	849	19.77 (12.27)	1.66 (1.55–1.78)
	LU	1,051	17.46 (12.81)	1.42 (1.33–1.51)
	NL	269	13.85 (10.54)	1.34 (1.20–1.47)
	PL	1,012	16.31 (11.45)	1.37 (1.28–1.47)

[a]Dispersion parameter alpha = 0.36 (95% CI 0.34–0.37); alpha = 0 would correspond to no overdispersion, i.e., a censored Poisson distribution.
[b]Direct comparisons between countries are difficult because of different approaches to recording frequent professional contacts. In BE, DE, FI, and NL, participants were instructed not to record professional contacts in the diary if they had more than 20 (BE) or 10 (DE, FI, NL) of them per day.
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Number of Contacts

A total of 97,904 contacts with different persons were recorded (mean = 13.4 per participant per day) in the diaries. On average, German participants reported the fewest daily number of contacts (mean = 7.95, standard deviation [SD] = 6.26) and Italians the highest number (mean = 19.77, SD = 12.27). The contact distributions in all countries are slightly skewed, the skewness statistics ranging from 0.62 in IT to 2.96 in DE (Figure S1). Analysis of the total number of reported contacts with a multiple regression model shows a consistent pattern of contact frequency by age, with a gradual rise in the number of contacts in children, a peak among 10- to 19-y-olds, followed by a fall to a lower plateau in adults until the age of 50 and a sharp decrease after that age (Table 1). Living in a larger household size was associated with higher number of reported contacts. Weekdays were associated with 30%–40% more contacts than Sundays. The influence of the country in which the survey was performed was also apparent (Table 1), even when adjusting for the main different recording formats we used in different countries (diary sizes and estimates of professional contacts) (see Table S3). The overdispersion parameter in the model was significantly different from zero, indicating the necessity to use a negative binomial model as opposed to a Poisson model.

Frequency, Intensity, and Location of Contacts

The intensity of contacts was measured in a number of ways, all of which were found to be highly correlated with each other (see Figure 1 for pooled data from all countries, Figure S2 for country-specific data). Contacts of long duration or of daily frequency were much more likely to involve physical contact. Approximately 70% of contacts made on a daily basis last in excess of an hour, whereas approximately 75% of contacts made with individuals who have never been contacted before lasted for less than 15 min. Approximately 75% of contacts at home and 50% of school and leisure contacts were physical, whereas only a third of contacts recorded in other settings were physical; approximately two-thirds of the persons contacted in multiple

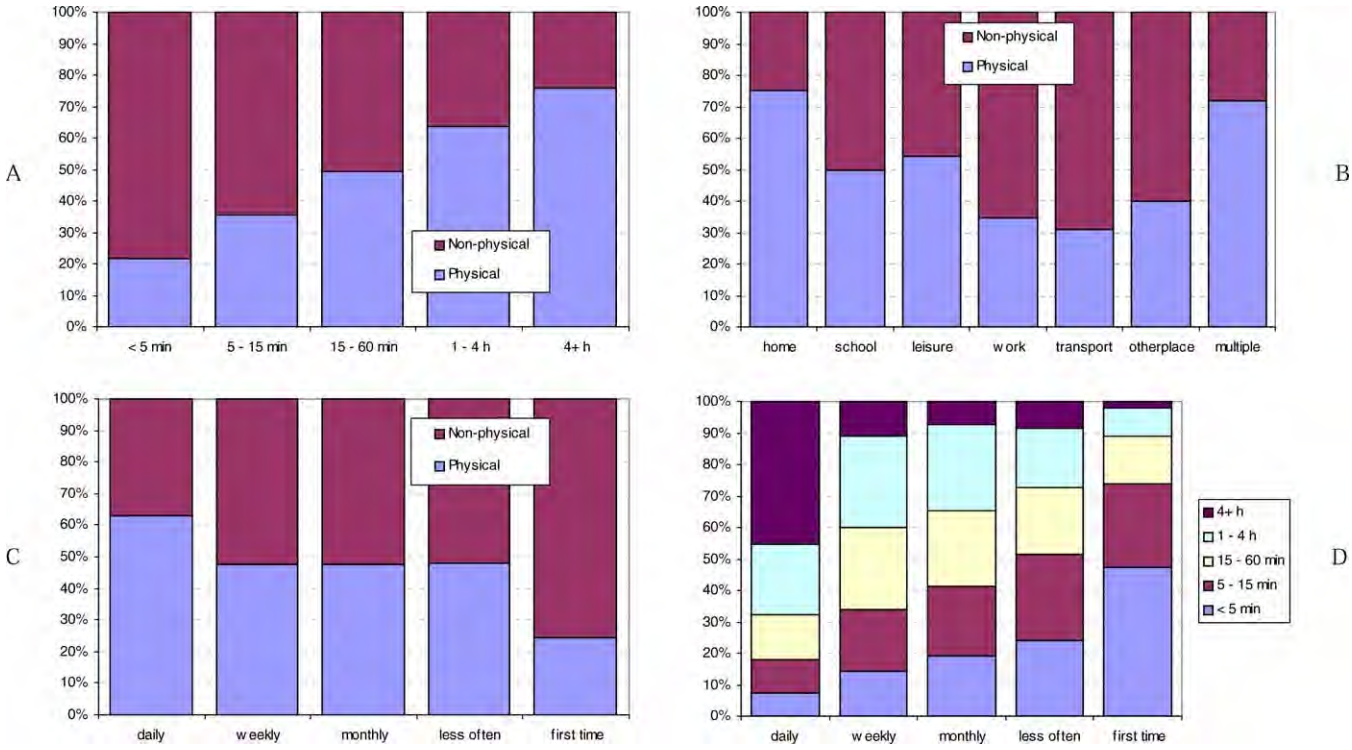

Figure 1. The Mean Proportion of Contacts That Involved Physical Contact, by Duration, Frequency, and Location of Contact in All Countries

Graphs show data by (A) duration, (B) location, and (C) frequency of contact; the correlation between duration and frequency of contact is shown in (D). All correlations are highly significant ($p < 0.001$, χ^2-test). The figures are based on pooled contact data from all eight countries and weighted according to sampling weights as explained in the Methods (based on household size and age).

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settings involved a contact at home, and so a high proportion were physical.

Mining the contact data for frequency, duration, and type of contact based on association rules of maximum length 3 using thresholds of 0.5% (about 500 contacts) on the occurrence, positive dependence, and a 5% significance level on the Chi-square test of dependence resulted in a total of 99 rules of which 46 were of length 2 (see Table S4). 75% of the contacts lasting 4 h or more involved physical contact and occurred on a daily basis (83%), while 83% of the first-time contacts lasting less than 5 min were nonphysical. First time and occasional contacts mostly lasted less than 15 min (lift values 3.3 and 1.8, respectively) and, when nonphysical, this association was intensified (lift values 3.6 and 2.6, respectively). Whether contacts were physical or not did not influence the association between contacts lasting at least four hours and occurring on a daily basis nor did it influence the association between contacts lasting from five minutes up to one hour and occurring on a weekly or monthly basis. Physical contacts and contacts lasting 1–4 h were the only characteristics that were symmetric—that is, they had the same level of confidence in both directions (66% and 64%, respectively). Overall, 67% of all physical contacts lasted for at least 1, while 56% of all physical contacts occurred on a daily basis. All previously reported rules had high lift-values and were significant at the 1% significance level. Due to the high degree of correlation between physical contact and other measures of intimate contact, in the remainder of the paper we use physical contacts as a proxy measure for high-intensity contacts.

Of all pooled reported contacts, 23%, 21%, 14%, 3%, and 16% are made at home, at work, at school, while travelling, and during leisure activities, respectively (Figure 2A). More than half of all reported contacts occur at home, at work, or at school. It is interesting to note, however, that on a population level the overall number of reported contacts made during leisure activities is very close to the number of reported contacts made at school. A higher proportion of physical contacts are made at home, and leisure settings are the second most frequently reported location for such high intensity contacts (Figure 2B).

Age-Related Mixing Patterns

Figure 3 shows the average number of contacts reported per participant with individuals of different age groups for each of the eight countries for all reported (Figure 3A) and physical contacts (Figure 3B) only (full contact matrix data can be found in Table S5). Apart from the remarkable similarity of the general contact pattern structure in the different countries, three main features are apparent from the data. First, the dominant feature is the strong diagonal element: individuals in all age groups tend to mix assortatively (i.e., preferentially with others of similar age). This pattern is most pronounced in those aged 5–24 years, and least pronounced in those aged 55–69.

Second, two parallel secondary diagonals starting at roughly 30–35 years for both contacts and participants are offset from the central diagonal. This pattern represents children mixing with adults in the 30–39 age range (mainly at home, see Figure S3) and vice versa. Older children mix with

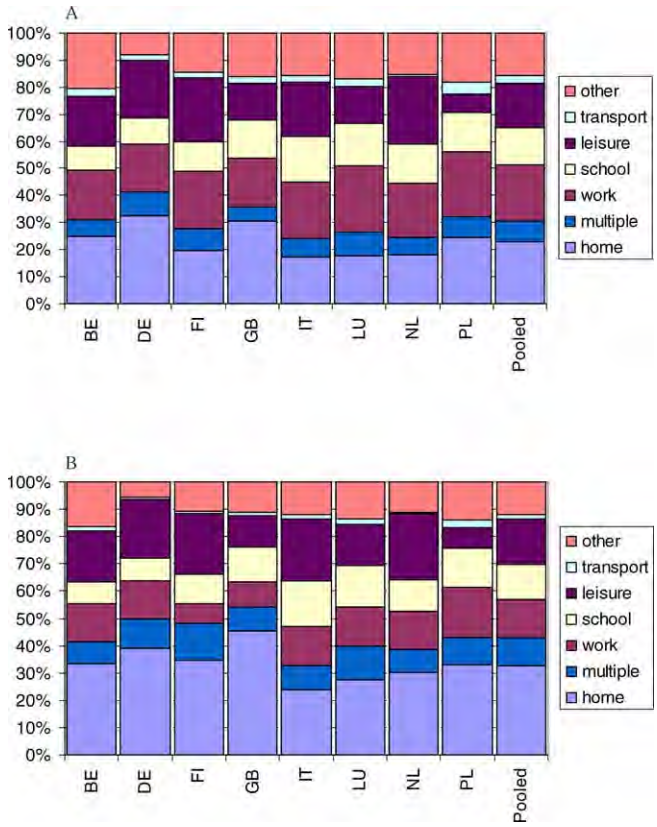

Figure 2. The Distribution by Location and by Country of (A) All Reported Contacts and (B) Physical Contacts Only

Sampling weights were used for each country. "Other" refers to contacts made at locations other than home, work, school, travel, or leisure. "Multiple" refers to the fact that the person was contacted during the day in multiple locations, not just a single location.

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middle-aged adults. Note, though, that the contact rates of the secondary diagonals at 30–35 years offset are an order of magnitude lower than the main assortative diagonal. Mixing between middle-aged adults and the elderly (above 60 y) was also apparent (see Figure S3).

The third feature is more apparent in the data for all reported contacts (Figure 3A) than for physical contacts only: a wider contact "plateau" of adults with other adults primarily due to low-intensity contacts, with many of these contacts occurring at work (see also Figure S4).

Simulated Initial Phase of an Epidemic

According to our mathematical model, the age distribution of cases during the initial phase of an epidemic of a new, emerging infection that spreads according to the reported social contacts in a completely susceptible population reveals a typical pattern that is similar across countries (see Figure 4). The highest incidence occurs among schoolchildren (ranging from 5- to 9-y-olds in NL to 5- to 19-y-olds in IT), and a less pronounced second peak in incidence occurs among adults (ranging from 30- to 34-y-olds in PL to 40- to 44-y-olds in FI). The high incidence among school-aged children results from their high number of contacts relative to other groups, and their tendency to make contacts within their own age group. The tendency to contact others within the same age group could potentially lead to a slow dispersion of infection across age groups. However, the contacts outside age groups are often with others about 30–35 years older or younger, and this tendency results in fairly rapid dispersion of infection across all age groups. Therefore, the observed contact patterns reveal that schoolchildren drive the epidemic in all age groups during the initial phase of spread for infections transmitted by droplets and through close contacts.

Discussion

Mathematical models are increasingly used to evaluate and inform infectious disease prevention and control policy. At their heart all models must make assumptions about how individuals contact each other and transmit the infectious agent. Until now, modellers have relied on proxy measures of contacts and calibration to epidemiological data. For instance, household size, class size, transport statistics, and workplace size distribution have been used in recent models to define the contact structure [2,3,33,34]. Our study complements those relying on proxy measures by using direct estimates of the number, age, intimacy levels, and distribution of actual contacts within various settings. The analysis of population-based contact patterns can help inform the structure and parameterisation of mathematical models of close-contact infectious diseases.

One of the most important findings of our study is that the age and intensity patterns of contact are remarkably similar across different European countries even though the average number of contacts recorded differed. This similarity implies that the results may well be applicable to other European countries, and that the initial phase of spread of newly emerging infections in susceptible populations, such as SARS was in 2003, is likely to be very similar across Europe and in countries with similar social structures.

Another major insight gained from our study comes from the observation that the contacts made by children and adolescents are more assortative than contacts made by other age groups. That is, most of the individuals contacted by children and teenagers are of very similar age, and these contacts tend to be of long duration. This pattern is likely to be the main reason why children and teenagers are and have been an important conduit for the initial spread of close-contact infections in general and for influenza in particular [11,14] and our preliminary modelling work confirms this.

Our study allows us to assess and quantify the risk of transmission in different settings. We took a number of different measures of "closeness of contact," including duration and frequency of contact and whether skin-to-skin contact occurred. These measures correlated highly with each other, such that the longer-duration contacts tended to be frequent and to involve physical contact (and vice versa). More-intimate contacts are likely to carry a greater risk of transmission. Furthermore, these types of contact tend to occur in distinct social settings: the most-intimate contacts occur at home or in leisure settings, whereas the least-intimate tend to occur while travelling. Thus, the risk of infection in these settings can be inferred to vary. This variation has important implications for contact tracing during outbreaks of a new infection. Our results suggest that if efforts concentrate on locating contacts in the home, school, workplace, and leisure settings, on average more than 80% of all contacts would be found.

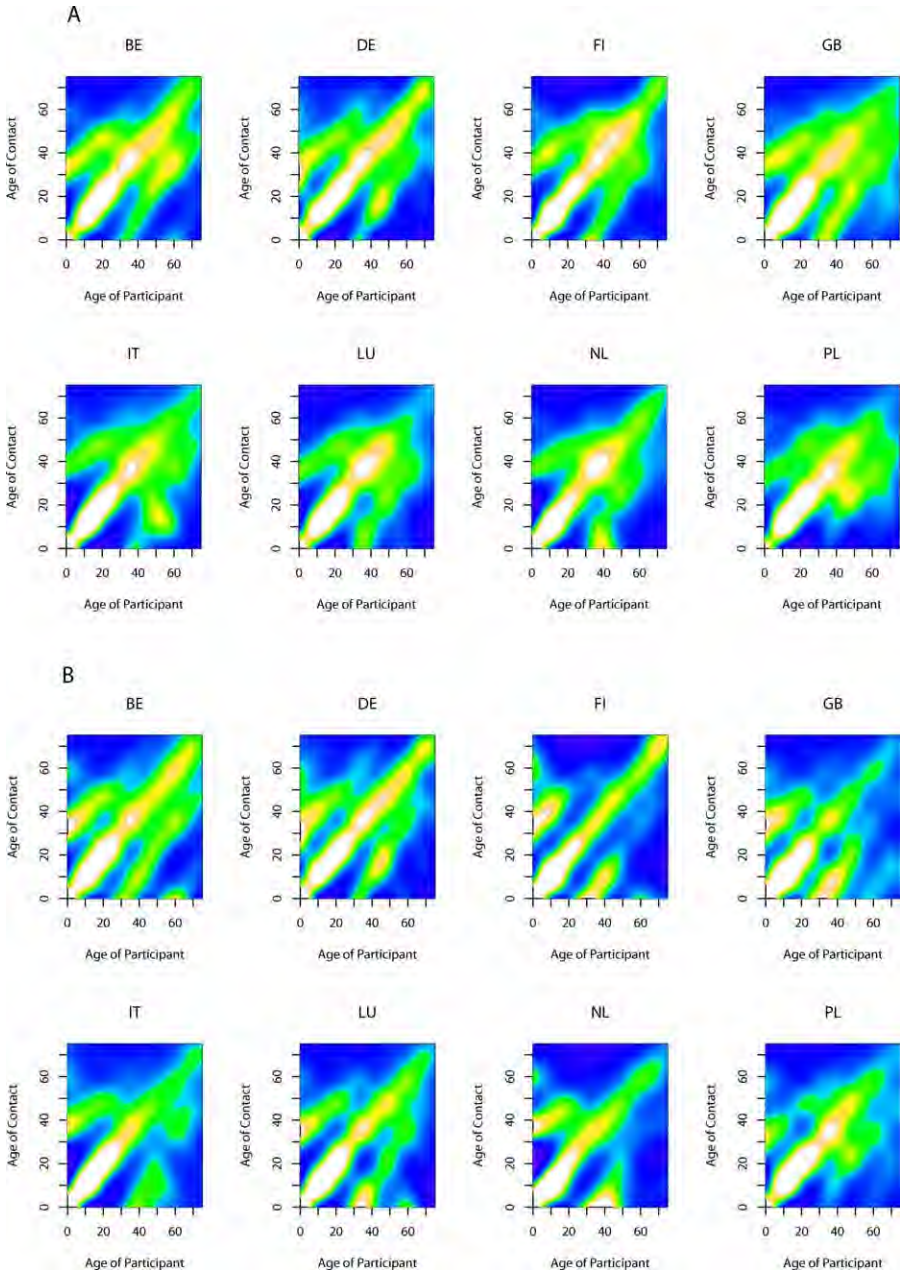

Figure 3. Smoothed Contact Matrices for Each Country Based on (A) All Reported Contacts and (B) Physical Contacts Weighted by Sampling Weights
White indicates high contact rates, green intermediate contact rates, and blue low contact rates, relative to the country-specific contact intensity. Fitting is based on a tensor-product spline to contact matrix data using a negative binomial distribution to account for overdispersion.
doi:10.1371/journal.pmed.0050074.g003

We have used simulations to expand on two particular types of contacts (physical and nonphysical) and to sketch the consequences of the observed contact patterns on the age distribution of incidence in the initial phase of an epidemic, when a new infectious disease is introduced into a completely susceptible population. As shown clearly by our simulations, the highest incidence of infection will occur among the younger age classes (5–19 y) for all countries. It is tempting to link such contact patterns to the observation during the 1957 Asian influenza A H2N2 pandemic that the first few generations of infection primarily affected those aged 11–18 y [35]. However, we note that our survey did not address the clustering of contacts; such clustering of contacts might result in less-pronounced differences in age-specific incidence than suggested by our calculations. Addressing the frequency of clustered contacts, duration and type of contact, differential impact of pathogen on different age groups, time correlation of contacts, and assortative mixing by demographic factors other than age should be key priorities for future research.

One of the major assumptions behind our approach is that talking with or touching another person constitutes the main at-risk events for transmitting infectious diseases. There may be other at-risk events that our methodology does not capture, such as being in a confined space or in close physical proximity with other individuals and not talking to them [23].

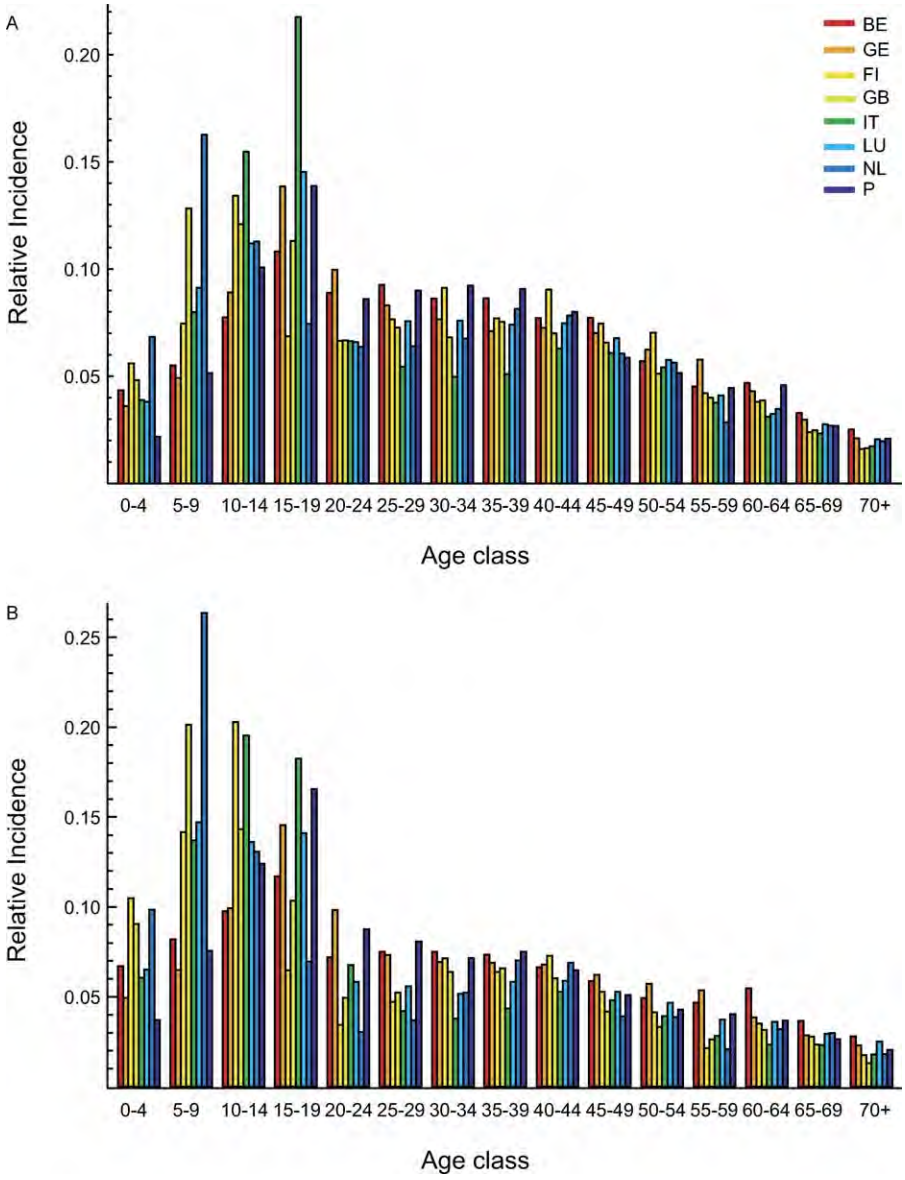

Figure 4. Relative Incidence of a New Emerging Infection in a Completely Susceptible Population, When the Infection Is Spread between and within Age Groups by the Contacts as Observed in Figure 3

For each country, we monitored incidence five generations of infection after the introduction of a single infected individual in the 65–70 age group; the incidence is normalized such that height of all bars sums to one for each country. (A) Results for all reported contacts; (B) for physical contacts only.
doi:10.1371/journal.pmed.0050074.g004

Such events are difficult to record or to measure without using intrusive and expensive surveillance methods, and are probably of lower risk than the communication events captured by our approach. Similarly, our framework does not apply to pathogens that, in addition to the respiratory route, can be also spread by other means, for example, the sewage contamination events for SARS [8]. Although we believe that it is plausible that the contact patterns observed in our study are predictive of disease transmission, further work is clearly needed to establish the types of contacts that represent transmission risks for different diseases and to determine the circumstances under which lower-intensity contacts could be epidemiologically relevant. The data reported in this study should not be considered a substitute for epidemiological studies that quantify, for instance, the intensity of transmission of influenza in households, schools, or other settings. However, this study does provide invaluable data on the relative importance of "leisure" and "other" contacts, which are very difficult to assess in other ways, and it highlights the relatively small contribution of personal contacts during travel based on our approach of defining a contact.

Using contact diaries in the general population was a feasible method for our specific study objectives, but as with all self-reported data, future research should validate our findings with different approaches, including interviews or direct observation. The latter might be particularly useful in assessing contacts of young children who spend time in day-care centres and kindergartens, because parental proxy reporting for young children is likely to be problematic.

Despite the limitations of self-reported egocentric data [36], contact diaries can provide extensive details regarding contact structures and have been used successfully for social network analysis [37]. Our contact diaries yielded detailed information about intimacy, frequency, and epidemiological relevance of contacts with an acceptable burden on respondents. In five countries, participants were given the opportunity to report whether they had any problems filling in the diary. The low proportion reporting problems (4% in adults, 4.9% in older children self-reporting contacts, and 4.9% in parents as proxy for children) suggest that the contact diary was readily accepted and understood by responding participants.

A further limitation of our study is that the comparison of contact patterns between countries is complicated by the variations of diary design (see Table S1), recruitment, and follow-up methodology (see Table S1). Our surveys were conducted in each country by different commercial companies with different recruitment and follow-up methods. Conducting surveys on contact behaviour and networks that entail a certain burden on participants and follow identical methodology in different countries is a challenging task, given that cultural factors in response also play a role. Further research is definitely warranted to determine optimal survey methodologies in different international settings, including developing countries, to improve comparability of contact data. Diaries used in BE, DE, FI, and NL instructed respondents not to record all of their professional contacts, but to provide an estimate if they had a lot of them. The reason for this instruction was to try to capture information from those people who make very large numbers of contacts (shop assistants and bus drivers, for instance), given that it might be very difficult or impossible for such people to fill out the full contact diary. This instruction may have lead to some underreporting of contact frequencies and thus have affected the distribution of age and circumstance of contacts for these four countries, although we have taken account of this possibility to some extent using a censored model. Additional analyses for these countries that combine and compare the estimated frequency of professional contacts with the diary data will provide additional insights about the number of contacts for all countries. The differences between diaries do not, however, affect the age-specific pattern, nor the similarity in age-specific patterns found across countries.

Our survey is, to our knowledge, the first population-based prospective survey of mixing patterns pertinent to the spread of airborne and close-contact infectious diseases performed in several European countries using a similar diary methodology. The quantification of these mixing patterns shows a remarkable similarity in degree of assortativeness, which likely results in similar patterns of spread in different populations. This finding represents a significant advance in our understanding of the spread of these infectious diseases and should help to improve the parameterisation of mathematical models used to design control strategies.

Supporting Information

Figure S1. Histogram of Number of Reported Contacts by Country

Found at doi:10.1371/journal.pmed.0050074.sg001 (7.7 KB PDF).

Figure S2. The Proportion of Contacts That Involved Physical Contact, by (a) Duration, (b) Frequency, (c) Location of Contact; and (d) Correlation between Duration and Frequency of Contact

Contacts were weighted by country-specific sampling weights in BE (A), DE (B), FI (C), GB (D), IT (E), LU (F), NL (G), and PL (H).

Found at doi:10.1371/journal.pmed.0050074.sg002 (84 KB DOC).

Figure S3. Smoothed Weighted Contact Matrices for Each Country Based on Reported Contacts Occurring in the Home Setting

White indicates high contact rates, green intermediate contact rates, and blue low contact rates. Fitting is based on a tensor-product spline to contact matrix data using a negative binomial distribution to account for overdispersion.

Found at doi:10.1371/journal.pmed.0050074.sg003 (282 KB PDF).

Figure S4. Smoothed Weighted Contact Matrices for Each Country Based on Reported Contacts Occurring in the Work Setting

White indicates high contact rates, green intermediate contact rates, and blue low contact rates. Fitting is based on a tensor-product spline to contact matrix data using a negative binomial distribution to account for overdispersion.

Found at doi:10.1371/journal.pmed.0050074.sg004 (254 KB PDF).

Table S1. Details of Survey Methodology in Each Country

Found at doi:10.1371/journal.pmed.0050074.st001 (52 KB DOC).

Table S2. Comparison of Household Size and Age Distribution of Census Data (2000) and Sample in BE, DE, FI, GB, IT, LU, NL, and PLRatio C/S (census versus sample), corresponds to the sampling weights used in the statistical analysis.

Found at doi:10.1371/journal.pmed.0050074.st002 (715 KB DOC).

Table S3. Relative Number of Reported Contacts Estimated by Different Negative Binomial Models (95% Confidence Interval in Brackets)

The results of this model comparison show that neither the censored nature of the data, nor the differences in how professional contacts were handled, substantially changes the model outcome. Note that all covariates have overlapping confidence intervals for models A and B, which are directly comparable, although censoring does improve model fit.

Found at doi:10.1371/journal.pmed.0050074.st003 (282 KB PDF).

Table S4. Association Rules of Length 2 for Type, Duration, and Location of Contacts with Minimal Support of 0.5%, Significant Positive Dependence (0.01 Significance Level)

Support, confidence, lift, and χ^2 values are given.

Found at doi:10.1371/journal.pmed.0050074.st004 (254 KB PDF).

Table S5. Contact Matrices of All Reported and Physical Contacts Consisting of the Average Number of Contact Persons Recorded per Day per Survey Participant Separately for Each Country

Found at doi:10.1371/journal.pmed.0050074.st005 (714 KB DOC).

Text S1. Example of the Diary Used in Great Britain

Found at doi:10.1371/journal.pmed.0050074.sd001 (49 KB PDF).

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Author contributions. JM, NH, MJ, JW, and WJE drafted the manuscript in consultation with all the other authors; the original idea and contact diary were conceived by WJE. JM conducted a pilot study on an adapted diary, and coordinated overall survey design and data collection. JM, MJ, PB, KA, RM, MM, GST, JW, JH, MST, and MR conducted the surveys in their respective countries. NH conducted the data mining and surface smoothing. JW and JH conducted the epidemic modelling. All authors approved the final manuscript.

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Editors' Summary

Background To understand and predict the impact of infectious disease, researchers often develop mathematical models. These computer simulations of hypothetical scenarios help policymakers and others to anticipate possible patterns and consequences of the emergence of diseases, and to develop interventions to curb disease spread. Whether to prepare for an outbreak of infectious disease or to control an existing outbreak, models can help researchers and policy makers decide how to intervene. For example, they may decide to develop or stockpile vaccines or antibiotics, fund vaccination or screening programs, or mount health promotion campaigns to help citizens minimize their exposure to the infectious agent (e.g., handwashing, travel restrictions, or school closures).

Respiratory infections, including the common cold, flu, and pneumonia, are some of the most prevalent infections in the world. Much work has gone into modeling how many people would be affected by respiratory diseases under various conditions and what can be done to limit the consequences.

Why Was This Study Done? Mathematical models have tended to use contact rates (the number of other people that a person encounters per day) as one of their main elements in predicting the outcomes of epidemics. In the past, contact rates were not based on direct observations, but were assumed to follow a certain pattern and calibrated against other indirect data sources such as serological or case notification data. This study aimed to estimate contact rates directly by asking people who they have met during the course of one day. This allowed the researchers to study in more detail different *patterns* of contacts, such as those between different groups of people (such as age groups) and in different social settings. This is particularly important for respiratory diseases, which are spread through the air and by close contact with an infected individual or surface.

What Did the Researchers Do and Find? The researchers wanted to examine the social contacts that people have in order to better understand how respiratory infections might spread. They recruited 7,290 people from eight European countries (Belgium, Germany, Finland, Great Britain, Italy, Luxembourg, The Netherlands, and Poland) to participate in their study. They asked the participants to fill out a diary that documented their physical and nonphysical contacts for a single day. Physical contacts included interactions such as a kiss or a handshake. Nonphysical contacts were situations such as a two-way conversation without skin-to-skin contact. Participants detailed the location and duration of each contact. Diaries also contained basic demographic information about the participant and the contact.

They found that these 7,290 participants had 97,904 contacts during the study, which averaged to 13.4 contacts per day per person. There was a great deal of diversity among the contacts, which challenges the idea that contact rates alone provide a complete picture of transmission dynamics. The researchers identified varied types of contacts, duration of contacts, and mixing patterns. For example, children had more contacts than adults, and those living in larger households had more contacts. Weekdays resulted in more daily contacts than Sundays. More intense contacts (of longer duration or more frequent) tended to be physical. Approximately 70% of contacts made on a daily basis lasted longer than an hour, whereas three-quarters of contacts with people who were not previously known lasted less than 15 minutes. While mixing patterns were very similar across the eight countries, people of the same age tended to mix with each other.

Analyzing these contact patterns and applying mathematical and statistical techniques, the researchers created a model of the initial phase of a hypothetical respiratory infection epidemic. This model suggests that 5- to 19-year-olds will suffer the highest burden of respiratory infection during an initial spread. The high incidence of infection among school-aged children in the model results from these children having a large number of contacts compared to other groups and tending to make contacts within their own age group.

What Do These Findings Mean? This work provides insight about contacts that can be supplemental to traditional measurements such as contact rates, which are usually generated from household or workplace size and transportation statistics. Incorporating contact patterns into the model allowed for a deeper understanding of the transmission patterns of a hypothetical respiratory epidemic among a susceptible population. Understanding the patterning of social contacts—between and within groups, and in different social settings—shows how diverse contacts and mixing between individuals really are. Physical exposure to an infectious agent, the authors conclude, is best modeled by taking into account the social network of close contacts and its patterning.

Additional Information. Please access these Web sites via the online version of this summary at doi:10.1371/journal.pmed.0050074.

- Wikipedia has technical discussions on the assumptions used in mathematical models of epidemiology (note that Wikipedia is a free online encyclopedia that anyone can edit; available in several languages)
- Plans for pandemic influenza are explained for the Government of Canada, the United Kingdom's Health Protection Agency, and the United States Department of Health and Human Services

REFERENCE 40

A high-resolution human contact network for infectious disease transmission

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The most frequent infectious diseases in humans—and those with the highest potential for rapid pandemic spread—are usually transmitted via droplets during close proximity interactions (CPIs). Despite the importance of this transmission route, very little is known about the dynamic patterns of CPIs. Using wireless sensor network technology, we obtained high-resolution data of CPIs during a typical day at an American high school, permitting the reconstruction of the social network relevant for infectious disease transmission. At 94% coverage, we collected 762,868 CPIs at a maximal distance of 3 m among 788 individuals. The data revealed a high-density network with typical small-world properties and a relatively homogeneous distribution of both interaction time and interaction partners among subjects. Computer simulations of the spread of an influenza-like disease on the weighted contact graph are in good agreement with absentee data during the most recent influenza season. Analysis of targeted immunization strategies suggested that contact network data are required to design strategies that are significantly more effective than random immunization. Immunization strategies based on contact network data were most effective at high vaccination coverage.

disease dynamics | network topology | public health | human interactions

Pandemic spread of an infectious disease is one of the biggest threats to society because of the potentially high mortality and high economic costs associated with such an event (1, 2). Understanding the dynamics of infectious disease spread through human communities will facilitate the development of much needed mitigation strategies (3). Schools are particularly vulnerable to infectious disease spread because of the high frequency of close proximity interactions (CPIs) that most infectious disease transmission depends on (3, 4). Infections that are transmitted predominantly via the droplet route, such as influenza, common colds, whooping cough, severe acute respiratory syndrome (SARS), and many others, are among the most frequent infectious diseases. Droplets from an infected person can reach a susceptible person in close proximity, typically a distance of less than 3 m (5, 6), making CPIs highly relevant for disease spread. Very little is known about the dynamic patterns of CPIs in human communities, however [but see Cattuto et al. (7)]. Here, we present data collected with a wireless sensor network deployment using TelosB motes (Crossbow Technologies Inc.) (8) to detect high-resolution proximity (up to 3 m) between subjects in a U.S. high school. The dataset represents a high-resolution temporal contact network relevant to the spread of infectious diseases via droplet transmission in a school.

Previous attempts to capture the contact networks relevant for infectious disease transmission have mostly been based on data collection using surveys, sociotechnological networks, and mobile devices like cell phones. Each of these approaches has advantages and disadvantages. Surveys manage to capture the interactions relevant for disease transmission but are often limited by small sample sizes (9) and are subject to human error (10). Sociotechnological networks can provide large long-term datasets (11) but fail to capture the CPIs relevant for disease transmission. The use of mobile devices aware of their location (or of other mobile devices in proximity) represents a promising third alternative. Using mobile phones to detect spatial proximity of subjects is possible with repeated Bluetooth scans (10), but the resolution is too coarse for diseases that are transmitted through the close contact route. Our approach is free of human error, captures the vast majority (94%) of the community of interest, and allows us to collect high-resolution contact network data relevant for infectious disease transmission.

Most efforts to understand and mitigate the spread of pandemic diseases (influenza in particular) have made use of large-scale spatially explicit models parameterized with data from various sources, such as census data, traffic/migration data, and demographic data (3, 4, 12–15). The population is generally divided into communities of schools, workplaces, and households, but detailed data on mixing patterns in such communities are scarce. In particular, very little is known about the contact networks in schools (16) even though schools are known to play a crucially important role in pandemic spread, mainly owing to the intensity of CPIs at schools. In what follows, we describe and analyze the contact network observed at a U.S. high school during a typical school day. Using an SEIR (susceptible, exposed, infectious, and recovered) simulation model, we investigate the spread of influenza on the observed contact network and find that the results are in very good agreement with absentee data from the influenza A (H1N1) spread in the fall of 2009. Finally, we implement and test various immunization strategies to evaluate their efficacy in reducing disease spread within the school.

Results

The dataset covers CPIs of 94% of the entire school population, representing 655 students, 73 teachers, 55 staff, and 5 other persons, and it contains 2,148,991 unique close proximity records (CPRs). A CPR represents one close (maximum of 3 m) proximity detection event between two motes. An interaction is defined as a continuous sequence (≥1) of CPRs between the same two motes, and a contact is the sum of all interactions between these two motes. Thus, a contact exists between two motes if there is at least one interaction between them during the day, and the duration of the contact is the total duration of all interactions between these two motes. Because the beaconing frequency of a mote is 0.05 s^{-1}, an interaction of length 3 (in CPRs) corresponds to an interaction of about 1 min (*SI Text* and references therein). The entire dataset consists of 762,868 interactions with a mean duration of 2.8 CPRs (~1 min), or 118,291 contacts with mean duration of 18.1 CPRs (~6 min)

Author contributions: M.S., M.K., J.W.L., P.L., M.W.F., and J.H.J. designed research; M.S., M.K., J.W.L., and P.L. performed research; M.S. analyzed data; and M.S. wrote the paper.

The authors declare no conflict of interest.

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(data available in *SI Methods*). Fig. 1*A* shows the frequency, *f*, of interactions and contacts of length *m* (in minutes) [*f*(*m*)]. The majority of interactions and contacts are very short (80th percentile of interactions at 3 CPRs, 80th percentile of contacts at 15 CPRs), and even though about 80% of the total time is spent in interactions that are shorter than 5 min, short contacts (<5 min) represent only about 10% of the total time (Fig. 1*B*).

The temporal mixing patterns observed are in accordance with the schedule of the school day [i.e., the average degree (number of contacts) peaks between classes and during lunch breaks] (Fig. S1). The aggregate network for the entire day can be represented by a weighted undirected graph, wherein nodes represent individuals and edges represent contacts (edges are weighted by contact duration). The topology of the contact network is an important determinant of infectious disease spread (17, 18). Traditional infectious disease models assume that all subjects have the same number of contacts, or that the contact network of subjects is described by a random graph with a binomial degree distribution. Many networks from a wide range of applications, including contact networks relevant for infectious disease transmission (19, 20), have been found to have highly heterogeneous degree distributions, however. Such heterogeneity is important because it directly affects the basic reproductive number, R_0, a crucially important indicator of how fast an infectious disease spreads and what fraction of the population will be infected. In particular, if ρ_0 is the incorrect estimate for R_0 in a heterogeneous network under the false assumption of a uniform degree distribution, the correct estimate is given by $R_0 = \rho_0 (1 + CV^2)$, where CV^2 is the squared coefficient of variation of the degree distribution (17, 21). Thus, the *CV* quantifies the extent to which contact heterogeneity affects disease dynamics.

The descriptive statistics of the school network with different definitions of contact are shown in Fig. 2. To account for the fact that the majority of the contacts are relatively short (Fig. 1*A*), we recalculated all statistics of the network with a minimum requirement for contact duration, c_m (i.e., all edges with weight $<c_m$ are removed from the graph). The network exhibits typical "small-world" properties (22), such as a relatively high transitivity (also known as clustering coefficient, which measures the ratio of triangles to connected triplets) and short average path length for all values of c_m. Assortativity, the tendency of nodes to associate with similar nodes with respect to a given property (23), was measured with respect to degree and role of the person (e.g., student, teacher). Interestingly, although both measures are relatively high, degree assortativity decreases and role assortativity increases with higher values of c_m. Because of the very high density of the contact network, a giant component exists for all values of c_m. Community structure (or modularity) is relatively high, increasingly so with higher values of c_m, indicating that more intense contacts tend to occur more often in subgroups and less often between such groups (24). We find a very homogeneous degree distribution with a $CV^2 = 0.118$ for the full network and slightly increased heterogeneity in the network with higher cutoff values c_m (Fig. 2*J*). The distributions of number of interactions, *c*, and the strength, *s* (the weighted equivalent of the degree) (25) are equally homogeneous (Fig. 3). Overall, the data suggest that the network topology is best described by a low-variance small-world network.

To understand infectious disease dynamics at the school, we used an SEIR simulation model (parameterized with data from influenza outbreaks; details presented in *SI Methods*), wherein an index case becomes infected outside of the school on a random day during the week and disease transmission at the school occurs during weekdays on the full contact network as described by the collected data. Each individual is chosen as an index case for 1,000 simulation runs, resulting in a total of 788,000 epidemic simulation runs. This simulation setting represents a base scenario, wherein a single infectious case introduces the disease into the school population. In reality, multiple introductions are to be expected if a disease spreads through a population, but the base scenario used here allows us to quantify the predictive power of graph-based properties of individuals on epidemic outcomes. We assume that symptomatic individuals remove themselves from the school population after a few hours. We find that in 67.7% of all simulations, no secondary infections occur and thus there is no outbreak, whereas in the remaining 32.3% of the simulations, outbreaks occur with an average attack rate of 3.87% (all simulations = 1.33%, maximum = 46.19%) and the average R_0, measured as the number of secondary infections caused by the index case, is 3.85 (all simulations = 1.24, maximum = 18). Recent work on disease spread on networks has identified the relationship between R_0, the network degree distribution, and the average probability that an infectious individual transmits the disease to a susceptible individual, T (18, 26). Based on this, R_0 would be valued at 4.52 (*SI Methods*). This value is higher than what we measure in the simulations because it is based on the assumption of continuous transmission, whereas the simulations exhibit discontinuous transmission attributable to weekends; during that time, the school is closed and the chain of transmission is effectively cut for 2 d. Finally, absentee data from the school during the fall of 2009 (i.e., during the second wave of H1N1 influenza in the northern hemisphere) are in good agreement with simulation data generated by the SEIR model running on the contact network (Fig. 4*A*).

A strong correlation exists between the size of an outbreak caused by index case individual *i* and the strength of the node representing individual *i* ($r^2 = 0.929$). The correlation between outbreak size and degree is substantially weaker ($r^2 = 0.525$) because at the high temporal resolution of the dataset, the de-

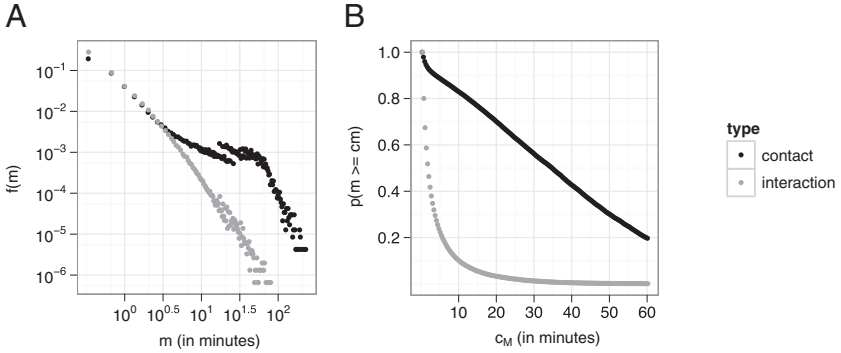

Fig. 1. (*A*) Normalized frequency, *f*, of interactions and contacts of duration *m* (in minutes) [*f*(*m*)] on a log-log scale. (*B*) Percentage, *p*, of total time of all CPIs by interactions and contacts with a minimum duration, c_m (in minutes). Most CPI time is spent in medium-duration contacts consisting of repeated short interactions.

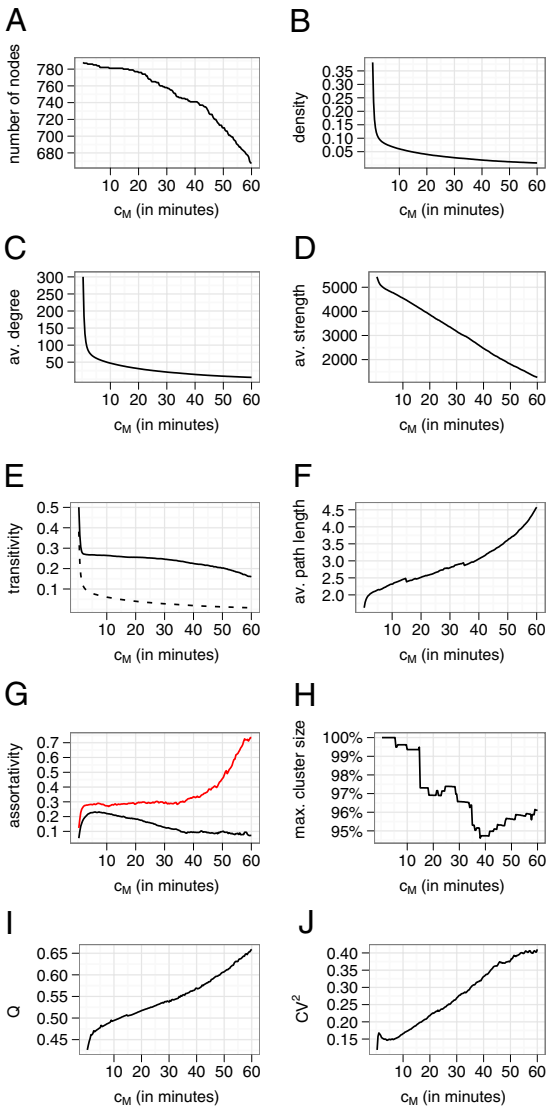

Fig. 2. Various statistics on the contact graph with minimum contact duration, c_m (i.e., the left-most point in each panel represents the full contact graph, the right-most point represents the contact graph that contains only contacts that are at least 60 min long). With increasing c_m, nodes drop out of the network if they have no contact that satisfies the minimum duration condition. (*A*) Hence, the reduction in the number, *V*, of nodes. (*B*) Density of the graph ($2E/[V*(V-1)]$), where *E* is the number of edges. (C) Average (av.) degree. (*D*) av. strength, where the strength of a node is the total number of CPRs of the node. (*E*) Transitivity (i.e., cluster coefficient) as defined by Barrat et al. (25) and expected value (mean degree/*V*) in a random network (dashed line). (*F*) Average path length. (*G*) Assortativity (23) with respect to degree (black line) and role (red line). (*H*) Size of the largest component as a fraction of total network size. max., maximum. (*I*) Modularity, *Q*, as defined by Reichardt and Bornholdt (39). (*J*) CV^2 of degree.

gree contains many short-duration contacts whose impact on epidemic spread is minimal. To estimate the sampling rate at which degree has maximal predictive power, we systematically subsampled our original dataset to yield lower resolution datasets. Fig. S2 shows that sampling as infrequently as every 100 min would have resulted in the same predictive power for degree as sampling every 20 s, whereas the maximum predictive power for degree would have been attained at ∼20 min. At this sampling rate, the 95% confidence intervals for the correlation between degree and outbreak size and the correlation between strength and outbreak size start to overlap (because of the high correlation between degree and strength; Fig. S2, blue line). These results suggest that high-resolution sampling of network properties such as the degree of nodes might be highly misleading for prediction purposes if used in isolation (i.e., without the temporal information that allows for weighting).

To mitigate epidemic spread, targeted immunization interventions or social distancing interventions aim to prevent disease transmission from person to person. Finding the best immunization strategy is of great interest if only incomplete immunization is possible, as is often the case at the beginning of the spread of a novel virus. In recent years, the idea of protecting individuals based on their position in the contact network has received considerable attention (11, 27, 28). Graph-based properties, such as node degree and node betweenness centrality (29), have been proposed to help identify target nodes for control strategies, such as vaccination; however, because of the lack of empirical contact data on closed networks relevant for the spread of influenza-like diseases, such strategies could only be tested on purely theoretical networks [or on approximations from other empirical social networks that did not measure CPIs directly (11)]. To understand the effect of partial vaccination, we measured outbreak size for three different levels of vaccination coverage (5%, 10%, and 20%) and a number of different control strategies based on node degree, node strength, betweenness centrality, closeness centrality, and eigenvector centrality (so-called "graph-based strategies"). In addition, we tested vaccination strategies that do not require contact network data (random vaccination, preferential vaccination for teachers, and preferential vaccination for students; *SI Methods*). To ensure robustness of the results to variation in transmission probabilities, all simulations were tested with three different transmission probabilities (*Methods*). Ten thousand simulations for each combination of vaccination strategy, vaccination coverage, and transmission probability with a random index case per simulation were recorded (i.e., total of 810,000 simulations) to assess the effect of vaccination. Fig. 4*B* shows which strategies led to significantly ($P < 0.05$, two-sided Wilcoxon test) different outcomes at all transmission probability values (results separated by transmission probability are presented in Fig. S3). As expected, all strategies managed to reduce the final size of the epidemic significantly. Compared with the random strategy, graph-based strategies had an effect only at higher vaccination coverage. Graph-based strategies did not differ much in their efficacy; in general, strategy-based strategies were the most effective. Overall, two main results emerge: (*i*) in the absence of information on the contact network, all available strategies, including random immunization, performed equally well and (*ii*) in the presence of information on the contact network, high-resolution data support a strategy-based strategy, but there was no significant difference among the graph-based strategies.

Discussion

In summary, we present high-resolution data from the CPI network at a U.S. high school during a typical school day. Notably, the month of the experiment (January) is associated with the second highest percentage of influenza cases in the United States for the 1976–1977 through 2008–2009 influenza seasons (second only to February). The data suggest that the network relevant for disease transmission is best described as a small-world network with a very homogeneous contact structure in which short repeated interactions dominate. The low values of the coefficients of variation in degree, strength, and number of interactions (Fig. 3) suggest that the assumption of homogeneity in traditional disease models (21) might be sufficiently realistic for simulating the spread of influenza-like diseases in communities like high schools. Furthermore, we do not find any "fat tails" in the contact distribution of our dataset, corroborating the notion (9) that the current focus on networks with such distributions is not warranted for infectious disease spread within local communities.

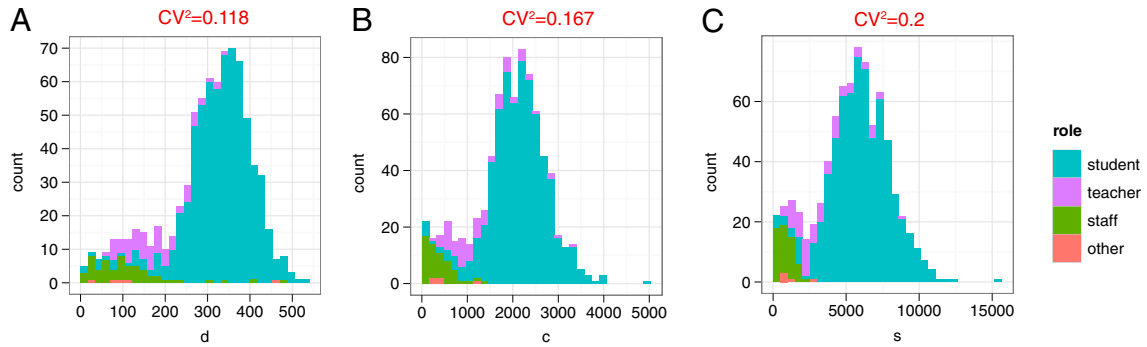

Fig. 3. Distribution and CV^2 of degree, *d* (*A*); number of interactions, *c* (*B*); and strength, *s* (*C*), based on the full contact network and colored by the role of individuals.

It is important to recognize the limitations of the data presented here, particularly in light of the fact that transmission of influenza-like diseases also occurs via other routes, for example, via contact with contaminated surfaces (30). Moreover, different pathogens as well as different strains of a particular pathogen might have different minimum requirements (both spatial and temporal) that need to be met for person-to-person transmission. At present, the data capture the contact network during a single day only. This is not an inherent shortcoming of the approach presented here, however, and long-term studies in the future could address how the large-scale structure of the contact network in a high school changes over time. Data collection at different schools with different demographic compositions would be helpful in clarifying if and how demographic compositions affect the properties of the network relevant for disease transmission. Wireless sensor network technology certainly allows further elucidation of the contact networks not only at different schools but in households, hospitals, workplaces, and other community settings.

With regard to immunization strategies, our simulation results suggest that contact network data are necessary to design strategies that are significantly more effective than random immunization to minimize the number of cases at the school caused by a single index case. Great care needs to be taken in interpreting these results for various reasons. First, the limitations of the data as discussed above mean that these results may not hold in other settings, underlining the need for further empirical network studies. Second, the simulations assume neither multiple introductions nor ongoing interactions of participants outside of the school. To what extent these assumptions, particularly the latter, are violated when a disease spreads through a community is unknown and remains to be measured. Third, future work needs to establish the robustness of the effect of vaccination strategies against errors in the measurement of graph-based properties. Fourth, and perhaps most importantly, a particular immunization strategy may be optimal for reducing the number of cases in one particular school but, at the same time, may not be optimal from the perspective of an entire community. Immunization strategies must also take into account medical, social, and ethical aspects (31). Thus, although we believe that data of the kind reported here can help to inform public health decisions, particularly as more data become available in the future, it is clear that one cannot derive public health recommendations at this stage directly from this study alone. We note, however, that our findings support the notion that graph-based immunization strategies could, in principle, help to mitigate disease outbreaks (11, 28).

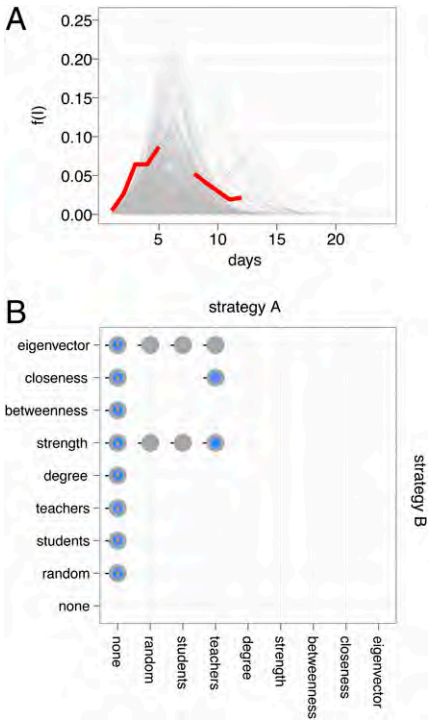

Fig. 4. (*A*) Absentee data (red) and data generated by the SEIR model (gray; 1,000 runs with R_0 >1 shown). Gray lines show frequency of infectious individuals, f(I); red lines show the combined frequency of students who reported, or were diagnosed with, a fever and teachers who were absent (gap in the line attributable to weekend). (*B*) Differences in effect of vaccination strategies. Colors represent vaccination coverage of 5% (orange), 10% (blue), and 20% (gray). A point at the intersection of strategy A and strategy B indicated that between those strategies, there was a significant difference ($P < 0.05$, two-sided Wilcoxon test) in the outbreak size at all transmission probability values at the given vaccination coverage. A black horizontal or vertical line points in the direction of the strategy that resulted in smaller outbreak sizes. Because of the symmetry of the grid, data points below the left bottom and top right diagonal line are not shown.

Methods

The mote deployment is described in detail in *SI Methods*.

Epidemic Simulations. To simulate the spread of an influenza-like disease, we used an SEIR simulation model parameterized with data from influenza outbreaks (12, 32, 33). In the following, we describe the model in detail.

Transmission occurs exclusively along the contacts of the graph as collected at the school. Each individual (i.e., node of the network) can be in one of four classes: susceptible, exposed, infectious, and recovered. Barring vaccination, all individuals are initially susceptible (more information on vaccination is presented below). At a random time step during the first week of the simulation, an individual is chosen as the index case and his or her status is set to exposed. A simulation is stopped after the number of both exposed and infectious individuals has gone back to 0 (i.e., all infected individuals have

recovered). Each time step represents 12 h and is divided into day and night. Transmission can occur only during the day and only on weekdays (i.e., apart from the initial infection of the index case, we do not consider any transmission outside of the school; although this assumption will not hold in reality, it allows us to focus exclusively on within-school transmission and to analyze the spread of a disease starting from a single infected case).

Transmission of disease from an infectious to a susceptible individual occurs with a probability of 0.003 per 20 s of contact (the interval between two beacons). This value has been chosen because it approximates the time-dependent attack rate observed in an outbreak of influenza aboard a commercial airliner (32). In particular, the probability of transmission per time step (12 h) from an infectious individual to a susceptible individual is $1 - (1 - 0.003)^w$, where w is the weight of the contact edge (in CPRs). On infection, an individual will move into the exposed class (infected but not infectious). After the incubation period, an exposed individual will become symptomatic and move into the infectious class. The incubation period distribution is modeled by a right-shifted Weibull distribution with a fixed offset of half a day [power parameter = 2.21, scale parameter = 1.10 (12)]. On the half day that the individual becomes infectious, the duration of all contacts of the infectious individual is reduced by 75%. This reduction ensures that if an individual becomes symptomatic and starts to feel ill during a school day, social contacts are reduced and the individual leaves the school or is dismissed from school after a few hours. In the following days, all contacts are reduced by 100% until recovery (i.e., the individual stays at home). Once an individual is infectious, recovery occurs with a probability of $1 - 0.95^t$ per time step, where t represents the number of time steps spent in the infectious state [in line with data from an outbreak of H1N1 at a New York City school (33)]. After 12 d in the infectious class, an individual will recover if recovery has not occurred before that time.

Based on these simulation settings and the finding that the average contact duration is 18.1 CPRs (*Results*), the transmissibility, T, as defined by Newman (18) and Meyers et al. (26), is $1 - (1 - 0.003)^{18.1*0.25} = 0.0135$. Furthermore, based on the framework established by Newman (18) and Meyers et al. (26), R_0 can be calculated as $R_0 = T \times \langle k_e \rangle$, where the average excess degree, $\langle k_e \rangle$, is $\langle k^2 \rangle / \langle k \rangle - 1 = 334.76$.

We assume that all exposed individuals developed symptoms. A high incidence of asymptomatic spread may affect infectious disease dynamics (34), but reports of asymptomatic individuals excreting high levels of influenza virus are rare (35). In addition, a recent community-based study investigating naturally acquired influenza virus infections found that only 14% of infections with detectable shedding at RT-PCR were asymptomatic and viral shedding was low in these cases (36), suggesting that the asymptomatic transmission plays a minor role. Similar patterns were observed for SARS-CoV, another virus with the potential for rapid pandemic spread: Asymptomatic cases were infrequent, and lack of transmission from asymptomatic cases was observed in several countries with SARS outbreaks (37).

Vaccination. The efficacy of vaccination strategies was tested by simulation. Vaccination occurs (if it occurs at all) before introduction of the disease by the index case. Vaccinated individuals are moved directly into the recovering class. We assume that the vaccine provides full protection during an epidemic.

Three vaccination strategies are implemented that do not require measuring graph-based properties; these strategies are called "random," "students," and "teachers."

Random. Individuals are chosen randomly until vaccination coverage is reached.

Students. Students only are chosen randomly until vaccination coverage is reached.

Teachers. Teachers only are chosen randomly until vaccination coverage is reached. If vaccination coverage is so high that all teachers get vaccinated before the coverage is reached, the strategy continues as the student strategy (see above) for the remaining vaccinations.

Five vaccination strategies are implemented that require measuring graph properties: These strategies are called "degree," "strength," "betweenness," "closeness," and "eigenvector." In all cases, individuals are ranked according to the specific graph property and chosen according to that ranking (in descending order) until vaccination coverage is reached.

Degree. Degree is calculated as the number of contacts during the day of measurement.

Strength. Strength is calculated as the total time exposed to others during the day of measurement.

Betweenness. Betweenness centrality, $C_B(i)$, of individual i is calculated as

$$C_B(i) = \sum_{s \neq t \neq i} \frac{\sigma_{st}(i)}{\sigma_{st}}$$

where s, t, and i are distinct individuals in the contact graph; σ_{st} is the total number of shortest paths between nodes s and t; and $\sigma_{st}(i)$ is the number of those shortest paths that go through node i (29). The shortest path is calculated using inverse weights.

Closeness. Closeness centrality, $C_C(i)$, of individual i is calculated as

$$C_C(i) = \frac{n-1}{\sum_{s \neq i} d_{si}}$$

where s and i are distinct individuals in the contact graph, d_{si} is the shortest path between nodes s and i, and n is the number of individuals in the graph (29). The shortest path is calculated using inverse weights.

Eigenvector. Calculation of eigenvector centrality is described by White and Smyth (38) through application of the page-rank algorithm with jumping probability 0. The measure captures the fraction of time that a random walk would spend at a given vertex during an infinite amount of time.

We tested three different levels of vaccination coverage: 5%, 10%, and 20%. These percentages apply to the entire population [i.e., a 10% vaccination coverage means that 10% of the entire school population is vaccinated, independent of the particular vaccination strategy (except for the strategy "none," which means no vaccinations occur]. In addition to the default transmission probability per CPR interval described above (i.e., 0.003), we tested lower (0.002) and higher (0.0045) transmission probability values.

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