Asymptomatic Transmission and the Infection Fatality Risk for COVID-19: Implications for School Reopening

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Asymptomatic infection occurs for numerous respiratory viral diseases, including influenza and coronavirus disease 2019 (COVID-19). We seek to clarify confusion in 3 areas: age-specific risks of transmission and/or disease; various definitions for the COVID-19 “mortality rate,” each useful for specific purposes; and implications for student return strategies from preschool through university settings.

Keywords. COVID-19; infection fatality risk; asymptomatic disease; school; children.

Four human coronaviruses cause common cold or mild influenza-like symptoms, while severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) cause severe and potentially fatal acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively [1, 2]. The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the seventh zoonotic human coronavirus, causing coronavirus disease 2019 (COVID-19) [3]. Influenza, parainfluenza, measles, and respiratory syncytial virus are among the other respiratory viruses of substantial human concern [4–6]. Despite their lethality to the general population (occasionally) and to susceptible elderly and/or very young or immunocompromised persons (more often), all these infections can be transmitted by individuals who exhibit no symptoms of the disease, a hallmark of infectious disease epidemiology. Yet, the role that asymptomatic infections play in the transmission and burden of COVID-19 is misunderstood. We seek to clarify the importance of asymptomatic SARS-CoV-2 infection, its relevance to measuring the infection fatality risk (as opposed to the case fatality risk or mortality rate), and how these concepts apply to school reopening and student safety.

ASYMPTOMATIC INFECTION

Recent estimates suggest that 15–45% of all SARS-CoV-2 infections are asymptomatic [7–9]. All others can be considered to have a presymptomatic phase in which individuals are infectious prior to being symptomatic. This distinction between “presymptomatic” individuals who are incubating the virus, but have yet to exhibit symptoms, and true asymptomatic cases who will never be symptomatic led to recent confusion in May 2020 with contradictory World Health Organization public statements [10]. There is mounting evidence to suggest that presymptomatic individuals have high viral loads and are responsible for a large proportion of transmission [11–13], whereas the role that true asymptomatic cases play in population-level transmission of SARS-CoV-2 is just now being clarified as cruise ship, military barracks, sports teams, churches, and other cluster outbreaks are reported [14].

Symptomatic persons may harbor high viral loads and be more likely to sneeze or cough, thereby projecting droplets and smaller aerosols more efficiently. Nonetheless, many symptomatic persons may self-segregate and voluntarily reduce the number of people they come into contact with [15], such that transmission risk may be highest at or just before symptom onset [11–14], or from individuals who are asymptomatic or only mildly symptomatic. Some persons with respiratory symptoms may still care for family members, participate in group social activities, and/or go to work, especially when sick-leave policies are constrained [15–17]. Minimizing transmission depends on wearing masks, practicing physical distancing (≥2 meters), safe hand and face hygiene, cleansing surfaces, avoiding crowds and crowding, outdoor activities when feasible, and aggressive viral testing and quarantine [18–24].

MEASURING MORTALITY: IT’S CONFUSING BUT DOES NOT HAVE TO BE

The frequency of asymptomatic infection in COVID-19 is related to obfuscation by popular and even scientific media vis-à-vis “mortality rates.” Wide variations in so-called mortality rates from COVID-19 are reported, but confusion exists regarding definitions and selection biases affecting both the numerator and denominator.
A true mortality rate is the number of deaths per total population per time interval, as with estimating true COVID-19–related deaths from excess mortality rates [26]. But many other so-called mortality rate estimates are more accurately termed a case fatality risk (CFR; or a case fatality rate if assessed over a defined time period) since they derive from denominators of tested persons, omitting persons with mild disease or without symptoms who were never tested from the denominator [27]. (Suboptimal access to antigen/polymerase chain reaction/viral testing has been the global norm.) CFRs may differ based on background population characteristics; Chinese and Italian CFRs were 2.3% and 7.2%, respectively, likely reflecting the ground population characteristics; treatment and only imperfect preventive measures, and if we assume an IFR of 0.5% and a US population of 331 million, then we could see nearly 1 million deaths (0.6 x 0.005 x 331 000 000) in the United States. The final size of the epidemic is expected to be even larger if the epidemic goes unchecked.

A comparison with influenza is useful. The CFR of COVID-19 is higher than the CFR of influenza [34, 35], and the COVID-19 IFR is about 100 times higher than the CFR of influenza [34, 35], and the COVID-19 IFR is about 100 times than the CFR of influenza [34, 35], and the COVID-19 IFR is about 100 times

### REOPENING SCHOOLS: CONSIDER ASYMPTOMATIC INFECTION AND MORTALITY RISKS

The issues of asymptomatic disease and IFR are highly relevant to school reopening decisions. Asymptomatic disease and mild disease that can resemble the common cold or influenza are common in children with COVID-19, and children have low CFRs [36, 37]. Principal concerns for SARS-CoV-2 infection in children include the infected child serving as a nidus of transmission to others, and rarely, severe disease in the infected child as with multisystem inflammatory syndrome in children (MIS-C) [37–39]. On average, children in the preschool and kindergarten to 12th grade (K-12) continuum come into contact with more people than the rest of the population; they typically do not adhere to hand hygiene and physical distancing, although mask use may be better encouraged and enforced if teachers and parents/guardians are motivated [40]. Thus, children are exceedingly good at spreading respiratory and fecal–oral infections. University students are generally young and healthy, and thereby also less likely to experience the severe COVID-19 disease, but they nevertheless pose a transmission risk to others in the community. University students who are in-residence in dormitories share risks like meningococcus, pertussis, and mumps, as occur in other crowded, high-risk environments (eg, barracks, factories, prisons, long-term care facilities, and cruise or naval ships).

Deaths in youth are far less frequent than is their representation in the general population. For example, 45% of the US population in 2019 were under 35 years of age, yet these represented less than 1% of COVID-19 deaths (Table 1). The principal concern with transmission in schools is that outbreaks can affect the older and/or more vulnerable individuals (eg, teachers, school workers, volunteers, grandparents, or immunocompromised children or adults) who are in proximity to school children. Also relevant is what we see each influenza season, namely school and family disruption of large numbers of children who are ill at any given time. Hence, it is incumbent on us all to reopen schools as safely as we can, to step up “gateway” testing opportunities (testing all children, staff, and faculty in the weeks just prior to school opening, with periodic retesting if feasible) if background incidence rates in a
Table 1. COVID-19 Deaths by Age, Compared With What Would Be Expected by the Proportions Represented in the US Population

| Age Group in Years | Number of Deaths (N = 95 608) | Proportion of Total, % | Proportion Expected if Similar Attack Rate by Age: US Census, % |
|--------------------|--------------------------------|------------------------|-------------------------------------------------------------|
| <1                 | 5                              | 0.02                   | 18.7                                                        |
| 1–4                | 3                              | 0.03                   | 18.7                                                        |
| 5–14               | 13                             | 0.14                   | 18.7                                                        |
| 15–24              | 116                            | 0.79                   | 26.7                                                        |
| 25–34              | 640                            | 3.07                   | 18.7                                                        |
| 35–44              | 1649                           | 6.5                    | 25.2                                                        |
| 45–54              | 4588                           | 12.7                   | 25.2                                                        |
| 55–64              | 11 439                         | 32.7                   | 22.6                                                        |
| 65–74              | 19 857                         | 36.2                   | 18.7                                                        |
| 75–84              | 25 520                         | 59.9                   | 6.6                                                         |
| ≥85                | 31 778                         | 66.2                   |                                                             |

Provisional COVID-19 deaths by age: https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Sex-Age-and-S9bhg-hcku; accessed 14 June 2020. Data through 10 June 2020. US Census 2019 estimates.

Abbreviation: COVID-19, coronavirus disease 2019.

In summary, asymptomatic transmission likely represents a substantial portion of total new infections, such that novel coronavirus IFRs are lower than some respiratory pathogens, although higher than for pandemic influenza [41]. Education and adherence may be most challenging in the very young student, as well as in the “invincible” adolescent, so how to enlist children themselves as allies in control of COVID-19 is a vital challenge. A more nuanced view of risk helps us maximize safety in reopening schools at every level of instruction, from preschool to university. While we should not be paralyzed with fear for our children (polio or measles are far worse), the COVID-19 IFR is still far higher than for influenza. Neither exaggerated fears for our children (Table 1) nor naïveté as to the menace of resurgent disease [42] among the most vulnerable are appropriate.

Notes

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References

1. Hui DSC, Zamula A. Severe acute respiratory syndrome: historical, epidemiologic, and clinical features. Infect Dis Clin North Am 2019; 33:869–89.
2. Bradley BT, Bryan A. Emerging respiratory infections: the infectious disease pathology of SARS, MERS, pandemic influenza, and Legionella. Semin Diag Pathol 2019; 36:152–9.
3. Banerjee A, Kulcsar K, Misra V, Friesen M, Mossman K, Bats and coronaviruses. Viruses 2019; 11:41.
4. Cantan B, Luyt CE, Martin-Loeches I. Influenza infections and emergent viral infections in intensive care unit. Semin Respir Crit Care Med 2019; 40:488–97.
5. Strebel PM, Orenstein WA. Measles. N Engl J Med 2019; 381:349–57.
6. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ 2019; 3665021.
7. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. Ann Intern Med 2020. Published online June 3, 2020. doi: 10.7326/M20-3012.
8. Nishiyama H, Kobayashi T, Miyama T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis 2020; 94:154–5.
9. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill 2020; 25:2000180.
10. Fernandez M. WHO walks back comments on asymptomatic transmission of coronavirus. Axios, June 9, 2020. Available at: https://www.axios.com/who-asymptomatic-coronavirus-69c56ec3-41e0-4e77-ab2a-d66761b4c7f.html. Accessed 12 June 2020.
11. He X, Lau EYH, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020; 26:672–5.
12. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-19. Nature 2020; 581:465–9.
13. Jing QL, Liu MJ, Yuan J, et al. Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. Lancet Infect Dis 2020; Published online June 3, 2020. doi: 10.1016/S1473-3099(20)30471-0.
14. Savvides C, Siegel R. Asymptomatic and presymptomatic transmission of SARS-CoV-2: a systematic review. medRxiv [Preprint]. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7310638/. Accessed 29 June 2020.
15. Edwards CH, Tomba GS, Sonbo Kristiansen I, White R, de Blasio BF. Evaluating costs and health consequences of sick leave strategies against pandemic and seasonal influenza in Norway using a dynamic model. BMJ Open 2019; 9:e027832.
16. Xue Y, Kristiansen IS, de Blasio BF. Dynamic modelling of costs and health consequences of school closure during an influenza pandemic. BMC Public Health 2012; 12:962.
17. Bleser WK, Miranda PY, Salmon DA. Child influenza vaccination and adult work loss: reduced sick leave use only in adults with paid sick leave. Am J Prev Med 2019; 56:251–261.
18. Pourbohloul B, Meyers LA, Skowronski DM, Krajden M, Patrick DM, Brunham RC. Modeling control strategies of respiratory pathogens. Emerg Infect Dis 2005; 11:1249–56.

19. West R, Michie S, Rubin GJ, Amlôt R. Applying principles of behaviour change to reduce SARS-CoV-2 transmission. Nat Hum Behav 2020; 4:451–9.

20. Chu DK, Akl EA, Duda S, et al. Physical distancing. West R, Michie S, Rubin GJ, Amlôt R. Applying principles of behaviour change to reduce SARS-CoV-2 transmission. Nat Hum Behav 2020; 4:451–9.

21. Wang Y, Tian H, Zhang L, et al. Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China. BMJ Glob Health 2020; 5:e002794.

22. Abaluck J, Chevalier JA, Christakis NA, et al. The case for universal cloth mask adoption and policies to increase supply of medical masks for health workers. SSRN: Social Science Research Network, April 1, 2020. Available at: https://ssrn.com/abstract=3567438 or http://dx.doi.org/10.2139/ssrn.3567438, Accessed 14 June 2020.

23. Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ. Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc Nail Acad Sci USA. Available at: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-23-united-states/. Accessed 29 May 2020.

24. Eikenberry SE, Mancuso M, Iboi E, et al. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. Infect Dis Model 2020; 5:283–308.

25. Aleta A, Martin-Corrall D, Pastore Y, et al. Modeling the impact of social distancing, testing, contact tracing and household quarantine on second-wave scenarios of the COVID-19 epidemic. medRxiv [Preprint]. May 18, 2020. doi: 10.1101/2020.05.05.20092841. Accessed 29 June 2020.

26. Weinberger DM, Chen J, Cohen T, et al. Estimating the early death toll of COVID-19 in the United States. JAMA Int Med. In press.

27. Lipstitch M, Donnelly CA, Fraser C, et al. Potential biases in estimating absolute and relative case-fatality risks during outbreaks. PLoS Negl Trop Dis 2019; 9:e0003846.

28. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. Published online March 23, 2020. doi: 10.1001/jama.2020.4683.

29. Kelly H, Cowling BJ. Case fatality: rate, ratio, or risk? Epidemiology 2013; 24:622–3.

30. Bendavid E, Mulaney R, Sood N, et al. COVID-19 antibody seroprevalence in Santa Clara County, California. medRxiv [Preprint]. April 14, 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.04.14.20062463v2. Accessed 29 June 2020.

31. Santa Clara County Public Health Coronavirus (COVID-19) Data Dashboard. Available at: https://www.sccgov.org/sites/covid19/Pages/dashboard.aspx. Accessed 29 May 2020.

32. Verity R, Okell LC, Dorigatti I, et al. Estimates of the case-fatality rate of COVID-19 in Italy. JAMA. Published online March 23, 2020. doi: 10.1001/jama.2020.4683.

33. Unwin HJ, Mishra S, Bradley VC, et al. State-level tracking of COVID-19 in the United States. Available at: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-23-united-states/. Accessed 29 May 2020.

34. Ioannidis J. The infection fatality rate of COVID-19 inferred from seroprevalence data. medRxiv [Preprint]. June 8, 2020. Available at: https://doi.org/10.1101/2020.05.13.20101253.

35. Giorgi GV, Kelly H, Ip DK, Wu JT, Leung GM, Cowling BJ. Case fatality risk of influenza A (H1N1pdm09): a systematic review. Epidemiology 2013; 24:830–41.

36. Presanis AM, De Angelis D, Hagy A, et al; New York City Swine Flu Investigation Team. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. PLoS Med 2009; 6:e1000207.

37. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020; 145:e20200702.

38. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020; 109:1088–95.

39. Walker DM, Tolentino VR. COVID-19: the effects on the practice of pediatric emergency medicine. Pediatr Emerg Med Pract 2020; 17:1–15.

40. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008; 5:e74.

41. Hadler J, Konty K, McVeigh KH, et al. Case fatality rates based on population estimates of influenza-like illness due to novel H1N1 influenza: New York City, May-June 2009. PLoS One 2010; 5:e11677.

42. Basu Z. Trump contradicts health officials on who can get a coronavirus test. Axios, May 11, 2020. Available at: https://www.axios.com/trump-coronavirus-testing-giroir-d83b4703-6d23-47ac-974e-972a868c85702.html. Accessed 12 June 2020.