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INVITED COMMENTARY

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 repiratory 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.

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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 [25]. 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 greater proportion of elderly afflicted in Italy [28]. A CFR is useful for measuring health-systems metrics (eg, delayed time to care, influence of comorbidities, or quality of healthcare), but they overestimate true mortality risks [29]. Surveys can guide more accurate assessments of the infection fatality risk (IFR; which also can be a rate over a defined time period), or risk of death among those symptomatically or asymptomatically infected, which is arguably more meaningful to considerations of societal reopening.

A Santa Clara County, California, quasi-representative Facebook-based survey of residents in early April 2020 suggested a range of 48 000–81 000 infected persons, or a population prevalence of 2.5–4.2% [30]. There were 140 deaths from COVID-19 as of 29 May 2020 [31]. While calculations are imperfect given time lags [32], the estimated IFR would be 0.17–0.29%.

The IFR is always lower than the CFR for the respiratory viruses. The CFR includes persons tested in the denominator, with symptomatic persons far better represented. The IFR is based on population-level denominator estimates, typically from surveys, such that the denominator better estimates the true infections, many of which would have been asymptomatic (or only mildly symptomatic) and would not have presented for testing. Epidemiologists and public health modelers use IFR to assess true lethality of a given infectious agent. Healthcare providers use CFR to assess quality of care and timeliness of clinical presentation and quality of care. When more representative, population-based serosurveys are available [33] and the true IFR can be estimated [34], we project that a United States–wide IFR of 0.1–1% will be confirmed. To put this into perspective, if we were to assume that approximately 60% of the population will eventually be infected as we gradually approach the herd immunity threshold (=1 – 1/R_0) over several years without a vaccine or effective 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 ($0.6 \times 0.005 \times 331\,000\,000$) 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 1–10/100 000 estimates of the IFR for the 2009 pandemic influenza H1N1pdm09 virus [35]. Better IFR estimates are needed with more valid, accessible, and affordable point-of-care diagnostics. We believe that therapies and vaccines are forthcoming, but these calculations remind us of the urgency of maintaining physical distancing, face covering, hand/face/surface hygiene, testing/quarantine, and crowd control until new tools for therapy and prevention are available and deployed.

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		
5–14	13		
15–24	116	0.79	26.7
25–34	640		
35–44	1649	6.5	25.2
45–54	4588		
55–64	11 439	32.7	22.6
65–74	19 857		
75–84	25 520	59.9	6.6
≥85	31 778		

Provisional COVID-19 deaths by age: https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Sex-Age-and-S/9bhg-hcku; accessed 14 June 2020. Data through 10 June 2020. US Census 2019 estimates.
Abbreviation: COVID-19, coronavirus disease 2019.

given community suggest the benefits of such an approach, and practice aggressive distancing, hygiene, and mask use in the school setting. Universal flu vaccine is a must, to minimize influenza burdens on schools in the December–March time frame (in the northern temperate zones).

Costs will be incurred for personal protective equipment such as masks (including pediatric sizes), shields (advisable for close-in work, as with a science or art class), and gloves for cleaning. Logistics can be altered, as with one-way flow in corridors and stairwells. Heating, ventilation, and air conditioning (HVAC) systems can be reconfigured and adjusted to increase outdoor air exchange and/or filtering of air. Gymnasiums or lunchrooms or libraries can be used as classrooms to improve physical distancing. Outdoor activities (and even outdoor classrooms) can be encouraged. Issues around music, arts, drama, and sports are complex. A myriad of risk-reduction methods can be used, acknowledging that risk of serious illness or death is most compelling for the contacts of infected students (both symptomatic and asymptomatic) far more than the students themselves. Immunologically vulnerable students may be best taught through distance-learning settings. Children and parents/guardians and teachers/staff all can be educated as to why and how to stay safe.

In summary, asymptomatic transmission likely represents a substantial proportion 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 naiveté as to the menace of resurgent disease [42] among the most vulnerable are appropriate.

Notes

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