An Evidence Base for School Health Policy during the COVID-19 Pandemic

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Objective: Children represent a small fraction of confirmed COVID-19 cases, with a low case fatality rate (CFR). In this paper, we lay out an evidence-based policy for reopening schools. **Methods:** We gathered age-specific COVID-19 case counts and identified mortality data for 14 countries. Dose-response meta-analysis was used to examine the relationship of the incremental case fatality rate (CFR) to age. In addition, an evidence-to-decision framework (EtD) was used to correlate the dose-response data with other epidemiological characteristics of COVID-19 in childhood. **Results:** In the dose-response analysis, we found that there was an almost negligible fatality below age 18. CFR rose little between ages 5 to 50 years. The confidence intervals were narrow, suggesting relative homogeneity across countries. Further data suggested decreased childhood transmission from respiratory droplets and a low viral load among children. **Conclusions:** Opening up schools and kindergartens is unlikely to impact COVID-19 case or mortality rates in both the child and adult populations. We outline a robust plan for schools that recommends that general principles not be micromanaged, with authority left to schools and monitored by public health authorities.

Key words: COVID-19; coronavirus; SARS-CoV-2; communicable disease; child & adolescent health; child transmission; school reopening policy
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Coronavirus disease 2019 (COVID-19) is communicable disease that was detected in Wuhan, China, in late 2019. Within a short time, it spread both rapidly and globally.[1,2] It is currently a world challenging pandemic that lacks a specific treatment. The presentation of disease can vary from being asymptomatic to varying degrees of severity of illness which may lead to acute respiratory distress syndrome (ARDS) and death.[3] Data to date indicates that children represent a small fraction of confirmed COVID-19 cases; less than 2% of reported infections in China, Italy, and the United States have been in people under 18 years old. In addition, the case fatality rate (CFR) is low in children due to a variety of possible factors.[4]

As the pandemic evolves worldwide, the following urgent questions need to be answered regarding children:

- How is COVID-19 affecting children?
- Are they getting the disease in a milder or asymptomatic form?
- Are they fully resistant to the disease?
- Do children play a role in the virus circulation and transmission to adult?

Answers to these 4 questions are needed to aid

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evidence-based policy-related decision-making for countries worldwide.

METHODS

The evidence in this paper was generated using a rapid evidence-to-decision framework (EtD) combined with a search on PubMed, pre-print sites, Google Scholar, and an analysis of publicly available data. The publicly available data relate to age-specific COVID-19 case counts and identified deaths gathered for 14 countries, including 9 European countries (Austria, Ireland, Netherlands, Norway, Switzerland, Sweden, Italy, Portugal, Spain), 4 Asian countries (China, South Korea, Qatar, Japan) and one from the pacific region (Australia). Data were extracted from either the country's respective surveillance system or its most recent situational reports for COVID-19 provided by health authorities as of October 2020.[4-16] Data for Qatar was sourced from the Ministry of Public Health Scientific Research and Reference Taskforce (SRRT) meeting on June 1, 2020. The data extraction process involved download of aggregate data from the sources mentioned in terms of incidence and mortality. Countries selected were based on data availability in the form required in the time period of this paper that were submitted in a report format to the SRRT of the Qatar ministry of Public Health in June 2020. PubMed searches were used to identify full text papers of interest to elucidate; search criteria were broad and included synonyms for children, childhood, and infancy as well as COVID19 and SARS-CoV-2. Relevant full text papers were retrieved based on abstract review.

Data Analysis

The publicly available data were used to look at the primary role of age on the severity of the disease, and ultimately, its fatality.[17] This was done by examining the incremental age-specific CFR when pooled across countries as this would give information regarding the homogeneity (or not) of these age-specific rates. The latter are expected to be relatively heterogenous if age is not the key driver of fatality as we would not expect the various risk factors to be consistent across countries by age-group.[18-20] If this variation is driven by age, and there is some evidence that this is the main driver of fatality in COVID-19,[21] then we can hypothesize the possibility of age-related physiological changes that the virus can take advantage of increasing with age, and therefore, expect this pooled analysis of incremental CFR will demonstrate homogenous results across countries when a dose-response analysis is done using age as the "dose." If confirmed, this information will explain why children get milder disease and can quantify the expected fatality in childhood. The baseline for all countries was an average age of 5 years. The age-specific CFR was computed as the percentage of deaths out of the detected cases within an age-group. Variance of the CFR was computed as shown in the equation below.[22]

$$SE_{CFRdiff} = \sqrt{\frac{a \times b}{(a+b)^3} + \frac{c \times d}{(c+d)^3}}$$

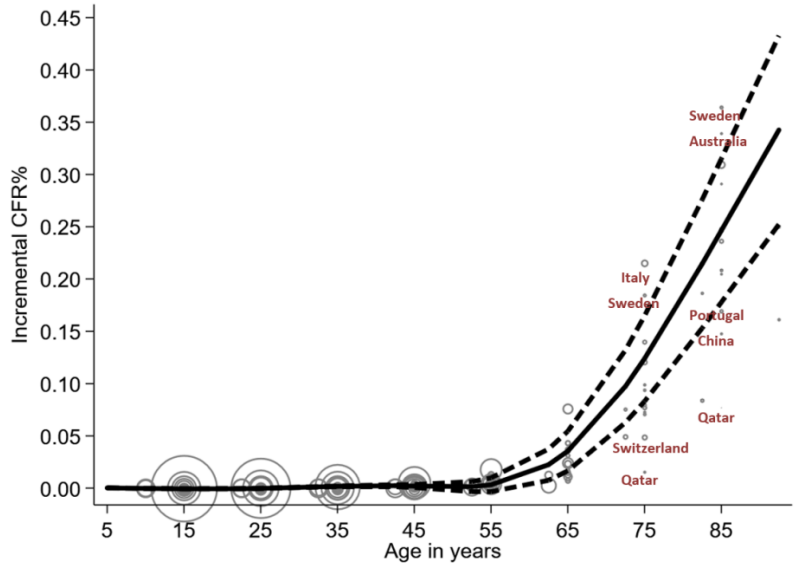
In this equation, d and c are the numbers of deaths and cases respectively for a particular age-group and a and b are the numbers for the 5-year average age. A dose response meta-analysis (DRMA) was conducted as a one-step procedure and we fit age and incremental CFR into an inverse variance weighted linear robust error meta-regression model using restricted cubic splines with 5 knots to approximate the potential non-linear relationship.[23] The weights were based on the variance of the incremental difference in CFR computed as the sum of the 2 age-specific CFR variances. We used Stata MP 15 (StataCorp, College Station, TX) for the analysis, with confidence levels of 95%.

RESULTS

COVID-19 Fatality in Children versus Adults

The dose-response analysis found that there was an almost negligible fatality below age 18. There were 591,445 COVID-19 cases out of which 42,286 fatalities were recorded across 14 countries included in the analysis. Results from the DRMA demonstrated that the CFR rises little between average ages 5 to 50 years. There was a non-linear relationship between age and CFR and a higher CFR was observed as age increased with the rise commencing at age 50-55 years. Thereafter, the CFR increases much more between the ages of 55 and 60 years, and more steeply thereafter (approximately 1% increase per year). The confidence intervals were relatively narrow suggesting homogeneity across countries (Figure 1). These results highlight

Figure 1
Relationship of the Incremental Case Fatality Rate to Age



Note.
Continuous line is the pooled estimate of trend and the dashed lines depict the 95% confidence interval. Based on our findings, it is unlikely that there are any transmission dynamics related or mortality related differences between elementary/primary versus secondary schoolchildren in relation to the aspects discussed above.

the fact that, although the CFR is thought to vary with the underlying health status of the specific population (eg, the presence of multiple comorbidities),[24,25] all countries were remarkably homogenous (as judged by narrow confidence intervals) in terms of CFR increment with age. If we view age as a proxy for underlying risk factors for death, it is tempting to conclude that this is an effect of other age-related risk-factors such as reduced immunity and comorbidities. However, it is exceedingly unlikely that across countries, the proportions with such risk factors by age group are similar. Therefore, we need to consider that age could be a primary driver of the CFR across the world, possibly indicating that age leads to physiological changes in some area that the virus can then leverage to exaggerate the inflammatory response.

A final point is that multisystem inflammatory syndrome in children (MIS-C), which is a Kawasaki-like pediatric illness that affects heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal organs, has been reported in childhood.[26] Children can develop MIS-C despite an asymptomatic course of COVID19. MIS-C typically manifests 3-4 weeks after SARS-CoV-2 infection and may explain why many children had positive antibodies to SARS- CoV-2, but negative RT-PCR at the time of MIS-C evaluation.[26] About half of individuals who developed the inflammatory syndrome did not have any underlying medical conditions.[26] This syndrome is rare and predominantly affects obese children over age 1 year.

Are Children More Likely to be Asymptomatic or Have Milder Disease?

Covid-19 is such a threat[27] because it can kill healthy adults in addition to elderly people with existing health problems and because it is transmitted efficiently with an infected person spreading the disease to 2 or 3 others (R naught "R0" about 2-3). Many people will shed the virus when only mildly ill or even when they are pre-symptomatic,[28] meaning the asymptomatic phase of the disease. Such cases may be considered to have asymptom-

atic infection, but they usually, in the majority of cases, end up being pre-symptomatic on the date of identification/report but do go on to develop symptomatic disease. The proportion of truly asymptomatic infections is unclear but appears to be relatively rare[29] and does not appear to be a major driver of transmission in the ongoing pandemic.[30] Most of such patients are identified through contact tracing and will have some clinical progression on follow-up. As an example, in a study of 23 patients who tested positive, 13 had asymptomatic infection, 10 of whom developed symptoms 7 days later.[30] In another study of 24 asymptomatic patients identified through contact tracing, only 7 remained free of clinical abnormalities, were younger (median 14 years), and had clearance of virus within 2-15 days;[31] the other 17 developed clinical or imaging evidence of disease.

The most common symptoms that pre-symptomatic patients go on to develop are fever (almost everyone), fatigue, and dry cough. However, fever might be low grade < 100.4°F/38°C in up to one-fifth of patients (especially younger ones). Although not highlighted in the initial cohort studies from China, smell and taste abnormalities (eg anosmia and dysgeusia) also have been reported as common symptoms in patients with COVID-19. Why some infections are truly asymptomatic or very mild is unknown.

Age seems to be a key factor and even symptomatic infection in children appears to be mild.[32] In a study of 10 children in China, symptom onset from exposure was within 2-10 days and clinical illness was mild – 8 had fever and the 2 without fever had a cough. Another report of 36 pediatric patients concurred with mild or moderate type of COVID-19, and there is a danger that the large proportion of mild cases may lead to difficulty in identifying cases or missed cases.[33]

The milder cases in younger patients are postulated to be tied to the aging lung environment where aged lungs counter the usual immune reaction with some tamping down of inflammation to avoid overreacting to environmental pollutants.[34] Therefore, the innate response is delayed in the elderly, ends up playing catch-up, and is exuberant leading to severe disease. There are other explanations, but by and large, children are able to clear the infection more efficiently and rapidly.[34]

Transmission Dynamics in Children

There is a growing body of evidence suggesting that children are at lower risk of getting infected.[35] Others say the incidence of infection in children is lower than in adults, partly because they have not been exposed to the virus as much — especially with many schools closed. Children do not get tested as often as adults, because they tend to have mild or no symptoms. In the municipality of Vo' in northern Italy, 86% of the population (2812 people) were tested after a resident died early on in the epidemic. All 217 children aged 10 or under tested negative. Of the 250 young people aged 11-20 who were screened, 1.2% were positive, compared with 3% for those 21 years and older.[36]

Viral Shedding

A study that examined viral shedding in asymptomatic cases found that children aged 0-14 years were overrepresented in asymptomatic carriers and that asymptomatic carriers had lower peak immunoglobulin M against COVID-19, but shorter ribonucleic acid (RNA) negative conversion.[37] The conversion was 12 days versus 16 days in pre-symptomatic and symptomatic COVID-19 patients.

Levels of virus in the respiratory tract, the main route via which the pathogen is transmitted, do not appear significantly different across age groups, in a study published by Christian Drosten, Director of the Institute of Virology at Berlin's Charite hospital.[38] However, translating the logarithmic viral load data into actual numbers yielded the following PCR counts for individuals positive for COVID-19 – 43,000 for those aged 1-10 years, 63,000 for 11-20 years, 183,000 for 21-30 years, and 164,000 for 31-40 years. When the authors tested the PCR viral count differences using the Kruskal-Wallis test they found a p-value of .008, which indicated a difference between the age groups.

On the other hand, data show that initial viral load (VL) at diagnosis in symptomatic children is comparable to those in adults, and that symptomatic children of all ages shed infectious virus in early acute illness.[39] Infectious virus isolation success was largely comparable to that of adults, although 2 specimens yielded an isolate at a lower VL (1.2 x 104 and 1.4 x 105 copies/ml) than what was observed in adults. COVID-19 shedding patterns of culture-competent virus in symptomatic children

resemble those observed in adults. Therefore, transmission of COVID-19 from children is biologically plausible. Considering the relatively low frequency of infected children at this time, biological or other unknown factors could reduce transmission in this population. Both large serological investigations and systematic surveillance of acute respiratory diseases are needed to understand the role of children in this new pandemic.

Risk from Children

We found a strong association between disease severity and COVID-19 transmission.[40] The symptom linked to an increased risk of disease transmission was fever, but other symptoms like cough, fatigue, or myalgia are not linked to a higher risk of transmission. In the Netherlands, the tracing of more than 700 contacts of patients with COVID-19 showed different infection rates depending on the patient's age.[41] For patients aged 18 and under, none of their contacts tested positive. In patients 19 years or older, however, 9% of their contacts were positive. School and daycare closures also could explain why children are not often the main source of infection with COVID-19. Other respiratory viruses can transmit from adults to children and back.

One study examined households with confirmed COVID-19 cases in Shenzhen, China.[42] Researchers found that children younger than 10 were just as likely as adults to get infected, but less likely to have severe symptoms. Another study analysed data from Hunan,[43] where the contacts of people with known infections had been traced and tested for the virus. The authors found that for every infected child under the age of 15, there were close to 3 people infected between the ages of 20 and 64. A third study of a cluster of cases in the French Alps describes one 9-year-old who attended 3 schools and a skiing class while showing symptoms of COVID-19, but did not infect a single person.[44] The boy had only mild symptoms and when tested was found to have levels of virus that were barely detectable. The low level of infection is thought to explain why he did not infect other people.

Finally, a systematic review that included 45 scientific papers concluded the following:[45]

- Children make up a small percentage of COVID-19 cases.
- They tend to have milder disease, or no symptoms and household transmission studies show they are rarely the index cases and seldom cause outbreaks.
- Even asymptomatic children can have viral loads but opening schools and kindergartens will not have an impact on the bigger picture of mortality.

Evidence from Re-opened Schools

Denmark was the first country to reopen schools in Europe, and others such as Norway, Germany, France, and the Netherlands followed. In Denmark, the virus's reproduction number rose from 0.6 to 1.0 after opening schools, but came down again within a week.[41]

In New South Wales (NSW) in Australia, schools have remained open. Analysis of 18 cases that occurred in 15 schools showed that of 735 children who had close contact, only 2 (0.3%) were infected. None of the 128 staff members who had close contact were infected.[46] The findings from a detailed Australian investigation suggests that spread of COVID-19 within NSW schools has been limited.[47] COVID-19 transmission in children in schools appears considerably less than seen for other respiratory viruses, such as influenza. In contrast to influenza, data from both virus and antibody testing to date suggests that children are not the primary drivers of the transmission of COVID-19 in schools or in the community. This is consistent with data from international studies showing low rates of disease in children. Data from the whole of NSW also demonstrate children (aged < 19 years) represent 4% of all cases of COVID-19 despite being approximately 23% of the population.

IMPLICATIONS FOR HEALTH BEHAVIOR OR POLICY

As initially suspected, we now have compelling evidence to support the conclusion that children with COVID-19 demonstrate only mild symptoms and rapidly recover in less than 10 days, while some remain asymptomatic. It is also evident that MIS-C is rare. The compilation of evidence suggests that transmission dynamics seem to be different between children and adults, and our interpretation of the evidence is that droplet transmission is a less likely route of spread of infection in children. Based on the evidence, we hypothesize that transmission through

surface contamination might play a role in children, based on the evidence suggesting that person-to-person contact in children does not play as significant of a role in disease spread as it does among adults. We suspect that the most likely transmission type among children is surface contamination.

It is now clear that children infected with COVID-19 have a lower viral load than adults in the respiratory tract. However, despite this finding, sick children should not attend school, and, as long as schools and kindergartens only contain healthy children, they should not become nodes of disease transmission.

School-going children must keep social distancing from grandparents and similar-aged household contacts because it is clear based on our analysis that age is the most important risk factor for severe disease; thus, we do not make a recommendation regarding parents with type 2 diabetes or obesity and stick to age as a more significant proxy for comorbidity.

These changes are easily implementable by schools and what may aid uptake is for schools to receive a notice to confirm their steps taken to comply with the measures emerging from this evidence base. These include:

- A mechanism to report contact details of symptomatic kids (fever, cough or any other respiratory symptom.
- Adequate infection control measures including morning check for symptomatic kids and temperature checks.
- Adequate social distancing in seating – physically spacing of kids in class.
- Provision of sanitary facilities for hand hygiene during operating hours in class and corridors and establish a hand hygiene routine.
- Staggering of school classes (opening and closure times) at different levels to avoid crowding at drop-off and pick-up including provision of a crowd management plan.
- Avoidance of mingling of each class level with other classes to keep in their bubble (eg, by staggering breaks and keeping these outdoors).
- Preventive measures to protect their vulnerable employees when they are at increased exposure to students with COVID-19 infection. These include masks, distancing regulations and hand sanitizing equipment.
- Information to families about keeping symptomatic children home.

Once these steps are taken, opening up schools and kindergartens is unlikely to impact COVID-19 case or mortality rates in the adult population. The plans for schools should not be micromanaged but left to the schools; the role of the ministry should be to assess school plans against compliance with the advice. However there is a need for evidence to make decisions, including research on the effects of reopening schools on community spread of COVID-19 and airborne transmission of the virus along with the relative effectiveness of strategies for mitigating the spread and the need for addressing these research questions concomitantly with the process of reopening schools. Health services are encouraged to put forward a monitoring scheme for schools' compliance against these principles. Perhaps environmental monitoring of surface contamination or sewage may be piloted in schools after re-opening as an added measure to assess trends.

The emergence of variants of SARS-CoV-2 has renewed discussion about school reopening. Based on knowledge to date, the World Health Organization[48] published the following conclusions regarding school reopening in January 2021:

- School closure should be implemented as a last resort, be temporary and only at a local level in areas with intense transmission.
- Authorities should check for new guidance, particularly with respect to the appearance of new and possibly more transmissible variants.
- In low-transmission areas, schools are unlikely to drive infection; in areas with widespread transmission, protective measures in schools are essential.
- Schools need outbreak prevention and management plans, including on ventilation, hand and surface cleaning, communication with parents, mask use, and physical distancing.
- Children aged 12 and older should wear a mask under the same conditions as adults. Physical distancing can be achieved by limiting class sizes, alternating shifts, and limiting mixing of classes.

- Stronger prevention measures might be necessary in secondary schools, and adolescents should limit their exposure risk outside school.
- Teachers are more likely to be infected outside schools than inside.
- During school closures, remote learning should be set up, regular schools services such as meals and immunization should be maintained, while mental health support should be enhanced.

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Human Subjects Approval Statement

This research project is based on previously published data, and it was exempted from review by Qatar University Institutional Review Board (QU-IRB). Research Ethics Approval Number is: QU-IRB 1434-E/20.

Conflict of Interest Disclosure Statement

The authors of this article declare they have no conflicts of interest.

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