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Children are unlikely to be the main drivers of the COVID-19 pandemic – a systematic review

Short title: Children and COVID-19 transmission

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Abstract

Aim: Many countries have closed schools and kindergartens to minimise COVID-19, but the role that children play in disease transmission is unclear.

Methods: A systematic literature review of the MEDLINE and EMBASE databases and medRxiv/bioRxiv preprint servers to 11 May 2020 identified published and unpublished papers on COVID-19 transmission by children.

Results: We identified 700 scientific papers and letters and 47 full texts were studied in detail. Children accounted for a small fraction of COVID-19 cases and mostly had social contacts with peers or parents, rather than older people at risk of severe disease. Data on viral loads were scarce, but indicated that children may have lower levels than adults, partly because they often have fewer symptoms, and this should decrease the transmission risk. Household transmission studies showed that children were rarely the index case and case studies suggested that children with COVID-19 seldom caused outbreaks. However, it is highly likely that children can transmit the SARS-COV-2 virus, which causes COVID-19, and even asymptomatic children can have viral loads.

Conclusion: Children are unlikely to be the main drivers of the pandemic. Opening up schools and kindergartens is unlikely to impact COVID-19 mortality rates in older people.

Key Words: Children, Coronavirus, COVID-19, Pandemic, Transmission,

KEY NOTES

- Children make up a small percentage of COVID-19 cases, but their role in transmission has been unclear and a systematic review was conducted.
- 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.

INTRODUCTION

In late 2019, a new highly infectious virus, severe acute respiratory syndrome coronavirus (SARS-CoV-2) was discovered in Wuhan, China[1]. The SARS-CoV-2 virus causes coronavirus disease 2019 (COVID-19), which typically presents with severe acute respiratory symptoms [2]. However, other manifestations, such as gastrointestinal symptoms,[3] and severe outcomes, including stroke, coagulation disorders and possibly hyperinflammation[4], have also been reported [5]. The World Health Organization (WHO) has classified the COVID-19 outbreak as a pandemic. By 11 May 2020, there had been more than 4,000,000 confirmed cases and nearly 300,000 deaths worldwide due to COVID-19[6].

Children often have a milder disease than adults and deaths are extremely rare[7], but children in many countries have been subjected to the same social confinement as adults. There is a growing interest in the role that children play in transmitting the virus that causes COVID-19 and this is referred to as COVID-19 transmission in this paper for the sake of simplicity. The issues around potential transmission by children has quickly become an issue, as countries need to know when to send children back to school as lock-down restrictions are eased. There have also been fears that opening up schools will lead to an increase in COVID-19 transmission[8].

However, the role of children in COVID-19 transmission is unclear. This paper reviews the current evidence on various aspects of COVID-19 transmission in children, following a systematic literature search of published papers in the MEDLINE and EMBASE databases. We also searched the medRxiv/bioRxiv preprint servers, which contain preprints, which are unpublished papers. This paper reviews the evidence for COVID-19 transmission *from* children and does not deal with adult-to-child transmission or intrauterine vertical transmission.

METHODS

Search process

Two experienced librarians at the Karolinska Institutet University Library, Stockholm, Sweden, performed a systematic literature review of the MEDLINE and EMBASE databases on 11 May 2020 to identify papers on COVID-19 transmission in children (Appendix S1). We used a broad range of search terms, such as transmission and transmit*, attack rate, infect*, incidence and prevalence, which were combined with childhood age keywords and words such as preschool, pupil and kindergarten. The search yielded 381 hits in MEDLINE and 381 hits in EMBASE. Although the numbers were identical for the two databases, they related to different publications. Removing the duplicates identified 508 scientific papers and letters. The titles and abstracts were screened and 40 publications were read in detail[7 9-47].

That search was complemented by a search of the medical preprint server medRxiv/bioRxiv on 12 May 2020, which yielded 192 unpublished preprints, including seven that were deemed relevant [48-54] (Appendix S2). In addition, we identified two more relevant unpublished preprints[55 56] when we reviewed the references lists of the publications that were identified by this second search.

There was no pre-specified protocols prior to the review.

RESULTS

Viral loads and levels in children

An unpublished preprint from Charité - Universitätsmedizin, Berlin [55], that used real-time polymerase chain reaction (PCR), reported the viral loads for 3,712 patients positive for COVID-19 This preprint has generally been interpreted as demonstrating an equal viral load in children above the age of one year and adults. 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 0.008, which indicated a difference between the age groups. However, they did not formally point out which age groups had the lowest viral loads. The fact that their postdoc tests failed to attain statistical significance was probably due to the large number of pairwise comparisons they carried out, instead of comparing children versus adults. The percentage of cases that tested positive for COVID-19 in this German study was lower in children (3.0%) than in adults (5.5%)[55]. Lower viral loads were also found in in children with underlying diseases[55]. Importantly, the German study mainly tested symptomatic individuals [55], which is of less relevance to school openings and closures.

Zhang *et al* examined viral shedding in asymptomatic cases and 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. The conversion was 12 days versus 16 days in pre-symptomatic and symptomatic COVID-19 patients[53].

L'Huillier *et al* reported similar viral loads in symptomatic children and symptomatic adults, but failed to compare the children and adults statistically[50].

In a recent letter to *Lancet Infectious Diseases*, Liu *et al* [57] showed that patients with severe COVID-19 had an average viral load that was 60 times higher than mild cases. That study did not distinguish between children and adults.

Our literature review did not identify any viral load studies that specifically looked at asymptomatic children attending kindergartens and schools.

Symptoms and physical transmission

Infectious diseases can be transmitted in a number of ways. These include bloodborne diseases, such as human immunodeficiency viruses and Hepatitis B, which can also be vertically transmitted during pregnancy. They also include airborne transmission, as in measles, faecal transmission, as in rotavirus diseases, and the droplet transmission identified in diseases like COVID-19.

Droplet transmission can occur through contact with surfaces touched by an infected individual, but it is more likely to occur because of sneezing, coughing and close contact. Children have less symptoms, such as coughing and sneezing, than adults[58] and this could suggest that the actual physical transmission of disease is lower in this age group.

In an unpublished study from Guangzhou, China, Luo *et al* reviewed 4950 close contacts and examined them according to mode of contact and clinical characteristics, using logistic regression [56]. This study found a strong association between disease severity and COVID-19 transmission ($p<0.0001$). The symptoms linked to an increased risk of disease transmission were fever, but not a cough, fatigue or myalgia.

Viral transmission can also occur when individual touch their eyes, nose and throat, if the hand contains viral particles. Schools and kindergartens all over the world are currently implementing hygienic hand washing to counteract that risk. We did not find any studies that examined if these measures decreased COVID-19 transmissions in children. In addition, we did not find any studies that examined whether children could infect other people with COVID-19 through faecal transmission.

Who do children transmit their disease to?

Many children are socially active and when they are playing this often involves physical contact[59]. Earlier research on respiratory disease transmission suggest that school children primarily

interact with individuals of the same age,[59] rather than older people. More time spent in kindergartens and schools may, therefore, decrease their exposure to older people, such as grandparents, who are more likely to die from COVID-19.

Attack rates

Our literature search failed to identify any data on attack rates *from* children, namely the proportion of exposed individuals that go on to develop COVID-19. Other literature has stated that two studies examined attack rates from children to adults, but that does not seem to be the case[12 52].

In a Chinese study of 391 COVID-19 cases, children were as likely to be infected as adults from a household contact with COVID-19 [12]. However, this paper did not present data on the attack rate when the index case was a child (personal communication with co-author Lessler, 13 May 2020). The second study, by Mizumoto *et al*, only reported that children were less likely to become infected[52], not that they had a lower or higher attack rate.

Family clusters

There is now extensive literature on household transmission involving children [31 54 28 37] and these reported that children were less susceptible to COVID-19 than adults at home [31]. When a paper by Choi *et al,* published online on 6 April 2020, summarised the literature, they found no cases of child to child or child to adult transmission[16]. However, a few reports have described family clusters where a child was identified with COVID-19 first, followed by other family members who tested positive [45 13]. Zhang *et al* reported a three-month-old child who was diagnosed prior to her parents [45], although it has been argued that this may have been due to a shorter incubation period in the child rather than the child being the index case in this family[15]. A study by Cai et al, cited in a paper by Cao *et al*[13], described a seven-year-old boy who is believed to have infected his mother with COVID-19 after a visit to Wuhan.

In an unpublished preprint, Zhu *et al* identified 31 household transmission clusters that children were involved in, in China, Singapore, the USA, Vietnam and South Korea[54]. In three (9.7%) households, the child was the index case. The authors compared this with household transmissions during the H5N1 influenza virus, where a child was the index case in 54% of households[54]. Zhu *et al* also cited two other studies of interest. One examined 66 family clusters and did not find any case where the child had been the index case. The other examined 419 household clusters and reported that there were no cases where the index individual was below age 15 years of age [54].

Real-world evidence

Real-world evidence points towards a limited spread of COVID-19 *between* children and *from* children. One nine-year-old boy attended three schools while symptomatic with COVID-19, but none of his 112 school contacts contracted the disease[17]. The Australian National Centre for Immunization Research in New South Wales described nine high-school students and nine staff with confirmed COVID-19. These 18 individuals had contact with 735 students and 128 staff and only two children may have contracted COVID-19 from these initial school cases, but no staff contracted COVID-19 from these 18 individuals[60]. So far there have been no reports of COVID-19 outbreaks in Swedish schools (personal communication, Anders Tegnell, State Epidemiologist, Sweden, 12 May 2020). This supports the argument that asymptomatic children attending schools are unlikely to spread the disease

DISCUSSION

This review showed that children constituted a small fraction of individuals with COVID-19[7] and that most had social contacts with peers or parents, rather than with older people who face a risk of severe disease. Data on viral loads were scarce, but those that were available indicated that children may have had lower levels than adults. Children tended to have milder or no respiratory symptoms and this probably decreased the risk of viral transmission. Household transmission studies showed that children were rarely the index case and case studies suggested that children with COVID-19 seldom caused outbreaks. Despite this, it also seems clear that asymptomatic children can have viral loads. It is also highly likely that children can transmit the disease.

Milder disease and potentially lower viral loads in children may prime adults who are infected, so that they develop a response to COVID-19 and are not overwhelmed by the infection. In the future, it would be interesting to explore if adults who have received the disease from a child are less likely to progress to severe disease than those adults who were infected by other adults.
It is notable that the German study by Jones *et al* found lower viral loads in children with underlying diseases[55]. Since underlying diseases do not protect against viral infections, one explanation could be that the clinical threshold for testing these children was lower than for children without pre-existing comorbidities, but it is also possible that these children were tested at a later stage, when viral levels had begun to declne[55]. There are now a number of reports that also suggest that children with comorbidities that test positive for COVID-19 have a good prognosis[36].

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. A small number of children may attend schools just before symptoms appear, because they do not realise that they are just about to become sick, but this should only account for a few cases. That said, more

studies are needed on viral loads in asymptomatic children, since data suggest that viral loads can be high in asymptomatic individuals, at least in elderly people[61].

The rationale for school closures is to limit the transmission of COVID-19 in society, but, as several authors have pointed out, the arguments put forward have not been compelling [10]. Although school closures may decrease the transmission of influenza, as children play a major role in the household transmission of influenza[62], this does not mean that school closures would limit COVID-19 transmission in society more than marginally. The adverse effects of school closures can include lack of education and disproportionally affect vulnerable and disadvantaged children. In addition, in some countries school nurses cater for the health needs of children, schools often offer subsidised free meals and they look after children for much of the day when parents work. Armitage *et al* have, therefore, suggested other measures than closing schools to decrease COVID-19 transmission, such as promoting hygiene and physical distancing in schools[10]. School closures also tend to increase child care obligations, especially of healthcare workers, as this group often have small children. Bayham and Fenichel have estimated that if mortality rates for COVID-19 increased by more than 17% - from 2.00% to 2.35% in their model - as a result of healthcare worker shortages, school closures would result in more deaths than the lives gained due to slower COVID-19 spread because of the school closures [11].

By now, it is clear that risk groups mainly consist of individuals aged 70 plus years and adults with certain underlying disorders, including cardiovascular disease, obesity and type 2 diabetes[2]. Opening up schools and kindergartens is unlikely to increase the transmission of COVID-19 to older people who need protection. Because children tend to have mild forms of the disease, if they infect other children this should not have an impact on the bigger picture of COVID-19 mortality. This review also found evidence that children primarily interact with peers of a similar age or with parents.

The main strength of this review was the systematic search of the MEDLINE and EMBASE databases, which identified more than 500 published scientific papers and letters, but also our

use of the medRxiv/bioRxiv preprint servers to identify unpublished preprints, which reflect the latest knowledge. However, unpublished preprints need to be interpreted with caution, because they have not yet undergone peer review. Given that the pandemic originated in China, a large proportion of the relevant papers concerned COVID-19 in that country and more data are needed from other countries.

It was beyond the scope of this review to examine factors that might protect people, including children, against COVID-19 transmission, such as wearing masks[63] and hand washing. In addition, the current paper did not explore the circumstances that predict such behaviour in children, as opposed to adults. Some data have indicated that the parents' socioeconomic background had an impact on wearing masks and hand washing [64]. Also, we did not include papers dealing exclusively with mathematical modelling [32 65 66].

CONCLUSION

The conclusion of this systematic review is that children are unlikely to be the main drivers of the pandemic. Opening up schools and kindergartens is unlikely to impact COVID-19 mortality rates in older people.

ABBREVIATIONS

COVID-19, coronavirus disease 2019;

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

PCR, polymerase chain reaction.

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CONFLICTS OF INTEREST

None.

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