Difference in SARS-CoV-2 attack rate between children and adults may reflect bias

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Brief summary

An apparent lower attack rate in children may reflect reduced exposure and methodological issues, including lower testing, rather than reduced biological susceptibility. Improvements in study design, data collection, and interpretation are required to better understand the epidemiology of paediatric COVID-19.

Abstract

The epidemiology of coronavirus disease 2019 (COVID-19) in children has been challenging to establish, owing to the high prevalence of asymptomatic infection in this population. Lower secondary attack rates in children compared to adults have been observed in household contact studies, but there is evidence this may reflect lower testing in children and reduced exposure, rather than a genuine difference in biological susceptibility. Additionally, children may shed infectious virus for a shorter period than adults and their antibody response may be less broad, with implications for both polymerase chain reaction and serological testing. Improvements in study design, data collection, and data interpretation are required to better understand the epidemiology of COVID-19 in children.

Key words

COVID-19, SARS-CoV-2, epidemiology, children

Text

The epidemiology of coronavirus disease 2019 (COVID-19) in children has been challenging to establish. It has been argued that children are less susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than adults, and play only a minor role in transmission.[1] A modelling study which analysed data from the first few months of the pandemic concluded that individuals aged under 20 years were approximately half as susceptible to infection as adults aged 20 years and older, and that interventions aimed at children and teenagers might only have a small effect.[2] However, these conclusions may be premature, and instead reflect the cryptic nature of the virus in children.

In stark contrast to adults, SARS-CoV-2 infection in children typically results in mild illness and mortality is very low.[3] The infection fatality ratio for children and adolescents is estimated to be 0.002%, compared to 0.1% for middle-aged adults, and ≥1% for adults aged ≥65 years.[4] However, long COVID (the presence of persistent symptoms following the acute phase of infection)[5] is under-appreciated in the paediatric population. In the United Kingdom, the 5-week prevalence of persistent symptoms may be as high as 12.9% (95% 10.4% - 16.0%) in children aged 2-11 years, compared to 22.1% (95% CI 21.2% - 23.2%) for the population overall.[6] Children may also be affected by a rare, multisystem inflammatory syndrome following infection with SARS-CoV-2.[7]

Nonetheless, asymptomatic infection is very common in children. Children are twice as likely as adults to be asymptomatic,[8] and the prevalence of asymptomatic infection may be as high as 50% in children and adolescents.[9] A study of paediatric cases from South Korea found most would probably have gone undetected had they not been tested as a consequence of contact tracing, and only 9% were diagnosed at symptom onset.[10] Symptom-based testing is therefore likely to miss paediatric cases.

Household contact studies have been characterised by marked heterogeneity in secondary attack rates. Some have reported children are much less likely to be infected than adults,[11] while others show similar attack rates.[12] However, some studies have only tested symptomatic contacts, and there is evidence children have been tested less than adults.[11] This represents an important source of differential bias. Paediatric cases may also be detectable for a shorter period than adult cases. In one prospective household contact study, serial polymerase chain reaction (PCR) testing revealed there was only a two-day window to identify one infected child.[13]

Given these challenges, serology may provide better insight into the susceptibility of children. A seroprevalence study of 6,098 persons aged ≥10 years conducted in a high-incidence area in Italy in May 2020, reported similar seropositivity in adolescents (25%) and young to middle-aged adults (23% - 26%).[14] Seropositivity was lower in those aged ≥60 years (18% - 22%), possibly reflecting high morbidity and mortality in this age group, and hence, survivorship bias. Symptomatic individuals and

their contacts were also tested by real-time PCR. Notably, the ratio between PCR-identified cases and those detected via serology was 1:7 for adolescents, compared to 1:3 for participants overall. The ratio was 1:1 in those aged ≥70 years, indicating marked age disparity with regard to the detection of cases.[14] A similar discrepancy was noted in a population-based study of over 11,000 children and adolescents in Bavaria, Germany, conducted between January and July 2020.[15] Seroprevalence was 6-fold higher than PCR-based testing had suggested. This is unsurprising, and infections in adults are also frequently under-detected. However, the study found no significant difference in seropositivity between those aged ≤6 years (0.84%), and those aged 7-18 years (0.98%). In contrast, official PCR-based testing had suggested younger children were much less affected (111 cases per 100,000 children aged ≤6 years, vs. 182 cases per 100,000 persons aged 7-18 years). Almost half of the seropositive children (47%) in this study had been asymptomatic.[15]

A repeated cross-sectional seroprevalence study of over 25,000 people in Brazil found a similar seroprevalence in children and teenagers (1.3% - 1.6%) and adults (0.6% - 1.9%) during the first survey in May 2020, but a higher seroprevalence in adults during the second survey in June 2020 (1.9% - 2.2% in children and teenagers vs. 2.1% - 3.7% in adults).[16] The increased seroprevalence in adults likely reflects greater exposure, since it was associated with an increase in the proportion of people leaving home each day.[16] This is consistent with data from China, which, at a time of widespread school closures, found persons aged 18-64 years were more likely to be infected outside the household, while children were more likely to be infected at home.[17] A seroprevalence study of over 61,000 people in Spain conducted between late April and early May 2020, found 3.4% of children had antibodies against SARS-CoV-2, compared to 4.4% - 6.0% of adults.[18] However, Spain's schools were closed for much of the year, and as such, these differences could reflect shielding. A household seroprevalence study (in which persons likely have more similar, but not equal exposure) conducted in Barcelona found seropositivity was similar between persons aged ≤14 years (17.6%) and those aged ≥15 years (18.7%).[19]

However, serology is not without limitations. The widespread use of serological testing is discouraged by the World Health Organisation, particularly in low-prevalence settings where false positives may become problematic,[20] but it likely has an important role to play in improving the quality of research. Household contact studies may be particularly enhanced, given the difficulty of identifying active infections in children, which limits the usefulness of PCR-based testing. However, because children demonstrate a less broad antibody response than adults, false negatives may be more likely.[21] In one intriguing case report, the three children of an infected couple repeatedly tested negative by PCR. However, IgG antibodies against the spike protein were found in plasma in one child, and anti-spike IgA in saliva in all three.[22] The authors noted routine virological and serological testing may fail to identify paediatric cases.[22]

These issues cast doubt on the conclusion of a recent systematic review and meta-analysis, which reported children are less susceptible to infection than adults.[23] An additional complication, which was not accounted for, is the influence of behavioural and environmental factors. Although the

authors of the meta-analysis hypothesised exposure may be similar for all household contacts, this is not supported by the literature. Partners of adult cases are more likely to be infected than other adults living in the same household.[24,25] Because schools have been closed for a considerable part of the year, adults have been more likely to be index cases than children. One would therefore expect higher secondary attack rates in adults owing to their closer physical contact with index cases, which does not necessarily imply lower biological susceptibility in children. Parents may also have tried to shield their children from infection. This may be particularly likely with regard to studies in which healthcare workers were over-represented.[26] Other studies demonstrate a clear influence of circumstantial factors. In a household study conducted in Singapore, children were twice as likely to be infected when their mother, rather than father, was the index case (11.1% vs. 6.7%).[27] A US study found children were more likely to be infected if they were children of the index case.[25]

An additional consideration with regard to determining exposure in household studies is the degree to which aerosol transmission occurs. If it were ubiquitous, exposure might be expected to be similar, and attack rates high, for all persons in the household. The fact that attack rates are higher in persons with close contact to index cases (e.g., spouses)[24,25] could suggest airborne transmission is infrequent. However, aerosols will be more concentrated at their source,[28] and so this does not rule out the airborne route. Additionally, some individuals may be "super-emitters" and biologically predisposed to emit more aerosols than others. In a study of the exhaled breath of 194 healthy subjects, it was found that 18% of participants accounted for 80% of the total number of aerosol particles produced.[29] This could mean that airborne transmission will also follow a Pareto distribution. There is some evidence to support this, with clustering observed within household studies. Ladhani et al. conducted a prospective seroprevalence study of the children of healthcare workers.[30] In a subset of this study, comprising 21 families in which at least one parent became infected, they noted marked clustering. Almost all children (95%) were seropositive in 9 families, while no children were seropositive in the other 12 families.[30] Aerosol transmission may therefore be an additional factor that could explain heterogeneity in household secondary attack rates.

The issues detailed so far, coupled with limited testing of children for much of the pandemic, may have created a perception that children are less susceptible to infection than in reality.[31] In the early stages of the pandemic, testing in many countries was restricted to people presenting with fever or respiratory symptoms who had recently returned from overseas travel or were known to have contact with a confirmed case. Although testing has since been expanded, children may present with atypical symptoms not meeting eligibility criteria. In some regions, children are still not routinely tested unless seriously ill.[32] Schools were also closed for much of the first year of the pandemic, markedly reducing children's exposure, and giving a misleading picture.

As previously noted, there may be a shorter window to detect cases in children compared to adults.[13] This may necessitate the use of additional methods to identify paediatric cases. Yuan et al. conducted a study to investigate the utility of anal swab testing for SARS-CoV-2.[33] They examined PCR test results for 212 children in Wuhan with suspected SARS-CoV-2 infection, from whom both throat and anal swabs were taken. Of the 78 children in which infection was subsequently confirmed, 24 (31%) were positive for both swabs, 37 (47%) only had positive throat swabs, and 17

(22%) only had positive anal swabs. Children who only had positive anal swabs were more likely to be asymptomatic than children who only had positive throat swabs (59% vs. 32%), although this did not reach statistical significance.[33] Anal swab testing could therefore be a useful adjunct to identify cases that would otherwise escape detection. Viral shedding in faeces appears to be prolonged compared to respiratory tract secretions,[34] and hence could provide a solution to the shorter window of detectability for paediatric cases.

Random testing also provides a much better picture of the extent to which children are involved in the pandemic. In contrast to early data - obtained during a period of widespread school closures - children currently account for a large proportion of cases. Random testing of the population in England indicates children and teenagers are now more likely to be infected than any other age group.[35] Government data also show children and teenagers in England are currently more likely to introduce the virus to households than adults, and are more than twice as likely to transmit the virus to other household members.[36]

The age-specific transmissibility of SARS-CoV-2 remains an important, unresolved question. Children have a similar (and possibly higher) viral load to adults,[37] but because children are more likely to be asymptomatic and may be infectious for a shorter period, it is reasonable to hypothesise the risk of transmission may be lower. However, any reduced risk may be offset by the high number of contacts children have at school. Contact tracing studies (conducted at a time of widespread school closures) suggest children and adults are similarly likely to transmit.[38,39]

In Victoria, Australia, 66% of infections in childcare centres and schools were limited to a single case.[8] This may seem reassuring, but must be interpreted in the context of the overdispersed nature of SARS-CoV-2 transmission. Between 5-20% of primary cases account for approximately 80% of secondary cases, and about 70% of people do not infect anyone.[39,40] Why so many people do not transmit is unclear, but it probably reflects a combination of biological and circumstantial factors, including opportunity, behaviour and environment (with some settings more conducive to transmission than others), biological predisposition to produce more or less aerosols, and the timing of infection. The Australian experience therefore does not suggest a reduced role for children in transmission, at least with respect to schools.

These observations stand in contrast to earlier conclusions about the role of children in the pandemic,[1] and suggest a need for re-evaluation. It is likely that children are more susceptible to SARS-CoV-2 infection than first thought, and they probably play an important role in community transmission. Improvements in study design, data collection, and data interpretation are required to better understand the epidemiology of COVID-19 in children.

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