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VIEWPOINT

Difference in Severe Acute Respiratory Syndrome Coronavirus 2 Attack Rate Between Children and Adults May Reflect Bias

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The epidemiology of coronavirus disease 2019 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 with adults have been observed in household contact studies, but there is evidence that this may reflect lower testing in children and reduced exposure, rather than a genuine difference in biological susceptibility. In addition, 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 coronavirus disease 2019 in children.

Keywords. COVID-19; SARS-CoV-2; epidemiology; children.

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 modeling study that analyzed data from the first few months of the pandemic concluded that individuals aged <20 years were approximately half as susceptible to infection as adults aged ≥20 years, 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 outcomes in adults, SARS-CoV-2 infection in children typically results in mild illness, and mortality rates are very low [3]. The infection fatality ratio for children and adolescents is estimated to be 0.002%, compared with 0.1% for middle-aged adults and ≥1% for adults aged ≥65 years [4]. However, "long COVID" (the presence of persistent symptoms after the acute phase of infection) [5] is underappreciated in the pediatric population. In the United Kingdom, the 5-week prevalence of persistent symptoms may be as high as 12.9% (95% confidence interval, 10.4%–16.0%) in children aged 2–11 years, compared with 22.1% (21.2%–23.2%) for the population overall [6]. Children may also be affected by a rare, multisystem inflammatory syndrome after 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 pediatric 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 pediatric cases.

Household contact studies have been characterized by marked heterogeneity in secondary attack rates. Some have reported that children are much less likely to be infected than adults [11], while others show similar attack rates [12]. However, some studies have tested only symptomatic contacts, and there is evidence that children have been tested less than adults [11]. This represents an important source of differential bias. Pediatric cases may also be detectable for a shorter period than adult cases. In 1 prospective household contact study, serial polymerase chain reaction (PCR) testing revealed that there was only a 2-day window to identify 1 infected child [13].

Given these challenges, serology may provide better insight into the susceptibility of children. A seroprevalence study of 6098 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 rates in this age group, and hence, survivorship bias. Symptomatic individuals and their contacts were also tested by means of real-time PCR. Notably, the ratio between PCR-identified cases and

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those detected with serology was 1:7 for adolescents, compared with 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 >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 underdetected. 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 that 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 >25 000 people in Brazil found similar seroprevalence in children and teenagers (1.3%–1.6%) and adults (0.6%–1.9%) during the first survey in May 2020 but 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, showed that 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 >61 000 people in Spain, conducted between late April and early May 2020, found that 3.4% of children had antibodies against SARS-CoV-2, compared with 4.4%–6.0% of adults [18]. However, Spain's schools were closed for much of the year, so these differences could reflect shielding. A household seroprevalence study (in which persons likely have more similar, but not equal, exposure) conducted in Barcelona found that seropositivity rates were 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 Organization, particularly in low-prevalence settings where false-positive results 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 an intriguing case report, the 3 children of an infected couple repeatedly tested negative by PCR. However, immunoglobulin G antibodies against the spike protein were found in plasma in 1 child, and anti-spike immunoglobulin A in saliva in all 3 [22]. The authors noted that routine virological and serological testing may fail to identify pediatric cases [22].

These issues cast doubt on the conclusion of a recent systematic review and meta-analysis, which reported that children are less susceptible to infection than adults [23]. An additional complication, which was not accounted for, is the influence of behavioral and environmental factors. Although the authors of the meta-analysis hypothesized that exposure may be similar for all household contacts, this is not supported by the literature. Partners of adult case patients 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 than children to be index case patients. One would therefore expect higher secondary attack rates in adults owing to their closer physical contact with index case patients, 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 overrepresented [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 patient (11.1% vs 6.7%, respectively) [27]. A US study found that children were more likely to be infected if they were children of the index patient [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 in close contact with index patients (eg, spouses) [24, 25] could suggest that airborne transmission is infrequent. However, aerosols will be more concentrated at their source [28], so this does not rule out the airborne route. In addition, some individuals may be "superemitters" 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 [30] conducted a prospective seroprevalence study of the children of healthcare workers. In a subset of this study, comprising 21 families in which ≥1 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 than in adults [13]. This may necessitate the use of additional methods to identify pediatric cases. Yuan et al [33] conducted a study to investigate the utility of anal swab sample testing for SARS-CoV-2. They examined PCR test results for 212 children in Wuhan with suspected SARS-CoV-2 infection, from whom both throat and anal swab samples were taken. Of the 78 children in whom infection was subsequently confirmed, both swab samples were positive in 24 (31%) , 37 (47%) had only positive throat swab samples, and 17 (22%) had only positive anal swab samples. Children who had only positive anal swab samples were more likely to be asymptomatic than those who had only positive throat swab samples (59% vs. 32%), although this difference did not reach statistical significance [33]. Anal swab sample testing could therefore be a useful adjunct in household contact studies to identify cases that would otherwise escape detection. Viral shedding in feces seems to be prolonged compared with respiratory tract secretions [34] and hence could provide a solution to the shorter window of detectability for pediatric cases.

Random testing is another technique that 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 that children and teenagers are now more likely to be infected than any other age group [35]. Government data also show that 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 hypothesize that their 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 that children and adults are similarly likely to transmit SARS-CoV-2 [38, 39].

In Victoria, Australia, 66% of infections in childcare centers 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% and 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 the virus is unclear, but it probably reflects a combination of biological and circumstantial factors, including opportunity, behavior 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 they suggest a need for reevaluation. 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 clarify the epidemiology of COVID-19 in children.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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