Clinical Infectious Diseases

REVIEW ARTICLE

A Meta-analysis on the Role of Children in Severe Acute Respiratory Syndrome Coronavirus 2 in Household Transmission Clusters

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The role of children in the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains highly controversial. To address this issue, we performed a meta-analysis of the published literature on household SARS-CoV-2 transmission clusters (n = 213 from 12 countries). Only 8 (3.8%) transmission clusters were identified as having a pediatric index case. Asymptomatic index cases were associated with a lower secondary attack in contacts than symptomatic index cases (estimate risk ratio [RR], 0.17; 95% confidence interval [CI], 0.09-0.29). To determine the susceptibility of children to household infections the secondary attack rate in pediatric household contacts was assessed. The secondary attack rate in pediatric household contacts was lower than in adult household contacts (RR, 0.62; 95% CI, 0.42-0.91). These data have important implications for the ongoing management of the COVID-19 pandemic, including potential vaccine prioritization strategies.

Keywords. children; SARS-CoV-2; COVID-19; transmission; household

At the time of writing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected >50 million people, resulting in >1 million deaths [1]. Large data analyses have shown that the elderly are particularly susceptible to severe forms of coronavirus disease 2019 (COVID-19) [2]. However, the role of children in the transmission of SARS-CoV-2 remains controversial [3–9]. During a typical influenza virus season, children have been identified as having the highest infection rate of any age group (up to 43%). Accordingly, children may play a major role in the spread of influenza virus and are a key target population for influenza vaccination to prevent infection and reduce transmission [10]. In the context of coronaviruses, pediatric infections with SARS-CoV-1, SARS-CoV-2, and Middle East respiratory syndrome are typically mild [9, 10]. Nevertheless, a lower incidence of clinical symptoms raises concerns that children could be an important, undetected source of SARS-CoV-2 in transmission in the community [8, 11]. Answering this question is of key importance to public health because it will help identify priority groups for vaccination. However, findings remain controversial, with some studies suggesting that children may play a key role in disease transmission and shed virus at equivalent titers to adults [12–17]. In contrast, others find little evidence of pediatric infections or spread [7, 8, 18–21]. Moreover, it is unclear if SARS-CoV-2 transmission differs among children of differing age groups.

Studying the source and route of viral transmission from children in the community is fraught with difficulties because of the multiple different potential sources of infection. Furthermore, it is thought that households are one of the most common settings in SARS-CoV-2 transmission [22]. Household transmission clusters therefore offer the unique opportunity to study viral transmission and susceptibility to infection in a more defined setting.

To address the role of children in the transmission of SARS-CoV-2, we performed a meta-analysis on household transmission clusters. We investigated prevalence of pediatric index cases in household transmission clusters of SARS-CoV-2 as well as the secondary attack rate of different age groups.

METHODS

Definitions

A household transmission cluster was defined as a group of ≥2 confirmed cases of SARS-CoV-2 infections in cohabiting individuals in whom the diagnosis of cases occurred

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within 2 weeks of each other. The index case was defined as the individual in the household cluster who first developed symptoms. Household contacts were defined as cohabiting individuals, typically family members, close relatives, housemates, or house helpers. An individual with laboratory confirmation of SARS-CoV-2 was considered to be infected. Household secondary attack rates were defined as the proportion of confirmed infections among all household contacts. Unless otherwise stated, adults were defined as individuals ≥18 years, whereas children were defined as individuals <18 years of age.

Data Collection

Following the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement for the reporting of meta-analysis [23], we searched published, deidentified data made available between December 1, 2019, and August 24, 2020. Information was accessed from the World Health Organization news [11], Google Scholar, PubMed, the *Lancet* COVID-19 resource center [12], *Clinical Infectious Disease Journal*, and *New England Journal of Medicine*. We searched for databases using the search terms ("COVID-19" OR "SARS-CoV-2" OR) AND ("household transmission" OR "family cluster" OR "household contact") AND ("transmissibility" OR "attack rate"). To identify missing studies, we checked the reference list for each selected paper. Studies that were duplicate publications, preprints, and/or reviews were excluded (Figure 1).

Our search strategy aimed to identify all articles that assessed the prevalence of children as index cases in a family SARS-CoV-2 cluster and/or the secondary attack rate of children and adults in household transmission clusters. Depending on the level of information available, studies were included in the index case analysis or the secondary attack rate meta-analysis.

All studies included in the index case analysis were household SARS-CoV-2 transmission clusters that (1) identified the index case of the cluster, (2) defined the number of infected contacts in the household, and (3) recorded the initial disease onset date of all cases in the cluster.

All studies included in the secondary attack rate meta-analysis were household SARS-CoV-2 transmission clusters that (1) defined the secondary attack rate within the cluster and (2) defined the age of contact cases in the cluster. Studies that did not meet bare minimum data required for the index case analysis nor the secondary attack rate meta-analysis were excluded (Figure 1). Where the same family cluster was included in more than published report, data were only extracted from 1 study. Collected data were verified by a second researcher.

Statistical Analysis

Susceptibility to infection was estimated by calculating the secondary attack rate for household close contacts associated with

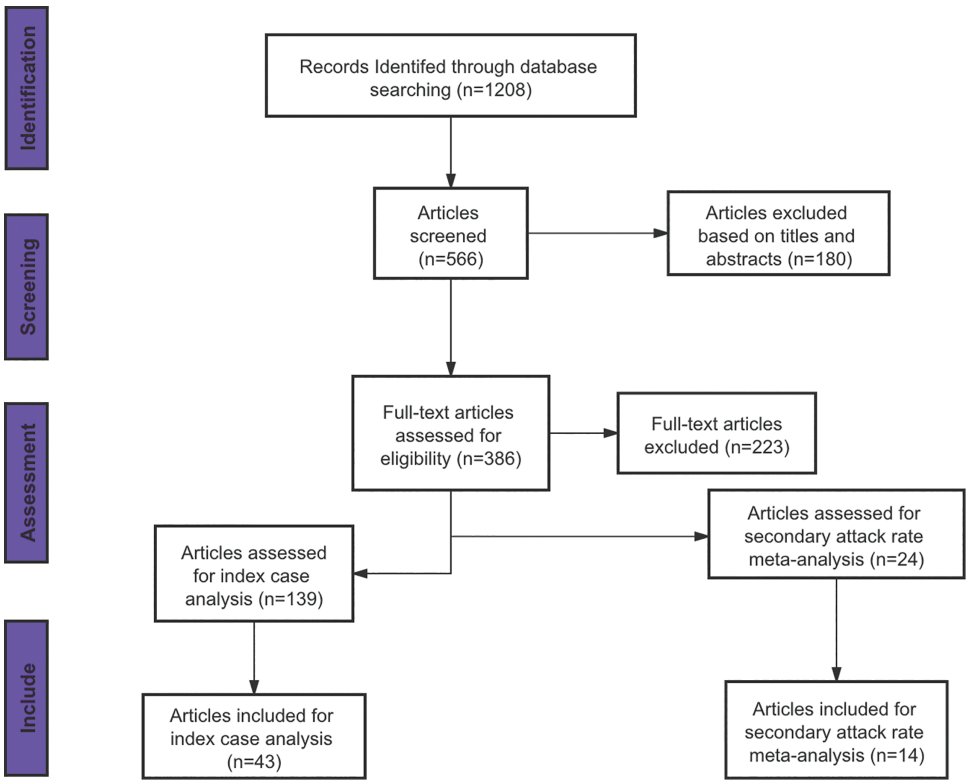

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram.

the index case in each transmission cluster. We estimated the relative risk (RRs) for SARS CoV-2 infection stratified by the age of household contacts for each study. We then pooled these RRs using a random effects model with DerSimonian and Laird weights [24]. We used a random effects model, equalizing the weight of the studies to the pooled estimate. Where relevant, we stratified the analysis by prespecified characteristics. Ninety-five percent confidence intervals (CI) were used to assess statistical significance in all models. The I^2 statistic was used to evaluate heterogeneity between studies. A threshold of $I^2 > 50\%$ was used as indicating statistically significant heterogeneity. All summary analyses and meta-analysis were performed using R statistical software (version 3.6.1).

RESULTS

We identified 1208 articles that described SARS-CoV-2 household transmission clusters, rejected 1151 articles from a lack of sufficient and or appropriate data, and derived a total of 57 articles. Household transmission clusters were drawn from cases in 12 countries: China, Japan, France, Germany, Italy, United States, Vietnam, Malaysia, Singapore, Morocco, Greece, and South Korea. Forty-three articles were included in the index case analysis [5, 25–66], whereas 14 articles were used in the secondary attack rate meta-analysis [66–79]. The full detail of all family clusters and characteristics of studies included in meta-analysis are shown in Supplementary Tables 1 and 2.

Children are Infrequently Identified as the Index Case of Household SARS-CoV-2 Clusters

In analysis of the cluster index cases, we included 43 articles, in which there were 213 SARS-CoV-2 transmission clusters; only 3.8% (8/213) were identified as having a pediatric index case (Table 1 and Supplementary Tables 1 and 3). Of 611 individuals in the 213 clusters, there were 102 children. These pediatric cases only caused 4.0% (16/398) of all secondary cases, compared with the 97.8% of secondary cases that occurred when an adult was identified as the index case in the cluster (Table 1).

The limited number of defined SARS-CoV-2 household clusters with children as the index case could have been influenced by the fact that COVID-19 in children is frequently asymptomatic [11]. Accordingly, it is possible that within a household cluster, children were not correctly identified as the index case of the infection (ie, the first to develop symptoms) and were instead mistakenly identified as a contact case. To exclude this possibility, we reanalyzed the data looking at household clusters where a pediatric contact case was SARS-CoV-2–positive but asymptomatic. In such a scenario, we assumed the child to be the "true" index case of the cluster. Clusters where the asymptomatic/symptomatic status of the contact cases was not described were excluded from the analysis. Even with this broader definition, only 39 (18.5%) children were identified as the index case in the household clusters (Table 2).

It is also possible that these data were influenced by the fact that early in the SARS-CoV-2 outbreak, infections were associated with travel to outbreak areas (ie, initially to Wuhan itself and later to the entirety of Hubei). Travel is much more likely to be undertaken by an adult in the family, potentially cofounding the results. To control for this factor, we reanalyzed the data, only including household transmission clusters where the index case had no history of travel or the whole family was associated with an outbreak area. Clusters where this information was not available were excluded from the analysis. This resulted in a total 152 clusters, 32 of which (21.1%) were identified as having a child as the index case in the cluster (Table 3).

A final factor that may have confounded this analysis is that, in some countries, a strict lockdown was imposed during the period of data collection. This would have limited the activity of children outside of the house and may therefore have artificially reduced the number of children identified as an index case. To control for this factor, a subanalysis was performed using only data collected when the regional area or country was not in a period of lockdown. In this subanalysis, only 3.0% of clusters were associated with a pediatric index case (Table 4, Supplementary Table 1).

Asymptomatic Index Cases are Associated With a Lower Secondary Attack Rate

We then further examined the household clusters identified in Table 1 where a child was identified as the index case to define the secondary attack rate of cohabiting family members

Table 1. Household Transmission Clusters of SARS-CoV-2 Stratified by the Age of the Index Case

Characteristics	SARS-CoV-2 Household Transmission Cases	
	Cluster (n = 213), No. (%)	Secondary Cases (n = 398), No. (%)
Child as the index case	8 (3.8)	16 (4.0)
Adult as the index case	205 (96.2)	382 (96.0)

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

Table 2. Household Transmission Clusters of SARS-CoV-2 Where any Asymptomatic, SARS-CoV-2 Positive Children are Assumed to be the Index Case of the Cluster

Characteristics	SARS-CoV-2 Household Transmission Cases	
	Cluster (n = 211), No. (%)	Secondary cases (n = 395), No. (%)
Child as the index case (including asymptomatic children)	39 (18.5)	80 (21.7)
Adult as the index case	172 (81.5)	315 (79.7)

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

Table 3. Household Transmission Clusters of SARS-CoV-2 Accounting for the Travel of Adults to Outbreak Areas

Characteristics	SARS-CoV-2 Household Transmission Cases	
	Cluster (n = 152), No. (%)	Secondary Cases (n = 264), No. (%)
Child as the index case	32 (21.1)	68 (25.8)
Adult as the index case	120 (78.9)	196 (74.2)

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

(Supplementary Table 4). Clusters where the total number of infected and uninfected family members were not recorded were excluded from the analysis. Accordingly, sufficient information was only available to calculate the secondary attack rate of 5 clusters with a pediatric index case (mean = 46.7%; standard deviation = 28.2%). Three of these index cases were <10 years and 3 index cases were aged 10 to 19 years. Only 22 clusters with an adult index case were eligible for this analysis (mean = 65.8%; standard deviation = 23.3%) (Supplementary Table 5). Therefore, there were insufficient case numbers to determine whether children are more or less able to transmit SARS-CoV-2 in a household setting compared with adult index cases.

It has previously been suggested that asymptomatic individuals may be less infectious than those who develop symptoms [7, 80, 81]. The prevalence of mild/asymptomatic infections in children may therefore affect the secondary attack rate in SARS-CoV-2 household clusters where a child was identified as the index case. To assess this possibility, we examined the secondary attack rate in household clusters where the index case was symptomatic versus the secondary attack rate in household clusters where the index case was asymptomatic (but known to be SARS-CoV-2–positive Figure 2). Asymptomatic index cases were associated with a significantly lower secondary attack in contacts than symptomatic index cases RR = 0.17 (95% CI, 0.09-0.29), although a significant overall effect was observed with heterogeneity (I^2 = 87%, P < .01).

Children Have a Lower Secondary Attack Rate Than Adults in Household SARS-CoV-2 Transmission Clusters

Several studies have suggested that children are less likely than adults to be infected with SARS-CoV-2 [20, 82]. However, small-scale studies can be biased by the fact that community testing is often only performed on symptomatic individuals, few of whom may be children.

We therefore used the second data set collected in this study to examine the secondary attack rate of children versus adults in household clusters where an adult was identified as an index case. In 11 observational studies of household transmission clusters, the secondary attack rate in tested pediatric household contacts (<18 years of age) was significantly lower than that in adult household contacts RR = 0.62 (95% CI, 0.42-0.91) (Figure 3).

In a subset analysis where additional information was provided on the age of the pediatric contact, younger children (<10 years) were no more or less susceptible to infection compared with older children (>10 years); RR = 0.69 (95% CI, 0.26-1.82) with no significant heterogeneity (I^2 = 33%, P = .17, Figure 4). Together, these data suggest that children (<18 years old) are less susceptible to SARS-CoV-2 infection in a household transmission cluster.

Table 4. Household Transmission Clusters of SARS-CoV-2 in the Absence of Regional or National Lockdown

Characteristics	SARS-CoV-2 Household Transmission Cases	
	Cluster (n = 199), No. (%)	Secondary cases (n = 366), No. (%)
Child as the index case	6 (3.0)	12 (3.3)
Adult as the index case	193 (97.0)	354 (96.7)

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

DISCUSSION

The transmission of SARS-CoV-2 to and from children has remained controversial throughout the course of the COVID-19 pandemic. In the present study, we recorded only a limited number of household transmission clusters (3.8%) where children (<18 years) were identified as the index case. This observation is supported by previous study from China, where a study of 66 family transmission clusters showed that children were never the first in the family to be diagnosed with COVID-19 [83]. Other reviews have also found limited evidence of children as the index cases in household transmission clusters [4, 20]. Indeed, in a family-based study by the Dutch National Institute for Public Health and the Environment, there were no indications in any of the 54 participating families that a child <12 years old was the source of COVID-19 within the family [84]. A more recent study of households in Tennessee and Wisconsin suggested that of 101 family SARS-CoV-2 clusters, only 14 had pediatric index cases [85].

There are multiple possible reasons as to why children may be infrequently identified as the index cases in household transmission clusters. This may reflect limited interaction of children outside the home during the period in question or the higher probably of an adult traveling to a COVID-19 endemic area than a child. An alternate hypothesis is that children are less susceptible to SARS-CoV-2 infection than adults. Indeed, this is consistent with our observation that in household transmission clusters, children were significantly less likely to acquire SARS-CoV-2 than their adult family members. Interestingly, we found that older children were not significantly more likely than younger children to acquire the virus, in contrast to previous pre-print suggestions [4].

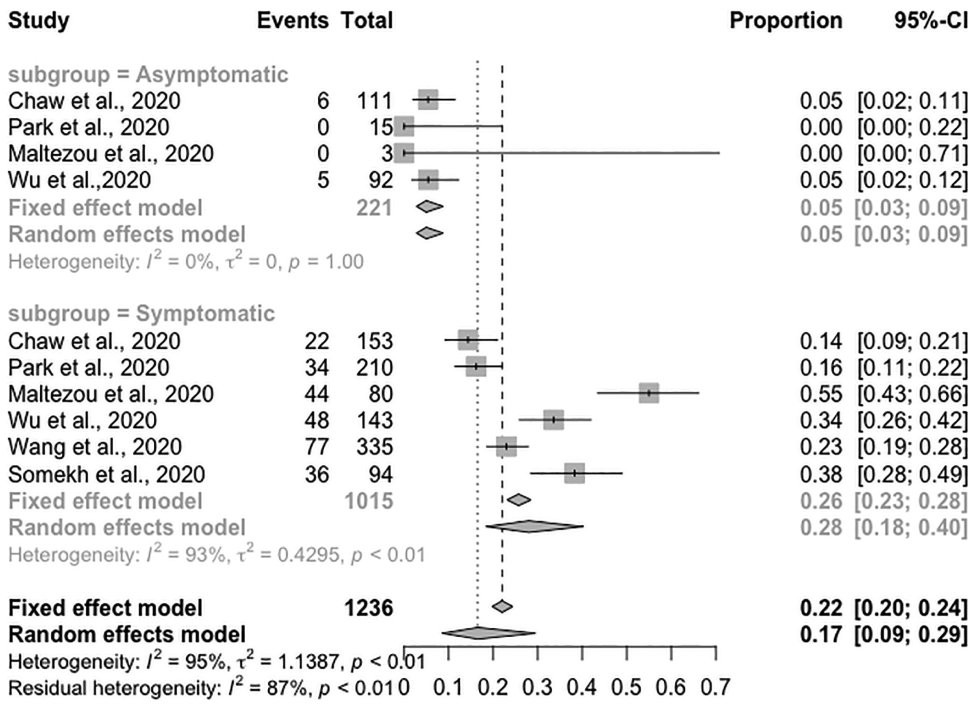

Figure 2. The secondary attack rate of household transmission stratified by severe acute respiratory syndrome coronavirus 2–positive symptomatic and asymptomatic index cases. Abbreviation: CI, confidence interval.

A reduced incidence of SARS-CoV-2 infection in children outside the home has previously been reported [2, 4, 8, 18, 86, 87]. Indeed, these data are congruent with survey data from Vo', Italy [88]. Here, all age groups were homogenously sampled yet no children tested positive for SARS-CoV-2 infection. This was despite the fact that at least 13 of these children lived together with infected family members [88].

Once infected, it remains to be determined whether children are more or less likely to transmit the SARS-CoV-2 to a family member as an infected adult. Although the mean number of infected household members was lower when a child was identified as the index case of the cluster, the low number of clusters eligible for inclusion in this analysis precluded any definitive conclusions. However, these data are consistent with recent US data suggesting that the secondary attack rate from pediatric index cases (18 years old) was less than that of adults (43% and 57%, respectively) [86]. It has previously been suggested that children are less likely to transmit SARS-CoV-2 compared with adults [7, 8, 18–20]. Such suggestions have remained controversial among other findings that children have equivalent

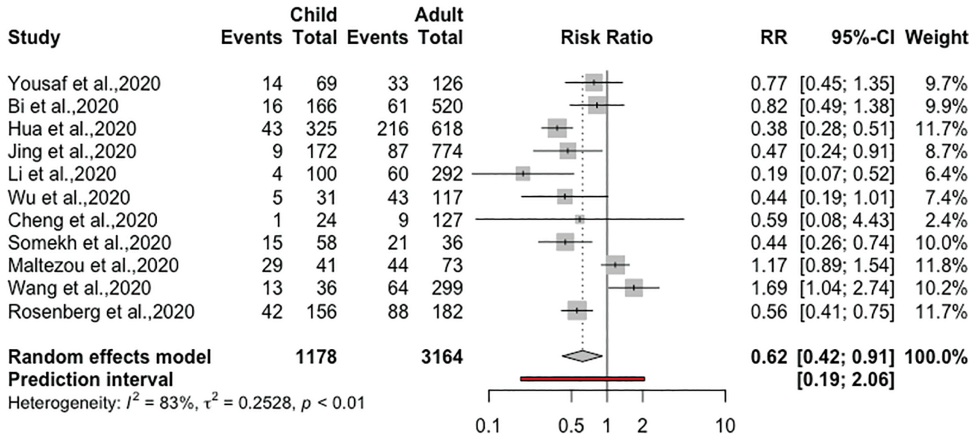

Figure 3. Relative risk (RR) for the secondary attack rate of children and adults in household severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission clusters. Events describe the number of SARS-CoV-2 positive individuals identified in the study. Abbreviation: CI, confidence interval.

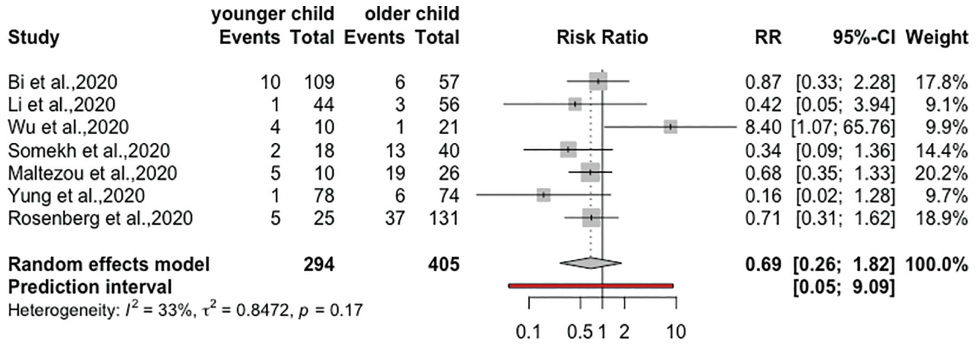

Figure 4. Relative risk (RR) for the secondary attack rate of younger and older children in household severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission clusters. Events describe the number of SARS-CoV-2 positive individuals identified in the study. Abbreviation: CI, confidence interval.

nasopharyngeal viral loads to adults [14, 16, 17]. However, reanalysis of the aforementioned studies has shown that (1) young children (<10 years old) did indeed have a significantly lower viral load [19], (2) that the comparison was being performed between children in the first 2 days of symptoms and hospitalized adults with severe disease [17], and (3) datasets included few children younger than 16 years [16]. Similarly, preprint suggestions that the risk of SARS-CoV-2 transmission to contacts is greatest from infected individuals <14 years old may be affected by limited case numbers in this age group (14/1489 total cases) [12].

Should children be less likely to transmit the virus, it is interesting to speculate the possible mechanism by which this occurs. There is an emerging body of evidence that mild or asymptomatic patients are less infectious than those with pronounced clinical symptoms [7, 13, 80, 81, 89]. Indeed, our meta-analysis showed that an asymptomatic index case was associated with a significantly lower secondary attack rate compared with a symptomatic index case. It is therefore tempting to hypothesize that children may be less infectious than adults infected with SARS-CoV-2 because of their more mild clinical manifestation of disease. However, such a hypothesis requires validation across a larger and more diverse dataset.

The present study was subject to several important limitations. First, because we were conservative during the data collection, only a limited number of studies were included, potentially contributing to the high I^2 value observed. This study also assumes that SARS-CoV-2 infections in the household contacts of infected individuals were the result of a direct transmission event. However, it is possible that the household contact acquired the virus from another source (eg, from community exposure) and that the first in the family to develop symptoms was not necessarily the index case. We were also unable to control for the chance of a "common exposure" where 2 individuals were infected by the same source at the same time, but 1 individual was incorrectly identified as the sole index case of the cluster because he or she was the first to develop symptoms. Indeed, this appears to have confounded the analysis of a series of family clusters identified in South Korea [5, 15]. It is also important to note that we were unable to differentiate between presymptomatic and asymptomatic infections and therefore the number of identified asymptomatically infected individuals may be overestimated. Finally, these data should not be extrapolated to SARS-CoV-2 transmission outside the home where children tend to make more social contacts than adults [18]. This could significantly influence transmission dynamics in the community setting, although our data are congruent with the low rate of SARS-CoV-2 transmission in Australian schools [90].

We are almost 1 year into the COVID-19 pandemic and many countries are still struggling to control outbreaks of SARS-CoV-2. At the time of writing, numerous countries in Europe have been forced into an additional lockdown. However, unlike the first lockdown many countries (including the United Kingdom and Germany) have elected to keep schools open. The data presented in this manuscript suggest that should children become infected at school during this period, they are unlikely to spread SARS-CoV-2 to their cohabiting family members.

There is now a growing body of evidence that a safe and effective vaccine will be soon be available. However, because of the global demands, SARS-CoV-2 vaccines are likely to be first administered to predefined priority populations. Although prioritizing the vaccination children against influenza has proved an effective tool in the reducing the spread of influenza virus in the community [10], our data suggest that a similar strategy would be unlikely to significantly decrease the household transmission of SARS-CoV-2.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. K. R. S. was supported by the Australian Research Council (DE180100512). K. R. S. reports speaker fees from Sanofi, Roche, and Novonordisk, outside the submitted work. A. C. B. receives

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