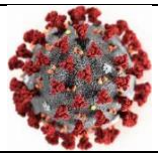
National COVID-19 Science Task Force (NCS-TF)



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The role of children (≤12 years of age) and adolescents (13-17 years of age) in the SARS-CoV-2 pandemic: A rapid review

Questions

This review updates the reviews in the policy briefs from 23 April 2020, 10 May 2020 and 12 August 2020.[1] It addresses three key questions about the epidemiology of SARS-CoV-2 infection and COVID-19 in children and adolescents. The review emphasizes the importance of trying to differentiate between different age groups: younger children, including infants and small children (0-5 years), school children (6-12 years) and adolescents (13-17 years). In this update, we assess available evidence relevant to children and adolescents, including new SARS-CoV-2 variants, which are more transmissible than the previous variants circulating in Switzerland. The key questions are:

1. How do children and adolescents present when infected with SARS-CoV-2?
2. Is the risk of children and adolescents becoming infected by SARS-CoV-2 comparable to that of adults? Does the probability of infection differ between age groups (0-5, 6-12, 13-17 years)?
3. Can children and adolescents transmit SARS-CoV-2 and is the risk comparable to that of adults? Does the probability of transmission differ between age groups (0-5, 6-12, 13-17 years)?

Appropriate preventive measures in schools should be in place. These are now dealt with in a separate policy brief

Summary, including new findings

Children of all ages and adolescents can be infected by, and can transmit, SARS-CoV-2. They usually have fewer and milder symptoms of SARS-CoV-2 than adults, which results in less testing and underdiagnosis. The precise relationship between age and the acquisition and transmission of SARS-CoV-2 remains unclear for two main reasons. First, there are inherent methodological challenges in differentiating between the biological effects of age and the external influences of level of community transmission and strength and nature of preventive measures. These challenges are exacerbated by poor reporting of contextual factors. Second, differences between studies in

[1] The role of children and adolescents (0-18 years of age) in the transmission of SARS-CoV-2: a rapid review (23 April 20; 10 May 20; 12 August 20 - EN)

analysis and reporting by age make it hard to synthesize findings across studies.

1. Younger children, school children and adolescents usually have fewer and milder symptoms of SARS-CoV-2 than adults and are less likely than adults to experience severe COVID-19. A hyperinflammatory syndrome, called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) in the USA can complicate recovery from COVID-19. Children and adolescents can experience prolonged clinical symptoms (known as long COVID, or post-acute sequelae of SARS-CoV-2 infection), but the frequency and characteristics are still under investigation. The severity of disease caused by new variants of SARS-CoV-2 in children and adolescents, in comparison with previous lineages, is under investigation.
2. The risk of becoming infected with SARS-CoV-2 is a combination of susceptibility (host biological factors), environmental factors associated with exposure type (work, shopping, schools etc.) and exposure intensity (level of community transmission and of preventive measures). In studies in which all household members are exposed to an infected person, the proportion becoming infected with SARS-CoV-2 increases with age. The detailed relationship between age and susceptibility to infection requires further investigation. More detailed epidemiological information about the factors influencing susceptibility of children and adolescents to the new SARS-CoV-2 variants is needed.
3. Infectious SARS-CoV-2 has been cultured in children as young as 7 days. Amongst diagnosed individuals tested at the same time point after symptom onset, SARS-CoV-2 viral load appears similar in children, adolescents and adults. The relationship between age, viral load and transmission across the full symptom spectrum of SARS-CoV-2 infection has not been comprehensively investigated because people with no, or mild, symptoms are seldom tested systematically. The relative transmissibility of SARS-CoV-2 at different ages remains uncertain, largely because of the challenges involved in disentangling the influences of biological, host and environmental factors. More detailed epidemiological information about the factors influencing transmissibility of the new SARS-CoV-2 variants in children and adolescents is needed.

More studies about the role of testing at all school levels and well-designed prospective longitudinal studies that can address questions about SARS-CoV-2 transmission at school and household level are urgently needed.

Main text

The role of children and adolescents in the transmission of SARS-CoV-2 is still uncertain. The uncertainties affect policy decisions, such as how to keep schools, kindergartens or day care facilities open safely and guidance about intergenerational contacts in general. Children and adolescents were observed early on in the pandemic to manifest mostly mild symptoms, with few cases of severe COVID-19, the disease caused by SARS-CoV-2 (Hoang et al., 2020; Morand et al., 2020; Mustafa and L, 2020). While a less severe course of infection is beneficial for young people, milder clinical manifestations are of public health importance if they result in unknowing and undetected infection transmission.

Understanding the characteristics of SARS-CoV-2 infection and spread by age is important for developing, adapting and improving control measures. There are ongoing debates, however, about the results and interpretation of research studies. Since January 2020, when COVID-19 was first described, the types of research evidence available and the design of research studies have

changed, allowing a reassessment of earlier findings. Many early studies had to rely, of necessity, on clinically apparent cases in healthcare settings with limited diagnostic testing. These studies made important observations, but underestimated the proportion of children amongst all COVID-19 cases because the milder symptoms resulted in under-detection of infection (Accorsi et al., 2021). Over time, it has become possible to design, conduct and analyze studies to reduce the risk of some of the biases in selection and measurement. Even so, the context in which a study is conducted (level of community transmission, control measures in place) cannot be changed. Differences between studies that attempt to address the same research question about SARS-CoV-2 in children may result both from differences in the circumstances under which studies were done and in study methodology.

We conducted an extensive literature review, with periodic searches of Pubmed and MedRxiv, up to January 21st, 2021, supplemented by inclusion of papers highlighted by experts until March 29th, 2021. The search strategy is described in the Appendix. Only studies in German and English were included in this report.

We screened 2778 studies up January 21st 2021 (peer-reviewed and preprints), of which 31 were deemed relevant to our review questions. From a manual search (also including reports and grey literature) we included another 36 articles (23 published, 13 not yet published or peer-reviewed or both). Of these 67 articles, 23 were case reports, 19 were cross sectional studies, 8 were cohort studies, 6 were narrative reviews or viewpoints, 10 were systematic reviews and 1 was a modelling study (see annex with tables on search and description of studies). Some studies cited in earlier versions of this review have been updated, where we found more relevant studies in recent searches.

The studies included describe the age distribution of study participants in very different ways. Reported age groups between studies often overlap, or report a finding for a wide age range, e.g. all below 18 years of age. It is not possible to summarize findings using consistent age categories or to adapt the results consistently according to school stage. Where the data are available, we try to report these for categories of younger children, including infants and small children (around 0-5 years), school children (around 6-12 years) and adolescents (around 13-17 years).

Question 1. How do younger children, school children and adolescents present when infected with SARS-CoV-2?

1.1 Severity of SARS-CoV-2 infection in children and adolescents

Pediatric SARS-CoV-2 cases were described in Wuhan, China in January 2020, at the beginning of the pandemic (Liu, Zhang, et al., 2020). Early studies and reviews reported that children of all ages and adolescents experienced mostly mild symptoms and few had severe disease requiring admission to intensive care (Morand et al., 2020, Mustafa and L, 2020, Lu et al., 2020, Dong et al., 2020, Castagnoli et al., 2020, Hoang et al., 2020).[2]

The reasons for the comparatively mild disease in children and partially in adolescents are still being investigated but Dong et al., 2020 proposed several possible explanations in March 2020:

- Reduced maturity and lower function of the ACE2 receptor on host cells in children than in adults (necessary for SARS-CoV-2 to infect cells)
- Children (<12 years of age) often experiencing respiratory infections (e.g., respiratory syncytial virus, other coronaviruses) in winter and thus possibly having higher levels of cross-reactive

[2] For regularly updated information about the clinical presentation of SARS-CoV-2 in children please see e.g. „Don't forget the bubbles".

immunity against SARS-CoV-2 than adults

- Young children potentially displaying a different immune response to pathogens (compared to adults) as their immune system is still developing
- Very young children are still in the stage of developing an immune system. Hence less immunopathology has been generally observed in this age group

Some reports from early in the pandemic, suggested that there might be an age-dependent risk of severe disease. The earliest studies have serious methodological limitations, however. Dong et al., 2020 reported slightly more severe or critical disease in infants (10.6% for <1 year olds) vs. 1-5 year olds (7.3%) (Dong et al., 2020). In this study, 2/3 of the suspected COVID-19 patients were not laboratory-confirmed. A report from the United States Centers for Disease Control and Prevention (CDC) reported on laboratory-confirmed COVID-19 cases in children <18 years, but data on hospitalization were only available for 29% of cases. Amongst those with data available, <1 year olds "accounted for the highest percentage (15-62%) of hospitalization among pediatric patients" (Team, 2020).

Several reviews, describing 32 different cases of neonatal SARS-CoV-2 infection in total, all show neonates mostly presenting with mild disease (Gordon et al., 2020, Dumpa et al., 2020, Sheth, Shah, and Bhandari, 2020, Kyle et al., 2020, Vardhelli et al., 2021). The respiratory symptoms described in some patients were generally consistent with their gestational age and could thus not be attributed to SARS-CoV-2. These findings are supported by small additional retrospective studies (Wei et al., 2020, Zhang et al., 2020) and a prospective national cohort study from the UK (Gale et al., 2021), describing mild SARS-CoV-2 disease progression in neonates. A case report by Nathan, Prevost, and Corvol, 2020 describes atypical presentations of SARS-CoV-2 in five infants "with poorly tolerated and isolated fever" and neurological symptoms. All recovered quickly and could be discharged 1-3 days after admission. Most reports of neonatal SARS-CoV-2 are case reports or small case series. Multicenter hospital-based studies, with more complete data and consistent case definitions, have been conducted more recently. A prospective cohort study from 260 hospitals in the UK, following 651 children and young adults (225/651 <1 year old) between 17 January and 3 July 2020, found that the risk of admission to intensive care was associated with age <1 month (odds ratio: 3.21, 95% CI:1.36-7.66) and age 10-14 years (odds ratio: 3.23, 95% CI: 1.55-6.99), compared with 15-19 year olds (Swann et al., 2020).

Studies carried out in hospital settings in different geographical locations might differ because the criteria for hospitalization of children and adolescents with COVID-19 differ. In some countries the aim is to monitor clinical progress, which results in admission of a wide spectrum of clinical manifestations, whilst in other countries only the sickest children are admitted.

A hyperinflammatory syndrome in children with COVID-19 has been described. It is called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in Europe and multisystem inflammatory syndrome in children (MIS-C) in the USA.[3] Jones, Mills, et al., 2020 reported the first case of an infant presenting with classic Kawasaki disease, who also tested positive for SARS-CoV-2 in April 2020. Shortly after, NHS England reported a small increase in critically ill children (Paediatric Intensive Care Society, 2020), based on a cluster of 8 children in South East England, with features associated with Kawasaki disease or toxic shock syndromes, most of whom had a history of exposure to COVID-19 or a positive test for SARS-CoV-2 (Riphagen et al., 2020). In a report of 99 cases diagnosed with MIS-C from New York, there were 31 in 0-5 year olds, 42 in 6-12 year olds and 26 in 13-20 year olds (Dufort et al., 2020). Presentation with any Kawasaki type symptoms was more common in those aged 0-12 years (31/73, 42%) than 13-20 years (3/26,

[3] For further information about PIMS-TS/ MIS-C please see this policy brief.

12%). PIMS-TS/MIS-C has still not been extensively studied, so the exact nature and strength of association with SARS-CoV-2 have yet to be established.

There is not yet conclusive evidence that young age is a particular risk factor for severe disease, owing in part to methodological limitations in the cited studies. There are also multiple small studies from around the world describing mild SARS-CoV-2 disease progression and low hospitalization rates, even in children with severe underlying health conditions such as cancer and immunosuppression (Balduzzi et al., 2020, Ferrari et al., 2020, Marlais et al., 2020, Boulad et al., 2020, Hrusak et al., 2020, Minotti et al., 2020, Rawson et al., 2021). These observations are shared by the PIGS (Pediatric Infectious disease Group of Switzerland), whose members collect and share observations of severe cases (study is still ongoing).

Preliminary data from a small study Italy suggest that children might, however, also be at risk of ongoing symptoms, referred to as long COVID or post-acute sequelae of SARS-CoV-2 infection (Buonsenso et al., 2021). Due to limited follow up and the absence of studies with control groups, the frequency, characteristics and prognosis of prolonged symptoms following SARS-CoV-2 infection remain uncertain.

1.2 Asymptomatic SARS-CoV-2 infection in children and adolescents, compared with adults

As children present with milder symptoms than adults, there are comparatively few data about the full spectrum of pediatric SARS-CoV-2 infection. A milder or completely asymptomatic course of disease progression is relevant for public health if these cases are infectious and go undetected.[4] It also contributes to under ascertainment of pediatric SARS-CoV-2 in routine surveillance data.

To determine the proportion of truly asymptomatic SARS-CoV-2 infections, the distinction between pre-symptomatic and a wholly asymptomatic course of infection is important. Researchers need to follow up participants for a sufficiently long time (e.g. 14 days after last exposure, or until RT-PCR negative) to exclude those who will develop symptoms. A systematic review of studies published up to 10 June 2020 provides information about the proportions of children of all ages and adolescents (<18 years) and adults in studies done in hospital settings in which patients were followed through the course of infection. In both groups, the majority of individuals with SARS-CoV-2 developed symptomatic disease. The proportions with persistently asymptomatic infection were: in children, 27% (95% CI 22-32%, 10 studies, 285 children) and in adults, 11% (95% CI 6-19%, 10 studies, 3228 adults) (Buitrago-Garcia et al., 2020). These proportions are likely to be underestimates of the proportion of truly asymptomatic infection in the general population because studies in hospitals preferentially include people with more severe disease. The children in hospital-based studies were generally diagnosed during investigations of household contacts of confirmed cases and were hospitalized for observation. Most studies in this review did not give detailed information about age, so it was not possible to examine differences between children of different age groups.

Asymptomatic infections can also be estimated in seroprevalence studies, although underestimation might occur because antibody levels are lower in those with less severe infection (Tan et al., 2020). In Switzerland, two studies have reported on SARS-CoV-2 symptoms in children. In Geneva, the SEROCoV-POP study, conducted between April 6 and June 30, 2020, found that 13% (77/590) of all participants with SARS-CoV-2 antibodies did not recall any SARS-CoV-2 symptom since January 2020. When stratified by age, the proportions reporting no symptoms were: 44% (4/9) aged 4-9 years; 26% (13/50) aged 10-17 years; 10% (28/278) aged 18-49 years. (Richard et al., 2020) Recall bias by participants reporting symptoms for themselves, or on behalf of young children, might have affected the absolute estimates of asymptomatic infection. Also, symptom reporting in

[4] People who do not develop symptoms of SARS-CoV-2 for the whole of their infection classify as asymptomatic. People who do not display symptoms when tested but develop symptoms later classify as pre-symptomatic).

children was less specific than in adults. With the exception of loss of taste or smell, symptoms were as common in seropositive as in seronegative children. In the Ciao Corona study in Zurich (n=2585), 73% of all children (age range 6-16 years) experienced any symptoms compatible with a SARS-CoV-2 infection between January and June 2020, with no difference between seropositive and seronegative children. Between July and November 2020, most children did not report symptoms compatible with SARS-CoV-2: 29% (29/101) of seropositive children and 22% (420/1923) of seronegative children. The authors suggest that children in the later period might have had fewer allergies and other infections. (Ulyte et al., 2021)

We did not find any studies reporting the frequency of asymptomatic pediatric SARS-CoV-2 infection caused by the new variants.

Question 2. Is the risk of children and adolescents becoming infected by SARS-CoV-2 comparable to the risk of adults? Does the probability of infection differ between age groups (0-5, 6-12, 13-17 years)?

The risk of becoming infected with SARS-CoV-2 is a combination of susceptibility (host biological factors), environmental factors associated with exposure type (work, shopping, schools etc.) and exposure intensity (level of community transmission and of preventive measures) and agent factors, including the variant of SARS-CoV-2. It is often difficult to disentangle the influences of these factors on the risk of children and adults becoming infected. Research studies about levels of SARS-CoV-2 infection in people of different ages therefore report on the total combined risk (susceptibility, exposure and pathogen factors) of infection. Interpretation depends on study methodology and the detail with which contributing factors are reported.

The risk of SARS-CoV-2 infection at different ages can be investigated in different study types. The least biased design would be to follow a random sample of the population with repeated frequent virological testing for SARS-CoV-2 to determine incidence at different ages and to place the findings in the epidemiological context in which the study was done. Repeated cross-sectional samples of a population can also give this information, assuming that the population structure remains stable. In contact tracing studies of transmission in households or during outbreaks the secondary attack rate in children and adults can be compared. In these studies, all household members theoretically have a comparable level of exposure. They are still at risk of chance effects and bias because adults are more likely to be the index case because they have symptoms more often. Different biases in household studies of secondary attack rate can result in underestimation or overestimation of the contribution of children (Accorsi et al., 2021). Seroprevalence studies give information about the proportion of people who have been infected since the start of the pandemic but do not give information about who infected whom, or when. Studies that use surveillance or registry data about cases that are diagnosed and reported should not be used to examine age differences in the risk of SARS-CoV-2 because children are less likely to be symptomatic and less likely to be tested in routine practice.

<u>2.1 Population studies/cross-sectional studies using virological testing</u>

The first detected case of COVID-19 in Italy was a resident from Vo', northern Italy, who died of pneumonia in February 2020 (Lavezzo et al., 2020). A 14-day quarantine was imposed at the beginning of a lockdown and a majority of the population was tested (85.9% at the first stage, 71.5% 14 days later) for SARS-CoV-2, irrespective of symptoms. There were no cases in 217 children aged 0-10 years and 3 cases in 250 11-20 year olds (1.2%), compared with 1.1% to 6.0% in adults in older 10-year age bands. This survey is at low risk of bias; nearly all residents were tested, there were no restrictions before the lockdown and children and adults lived in the same households. The COVID-19 Infection Survey (CIS) where randomly selected members of the British population aged 2 years and older, submit repeated swabs for SARS-CoV-2 testing, has found differences in SARS-CoV-2

positivity over time. Greater increases in positivity in children aged 2 to 24 years than in older adults coincided with school opening in September 2020 (Children's Task and Finish Group, 2020).

2.2 Contact tracing/household studies

We identified three relevant systematic reviews. Viner et al., 2021 included 18 studies based on contact tracing in any setting up to July, 28th 2020. They found a lower risk of infection for younger children <10 years of age (odds ratio, OR 0.52, 95% CI 0.33-0.82)) than adults (reference group), but not for older children and adolescents >10 years of age (OR 0.72, 95% CI 0.46-1.10). Zhu et al., 2020 included 14 household studies up to 24th August 2020 (4 of which were included by Viner et al., 2021), with comparable findings. The risk of infection was lower among all <18 year olds than in adults (relative risk, RR 0.62, 95% CI 0.42-0.91). Madewell et al., 2020 analyzed 15 household studies up to October, 19th 2020 (7 of which were also included in Viner et al., 2021. They compared the SAR within each study and found the summary proportion of participants with SARS-CoV-2 was higher in adult contacts (28.3%, 95%CI, 20.2%-37.1%) than in child and adolescent contacts of all ages (<18 years of age) (16.8%; 95%CI, 12.3%-21.7%).

Most of the studies in these reviews were conducted during times of strict social distancing. There is a risk of bias in levels of exposure for adults and for children. Adults were at risk of infection outside their homes e.g. while shopping or at work, whilst children stayed mostly at home. Children were, however, likely in contact with adults within the families. A limitation of these reviews is the different age groups studied, resulting in large, and sometimes overlapping groups.

Some household studies (some of which are included in the systematic reviews) distinguish between narrower age groups. A cohort study by Li et al., 2020 analyzing 392 household contacts of 105 index patients in China, calculated secondary attack rates of 2.3% (1/44) for younger children (aged 0-5 years), 5.4% (3/56) for school children and adolescents (aged 6-17 years) and 17.1% (60/292) for adults. In Singapore, Yung et al., 2020 described 213 children in 134 households, of which 13 became infected with SARS-CoV-2: 0-4 years old, 1.3% (1/77); 5-9 years, 8.1% (6/68); and 10-16 years, 9.8% (6/55). Somekh et al., 2020 also found older children and adolescents (aged 5-17 years) in family household settings in Israel being 61% less likely to be infected with SARS-CoV-2 than adults, with the risk for younger children 0-4 years of age being 47% lower than the risk for adults.

2.3 Seroprevalence studies

We found several seroprevalence studies. Studies conducted in nationally representative samples of the population using methods that reduce the risks of bias in selection, measurement and analysis of antibody status will provide the most robust estimates of cumulative incidence up to the time at which the survey was done (Accorsi et al., 2021). Differences between studies that are at low risk of methodological biases are then more likely to be explained by contextual factors, such as levels of exposure to infection.

In a nationally representative seroprevalence survey in Spain (April-May 2020), seroprevalence was lowest in the youngest age groups (Pollan et al., 2020). This study was done when a strict national lockdown was imposed in Spain with schools and kindergartens closed and children were mostly exclusively at home.[5]

[5] Other population-based seroprevalence studies have been published since summer 2020 (e.g. Hippich, Holthaus et al. 2021; Konsortium der Medizinischen Universität Graz, 2020). Hippich et al., 2020, reported similar seroprevalence in 0 to 6 years (66 of 7,821, 0.84%) and children aged 7 to 18 years (14 of 1,425, 0.98%) from April to July 2020 in Bavaria, Germany. Seroprevalence was 6 times higher than numbers of diagnosed and reported SARS-CoV-2 cases in children, but no adults were tested in that study. The same applies to the Austrian study by the Konsortium der Medizinischen Universität Graz, 2020, where the prevalence in students (0.37%, 95% CI 0.26-0.53%) was compared to the prevalence of their teachers

In Germany, Debatin et al., 2020 invited volunteers through newspaper and social media adverts and analyzed antibody levels in 5042 parent-child pairs in April-May 2020 during a strict lockdown (schools were closed and children and parents were almost exclusively at home, but children from essential workers could still attend daycare facilities). They found a higher proportion of parents (1.8%; 95%CI: 1.3-2.4%) than children (1-5 years, 0.6%; 95%CI: 0.3-1.3) with SARS-CoV-2 antibodies. Torres et al., 2020 analyzed a school outbreak of 52 RT-PCR positive cases in Chile and measured seroprevalence in a random sample of students and staff 8-10 weeks after the outbreak. The index case was a staff member in the pre-school department. The authors thought it likely that the staff member infected both pre-school children at school and parents and colleagues during parent-teacher meetings. They found 16.6% (95% CI 12.1-21.9%) of staff had antibodies. A higher percentage of younger children (pre-school 12.3%, 95% CI 7.8-18.6%) than high school students (5.7%, 95% CI 3.6-8.9%) had antibodies.

2.4 Studies done in Switzerland

The SEROCoV-POP seroprevalence study in Geneva, Switzerland analyzed randomly selected participants from a past cohort study and their household members (>5 years old) in April-May 2020. The risk of antibody positivity for children <10 years of age was lower (risk ratio 0.32, 95%-CI: 0.11-0.65) than that for adults >20 years of age. Seroprevalence among children aged 10-19 years was similar to that of >20 year olds (risk ratio 0.86, 95%-CI: 0.57–1.22) (Stringhini et al., 2020). As this was a retrospective study that was conducted when Swiss schools were closed, individual sources of infection were not analyzed. The lower risk in children could be due to less exposure to SARS-CoV-2 than adult household members. Another survey round was done in November-December 2020, after the second peak of the pandemic. Seroprevalence became similar for school children and adolescents (6-11 year olds, 22.8%, 95%-CI 18.7-27.1%; 12-17 year olds, 23.6%, 95%-CI 19.6%-28.0%) and adults (25-34 years, 25.9%, 95%-CI 21.8-30.2%), but was lower for children aged 0-5 years (14.9, 95% CI 10.7-19.6) (Stringhini et al., 2021). During the study period, Geneva imposed a regional lockdown, where most shops were closed, but schools and the border were open and inter-cantonal travel to cantons with less strict measures was common.

Question 3. Can children and adolescents transmit SARS-CoV-2 and is the probability of transmission comparable to that of adults? Does the probability of transmission differ between age groups (0-5, 6-12, 13-17 years)?

Children and adolescents can transmit SARS-CoV-2 in both household, school and out of school settings. The relative transmissibility of SARS-CoV-2 at different ages remains uncertain, largely because of the challenges involved in disentangling the influences of biological, host and environmental factors. For example, school children and adolescents are more mobile and generally have more close contacts among themselves than younger children (Mossong et al., 2008).[6] On the other hand, measures aimed at limiting virus transmission, such as wearing masks in school settings, have been more widely recommended and implemented among adolescents than school children ≤12 years old. The timing of studies is an important consideration. For example, in Switzerland, restrictions in extra-curricular activities in early 2021 were limited to children older than 12 years. If this type of information is not reported, study findings may be misinterpreted.

There are different study designs to investigate the infectiousness and resulting transmission potential at different ages. Comparisons between children and adults in estimates of viral load, which are usually based on RT-PCR cycle threshold values, can indicate differences in infectiousness.

(0.57%, 95% CI 0.25-1.32%), but not with adults in the same households again, excluding the household settings. This weakens the certainty of these studies' findings.

[6] https://www.fhi.no/en/op/novel-coronavirus-facts-advice/facts-and-general-advice/advice-and-information-for-children-and-adolescents/

These studies provide partial information because the probability of transmission is also influenced by the probability of being diagnosed, by levels of symptoms (e.g. cough increases the risk of aerosol transmission) and by physiological features (e.g. children having less lung capacity than adults). Studies that estimate the secondary attack rate can also be used to study transmission from a child or adult to their close contacts (either in households or schools). Methodological issues in study design, which generally arise from misclassification of the index case or the contact, can result in biased estimates, however (Accorsi et al., 2021). Since children display fewer symptoms than adults (see question 1), they might be less likely to be classified as an index cases and more likely to be classified as a contact, which would underestimate the transmission risk from children. Environmental factors (e.g. culture, community transmission, lockdown without any contacts except essential contacts e.g. while shopping or at work) also make extrapolation to different settings difficult and might lead to an overestimation of transmission if the contacts were actually infected elsewhere. Regular repeated testing of people within households can identify the first infected person in a chain of transmission, which helps to understand who infected whom. Even this study design can only be interpreted appropriately if the epidemiological context is reported.

3.1 Laboratory-based studies of infectiousness

L'Huillier et al., 2020 showed that infectious SARS-CoV-2 can be isolated from children as young as 7 days old. Amongst 23 children <16 years old in Geneva, virus was cultured in 12. The same group in Geneva found comparable viral load levels, by age group, in laboratory samples taken within 5 days of symptom onset and tested between March-May 2020 (53/405 aged <16 years) Baggio et al., 2020. In a large study of samples sent to a laboratory in Germany, Jones, Mühlemann, et al., 2020 used two different testing systems, and found an association between increasing age and increasing viral load on one (Roche Cobas system), but a negative association on the other system (Roche LC480 system). Jones, Mühlemann et al. 2020 did not specify the type of specimen from which the viral RNA was isolated in adults and in children. As Zou et al., 2020,Yu et al., 2020 and Wang et al., 2020 show, RT-PCR cycle threshold values, which were used to calculate the viral loads of different specimens, are not comparable. A different statistical analysis of the same data found that viral load increased with age (Held, 2020).
These studies do not allow the relationship between age and viral load to be determined across the full spectrum of SARS-CoV-2 infection. A major limitation of studies based on collections of samples in diagnostic laboratories is that inclusion in a study depends on having been tested. Since testing for SARS-CoV-2 concentrates on detection of infection in people with symptoms, children who are included in these sample collections are unlikely to be representative of all those infected. The study by Baggio et al., 2020 is restricted to a defined group of symptomatic people, but the study by Jones, Mühlemann et al. 2020 does not stratify the results about age and viral load by the severity of the patient's symptoms.

Prospective studies that reduce the risk of selection bias by including representative samples across the spectrum of SARS-CoV-2 infection, and document age, symptom status, specimen and assay type, viral load and culturability would allow a more detailed assessment, since severity of disease is potentially directly associated with infectiousness, viral loads and thus SARS-CoV-2 transmission (Luo et al., 2020; Liu, Yan, et al., 2020; Han et al., 2020; Zheng et al., 2020).

3.2 SARS-CoV-2 studies in family and schools/day care centers

A meta-analysis by Zhu et al., 2020 analyzing household clusters up to August, 24th 2020 found that a child or an adolescent (<18 years) was identified as the first case in 4% (8/13) of these clusters. The pediatric index cases also led to fewer secondary cases than adult index cases (4% vs. 96% of 398 secondary cases). Acknowledging the potential undercounting of children as index cases, the authors included asymptomatic children as possible index cases, and the proportion of clusters with an index case <18 years increased to 19% (30/211) and the proportion of secondary cases increased to 22% (80/395 contacts). A regularly updated review that includes studies with contact tracing data

up to January 21st, 2021 reported very limited transmission from younger children in school settings, but found potential outbreaks in school children and adolescents (without further clarification of the respective age groups), especially during times of higher community transmission (Boast, Munro, and Goldstein, 2020).

Several studies have described large clusters of SARS-CoV-2 involving schools and school camps. Fontanet et al., 2020 described an outbreak of SARS-CoV-2 in a school in northern France in early 2020. In a serosurvey in one high school, seroprevalence higher in adolescents (82/205 in 15-17 year olds) than adults (88/415 in ≥18 years olds). As neither the sampling methodology is known nor were the supposed index cases laboratory confirmed SARS-CoV-2 cases, the extent of spread in the school compared with outside is not known. Further studies by Szablewski et al., 2020, Pray et al., 2020 and Stein-Zamir et al., 2020 describe clusters of cases in overnight camps/retreats in the USA and a school in Israel. While Pray, Gibbons-Burgener et al. 2020 and Stein-Zamir et al., 2020 describe outbreaks in high schools (ages 12 and older), the camp outbreak described by Szablewski et al., 2020 included children and adolescents aged 6-17 years and found similar attack rates in 6-10 year olds (51/100, 51%) and 11-17 year olds (180/409, 44%). Outbreak investigations did not test close contacts before or after camps (Szablewski, Chang et al. 2020 and Pray, Gibbons-Burgener et al. 2020) or provide information about contact histories with other potential cases (Stein-Zamir, Abramson et al. 2020) so the numbers of cases infected outside the camps or schools are not known.[7]

Other studies from schools have found limited transmission when community transmission was comparably low, even in secondary education facilities. Potential protective measures in most reports were not described. In Singapore, Yung et al., 2021 described three school settings in which no child contacts became infected: 0/8 symptomatic contacts of an infected 12 year old; 0/34 symptomatic contacts of an infected 5 year old; and 0/77 preschool pupils where a total of 16 staff members were infected (Yung et al., 2021). In Australia, 18 index cases (9 students and 9 teachers) in 15 different schools (primary and high schools) had close contact with 735 fellow students and 128 staff. None of the 128 staff contracted SARS-CoV-2 and the 2 initial cases (1 student and 1 staff) only infected two fellow students (one in a high school, and one in a primary school). At the time of the study, children were advised to receive online learning at home, so reduced attendance could have influenced transmission (NCIRS), 2020). Heavey et al., 2020, describe six index cases in schools in Ireland before preemptive school closures during the 2020 spring wave. Three students, aged 10-15 years, and three adults did not infect any of the 1001 child contacts tested (924 school contacts, 77 non-school-related contacts), including those with only mild symptoms. Ehrhardt et al., 2020 described 137 index cases aged <19 years in Baden-Württemberg, Germany from May-August 2020. From more than 2300 contacts, 11 infections in classmates were found (three in childcare facilities, one in elementary school, 4 in secondary school and three in vocational school). None of these secondary cases infected any other students. There were several hygienic control measures in place (e.g. reduced class size, exclusion of sick children, etc.). Link-Gelles et al., 2020 and Yoon et al., 2021 also found a low risk of infection from adult and pediatric index cases in childcare settings in Rhode Island, USA and South Korea.

A study from the England (Ismail et al., 2021) reports on 177 COVID-19-associated events in educational settings (preschool, primary and secondary) involving 130 confirmed cases in children and 213 in staff members. Most outbreaks were small (median number of cases, 2, interquartile range 2-5). The maximum size of outbreaks was lower when the index case was a child (median 1,

[7] Media reports describe several SARS-CoV-2 school outbreaks in Germany. Most of these reports describe cases appearing at schools but do not provide enough information to determine the source or direction of transmission. In one secondary school, transmission was proven to have happened at school with one person infecting 25 students and 15 teachers. There is no data about the age of the index case. The case study suggests that adolescents can become infected in school settings when protective measures (masks etc.) are not taken. (https://www.abendblatt.de/hamburg/article231223608/Corona-Ausbruch-an-Schule-Eine-Person-steckte-Dutzende-an.html)

maximum 6) than when the index case was a staff member (median 1, maximum 12). Although the number of cases was low overall, there was a strong association with regional incidence of reported COVID-19; for every 5 new cases per 100000 inhabitants the risk of an outbreak increased by 72% (95% CI 28-130). In most outbreaks, a staff member was the index case (staff to staff in 26/55 outbreaks, staff to student in 8/55 outbreaks, student to staff in 16/55 outbreaks, and student to student in 5/55 outbreaks). The same pattern of index cases was seen in Georgia, USA, where nine clusters were described in elementary schools from December 2020-January 2021. Of these nine clusters four were started by teachers, one by a student and four were unknown. (Gold et al., 2021)

In schools, as in other settings, however, children might be under-counted as the index case because they are less likely than adults to present with symptoms.

3.3 Studies of new SARS-CoV-2 variants

The characteristics of SARS-CoV-2 variants of concern, such as B.1.1.7, first identified in England, in different age groups are not yet known.

The British Children's Task and Finish Group describes an increase in infection prevalence between September-October 2020, which was most marked in the age group 16/17-24, followed by 12-16 year olds, based on the ONS COVID-19 Infection Survey. The School Infection Survey, conducted in November 2020 found that despite more testing the level of infection in schools is low even in times of high community transmission (students, 1.24%, 95%-CI 0.96-1.58%; staff, 1.29%, 95%-CI 0.96-1.68%) (Group, 2020). This report was written before the increased transmissibility of B.1.1.7 was confirmed. A modeling study by Volz et al., 2021 predicted that under 20 year olds could have been affected more by the new SARS-CoV-2 variant B.1.1.7 than by the previous variants, but this could have resulted from increased transmission when schools were open during a lockdown period, from increased susceptibility, or from increased symptoms leading to more testing. Further research about the impact of B.1.1.7 on children is needed.

3.4 Studies done in Switzerland

In addition to the laboratory-based studies (section 3.1), a longitudinal seroprevalence study has been done in schools in Zurich (Ciao Corona study) in June/July and October/November 2020 (Ulyte et al., 2021). The study follows children aged 6-16 years in 55 schools and 275 classes during a period when hygienic measures were in place (e.g. mask wearing for teachers and students >12 years of age). In 7 classes in 5 schools ≥3 students had SARS-CoV-2 antibodies, in periods of moderate to high community transmission, when seroprevalence itself increased from 2.4% to 4.5% in schools. It is not known whether the students were infected as part of an outbreak, or were sporadic cases, nor whether the infections were acquired or transmitted in the school.

In the Canton of Vaud, schools are investigated if ≥2 SARS-CoV-2-positive children are detected in the same school within 5 days (personal communication, Valérie d'Acremont). During 3 weeks in January-February 2021, testing was carried out in 32 of 6135 (0.5%) classes: 325 of 124,818 (0.3%) children and adolescents were tested, of whom 18 (5.5%) were positive. Of the diagnosed cases, ⅔ were in primary schools, ⅓ in secondary schools and none were in post-compulsory schools. Three primary school classes were put in quarantine. Clusters of ≥5 persons occurred once in one class and once in teachers from one school in which no case in children was found.

Conclusions

Children are susceptible to SARS-CoV-2 infection and also transmit the disease. The extent of transmission depends on various factors, including for example the level of community transmission, the measures implemented and also biological factors (possible less transmission among younger children; type of variant present). The precise role of children and adolescents in the overall transmission still requires further investigation, especially as there is a lack of more

detailed epidemiological information on the transmission dynamics of the new SARS-CoV-2 variants. More testing amongst children of all ages and adolescents, and well-designed longitudinal studies in school and household settings, are urgently needed. Appropriate preventive measures should be consistently implemented in schools.

Authors: Margarethe Wiedenmann, Nicola Low and members of expert groups

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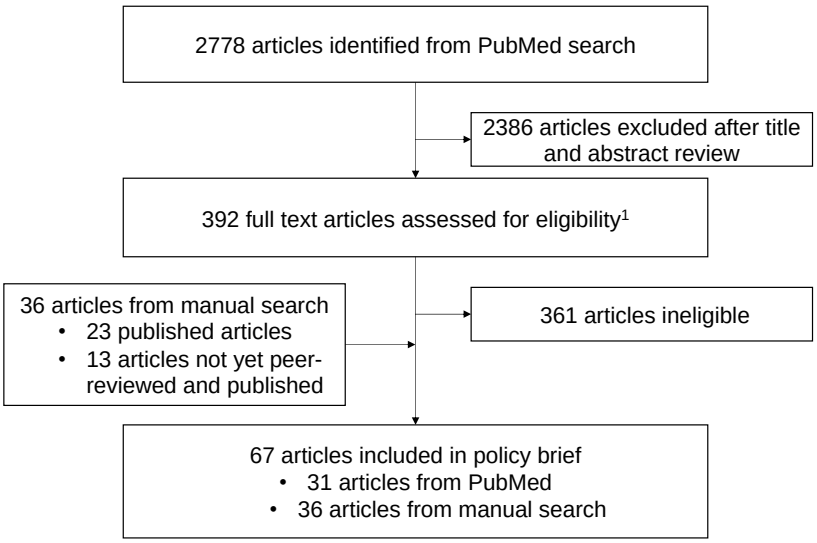
1. Search strategy

We searched Pubmed using the following search terms “COVID-19”, "SARS-CoV-2", "novel coronavirus” and "attack rate", "secondary attack rate", "infectiousness", "transmission rate", "transmission" and “children” or "pediatric patients”. We also combined this search with “kindergarten”, “creche”, “preschool”, “elementary school”, “secondary school” or “high school”. We also added the SARS-CoV-2 search terms to "asymptomatic", "presymptomatic” and "attack rate", "secondary attack rate", "infectiousness", "transmission rate", "transmission" or "viral shedding".

2. Flow chart of identified and included studies



[1] Eligibility: language (English, German): study design (case reports, cross sectional studies, cohort studies, modelling studies, reviews/viewpoints: preprints, peer-reviewed studies); study population (children and adolescents (<18 years old)); settings (households, schools/day care centres/camps, community))

3. Table of characteristics of included studies

Author	Study Type	Country	Number of Study Participants	Age range of included participants	Number of Studies (in Reviews)	Comments
Baggio, S. et al. (2020)	Cohort Study	Switzerland	53 <16y old, 352 ≥16 y old	0-82 y old	n/a	Laboratory based study among symptomatic children and adults
Balduzzi, A. et al. (2020)	Case Report	Italy	5	not reported	n/a	Observational report in a paediatric hemato-oncology department
Boast, A. et al. (2021)	Systematic review	n/a	n/a	n/a	not reported	Rapid literature review of pertinent paediatric literature
Boulad, F. et al. (2020)	Cross Sectional Study	USA	20 children, 13 caregivers	not reported	n/a	Observational study in a paediatric hemato-oncology department
Buitrago-Garcia, D. et al. (2020)	Systematic	n/a	n/a	n/a	94	Living systematic review and metananalysis on
Buonsenso, D. et al. (2020)	Cross Sectional	Italy	129 children	mean 11 ± 4.4 years	n/a	Observational study in children with confirmed SARSCoV2 infection
Castagnoli, R. et al. (2020)	Systematic	n/a	n/a	n/a	18	Systematic review of studies on children with confirmed SARSCoV2
Debatin, K.-M. et al. (2020)	Cross Sectional	Germany	2466 children, 2466	0-10 years old for	n/a	Seroprevalence study in children and parents (interim analysis)
Dong, Y. et al. (2020)	Cross Sectional Study	China	2135	n/a	n/a	Nationwide observational study of confirmed and suspected paediatric cases
Dufort, E. M. et al. (2020)	Case Report	USA	99	0-20 y old	n/a	Observational report of confirmed and suspected paediatric cases
Dumpa, V. et al. (2020)	Narrative Review/Case report	n/a	n/a	n/a	8	Case report and narrative review on SARSCoV2 infection in neonates
Ehrhardt, J. et al. (2020)	Cross Sectional Study	Germany	137 index cases, >2300 contacts	0-19 y old	n/a	Observational study in SARSCoV2 infected children attending daycare/school and their contacts to evaluate transmission
Ferrari, A. et al. (2020)	Case Report	Italy	21	0-18 y old	n/a	Observational report in a paediatric hemato-oncology departments
Fontanet, A. et al. (2020)	Cohort Study	France	326 adolescents and school staff, 345 parents and siblings	not reported	n/a	Retrospective cohort of high-school students, their families and school staff (COVID19 cluster)
Gale, C. et al. (2020)	Cohort Study	UK	66	0-30 days old	n/a	National observational study in neonates with SARSCoV2 infection
Gold, J. A. W. et al. (2020)	Case Report	USA	32 children, 13 educators	not reported	n/a	Observational report of SARSCoV2 infections in students and teachers (COVID19 clusters)
Gordon, M. et al. (2020)	Systematic Review	n/a	n/a	n/a	8	Rapid literature review of neonatal SARSCoV2 infections
Group, Children's Task and Finish (2020)	Narrative Review/Viewpoint	UK	n/a	n/a	n/a	Review of available data on children, schools and transmission in UK
Han, M. S. et al. (2020)	Case Report	South Korea	12	27 days to 16 years old	n/a	Laboratory based study among asymptomatic and mildly symptomatic children
Heavey, L. et al. (2020)	Case Report	Ireland	6 index cases (3 children and 3 staff members), 1025 contacts	not reported	n/a	Observational study in SARSCoV2 infected children attending school and school staff to evaluate trasmission
Held, L. (2020)	Narrative Review/Viewpoint	n/a	n/a	n/a	n/a	Reanalysis of data presented in ref Jones, TC et al (2020)
Hippich, M. et al. (2020)	Cross Sectional Study	Germany	11884 children	median 3.2 y (IQR 2.2 - 5.1 y)	n/a	Seroprevalence study in children

Author	Study Type	Country	Number of Study Participants	Age range of included participants	Number of Studies (in Reviews)	Comments
Hoang, A. et al. (2020)	Systematic Review	n/a	7780 children	n/a	131	Systematic review of studies on children with confirmed SARSCoV2 infection
Hrusak, O. et al. (2020)	Case Report	25 countries	200 children	not reported	n/a	Multinational survey in a paediatric hemato-oncology departments
Ismail, S. A. et al. (2020)	Cohort Study	UK	928 000 (median student number)	0-18 y old	n/a	Observational study of SARSCoV2 infection clusters and outbreaks in schools
Jones, T.C. et al. (2020)	Case Report	Germany	5524 children tested	0-19 y old	n/a	Laboratory study of routine testing samples for SARDCoV2
Jones, V.G. et al. (2020)	Case Report	USA	1	0.5 y old	n/a	Case report describing Kawasaki-like syndrome in an infant
Konsortium der Medizinischen Universität	Cohort Study	Austria	10 464 students and teachers	not reported	n/a	Monitoring study in 243 schools
Kyle, M.H. et al. (2020)	Narrative Review/Viewpoint	n/a	35	newborns	17	Review of studies reporting on children born by mothers with SARSCoV2 infection
L'Huillier, A.G. et al. (2020)	Case Report	Switzerland	23	median 2 y (IQR 3.8–14.5 y)	n/a	Laboratory based study on children infected by SARSCoV2
Lavezzo, E. et al. (2020)	Cross Sectional Study	Italy	234 children 0-10y, 28907 overall	all age groups	n/a	Population based study
Li, W.B. et al. (2020)	Case Report	China	105 index cases, 392 household contacts	median 51 y (IQR 39-60y)	n/a	Observational study to evaluate household transmission
Link-Gelles, R. et al. (2020)	Cohort Study	USA	30 pediatric cases, 22 adult cases	not reported	n/a	Statewide observational program in child care programs to identify SARSCoV2 infections
Liu, W. et al. (2020)	Cross Sectional Study	China	366	0-16 y	n/a	Oservational report in children with SARSCoV2 infection
Lu, X. et al. (2020)	Case Report	China	171	0-16 y	n/a	Oservational report in children with SARSCoV2 infection
Luo L. et al. (2020)	Case Report	China	4950, 783 children	median 38 y	n/a	Observational study evaluating transmission between close contracts
Madewell et al. (2020)	Systematic Review	n/a	77758	old	54	Systematic review of studies on household transmission
Marlais et al. (2020)	Cross Sectional Study	11 countries	18	6-14 y	n/a	Observational study in immunosuppressed children with SARSCoV2 infections
Minotti et al. (2020)	Systematic Review	n/a	4 children, 106 adults	not reported	16	Systematic review of studies in immunosuppressed children and adults with SARSCoV2 infection
Morand et al. (2020)	Narrative review/viewpoint	n/a	n/a	n/a	n/a	Narrative review about SARSCoV2 infection in children
Mustafa, N. M. et al. (2020)	Systematic review	n/a	n/a	n/a	17	Systematic review of studies describing clinical picture and transmission of SARSCoV2 in children
Nathan, N. et al. (2020)	Case Report	France	5	<3 months old	n/a	Observational report of infants with SARSCoV2 infection
National Centre for Immunisation Research and Surveillance (NCIRS)	Case Report	Australia	863	not reported	n/a	Observational study evaluating transmission between SARSCoV2 infected school children and staff and their contacts
Pollan, M. et al. (2020)	Cross Sectional Study	Spain	6627 children, 45331 adults	all age groups	n/a	Nationwide population based seroprevalence study

Author	Study Type	Country	Number of Study Participants	Age range of included participants	Number of Studies (in Reviews)	Comments
Pray, I. W. et al. (2020)	Cross Sectional Study	USA	127 children and 25 staff members	14-45 y old	n/a	Observational study about a summer school outbreak
Rawson, A. et al. (2020)	Case Report	USA	2	13y and 18y old	n/a	Observational report of immunosuppressed children with SARSCoV2 infections
Richard, A. et al. (2020)	Cross Sectional Study	Switzerland	902 children, 7442 adults	5-94y old	n/a	Population based seroprevalence survey
Riphagen, S. et al. (2020)	Case Report	UK	8	6-14y old	n/a	Observation report of Kawasaki-like syndrome in children with SARSCoV2 infection
Sheth, S. et al. (2020)	Narrative Review/Viewpoint	n/a	326 mothers-children pairs	newborns	39	Review of studies reporting on children born by mothers with SARSCoV2 infection
Somekh, E. et al. (2020)	Case Report	Israel	58 children, 36 adults	6-48 y old	n/a	Observational study on identified family clusters of SARSCoV2 infection
Stein-Zamir, C. et al. (2020)	Cross Sectional Study	Israel	1164 students, 152 staff	≥12 y old	n/a	Observational study about a high school outbreak
Stringhini, S. et al. (2020)	Cross Sectional Study	Switzerland	455 children, 2311 adults	≥5 y old	n/a	Population based seroprevalence study
Stringhini, S. et al. (2021)	Cross Sectional Study	Switzerland	1014 children, 2986 adults	all age groups	n/a	Population based seroprevalence study
Swann, O.V. et al. (2020)	Cohort Study	UK	651	median 4.6y (IQR 0.3-13-7y)	n/a	Observational cohort study in 260 hospitals describing characteristics of hospitalised children infected with SARSCoV2
Szablewski, C.M. et al. (2020)	Cross Sectional Study	USA	344 children and staff	6-19y for campers, 14-59y for staff	n/a	Observational study about a camp outbreak
Team, CDC Covid-Response (2020)	Cross Sectional Study	USA	2572	0-17y	n/a	National observational study in children with SARSCoV2 infection
Torres, J.P. et al. (2020)	Cross Sectional Study	Chile	1009 students, 235 staff	10.8±4.1 y for students, 48.8±10.4y for staff	n/a	Observational study about a school outbreak
Ulyte, A. et al. (2020)	Cohort Study	Switzerland	2831 students	6-16y	n/a	Seroprevalence study in school children
Vardhelli, V. et al. (2020)	Systematic review	n/a	793 neonates	newborns	45	Systematic review of studies reporting on children born by mothers with SARSCoV2 infection
Viner, R. M. et al. (2020)	Systematic review	n/a	41640	n/a	32	Systematic review on susceptibility and transmission of children to SARSCoV2 compared to adults
Volz, E. et al. (2020)	Modelling Study	UK	n/a	n/a	n/a	Modelling study about the B 1.1.7 variant of SARSCoV2
Wei, M. et al. (2020)	Cross Sectional Study	China	9	0-1y old	n/a	Observation study in hospitalised infants with SARSCoV2 infection
Yoon, Y. et al. (2020)	Case Report	South Korea	1 index case, 190 contacts	4y old	n/a	Observational study examining transmission of SARSCoV2 from infected toddler to contacts
Yung, C.F. et al. (2020)	Case Report	Singapore	223 adult index patients, 213 child contacts	0-16y for children	n/a	Observational study examining household transmission of SARSCoV2 from adults to children
Yung, C.F. et al. (2021)	Case Report	Singapore	3 index cases (2 pediatric, 1 adult), 119 contacts	5y, 12y old	n/a	Nationwide contact surveillance and contact tracing study on SARSCoV2 infections in schools
Zhang, Z.J. et al. (2020)	Case Report	China	4	0-28 days old	n/a	Observational report of neonates with SARSCoV2 infection
Zhu et al. (2020)	Metaanalysis	12 countries	213 clusters	n/a	57	Metaanalysis of studies describing household transmission clusters of SARSCoV2