Article

SARS-CoV-2 infection in children - a review on clinical disease, transmission and school closures

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Abstract

Coronavirus Disease 2019 has significant impact on societies and healthcare systems worldwide, but interestingly, children are less affected than adults. Infections with the severe acute respiratory syndrome coronavirus 2 have been reported in all age categories, including neonates, but occur less often in young children compared to adults. Moreover, the vast majority of children has mild disease and mortality is low. Immunocompromised children appear to have a higher risk of being admitted when infected and infection appears more severe in children with combined immunodeficiencies and immune dysregulation, in comparison to other immunodeficiencies such as antibody deficiencies. Children are less susceptible to infection than adults, and infectiousness appears to be either reduced or comparable. Vertical transmission is possible, but the risk hereof is very low. School closures have significant adverse impact on children, and because school outbreaks are relatively uncommon and strongly associated with regional incidence, school closures should be a last resort. Whether new variants of the virus might significantly change transmission dynamics remains unclear, and spread of these variants should be monitored carefully.

Introduction

The first case of Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was detected in Wuhan, China, in December 2019. Since then, the virus has spread rapidly, was characterized as a pandemic by the World Health Organization (WHO) in March 2020 and has caused more than 80 million cases including 1.8 million deaths as of January 1st 2021 (1). In Belgium, 649.453 cases were confirmed in this period, leading to 19.667 deaths (2).

From early on, children were shown to be less affected than adults. However, a number of questions remain, mainly regarding clinical disease in children with underlying immunodeficiencies, and the role of children in transmission. In this narrative review, we discuss the spectrum of clinical disease in children, with specific focus on immunocompromised children. Next, we review the existing literature on transmission in children and discuss the implications of these data on decisions regarding closing of schools.

COVID-19: clinical disease in children

None of the first reported cases were children, and early on in the pandemic, it was found that, although children of all ages were susceptible, clinical disease was much less severe than in adult patients (3). Even though testing strategies have changed significantly with increased availability over time, young children remain underrepresented among COVID-19 cases. The European Centre for Disease Prevention and Control (ECDC) reported that children aged 1-4 years represented only 1.3% of the cases, and that 4.2% of the cases occurred in children aged 5-11 years, while they represent 3.8% and 6.8% of the population, respectively (4). This is different for older children, where the proportion of cases is roughly equal to the proportion of the population they represent (4). However, children of all ages are substantially underrepresented in severe outcomes such as hospitalisation, intensive care unit (ICU) admission, ventilatory support requirement or death (4).

During the first epidemic wave from March 15th to June 28th extensive laboratory, school and hospital surveillance was performed in Belgium, showing a similar pattern (5). For most of the period investigated, schools were closed, especially for secondary school students. Although children made up about 20% of the population, they only constituted 10% of all tests. In addition to the fact that they were tested less frequently than adults, the positivity ratio was lower (1.8% in children versus 6.3% in adults). Moreover, infection with SARS-CoV-2 in children was less often a reason for hospital admission: only 1.6% of hospitalised patients in Belgium was less than 18 years old, whereas 3% of all positive test results were from children. Among hospitalised children, infants less than 1 year were overrepresented. Not only was the admission rate per 100.000 individuals higher in children less than 1 year compared to older children, the admission rate per 100 positive tests was also higher, suggesting that the youngest category of patients is hospitalised more readily in case of infection. The majority of hospitalised children (81%) did not suffer from severe complications and only 3% needed intensive care. Median hospital stay was only 3 days. Of all COVID-19 related deaths in Belgium, only 0,04% was younger than 25 years (8 out of 19.667 in the period December 1st 2019 up to January 1st 2021 while they represented 28% of the population on January 1st 2020 (6).

The proportion of asymptomatic children is estimated to be between 14.6 and 42% (7). A systematic review of 20 studies describing clinical presentation and outcomes in 1810 children showed that the majority (72%) had mild disease, while 21% of children had moderate disease severity and 7% was severely or critically ill. Mortality in these studies was 0.3% (8). Disease severity is probably overestimated in these studies, as most included only hospitalised patients, and are therefore biased towards the more severe spectrum.

Of children presenting with symptoms, fever and cough are most common, occurring in 46% to 64.2% and 32% to 55.9% of children, respectively. Symptoms such as rhinorrhoea, headache, sore throat, fatigue/myalgia and gastrointestinal symptoms including diarrhoea and vomiting can occur as well, but less frequently, in 10% to 20% of children (7, 9). However, fever and cough are indications for testing in many countries, which might have resulted in overestimation of the prevalence of these symptoms. When compared to adults in a study from China, children were found to present more frequently without symptoms (20% versus 5.5%), and less frequently with fever (57.1% versus 72%) (10).

A comparison of children who were admitted to either the general ward or the PICU in a hospital in New York showed that age ≥12 years was associated

with admission to ICU, while comorbidities such as prematurity, respiratory disease, congenital heart disease, diabetes mellitus, immunosuppression or kidney disease were not (11). These data suggest that adolescents are at higher risk of severe disease than younger children. A multinational European study showed that age of less than 1 month was associated with ICU admission (12). In Belgium, however, clinical surveillance during the first epidemic wave showed that infants younger than 1 year had a lower risk of complication (pneumonia, bacterial or fungal superinfection, ICU admission or acute respiratory syndrome) than older children (5). Indeed, neonatal SARS-CoV-2 infection is rare, mortality is low, and short-term prognosis in this group seems favourable (13-16).

Multisystem inflammatory syndrome

In April 2020, clinicians in the United Kingdom (UK) observed increased reports of previously healthy children presenting with a severe inflammatory syndrome in areas with high community transmission, two to four weeks after the initial peak of infections (17). This post-COVID inflammatory syndrome was termed Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in the UK (18) and multisystem inflammatory syndrome in children associated with COVID-19 (MIS- C) in the United States (US) (19).

Children present with prolonged fever and abdominal symptoms such as abdominal pain, vomiting and diarrhoea. Cardiovascular manifestations are present in 50-87% and rash in about half of the patients (20, 21). Clinical presentation is variable, with some children presenting with very high inflammatory markers but relatively mild disease, and others with profound shock. Kawasaki features are present in some children, with 5-22% of children meeting the criteria for complete Kawasaki, and 9-36% developing coronary aneurysms(20, 22, 23). Lymphopenia and high inflammatory markers are common. Median age is 8-11 years, and children from Asian and Afro- Caribbean backgrounds appear to be overrepresented (20, 23).

This syndrome of post-COVID inflammation is rare, estimated at less than two per 10000 COVID-19 cases (24). Although patients are frequently admitted to the ICU, length of stay is usually less than a week, and mortality is low, approximately 2% (22, 23). Most patients are treated with immunoglobulins or steroids, to halt the inflammation. However, effectiveness of these therapies needs to be investigated in ongoing clinical trials (25).

COVID-19 in immunocompromised children

Data from SARS-CoV-2 infection in patients with immunodeficiencies remain scarce. Moreover, patients with immunodeficiencies are a very heterogeneous group, and the course of SARS-CoV-2 infection is probably different depending on the specific part of the immune system that is affected. While a significant proportion of patients with life-threatening COVID-19 pneumonia were shown to have defects in type 1 interferon pathways, and patients with such a defect are clearly at higher risk of severe disease, similar linkages of specific immunodeficiencies to disease severity will be difficult to assess, since most of these conditions are rare (26).

Evidence from adults suggests that patients with both primary and secondary immunodeficiencies experience greater morbidity and mortality (27), although early reports described a favourable outcome in the majority of patients (28). A more recent description of SARS-CoV-2 infections in patients with immunodeficiencies, reported by the UK Primary Immunodeficiency Network registry demonstrated increased morbidity and mortality, with a case fatality rate of 31.6% in patients with primary, and 39.2% in patients with secondary immunodeficiency (29).

Studies reporting infection rates and outcomes of SARS-CoV-2 infection in children with immunodeficiencies are even rarer. A number of case reports with a total of 14 children, including common variable immunodeficiency patients, patients on prednisolone and patients receiving chemotherapy, showed asymptomatic or mild course in all patients, with none requiring admission (30-32). Testing of sera from 485 children with immunocompromising conditions, including oncologic diagnoses, solid organ transplant, bone marrow transplant, primary immunodeficiency, and rheumatologic conditions or inflammatory bowel disease on systemic immunosuppression showed a seroprevalence of 1%, similar as in general paediatric population. Moreover, only one patient was admitted with mild disease (33). Analysis of 21161 paediatric COVID-19 cases in the national registry in Mexico showed that while children with immunodeficiencies were less likely to be diagnosed with SARS-CoV-2 infection (adjusted prevalence ratio 0.773, 95% CI 0.664-0.882), they were more likely to develop pneumonia and be admitted (34). While the reduced infection rate might be the explained by an increased proportion of these patients having shielded, the increased risk of hospitalisation suggests that immunodeficiency might be associated with an increased risk of more severe disease in children.

The largest study reporting COVID-19 in children with immunodeficiencies reported an analysis of 2754 patients with primary immunodeficiencies in Iran, who were tested for SARS-CoV-2 infection if they presented with cough, fever and dyspnoea. They confirmed infection in 19 patients, resulting in an increased incidence of 1:144 compared to 1:178 in the total population (35). Infection appeared more common in children with combined immunodeficiencies and immune dysregulation, as opposed to other immunodeficiencies such as antibody deficiencies. Infection was not observed in patients with innate or complement deficiencies. However, the number of patients was too small to draw definitive conclusions. The mortality in this cohort was high, 8 out of 19 patients (42%) died. The majority of these had combined immunodeficiency and were not treated with haematopoietic stem cell transplantation (HSCT), potentially indicating the importance of cellular immunity. Although medical care was probably not optimal for these patients (the authors mention HSCT is not available), this indicates potential severity of COVID-19 in this subgroup of patients.

SARS-CoV-2 transmission in children

Whether or not children play a significant role in SARS-CoV-2 transmission has been a topic of much debate. As described earlier, clinical disease is less frequent and less severe in children compared to adults. However, whether this is due to reduced susceptibility to infection, or other factors, is not an easy question to answer. Moreover, it soon became clear that asymptomatically infected individuals could transmit the virus, which raised the question to what extent children contribute to spread of the virus, knowing that for many respiratory viruses, e.g. influenza, children are the main drivers of transmission (36). However, accumulating data is now pointing towards a minor role of children in SARS-CoV-2 transmission. In order to unravel the role of children in SARS-CoV-2 transmission, we discuss their susceptibility and infectiousness separately. Hereafter, we review the available information regarding vertical transmission.

Susceptibility of children to infection with SARS-CoV-2

In a seminal study from Iceland, 6% of the population was tested early in the pandemic. The investigators performed both targeted testing of symptomatic people and persons from high-risk areas or individuals with COVID-19 contact (n=9199) and random population screening (n=13080). In the targeted testing, 6.7% of children under the age of 10 tested positive, compared to 13.7% in older individuals. However, children were probably underrepresented in this group because they are more frequently asymptomatic. In the random population screening group, all children under 10 tested negative, while 0.8% of persons 10 years or older tested positive (37). This indicated that children were less susceptible to infection. Moreover, differences in viral load and duration of Polymerase Chain Reaction (PCR) positivity could potentially explain some of the difference between the groups (38, 39).

Instead of testing for presence of the virus by PCR, population-based seroprevalence studies could overcome some of these issues. Several cross-sectional population-based seroprevalence studies have been performed. The majority of these studies found lower seroprevalence rates in children compared to adults, with generally lower seropositivity in young children compared to adolescents (40-43). A large study in the US, using a convenience sample of 16025 serum samples, of which 1203 (7.5%) were obtained from children showed lower seroprevalence in children compared to adults in six states, similar levels in two states and higher levels in two states (44). Weighed mean seropositivity rates, calculated based on the data provided in the paper were 1.8% for children and 3.2% for adults. However, seroprevalence studies have a number of drawbacks. Antibody levels are higher in individuals with

more severe disease, and young children might induce lower levels, thereby underestimating the true rate of previous infection. Moreover, people from different age groups vary significantly in their behaviour and therefore risk of contact with SARS-CoV-2 infected individuals, which will influence the outcome of these studies, making it difficult to estimate the true susceptibility of children for SARS-CoV-2 infection compared to adults.

Household investigations are an elegant way to circumvent some of these hurdles. Because the contacts are well defined, and exposure is assumed to be comparable between adults and children, household contact investigation allows one to compare secondary infection rates between children and adults and therefore their relative susceptibility.

We found sixteen household studies that systematically tested household contacts by PCR and compared secondary infection rates in children versus adults (see table 1). Eight of these studies found a lower secondary infection rate in children and seven found no difference between children and adults. One study found an increased secondary infection rate in children (45). However, in this last study, there was a significant difference between children 0-9 years-old (3 out of 57 contacts tested positive, 5.3%) compared to children 10-19 years-old (43/231 positive, 18.6%). A meta-analysis on this subject confirmed that children younger than 10 to 14 years are less susceptible to infection with SARS-CoV-2 than adolescents and adults with an odds ratio of 0.52 (CI 0.33-0.82) (46).

Table 1. *Susceptibility of children for SARS-CoV-2 infection, compared to adults, based on household investigations.*

Study	Age children (year)	Children Infected/total tested (%)	Adults Infected/total tested (%)	Country
Bi 2020(105)	0-9	11/148 (7.4)	67/837 (8.0)	China
	10-19	6/85 (7.1)		
Grijalva 2020(63)	<12	18/32 (56.3)	70/129 (54.2)	US
	12-17	14/30 (46.7)		
Hu 2020a(64)	0-14	22/936 (2.4)	187/7223 (2.6)	China
Hu 2020b(106)	0-14	10/216 (4.6)	49/1128 (4.3)	China
Hua 2020(107)	<15	43/325 (13.2)	108/510 (21.2)	China
Jing 2020(108)	0-19	9/171 (5.3)	88/599 (15.7)	China
Lewis 2020(109)	<10	3/29 (10.3)	33/120 (27.5)	US
	10-17	16/39 (41.0)		
Li 2020(110)	0-5	1/44 (2.3)	60/292 (20.5)	China
	6-17	3/56 (5.4)		
Park 2020(45)	0-9	3/57 (5.3)	1202/10304 (11.7)	South Korea
	10-19	43/231 (18.6)		
Rosenberg 2020 (111)	0-5	5/25 (20.0)	88/182 (48.4)	US
	5-18	37/131 (28.2)		
Somekh 2020(112)	0-4	2/18 (11.1)	21/36 (58.3)	Israel
	5-17	13/40 (32.5)		
Van der Hoek 2020(113)	1-5	2/19 (10.5)	23/67 (34.3)	The Netherlands
	6-11	7/44 (15.9)		
	12-17	15/44 (34.1)		
Wang 2020a(114)	0-17	13/36(36.1)	64/92 (69.6)	China
Wang 2020b(115)	0-17	2/10 (20.0)	130/201 (59.7)	China
Wu 2020(116)	0-3	4/10 (40.0)	43/112 (38.4)	China
	4-18	1/21(4.8)		
Yousaf 2020(117)	<18	14/69 (20.3)	33/126 (26.2)	US

Although household studies are probably the most robust method to assess susceptibility to infection, there are a number of issues. For example, it is difficult to ascertain whether the person who presented first was indeed the index case, or whether this person was infected by another, asymptomatic or mildly symptomatic, household member. Alternatively, as shown by Kim et al., multiple infected individuals from one household could instead be infected by a common index patient outside the household (47). Indeed, antibody testing in quarantined household contacts of adult COVID-19 cases in Spain showed similar seroconversion rates for children and adults (17.6 and 18.7%, respectively) (48). Another analysis of 30 households with adult COVID-19 index patients also showed similar seroconversion rates in children (28/53, 52.8%) compared to adults (16/27, 59.3%) (49).

People from different age groups differ in their behaviour, and might also differ in their adherence to physical distancing and hygiene measures. This could alter their risk of exposure to SARS-CoV-2, even within households. However, looking at the available evidence to date, it seems highly likely that young children have a reduced susceptibility to SARS-CoV-2 infection compared to adults. This finding is supported by two modelling studies. Fitting of an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea demonstrated that susceptibility of infections was approximately half in individuals under 20 years of age, compared to older people (50). Another modelling study on transmission in 14622 individuals who were close contacts of 870 COVID-19 patients showed that susceptibility of children younger than 13 years old was significantly reduced compared to adults (OR 0.41, 95% CI 0.26-0.63) (51). The reason for this reduced susceptibility remains to be elucidated, but reduced expression of the angiotensin-converting enzyme 2 (ACE2) receptor in children younger than 10 years of age could play a role (52).

Infectiousness of children with SARS-CoV-2 infection

Nasopharyngeal samples of children with PCR-confirmed COVID-19 were tested in cell culture and demonstrated culture-competent virus in 12 (52%) of 23 children (53). However, in order to assess the true infectiousness of children compared to adults, it would be important to compare secondary infection rates stratified by age of the index patient. Unfortunately, there are few data available to answer this question.

Children are less often shown to be the index case in household clusters: in an analysis of 4021 households with one or more IgG positive child and one or more IgG positive adult, the first adult and child tested positive at the same time in 55.9%, the adult had the first positive result in 35.7%, and the child had the first positive result in only 8.4% of the households (54). Another study showed that in 31 household transmission clusters, only 3 out of 31 index cases (9.7%) was a child, where this was 30 out of 56 (54%) in H5N1 influenza (55). A similar result was found in another study, where in only 3 out of 39 (8%) of households a child was the first to develop symptoms (56). However, this could be biased due to the higher proportion of infected children presenting asymptomatically.

A study in a Parisian hospital showed a lower attack rate amongst health care workers in the paediatric setting compared to the adult setting (2.3 versus 3.2% respectively, p=0.0022), although this was probably a reflection of the lower number of COVID-19 admitted cases and potentially a difference in adherence to personal protective equipment and physical distancing measures (57). Large-scale comparison of self-reported incidence rates amongst child care providers in the US (within the context of already implemented significant mitigation measures) showed no difference with background transmission rates, therefore suggesting that exposure to child care does not entail an increased risk for COVID-19 (58). This finding is supported by a French seroprevalence study in children and day-care staff, which suggested that intrafamily transmission was more common than transmission in day-care centres (59). The probability of transmission is highest in contacts of the same age, particularly for children up to 14 years old and adults aged 65 years and older (60). However, this might mainly reflect the nature of behaviour and interactions of certain age groups.

In a Korean study, 5320 contacts of 22 children with confirmed COVID-19 were tested, with only two secondary cases detected, and investigation of transmission from paediatric cases in Norwegian primary schools found no secondary cases (61, 62). Analysis of 191 household contacts of 101 index patients in the US showed that if the index case was less than 12 years old, the secondary infection rate was 53% (9/17), and 38% (11/29) if the index case was 12-17 years old. This was not significantly different from adult index cases, where the secondary infection rate was 57% (82/145) (63). Although this study is valuable because of the direct comparison of secondary infection rates between children and adults, the small number of paediatric index patients and the high secondary infection rate suggests some selection bias, impeding extrapolation. A similar study in China showed a secondary infection rate of 1% (2/193; 95% CI 0.1-3.7) if the index patient was a child, compared to 2.6% (207/7966) if the index patient was an adult, which was not significantly different (64). This was supported by a modelling study on transmission in 870 COVID-19 patients and 14622 close contacts, which found no difference between infectiousness of children and adults (51). However, a more recent household study from Israel showed a reduced relative infectivity of children of 63% (95% CI 37-88%), compared to adults (65). Most studies comparing children and adults do not separately assess children <10 years of age, who might be less infectious than older children. In summary, infectiousness of children with SARS-CoV-2 is difficult to establish reliably, but appears to be similar or reduced compared to adults.

Whether or not faecal shedding of virus contributes to transmission remains unclear. There is ample evidence of prolonged viral shedding in stool, with multiple reports describing children who test positive by PCR on faecal samples for up to five weeks after testing negative in samples from the respiratory tract (66-69). However, there are only sporadic reports of replication-competent virus being isolated from stool (70).

Vertical transmission of SARS-CoV-2

The possibility and relevance of vertical transmission is still debated. Although the ACE2 receptor is expressed abundantly in the placenta, it was hypothesized that physiological mechanisms exist to prevent transplacental transmission of SARS-CoV-2 (71). Since the start of the pandemic, the lack of information on this subject has created uncertainty and concern. Presence of SARS-CoV-2 has been confirmed by PCR on placentas, amniotic fluid, umbilical cord blood, vaginal secretions and breast milk (72, 73). Percentages of positive SARS-CoV-2 PCR in neonates born to mothers with COVID-19 vary from 0% to 8% (72-75). However, although there have been cases described where positive test results were reported simultaneously in placental and neonatal samples, indicating that vertical transmission occurs, it cannot be stated unequivocally that confirmed neonatal infections are due to vertical transmission in a majority of cases (73). Congenital malformations related to maternal COVID-19 have not yet been reported. Reviews on the transmission of SARS-CoV-2 in breast milk show that 0% to 13.2% of milk samples tested with PCR were positive (76, 77). However, replication competency of the virus was not confirmed in these samples. In none of the neonates who tested positive it could be established with certainty whether transmission took place through breast milk, through droplets during close contact, during passage of the birth canal or via the placenta. Therefore, it is recommended that mothers with COVID-19 should be encouraged to breastfeed, as the benefits seem to substantially outweigh the potential risk for transmission, especially considering the immunomodulating effects of breast milk (77, 78).

Closing schools in order to reduce transmission: a last resort

School closures have been implemented to reduce transmission, but the negative effect of this measure on children is significant. Here, we discuss the available data on SARS-CoV-2 transmission in educational settings, the impact of school closures on children and on transmission, and the pros and cons of this intervention.

Accumulating data suggest that transmission in schools occurs, but that it is relatively uncommon. Twelve out of 17 countries (71%) who responded to an ECDC survey, reported transmission clusters in educational settings, the majority of which occurred in secondary schools, followed by primary schools and preschools. The number of cases involved in each cluster was usually less than 10, although clusters with up to 80 cases were reported (4). Analysis of notified cases from January until August in Germany showed that

school outbreaks re-occurred after schools reopened, but these were few and small. Out of 8841 COVID-19 outbreaks, 48 (0.5%) occurred in schools, and included 216 cases, of which almost half was older than 21 years old (79). A large prospective epidemiological study in England, analysing national surveillance data from cases occurring in students and staff after reopening of schools after the first lockdown in July showed that infections and outbreaks were uncommon. Importantly, there was a strong association with regional COVID-19 incidence, and measures to mitigate community transmission should be implemented to protect educational settings (80). This notion was confirmed in a modelling study of transmission data from Germany and Scandinavian countries, which showed that school closure caused a visible reduction in on transmission, but that reopening of schools is feasible as long as community transmission levels are low (81).

School surveillance was started in Belgium when schools reopened after the summer holidays (5). Several additional mitigation measures were imposed on population level and schools remained closed after the autumn break for an extended period. During this period of 15 weeks, from all children less than 6 years old, 0.2% tested positive by PCR. This was 2.8% and 4.5% in all children aged more than 12 years and staff, respectively. Similar to other countries, the pattern of confirmed cases in children follows, rather than precedes the pattern of infections in the general population in Belgium.

Secondary infection rates in schools are generally low (82-84). Early data from Ireland, from before schools closed in March 2020 did not show any paediatric transmission, although the overall number of cases was low and the number of paediatric cases was probably underestimated because only symptomatic individuals were tested (89). Epidemiological data from New South Wales, where most schools remained open during the first epidemic wave, showed that the secondary attack rate was low at 1.2%, and schools did not contribute significantly to SARS-CoV-2 transmission (28). However, large school outbreaks are reported occasionally; one such outbreak occurred in Israel just after schools reopened with attack rates of 13.2% in students and 16.6% in staff (85). Belgian data show that less than one fifth of the cases in school are a result of transmission inside the school (5).

It has been challenging to estimate the relative effectiveness of school closures, compared to other mitigation efforts. However, consensus amongst most studies is that closing schools reduces transmission, but is most effective when implemented in combination with other interventions. A modelling study from the Netherlands showed that closing schools for children aged 10-20 years is expected to reduce the reproduction number by 8%, while closing schools for children aged 5-10 years would reduce the reproduction number by 5% and reducing contacts among children aged 0-5 years is expected to have negligible effect (86). This suggests that closing secondary school would have most impact on transmission. Whether new variants of the virus, such as recently identified in the UK and South Africa, might change these dynamics remains unclear, and transmission should therefore be monitored carefully, with appropriate adjustments of policies if necessary, based on evolving evidence. The variant that was first encountered in the UK on 20 September 2020 was designated as Variant of Concern (VOC) on 18 December 2020. Whereas it constituted initially only 1 in 4 tests, the proportion of the new variant increased to almost two thirds in London in only three months' time (87). It was estimated that individuals infected with this VOC 202012/01 transmit the virus to 11% to 15% of contacts, leading to a secondary attack rate that is 10% to 70% higher than in cases with the wild type virus (88). The increased transmissibility does not affect any age group in particular, as was shown by a surveillance study in the UK (89). During an outbreak of COVID-19 in a school in Rotterdam, The Netherlands, students, teachers and household contacts were tested for the new variant. Preliminary results showed that 10% tested positive and approximately 40% of these infections was due to the new variant (90). In Belgium, four possible cases of the VOC 202012/01 were identified, but definite results were not yet available on December 25th (91).

Given the low prevalence and reduced severity of COVID-19 in children, exposure of teachers and other staff should be a major concern. A significant proportion of school employees in the US (39.8-51.4%) was estimated to be at increased risk of severe COVID-19 according to CDC guidelines (92, 93). However, studies from England, Norway, Denmark, Sweden and The Netherlands demonstrated that teachers did not have an increased risk of COVID-19 compared to other professions(4, 94-97).

UNESCO reports that in late April 85% of learners worldwide were affected by school closures due to SARS-CoV-2 (98). Closing schools has significant adverse impact on children, not only because they miss out on important learning opportunities, but also because of reduced interaction with peers, the lack of structure and daily rhythm and for some children school meals, with significant impact on well-being and child protection (99). There is evidence of increased vulnerability and domestic violence for children when schools are closed (100). In The Netherlands an increase of child abuse of 81% was reported by an online assistance tool, and was confirmed by National Prevalence Studies of Abuse in Children and Adolescents where child abuse was estimated to have more than doubled, especially in the category of emotional neglect (101). Children with special needs and from less advantaged backgrounds are more likely to suffer, with the risk of aggravating existing inequalities in society (99). Moreover, the economic costs of schools closures are estimated to be substantial, mainly due to reduced parental economic activity (102).

In order to open schools safely, it is crucial that physical distancing measures are in place in order to prevent crowding, and that children and staff are trained to strictly apply hygiene measures in order to prevent transmission. Concrete advice on these measures, including formation of so-called 'bubbles' is now available from several resources (4, 103). Moreover, efficient testing and tracing should be implemented in order to prevent onward transmission if cases occur. A modelling study estimated that in order to prevent another wave of infections, 75% of individuals with symptomatic infection would need to be tested, assuming that 68% of contacts could be traced, and all positive cases would need to be isolated (104).

In conclusion, schools play a limited role in transmission if mitigation measures are implemented, and should only be closed as a last resort because of significant harm to children's mental health, educational opportunities and social development.

Conclusion

Young children are proportionally less often affected by SARS-CoV-2 infection than adolescents and adults. Moreover, children are underrepresented in admissions, complications and mortality. Asymptomatic infection appears to be common in children and although adolescents and immunocompromised children seem to be at higher risk of severe disease, short-term prognosis for children is favourable, even in the rare and clinically variable entity of multisystem inflammatory syndrome. Evolving evidence shows reduced susceptibility and similar or reduced infectiousness of children compared to adults and a very low risk of vertical transmission. Secondary attack rates in schools are low and patterns of infection in school aged children generally follow population incidence. Educational staff does not appear to have a higher risk of infection with SARS-CoV-2 compared to other professions. On the other hand, children's mental health, educational opportunities and development can be significantly impeded by school closures, which should therefore remain a last resort. Transmission dynamics might change with the spread of new variants and vigilance is required. In the future, less invasive and faster testing methods might contribute to close monitoring of transmission and facilitate health policy decisions.

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