COVID-19 in children: current evidence and key questions

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# Abstract

## Purpose of review:

SARS-CoV-2 infection in children has been less well characterised than in adults, primarily due to a significantly milder clinical phenotype meaning many cases have gone undocumented by health professionals or researchers. This review outlines the current evidence of the epidemiology of infection in children, the clinical manifestations of disease, the role of children in transmission of the virus, and the recently described hyperinflammatory syndrome observed later during the first phase of the pandemic.

## Recent findings:

International seroprevalence studies have found younger children to have lower prevalence of antibodies to SARS-CoV-2, indicating they have not been infected as much as adults. This may be due to shielding by school closures, or by a reduced susceptibility to infection, as indicated by a significantly lower attack rate in children than adults in household contact tracing studies. The most well recognised symptoms in adults of cough, fever, anosmia and ageusia are less frequent in children, who may often present with mild and non-specific symptoms, or with gastrointestinal symptoms alone. Risk factors for severe disease in children include chronic lung, cardiac or neurological disease, and malignancy. However, the absolute risk still appears very low for these cohorts. A new hyperinflammatory syndrome has emerged with an apparent immune aetiology.

## Summary:

Important questions remain unanswered regarding why children have mild disease compared to adults; how children of different ages contribute to asymptomatic community transmission of the virus; and the pathophysiology of and most appropriate investigation and treatment strategies for the novel hyperinflammatory syndrome.

# Keywords

COVID-19

SARS-CoV2

Children

Paediatrics

Transmission

Paediatric Multisystem Inflammatory Disorder

# Introduction

It has been clear from the first Chinese reports that COVID-19 is a different disease in children and young people than in adults. The primary effect of age as a predictor for both case numbers and severity of illness has been replicated in many countries, leading to questions about how the pathophysiology and disease course differs in children and adults. Whilst much has been learned about the epidemiology and clinical features of infection in children, many important questions remain unanswered which have implications for treatment strategies and infection control policies. This review outlines the current evidence of the epidemiology of infection in children, the clinical manifestations of disease, the role of children in transmission of the virus, and the recently described hyperinflammatory syndrome observed later during the first phase of the pandemic.

# Epidemiology

Since the initial reports from China at the beginning of the epidemic[1], children have been underrepresented in case figures from around the world, making up only 1% of confirmed cases in the UK as of the start of May 2020 [2]. Collated European data shows children under 10 accounted for 1.9% of cases and children aged 10 – 19 3.7% [3]. The low number of cases in children is partly a reflection of their significantly reduced severity of acute infection compared to adults, meaning that children were less frequently unwell enough to present to hospital for testing in early phases of the pandemic. Children also less frequently present with symptoms meeting the case definition for COVID-19 so qualifying for testing. However, a study early in the pandemic from Iceland found extremely low rates of infection in young children, with only 6.7% of children tested from high risk groups being positive compared to 13.7% of those aged over 10yrs, and none testing positive from invitation population screening compared to 0.8% of those over 10 years [4]. In the town of Vo, Italy, over 70% of the population was screened at 2 intervals 14 days apart, and no positive cases in children <10 years were found, despite 13 of them cohabiting with individuals who tested positive[5]. The background prevalence in the population was 2.6%.

Nationally representative seroprevalence has helped to understand better how frequently children have been infected during the pandemic to date. A large study of over 60,000 people in Spain found significantly fewer children to be seropositive than adults (ranging from 1- 3% compared to >5% of adults) [6]. A representative sample from Geneva, Switzerland found only one positive child less than 10 years of age, which was equivalent to a relative risk of 0.3 for having acquired infection. There were no significant differences between children ages 10 – 19 and more mature adults in this study [7]. Pre-print serosurveillance data from a high incidence area of Lombardy, Italy demonstrates increasing seroprevalence with age [8].

During the first wave of the pandemic that children were less affected than adults, as represented in case numbers and seroprevalence. This may be due to a number of factors, including reduced susceptibility to acquiring the infection. Social factors such as protection from community transmission by early school closures may play a small part, although the majority of transmission events following national lock downs occurred within households, from which children were not shielded. In more recent months, an increasing proportion of positive cases are amongst young adults and children, although this may be a feature of a decreasing burden of disease amongst the elderly who are taking more care to be socially distant.

# Transmission

Early in the pandemic it became clear that children were spared from the worst of the clinical effects of COVID-19. This has led to intense interest into whether children can silently spread infection in households and society. This is because children are thought to be significant amplifiers of many respiratory viral infections such as influenza, where control measures have been designed to prevent such transmission. For example plans for school closures are considered a key non-pharmaceutical intervention for control in an influenza pandemic [9].

## Susceptibility to infection

Initial evidence of contact tracing data from Shenzhen in China appeared to show children becoming infected at a similar rate to adults within households, but being less likely to become symptomatic [10]. However, subsequent data has consistently demonstrated that children are less susceptible to becoming infected with SARS-CoV-2 than adults given equal or similar exposure, as determined through household cluster evaluation. Studies from Guangzhou [11]and elsewhere[12] in China both demonstrated significantly lower odd ratios (OR)of a child becoming infected within households (OR of 0.2 and 0.3 respectively), which has been bolstered by subsequent data from the USA [13], Israel [14] and the Netherlands (including testing with serology) [15]. A pre-print of a meta-analysis of several studies across all settings suggests a pooled OR of 0.56, and when this was restricted to household contacts only a pooled OR of 0.41 [16] . As the odds of becoming infected appear to increase with age, it is likely that younger children are less susceptible to older adolescents. This would be consistent with epidemiological data showing increased case numbers in those aged 15 – 18 compared to children under 10 years.

## Contagiousness

The question of how infectious a child may be once there is active infection has been difficult to elucidate. In the Netherlands and Iceland, tracing data has found that transmission from children to other children or adults has been very rare, with the majority occurring between adults, and sometimes from adults to children[17,18]. However, as these studies are generally biased towards testing of symptomatic individuals, it is possible that transmission between children could have been overlooked, or that due to school closures children have not had sufficient exposure to become infected and transmit onwards. Lack of evidence of significant transmission within school environments [19–21] implies limited transmission from children as index cases, described in more detail below. Studies from South Korea using systems analysis of index cases and linked secondary cases found children under 10 to be significantly less likely to result in secondary transmission than adults, but those aged 10 – 19 to be as, or more likely to result in secondary transmission [22]. However, a subsequent publication which corrected for shared exposure (index child and their secondary case both having been exposed to the same initial infection event) found only one transmission event from over 100 positive cases [23]. However, this very low rate of secondary infection is in the setting of immediate quarantine of the infected child, including carers wearing full airborne protection PPE.

## Viral dynamics

Insights into the viral dynamics of children with COVID-19 have proved complex. A study from Switzerland found children to have relatively comparable viral loads and culturable virus to adult patients with COVID-19. However, the relatively low number of children sampled, who were those who happened to be tested at the laboratory for uncertain clinical indications, opens the question as to whether this sample derived from children who likely had more severe symptoms is generalisable [24]. A study looking solely at children with mild to moderate symptoms found that children under 5 years had significantly higher viral loads than adults, although older children had comparable levels to adults [25]. This study only compared cycle threshold values for viral RNA, and not live virus. Pre-print data from a large patient cohort in Germany (although with low numbers of children) found children to have slightly lower viral loads than adults [26]. Whether this difference is clinically significant is uncertain, and as the cohort were patients who had been tested at the participating laboratories for unspecified clinical indications, it is not clear whether the children had comparable disease to the adults in the study, nor whether the sample of children included is more broadly representative. A further study found similar viral loads in children to adults, including a small number of asymptomatic children [27].

## Transmission within schools

Interest in schools has intensified as many northern hemisphere societies plan for their reopening following a summer break, with many having been closed for over 6 months. Several studies have been conducted into transmission of COVID-19 within the school environment from around the world. Early data from France in a secondary school located in an area of high transmission documented a very high rate of seroprevalence in a high school, at over 40% of pupils and staff. This was much higher than the 10.9% of pupil’s family members, implying a significant amount of transmission occurred within the school environment. However, 205 out of the 242 children in the study were aged 15 or over, with only 1 of the 37 children aged 14 years or under being seropositive [28]. In contrast, a study from the same area within a primary school found no evidence of transmission within the school environment and higher seropositivity in the households of pupils (12%) than in school pupils (8.8%) [29]. Contact tracing from Ireland of 3 children and 3 teachers with COVID-19 found only one secondary case from over 1000 contacts, from a teacher to another adult outside the school environment [19]. Only symptomatic contacts were tested leaving open the possibility of some asymptomatic positive contacts. Data from Singapore from several cases in school found no secondary cases amongst children, including following an outbreak among staff at a daycare centre [20]. Contact tracing from New South Wales, Australia, found very limited evidence of onward spread within the school environment, with only 18 secondary cases found from an initial 25 index cases (15 children and 12 adults) despite 44% of contacts having been tested regardless of symptoms. The highest secondary attack rate was between adults at 4.4% [21]. A serological survey of an outbreak in Chile following an index case in a primary school teacher found a seropositivity of 9% in younger pupils and 16% of staff[30]. As the area experienced a high rate of transmission during the study period, it is not clear what proportion of the infections were acquired in the school.

Israel, following an initially successful campaign to suppress COVID-19, experienced a surge in case numbers following the opening of schools simultaneously with the opening of many other parts of society. A study from a secondary school there reports a large outbreak, affecting 13% of 153 of 1164 (13.2%) pupils and 25 of 152 (16.6%) staff members [31]. Whilst the study cannot determine the chain of transmission, nor the routes into the school, it does demonstrate that in areas with high rates of community transmission that SARS-CoV2 can successfully transmit in a school environment. Early data from Public Health England analyses into cases of COVID-19 in schools following their partial reopening in June 2020 found 67 cases, and 30 outbreaks (consisting of 2 or more cases) of which 22 consisted of transmission between staff members, or from a staff member to a child. Outbreak size was strongly correlated with level of community transmission [32].

# Clinical illness

## Signs, symptoms and investigations

Many studies have reported on the clinical signs and symptoms of children with acute infection with SARS-CoV-2. It should be noted that most children in these reports were unwell enough to seek medical attention, primarily in acute hospitals, so data is skewed towards those with the most severe illness. Data is still lacking on the true proportions of children who develop no symptoms at all, those who develop mild symptoms (myalgia, headache, rhinorrhoea etc) which would not meet formal case definitions for COVID-19, and those who would be classed as symptomatic according to case definition (persistent cough, fever or shortness of breath).

Despite study populations being skewed towards children with more severe illness, symptoms remain significantly milder than in adults. Fewer children appear to have classic symptoms, with most studies reporting 50% of children having cough or fever, and early data from the USA suggesting 74% to have at least one of those symptoms [33]. Upper respiratory tract symptoms such as rhinorrhoea or sore throat are present in between 7 – 22% of children [34,35]. Non-respiratory symptoms are relatively common, with at least 10% of children having diarrhoea and/or vomiting [33,36]. Ascertaining the true proportion of asymptomatic cases has not to this point in time been done effectively or systematically, as by their nature they are likely to be undercounted. Prospective testing strategies so far used for research have also been used to inform infection control during the pandemic, thereby preventing true studies of asymptomatic transmission. Despite this, Chinese cohorts have found between 4% [37] and 16% [36] to be asymptomatic. Data from Italy found 21% of patients to be asymptomatic[35]. As these studies were performed cross sectionally without follow up, we cannot be sure what proportion of these children later developed symptoms. Many studies of COVID-19 also have poor definitions of “asymptomatic”, with some discounting any symptoms which would not meet case definition criteria. Studies of seroprevalence with retrospective symptom surveys have found an asymptomatic proportion as high as 50% [29,30], however these are subject to significant recall bias.

Laboratory tests conducted during hospital visits similarly show a much milder picture in children than adults. Lymphopenia is uncommon, and inflammatory markers rarely significantly raised with CRP often normal or mildly elevated (e.g. 30mg/L) [34,35]. Imaging of the chest is normal in up to 35% of patients[38], and where CT scans have been performed, they rarely show severe involvement, with few reports of ground glass shadowing or halo signs [39]. Of note, abnormal chest imaging has been detected even in children not currently displaying clinical symptoms of disease [40]. Chest imaging is not considered necessary for the diagnosis of COVID-19 in children [39].

## Outcomes and risk factors

Whilst rare, serious illness does occur in a small number of children. In a large cohort from China, 6% of cases were classed as severe, or critical (with severe defined as an oxygen requirement) [37]. Data from a pan European consortium demonstrated that the presence of comorbidities was a risk factor for admission to paediatric intensive care), with the most common being chronic lung disease, congenital heart disease, neurological disease or malignancy [41]. Intensive care admission is rare, with only 70 cases being admitted in the UK as of June 23rd 2020 since the beginning of the pandemic [42]. Age appears to be a risk factor, with young infants and older adolescents at higher risk of severe disease [34,41,43]

Children with comorbidities do appear at higher risk of severe disease, but in general the risk remains low. Reports of small cohorts of children with inflammatory bowel disease[44], cancer[45] and chronic kidney disease [46] who have tested positive for SARS-CoV-2 have all had a mild clinical course. Determining the true relative risk is difficult due to low case numbers, but one study has calculated an odds ratios for PICU admission of 3.1 (1.2 – 8.2) for chronic lung disease, 2.9 (1.0 – 8.4) for congenital heart disease and 2.8 (1.0 – 7.9) for neurological disease [41].

# Paediatric Multisystem Inflammatory Syndrome Associated with COVID-19

Late in May 2020 reports emerged from around the world of a surge in cases of children with symptoms resembling Kawasaki disease, but with profound multi-organ dysfunction and shock [47,48]. This surge followed 4 weeks after the initial peak of the COVID-19 pandemic in the same areas. The UK Royal College of Paediatrics and Child Health established a working case definition for Paediatric Inflammatory Multi-System disease Temporally Associated with COVID-19 (PIMS-TS) [49], which was also described in the US [50] and by the World Health Organisation [51] as Multi-system Inflammatory Syndrome in children associated with COVID-19 (MIS-C). The median age of children affected tends to be between 8 and 10 years of age [52,53].

Post-COVID multisystem inflammation in children is extremely rare. Only 78 cases were admitted to PICU in the UK up until May 10th 2020 [54]. Given an estimated seroprevalence among children of 4%, this would equate to an incidence of less than 2 cases per 10,000 cases of COVID-19 in children. Peaks of cases have occurred 2 – 4 weeks after the peak in incidence of COVID-19 [53], and almost all children from various reported cohorts are positive for SARS-CoV-2 IgG [48,52]. Children from a Latino, Black, Asian or other minority ethnic background are overrepresented in the cohorts described so far [48,52,53]. The pathophysiology of this inflammatory syndrome has not yet been well established.

Symptoms of this syndrome include prolonged fever, and abdominal symptoms in the early phase (including abdominal pain, diarrhoea and vomiting). Features of Kawasaki disease are variably present, with proportions of children meeting full AHA criteria for KD ranging from 5%[55] to 22%[52] (depending on case definition used). Shock is common, as is profound acute myocardial dysfunction. Coronary artery dilatation to some degree has been reported between 8%[53] and 14%[52] of cases. Inflammatory markers are significantly raised, including D dimers, ferritin and CRP [56].

The syndrome appears to be heterogeneous and as yet there is no international consensus regarding disease classification. The UK based description classified the condition into 3 groups: those with raised inflammatory markers but relative mild clinical disease, those with profound shock and multi-organ dysfunction, and those with classical features of Kawasaki disease[52]. The US CDC used latent class analysis to categorise differently; those with profound shock and organ dysfunction, those testing positive for acute SARS-CoV-2 infection with respiratory distress and ARDS, and those with classical features of Kawasaki disease [55]. Immunological phenotyping would suggest that severe COVID-19 with ARDS is a distinct entity to PIMS-TS/MIS-C [57], which may have important therapeutic implications.

It is unknown which therapies may be effective for PIMS-TS/MIS-C, and whether differing phenotypes require different therapies. A UK expert group consensus process available via pre-print agreed intravenous immunoglobulin (IVIG) as the suggested first line therapy, and also agreed there was equipoise for clinical trials to compare IVIG with high dose corticosteroid as first line therapy [58]). These therapies are now offered to children in the UK RECOVERY platform trial for people of all ages with COVID-19 [59] as this is a critical global question due to the short supply and cost of immunoglobulin treatment. Second line therapies proposed and used have included IL-6, TNF and IL-1 blockade, with IL-6 blockade currently being tested as a second line agent in paediatric inflammatory syndrome within the RECOVERY protocol.

Prognosis for this condition is generally good, with most children having a rapid recovery in clinical and myocardial function. The mortality rate of an already rare condition is around 2%[53,54,56].

# Unanswered questions

Whilst it is clear children predominantly suffer mild illness from COVID-19, the reasons why remains unclear. There is some evidence that children express lower levels of the ACE2 protein (where SARS-CoV-2 enters cells) in nasal epithelium, with expression increasing throughout childhood [27,60].The clinical relevance of the difference is not established, particularly as there does not appear to be a difference in viral load associated with ACE2 expression [27]. There are reports of cross reactivity of T cell mediated immunity to SARS-CoV-2 which are based on previous exposure to other, non-severe human coronaviruses (hCoV) [61]. This would support the hypothesis that due to frequent seasonal exposure to similar viruses children have some pre-existing immunity to help protect against severe lower respiratory illness due to SARS-CoV2. If true, this hypothesis could also in part explain the “U shaped” gradient of severity. Intensive care admissions are reported to be more frequent in infants under 1 year who may have minimal pre-existing hCoV exposure, and are also higher in older teenagers whose immunity to these viruses acquired in early childhood may have waned [33,41].

The potential role of school environments in contributing to wider community transmission of SARS-CoV2 is still unknown. Most studies to date are small or occurred in communities with relatively low levels of transmission. The chain of transmission is often unclear, although infected adult staff members appear to have been the main propagators of infection. Whilst Sweden kept schools for those under 16 years open throughout the pandemic, testing was low and focussed only on those with severe symptoms in the early stage. This means that while very few children became unwell[62] it is not certain to what extent children contributed to wider community spread of disease. In particular, the role of silent asymptomatic spread needs to be addressed. Whilst a substantial proportion of children may be asymptomatic [30], there is some clinical evidence that transmission risk is correlated to symptom severity, with asymptomatic individuals transmitting least [63].

The mechanisms behind paediatric inflammatory syndrome due to COVID-19 are still not well understood. The delay between acute infection and onset of hyperinflammatory response hints at a distinct immune aetiology. This is supported by peripheral immunophenotypes which demonstrate elevated levels of IL-β and IL-6, as well as high CD64 expression on neutrophils and monocytes during the acute phase of the illness [64]. Detailed immunological analysis confirms features highly distinct from those of either Kawasaki disease or acute SARS-CoV-2 infection [65], including autoantibodies against lymphocyte activation processes, phosphorylation pathways and cardiac development. Further research is required to establish the pathophysiology and most appropriate therapies for this condition.

# Conclusion

SARS-CoV-2 appears to infect children less readily than adults and causes significantly more mild disease. Many children seem to be asymptomatic, but the true proportion is unknown. Critical illness occurs but is rare, and comorbidities such as neurodisability, chronic lung disease or existing cardiac disease increase the risk of requiring intensive care admission. Mortality is extremely rare. Children do not appear to have played a significant role in amplifying transmission of COVID-19 so far and transmission in schools appears predominantly low, although in the setting of widespread community transmission outbreaks have occurred. A rare, newly-described inflammatory condition may occur as a delayed immune response to the virus, which can result in severe myocardial dysfunction, shock, and rarely death. Important questions remain regarding the mechanisms protecting children from severe disease, their role in community transmission and the pathophysiology and treatment of the post COVID-19 multisystem inflammatory syndrome.

# Summary points

* SARS-CoV-2 infection causes mild disease in the majority of in children. Symptoms may be non-specific and difficult to distinguish from other respiratory or non-respiratory viruses.
* Children do not appear to have played a significant role in propagation of the first wave of the pandemic. Evidence suggests they are less susceptible to acquiring the infection then adults.
* A novel post COVID-19 hyperinflammatory syndrome has emerged in children with an immune phenotype distinct from both acute SARS-CoV-2 infection and Kawasaki disease.
* Important questions remain regarding the mechanisms which protect children from severe infection, their role in asymptomatic transmission of the virus, and the aetiology, diagnosis and treatment of the novel hyperinflammatory syndrome.

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# Conflicts of Interest

None relating to this manuscript.

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