COVID-19 - research evidence summaries

Research & Evidence team
Here we provide a summary of key evidence regarding COVID-19 in children and young people.

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Table of contents

- Introduction
- Epidemiology
- Transmission
- Clinical features and investigations
- At risk groups
- Neonatal
- Therapeutics
- Prognosis
- Summary
- Notable evidence
- References
- Downloads

Introduction

This summary was produced in partnership with The Don't Forget the Bubbles team, and based on published and pre-print studies identified in our rapid review. We completed the final update to this summary on 22 July 2021, according to the
Published date on 28 June 2021 and JCVI guidance from 19 July 2021.

From now, we will add details of key studies only in the section, Notable evidence.

The initial phase of this rapid review, which began in April 2020, involved a comprehensive look at all studies regarding COVID-19 in children and young people. On 1 July 2020 we refined our search process to update the summary with studies considered to be good quality or of high impact. A full summary of all the papers identified on COVID-19 and children published to date is hosted by Don’t Forget the Bubbles.

The evidence found during the initial six-month period can be downloaded below together with search strategies and inclusion criteria used to identify papers during both periods.

Some included studies, indicated in the reference list [1], provide preliminary findings that were not certified by peer review; these findings should be treated with due caution.

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**Epidemiology**

**Can children and young people suffer from COVID-19 disease?**

COVID-19 disease has been reported in children and young people of all ages, including shortly after birth.1 2 3 There have been far fewer confirmed cases of COVID-19 disease in children than adults (children consistently make up 1-5% of total case numbers in reports).4 5 6 7 8 9 10 11 12

Publications about acute infection suggest that there are comparatively few children infected by SARS-CoV-2 and thus suffering from COVID-19 disease in the community.4 12 13 14 15 Community surveillance systems suggest teenagers are more susceptible to COVID-19 disease than younger children.12 16

**Does COVID-19 affect children and young people in the same way as adults?**

Infection with SARS-CoV-2 appears to take a milder course in children than in adults: most infected children present with mild symptoms or are asymptomatic.1 4
and very few (c. 1%) develop severe or life threatening disease. In the absence of widespread community or serological testing, it is uncertain what the proportion with sub-clinical symptoms is.

Within households, secondary attack rates in children have generally been shown to be lower than in adults, suggesting that they have a reduced susceptibility to infection. It is speculated that differences in the expression of Angiotensin Converting Enzyme 2 Receptor may play a role in altering the susceptibility of children to infection.

More recently, understanding of the innate and adaptive immune response to SARS-CoV-2 has been progressed. Australian and American studies have demonstrated a reduction in monocyte and dendritic cells after SARS-CoV-2 infection in children, which recover in convalescence. Interestingly, they also showed that there is a significant increase in CD63+ neutrophils (which are associated with the release of pro-inflammatory mediators) which has not been shown in adult studies, suggesting that there may be differences in the innate immune response to infection in adults and children.

A UK study has shown that children not previously infected with SARS-CoV-2 have much higher levels of cross-reactive IgG antibodies between “common cold” human coronaviruses and SARS-CoV-2 compared to young adults. Differences in antibody response to SARS-CoV-2 infection have been shown with young children having higher anti-S IgG antibodies compared to teens (the S protein of SARS-CoV-2 binds to the cellular receptor for viral entry to the cell) and increasing levels of anti-N IgG antibody with age. N protein release requires lysis of infected cells so lower levels of anti-N antibody may reflect the milder disease course in children. Understanding the antibody response in different age groups is important when considering how to screen for previous exposure to SARS-CoV-2 and to gain more complete understanding of the epidemiology of the disease, as demonstrated in a large serosurveillance study from the Netherlands. An Italian study has looked at the relationship between the presence of neutralising antibodies (NAbs) with viral load of SARS-CoV-2 and viral clearance in children. NAbs are not found in all children with SARS-CoV-2, but when present a lower viral load is found, along with more rapid viral clearance. At this point in time the clinical utility of antibody testing is unclear.

Deaths in children due to COVID-19 have been extremely rare: mortality seems to
be consistent at around 0.01-0.1% (similar to the incidence seen every year with seasonal influenza). 12 17 24

What role does ethnicity have in COVID-19 infection?

The impact of ethnicity in COVID-19 infection has not been fully elucidated. However, it has been noted that a high proportion of neonates affected by COVID-19 infection are from Black, Asian or minority ethnic groups. 41 The largest UK study of children with COVID-19 in hospital found that children of Black ethnicity were over-represented compared to the population representation and that Black ethnicity was associated with an increased likelihood of requiring critical care admission. 42 A school-based UK study has also found that children of non-white ethnicity had a higher rate of seropositivity for SARS-CoV-2 antibodies. 43 A US study of 135,800 children found that whilst children of black and Hispanic ethnicity were less likely to have undergone testing for SARS-CoV-2 than Caucasian children, when they were tested they were more likely to be SARS-CoV-2 positive, which has been corroborated in other large series. 44 45 46 It was found that 69% of children with Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) in the UK were of Black or Asian race. 47 The reasons for these differences are not clear, either within the context of the UK or globally. Further work to understand the role of ethnicity is required.

Transmission

Are children as likely as adults to acquire COVID-19?

Evidence suggests that children may be less likely to acquire the disease. 4 13 14 24 39 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 This is supported in countries that have undertaken widespread community testing, where lower case numbers in children than adults have been found. 4 14 16 63 64 65 Between 16 January and 3 May 2020, 35,200 children in England were swabbed for SARS-CoV-2 and 1408 (4%) were positive. Children under 16 years old accounted for only 1.1% of positive cases. 60 Previous infection with other types of coronaviruses has not been shown to be protective against SARS-CoV-2. 66

Can children transmit the virus?

The importance of children in transmitting the virus is difficult to establish, particularly because of the number of asymptomatic cases, 65 67 68 but there is
some evidence that their role in transmitting the virus is limited and older ‘index case’ age has been associated with an increased rate of secondary infections. Early studies of multiple family clusters have revealed children were unlikely to be the index case, in Guangzhou, China, Israel and other countries. A SARS-CoV-2 positive child in a cluster in the French Alps did not transmit the virus to anyone else, despite exposure to more than 100 people.

In the Netherlands, separate data from primary care and household studies suggests SARS-CoV-2 is mainly spread between adults and from adult family members to children, this is supported by a similar Greek study. A family-based Norwegian study has shown that whilst adults are most often the index case within a family, the onward transmission of SARS-CoV-2 within a family is highest when the index case is an adult or a child aged 0-6 years, possibly due to the close contact that occurs between younger children and others in the family. An American study has analysed variables which may be associated with a higher secondary household attack rate and has found that higher living density, being a partner of the index case, having a BMI >30Kg/m2 and the index case being non-white are significantly associated with higher secondary attack rates.

In an epidemiological study where 1155 contacts of six COVID-19 positive cases in an Irish school were screened, there was no or minimal evidence of secondary transmission of COVID-19 from children to other children or adults, with the findings mirrored in studies from Singapore, Germany and the USA. A German study screened contacts of 137 children who attended school for at least one day when presumed infective (i.e. one day before symptoms started), before the child isolated. Six index cases were found to have infected 11 additional pupils, with no onward transmission identified for the other 131 children who attended school.
However, viable SARS-CoV-2 virus has been isolated from symptomatic children with COVID-19\textsuperscript{92} and there is some evidence of transmission from asymptomatic children to others.\textsuperscript{13,54} Analysis of large outbreaks of COVID-19 disease in summer camps were unable to differentiate between transmission from adults to children and between children themselves, but up to 90\% of exposed attendees who had not previously had COVID-19 contracted the virus.\textsuperscript{93,94} It is likely that multiple chains of contact account for the high infection rates and supports the notion of limiting contact outside classrooms and having “bubbles” for schools, to reduce the exposure of individuals to the virus.

Fastidious additional measures including daily temperature checks, face-masks at all times, desk spacing, half-day schooling and staggered arrival and departure time have been cited as interventions which may have resulted in low transmission rates in Hong Kong.\textsuperscript{95} This is supported by an Israeli study into a secondary school outbreak of two separate cases of COVID-19 in students, 13.2\% of students and 16.6\% of staff subsequently tested positive for SARS-CoV-2. Untangling the modes of transmission (increased community spread due to loosening of lockdown restrictions vs school contact) was not possible but avoiding poorly ventilated closed spaces, crowded areas and close-contact settings is recommended.\textsuperscript{96-100}

An Australian study in secondary schools shows a low rate of child to child transmission (0.3-1.2\%), with adult to child (1.5\%) and adult to adult (4.4\%) transmission being more common,\textsuperscript{101} something which is reflected in other transmission studies.\textsuperscript{102} Low community prevalence levels in combination with effective contact tracing enabled a rapid response, which may explain why the levels of onward infection appear to be much lower in this study.

Public Health England collected data on transmission related to school settings during June 2020, when a limited number of school years were invited to return to school. Nationally there were 198 confirmed cases related to educational settings and 1.6 million (mainly primary school aged) children were reported to have returned to school. When the index case was a child the maximum number of secondary cases was two, compared to nine when the index case was a staff member. When outbreaks were reported this was significantly associated with increased rates of regional prevalence and clustering was seen in staff members but not students.\textsuperscript{43,103} A US study reported that index cases are more commonly staff than secondary students and that secondary attack rates are higher after
members of staff are the index case, when indoor sports settings are included. However, indoor sports were associated with the highest rate of secondary cases, and caution around sports training and transport to and from matches should be taken.

The data that continue to be published throughout the world demonstrate that children are unlikely to contract COVID-19 from contact within schools and that household transmission is the mode of contact which is most likely to result in the spread of COVID-19. Overall this is very reassuring for children returning to school but highlights the importance of household isolation when a person within the household is positive for COVID-19. Maintaining interventions including social distancing, hand washing and, when appropriate, wearing masks, appear to be effective measures to reduce in-school transmission of COVID-19.

A US study comparing the change in overall incidence of COVID-19 in children between ongoing remote teaching and a return to in-person teaching of children of all ages found an increase in incidence 20 days after schools re-opened for in-person teaching. This was more marked for children in high school. There are several confounders within the study which may impact the results (higher starting incidence of COVID-19 in areas with in-person teaching, community rates not described, different public health policies).

Importantly for adults aged 65 years and under, living with children of any age is associated with a lower risk of dying from COVID-19 and for adults over 65 years there is no effect on mortality. There is a slight increased risk of developing COVID-19 infection for adults 65 years and under when living with children aged 12-18 years old but this is not associated with needing admission to hospital, ICU or death.

This summary is based on published and pre-print literature. For up to date ONS data on community prevalence levels please see the Office of National Statistics. These data will be included in the summary if published and added to the medical databases.

**What is the duration of viral shedding in nasopharyngeal or throat swabs?**

The duration of viral shedding (in nasopharyngeal or throat swabs) has been reported in children to range from 6-22 days, with mean reported at 12 days vs. median eight days. Saliva has been assessed as an alternative
Can children transmit the virus through their stool?

Several studies have now shown that SARS-CoV-2 can be detected by PCR in the stool of affected infants for several weeks after symptoms have resolved; faecal swabs have been found to be positive for a longer duration than nasal swabs,\textsuperscript{120,123,124} with stool shedding reported to be more than 30 days.\textsuperscript{125,126,127} This has raised the possibility of faecal-oral transmission. Research from Germany did not identify any live, culturable virus in stool despite viral RNA being detectable, suggesting this represents viral debris rather than active virus.\textsuperscript{128}

Subsequent reports, however, indicate that there has been infectious virus in stool identified,\textsuperscript{129} but how much and how infectious is not yet clear as it is not quantified. This would suggest that faecal-oral transmission theoretically is possible, but we would need more evidence to really know the ramifications of this. Hand hygiene remains essential to reduce the spread of the virus from droplets arising from either the respiratory or GI tract. Further studies are needed.

How do new variants of COVID-19 affect children?

Early population data suggest that the SARS-CoV-2 variants are more infectious to the general population, including children.\textsuperscript{130,131,132,133} However, there is no evidence of children being at increased susceptibility to new variants compared to adults, or to be more severely affected by new variants,\textsuperscript{134} nor of any associated increased risk of developing PIMS-TS. The evidence base around this is rapidly growing. For up-to-date information on trends in England please see the ONS website.

What is the role of testing in children?

Until recently, testing in children has been focused on diagnosis of the presence or absence of SARS-CoV-2 using nose and throat swabs in children who are symptomatic. Rapid diagnostic tests, either based on the presence or absence of a SARS-CoV-2 antigen (e.g. lateral flow device) or on rapidly expanded viral RNA (loop mediated isothermal amplification - LAMP) have started to be considered for use in screening, rather than diagnosis. The asymptomatic testing that has been undertaken in Liverpool excluded children under the age of 11 years so few data are available from this group, and children have not been included in the

A Swiss study has evaluated a rapid diagnostic antigen test using Buccal swabs compared to Buccal PCR. There was a low prevalence of 0.2% (assessed using PCR) during the study period. The specificity of the rapid antigen test was 99.4% in children and the low level of PCR positive children meant that the sensitivity could not be determined. A Spanish study demonstrates that whilst the sensitivity of a rapid antigen test performed in children is lower than PCR, when this is put into the context of low to moderate prevalence of COVID-19, the positive and negative predictive value of the test remains very good (100% PPV and 99% NPV).

A study from Hong Kong suggests that the viral load of SARS-CoV-2 in children’s saliva correlates better with the presence of symptoms and immunological markers of COVID-19 than the viral load detected by nasopharyngeal swabbing.

Further data on children are required to determine the use of rapid diagnostic tests in hospital and community settings and to determine the optimal method of sampling in children.

**Clinical features and investigations**

**What are the symptoms of COVID-19 disease?**

Disease presentation can range from no symptoms (asymptomatic) in approximately a third of children to severe pneumonia requiring ITU admission. When there are clinical features, they are non-specific and similar to other viral respiratory infections. The most common presenting features, present in more than 50% of cases, are cough and fever; upper respiratory tract symptoms (such as sore throat and rhinorrhoea) occur in 30-40% of patients; diarrhoea and vomiting present in approximately 10% of cases. There are reports of infants presenting with fever but no respiratory symptoms. Less commonly reported symptoms include thoracic pains, somnolence, febrile convulsions, lower limb pains, cutaneous manifestations, ocular manifestations consistent with viral conjunctivitis and thrombotic sequelae. A higher than expected rate of appendicitis has been noted in patients with SARS-CoV-2 in small case series, warranting further evaluation of any potential
Differences in immune responses may play a role in influencing the severity of symptoms. Please see ‘What is PIM-TS’ below for further information about the symptoms of the hyper-inflammatory response syndrome.

Are there any signs that could help differentiate COVID-19 from other childhood respiratory viral infections?

There appears to be little in the way of clinical signs in children to differentiate COVID-19 from other childhood respiratory virus infections, and COVID-19 has been detected in combination with other viral and bacterial infections. There are some cases indicating possible association with skin manifestations in patients with suspected or confirmed COVID-19 (but please note, this case series does not describe the age of patients so includes adults), which may persist for some time once other symptoms have resolved and include acral areas of erythema oedema with some vesicles or pustules, other vesicular eruptions, urticarial lesions, other maculopapular lesions, livedo or necrosis. Dermatological exanthem, maculopapular and chilblain like lesions associated with COVID-19 have also been reported in children. The finding of the presence of SARS-CoV-2 in the endothelium of dermal vessels in skin biopsies of children and adolescents with acute chilblains confirms that these (chillblain) lesions are a manifestation of COVID-19.

What is PIMS-TS?

An emerging phenomenon of a hyperinflammatory response syndrome, resembling Kawasaki Disease Shock Syndrome (KDSS), was reported in a case study describing a six month old who was treated for Kawasaki Disease (KD) and then subsequently was found to test positive for SARS-CoV-2. Further studies were reported in the UK, including a case series indicating that it can mimic appendicitis, with inflammation of the terminal ileum, Italy and France, as well as the US and Luxembourg.

The RCPCH have produced a case definition for the Paediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS) which can be found here. The CDC have subsequently named the same syndrome Multisystem Inflammatory Syndrome in children (MIS-C) with a slightly different
Symptoms reported include abdominal pain, vomiting and diarrhoea, with persistent high-grade fever and frequently progress to shock with cardiac involvement requiring ICU admission for inotropic support, mechanical ventilation and, in a small number of patients, ECMO. Children tend to have high inflammatory markers, cardiac involvement, e.g. myocarditis, maculopapular rashes, non-suppurative conjunctivitis and encephalopathy. There have been a handful of fatalities reported.

Children with PIMS-TS/MIS-C have been treated with supportive care only, IVlg, IV corticosteroids, anakinra, infliximab, tocilizumab, siltuximab and rituximab but the current indications for each therapy are not currently clear. Coronary artery aneurysms have been described in up to 40% of children with PIMS-TS, with this appearing to be more common in children admitted to PICU. Routine screening for coronary artery aneurysms is recommended at one to two weeks and four to six weeks after presentation.

A possible temporal association with SARS-CoV-2 infection has been hypothesised because many children that were tested for SARS-CoV-2 infection were either positive by PCR or serology. The first epidemiological surveillance study of PIMS-TS in France supports a casual link with COVID-19 following four-five weeks behind the clinical illness and a further analysis of temporal causality suggests that viral infections including SARS-CoV-2 are associated with the diagnosis of KD. Geographic and temporal trends in the USA have demonstrated an association between the incidence of SARS-CoV-2 and the incidence of MIS-C, strengthening the argument for causality.

One of the most detailed reports of 58 children diagnosed with PIMS-TS demonstrate that it can have a wide spectrum of symptoms, signs and severity and overlap with KD, KDSS and toxic shock syndrome (TSS). Differences in clinical and laboratory profile compared with KD, KDSS and TSS suggest that PIMS-TS is a unique entity, potentially arising from a maladaptive acquired immune response to the SARS-CoV-2 infection.

The centre for disease control analysed 570 patients with MIS-C and, using latent class analysis to group the patients according to their symptoms, found three clusters. The first (36%) were an older group (median age nine years) with multi-organ involvement, particularly cardiovascular and gastro-intestinal, with
very few fulfilling the diagnostic criteria for Kawasaki Disease. There was a high proportion of children with shock in this group and there was a mortality rate of 0.5%. The second (30%) had primarily respiratory symptoms in-keeping with acute COVID-19 infection and there was a case fatality rate of 5.8%. The third cluster (35%) were younger (median six years) and predominately associated with mucocutaneous lesions and rash. These children were less likely to have cardiovascular involvement. Coronary artery dilatation or aneurysms were seen in all three groups, highlighting the need for echocardiogram as part of the assessment of these children. Routine cardiac MRI after recovery from PIMS-TS did not show persistent myocardial dysfunction in a small study of five patients and children appear to return to their baseline functional levels by 30 days after discharge. Within the USA, MIS-C has been observed to disproportionately affect Hispanic and Black children and young people, the reasons for which aren’t fully understood but are likely to be multifactorial.

Further information can be found on the management of children presenting in this manner. The document details information on how to include cases you might be managing into research studies, including ISARIC-CPP/UK, DIAMONDS and the RECOVERY trial.

**Are children from a BAME background at a higher risk of severe disease from acute COVID-19 infection?**

Children from a BAME background seem to be at higher risk of severe disease from acute COVID-19, which is consistent with adult literature. BAME children are significantly over-represented in case reports/series of PIMS-TS. Also see the Epidemiology section to see the role of ethnicity in infection.

**How long after being exposed to SARS-CoV-2 does a child develop symptoms?**

The assumed incubation period (time from exposure to index case to developing symptoms) varies in different studies: it has been reported to be between 2-10 days, with median (and mode) of seven days, vs. 24h – 28d, vs. mean of 10 days (IQR 7.75 – 25.25).

**Can a child be asymptomatic but still have COVID-19?**

Yes, there are reports of asymptomatic cases with positive laboratory confirmed COVID-19. In the absence of widespread community or serological data, the proportion of children who do not have any symptoms or
have sub-clinical symptoms is unclear, but it is likely to be around a third of infected children.\textsuperscript{68 209} Testing of 120 asymptomatic cancer patients in a US cancer centre revealed 2.5% to be positive (vs. 14.7% of their care givers).\textsuperscript{53}

**What are blood and imaging tests of children with COVID-19 likely to show?**

Laboratory findings are non-specific, and often normal. They may include slightly elevated inflammatory markers including c-reactive protein,\textsuperscript{26} and raised liver transaminases.\textsuperscript{119 145 210} Lymphocytopenia is seen,\textsuperscript{3 151 211} but more children appear to have raised or normal lymphocyte counts.\textsuperscript{77 119 140 141 145 212 213}

Radiological investigations in infected children can be normal in up to 10%, and is associated with mild disease not requiring PICU.\textsuperscript{119 149 152} Common abnormal findings include increased peribronchovascular markings, bronchial thickening (58%), consolidation (35%), ground glass opacities (19%) and interstitial changes (16%). Pleural effusion, pneumothorax and atelectasis are uncommon features of COVID-19.\textsuperscript{22 119 144 145 152 211 214 215 216 217 218} These findings are non-specific and do not enable radiological differentiation between COVID-19 and other respiratory viruses, which have a similar picture.\textsuperscript{219}

Computed Tomography (CT) of the chest has been used as a rapid diagnostic tool by some centres and, when performed, over 90% are reported to have features of lower lobe ground glass opacification (88%) and consolidation (58%). It is worthwhile noting that CTs were performed on a selective group of patients, are not recommended as a method of diagnosing COVID-19 and should be reserved for complex cases.\textsuperscript{218} CT changes have been reported in asymptomatic positive children.\textsuperscript{212}

There are several cases of reported co-infection of SARS-CoV-2 and other respiratory viruses, which illustrates that the identification of another respiratory pathogen should not preclude SARS-CoV-2 testing in children.

**If a swab is negative for COVID-19 infection is it possible that a child has COVID-19 infection?**

We know that virtually no test is perfectly sensitive (correctly picks up all people with the disease) or specific (correctly picks up all people who don’t have the disease) and the same is true for COVID-19.\textsuperscript{220} The test that is used to confirm whether someone has COVID-19 infection or not uses swabs from the back of the nose and throat. These are used to look for COVID-19 genetic material in the cells
that have been picked up, using a technique called reverse transcriptase polymerase chain reaction (RT-PCR). It is possible to still have COVID-19 infection even if the RT-PCR does not detect COVID-19 genetic material, particularly very early or very late in the disease.221

**At risk groups**

**Are there any groups that are at higher risk of developing severe COVID-19 illness?**

Whilst children with comorbidities are still at low risk of developing severe disease after SARS-CoV-2 infection compared to adults, there is evidence that children with co-morbidity have a higher risk of developing severe disease compared to children without co-morbidity.222 223 224 225 226 A national Italian study of 3836 cases reports a mortality rate of 0.1% with all children who died having co-morbidities.12 In reports of children with immunosuppression, cancer therapy have not shown it to be a significant risk factor for severe disease.227 228 229 230 231 232 233 234 235 236 237 238 Contact tracing on a dialysis unit who had contact with a member of staff who tested positive found three children to be positive, but only one had symptoms.239 A case report of a child with cystic fibrosis who contracted COVID-19 from his grandfather, identified though contact tracing, also remained asymptomatic.240 There is a case report of COVID-19 pneumonia triggering acute chest syndrome in an adolescent with known sickle cell disease on daily hydroxyurea.241

A European study of 37 asthma centres reported no children with severe asthma being admitted to hospital with COVID-19. Four of the countries included in the study, including the UK, had recommended shielding for a very small minority of children with the most severe asthma, however the other twenty-one countries had not, suggesting that severe asthma is not a risk factor for severe COVID-19 infection.242 A multinational study of 105 children with Cystic Fibrosis (95 with confirmed SARS-CoV-2 on RT-PCR) found that almost a third were asymptomatic and 70% were managed in the community. Those who were admitted to hospital required supplemental oxygen and tended to be the children with reduced lung function or reduced body mass index, compared to children in the community. One child required care in PICU and one child died approximately six weeks after being diagnosed with COVID-19 due to worsening underlying lung disease.243

On screening patients and caregivers with cancer in one of the largest paediatric
cancer centres in the US, 20 of 178 paediatric patients tested positive. Only one (5%) required hospitalisation for symptoms of COVID-19, with none requiring critical care.53

CDC data from the USA reports that a high proportion of cases needing admission had at least one co-morbidity (most commonly respiratory).5 Further data from Italy20 and the US153 244 also finds that children with co-morbidities are over represented in those admitted to hospital, though most were reported to have mild illness. Children under one year of age appear to be more likely to be admitted to hospital with COVID-19 than those in older age groups.5 12 208 245 246

The USA has reported only 121 out of a total of 190,000 deaths associated with SARS-CoV-2 in people under 21 years of age until 31 July 2020. Of these 121, 70% occurred in children aged 10-20 years old (41% of the total were 18 years and above); with 74% in children of Hispanic or Black ethnicity. It was found that 75% of the children who died had co-morbidities which included asthma, obesity, neurological and cardiac conditions.247 The contribution of SARS-CoV-2 to death is unclear in this study, 35% of the total deaths occurred before the child or young person/adult could be admitted to the Hospital. There were 15 cases which met the definition for the multisystem inflammatory syndrome in children.

A UK study of 651 hospitalised children with COVID-19 found that six children died and all had significant severe co-morbidities.42 Studies have looked at other individual co-morbidities such as the impact of learning difficulties, however a lack of focus on children means that the application of the findings to children and young people is not possible.248 Further data on the impact of co-morbidities in a robust comparative way that is specific to children is required to understand the impact of co-morbidities in developing severe disease after SARS-CoV-2 infection.

In a US study of 20714 children with confirmed SARS-CoV-2, 2430 (11.7%) were admitted to hospital with COVID-19. 31% of those admitted to hospital and 3.7% of all recorded children had severe disease (requiring ICU, mechanical ventilation or causing death) and there were increased odds of severe disease in children aged 2-11 compared to children over the age of 12 years. The presence of co-morbidity was also identified as a risk factor for severe disease.249

The RCPCH have provided guidance on clinically extremely vulnerable children and young people.
This guidance continues to be reviewed as new evidence emerges.

**What are the characteristics of children admitted to PICU?**

Severe illness is far less frequent in children than adults, but it is still significant in a very small number of children and young people. Most studies describing severely unwell children combine those who are on PICU with either SARS-CoV-2 infection with those who have PIMS-TS. Approximately 20% of hospitalised children with COVID-19 require PICU admission, 8% require inotropic support and 9% require respiratory support. Extra-corporeal membrane oxygenation has been used in a very small number of children with COVID-19 (approximately 2% of children admitted to PICU).

Age: Children who have been admitted to PICU have been seen in two peaks - premature babies and those under one month of age and older children who are more commonly diagnosed with PIMS-TS.

Co-morbidities: up to three quarters of children admitted to PICU have a co-morbidity and children with co-morbidities are more likely to require ventilation. The literature suggests that children may be at higher risk of requiring PICU admission if they are medically complex; have long-term dependence on technological support including tracheostomy; have developmental delay; have genetic abnormalities; have respiratory co-morbidity; have cardiac co-morbidity or are obese. Children who are positive for SARS-CoV-2 have also been admitted to PICU for potential sequelae of the infection including diabetic ketoacidosis and status epilepticus.

Ethnicity: Children of black ethnicity have been noted as being over-represented compared to the general population for both the requirement to be admitted to hospital and the requirement for PICU care. The reasons for this are not clear.

Presentation: Children presenting to hospital with pyrexia, symptoms and signs of lower respiratory tract infection, acute respiratory distress syndrome or radiological evidence of pneumonia are noted to be more likely to require PICU admission.

Co-infections: Viral co-infection has been cited as a potential risk factor for PICU admission.

The overall English mortality rate in children with confirmed SARS-CoV-2 on RT-PCR is 0.3% (eight children), half of whom who had multiple co-morbidities and
the other half who died of other causes with SARS-CoV-2 as an incidental or indirect contributor to death.60

In summary, studies from PICU admissions in Europe and the USA have found that those with comorbidities are over-represented, most commonly respiratory, complex neurodisability – groups which are otherwise at increased risk of complications from all respiratory viruses.254 It is not clear if the SARS-CoV-2 infection was causal, contributory or incidental to the ICU admission (or even acquired after PICU admission). The rates of complications from SARS-CoV-2 infection do not appear disproportionate to those from other respiratory viruses in this early data.255

**Neonatal**

**Are neonates at increased risk of severe disease?**

Many case reports/series have been published looking at the outcomes of pregnant mothers with COVID-19 and their newborn babies. Mothers and their babies in general appear to do well, with few reports of neonates requiring NICU admission.256 257 Early studies suggested that neonates without comorbidities are not at an increased risk of severe disease.258 259 260 However, recent European and UK studies have reported that age under one month and prematurity are risk factors for PICU admissions.27 41 42 It is noted in a series of four neonates infected after birth that half had additional infections and highlights the importance of screening for additional infections.261

**Can COVID-19 increase the risk of pre-term birth, if the mother acquires it in the late second or third trimester?**

There is a small increase in the rates of preterm or earlier birth262 and signals of an increase in the rates of foetal loss/stillborn delivery.263 264 265 266 267 A small case series suggests that SARS-CoV-2 at high viral loads may affect the placenta of late third trimester pregnancies but the evidence for this is very weak.268 A meta-analysis has found that the rate of maternal death and stillbirth has increased during the pandemic but that a change in the rate of pre-term birth has not been observed.269

**Can the virus be transmitted vertically?**

The vast majority of newborns have not acquired COVID-19 themselves and not
had adverse outcomes after maternal COVID-19. However, a systematic review reveals that SARS-CoV-2 has been isolated from the placenta, cord blood, rectal and nasopharyngeal swabs of a small proportion of babies born to mothers with 3rd trimester COVID-19 suggesting that vertical transmission, whilst rare, can occur.

There are a few cases of infants delivered to COVID-19 positive mothers, who have elevated SARS-CoV-2 IgM after birth, which may indicate intrauterine transmission but this is not clear because these babies tested negative on swab PCR and false positives with IgM are not uncommon. There have also been cases of newborns and very young infants testing positive shortly after birth (including several at or before 12 hours of age) however they have not suffered any known significant complications of the disease and mostly required minimal respiratory support. There is evolving evidence that neonates born to mothers who have had COVID-19 in the last two months of pregnancy have both passive and active immunity to SARS-CoV-2 but this may only last for a few weeks after birth. Current evidence supports the WHO guidance that babies born to mothers who have COVID-19 are very unlikely to contract the virus or to develop severe illness if they do so. It is therefore recommended that mothers should be supported to have skin-to-skin contact with their baby and to share a room.

**Can the virus be transmitted or through breast milk?**

Many reports of breast milk from COVID-19 positive mothers found that the breastmilk tested negative for COVID-19. There are a small number of reports of viral RNA being found in breast milk, but it is unclear if this positive result reflects live, infectious virus and whether the source was the mother or infant who subsequently tested positive for the virus.

Subsequent data suggests pasteurisation eliminates the virus from breast milk and also that PCR positive breast milk does not seem to represent live, replicating virus. Further large-scale studies are needed to draw firm conclusions.

Interestingly, antibody testing of breastmilk collected in 2018 has shown cross-reactivity with SARS-CoV-2 antibody and mothers who have had symptoms of COVID-19 have higher levels of SARS-CoV-2 S1+S2 reactive IgA and IgM in their
breastmilk. Mothers who were vaccinated and are vaccinated against Influenza have also been shown higher antibody levels. The protective implications of this are not yet clear for neonates but the data supports encouraging breastfeeding and highlights the importance of maternal vaccination.

WHO continues to recommend breastfeeding with appropriate precautions for COVID-19 positive mothers.

**Does having COVID-19 in pregnancy cause any long-term problems for the baby?**

We do not currently have sufficient evidence to draw conclusions on this.

**Therapeutics**

**What treatments are available for children with COVID-19?**

For those without severe disease, which will be most children, supportive management (ensuring oxygenation, hydration and nutrition) is appropriate. For more information, please see the RCPCH guidance on the clinical management of children admitted to hospital with suspected COVID-19.

There are many ongoing studies; within the UK, there is the RECOVERY trial which is now recruiting neonates and children who are severely unwell with COVID-19.

Currently, children with an acute respiratory presentation of COVID-19 can be recruited to arms of 'no additional treatment' or Azithromycin and/or convalescent plasma. Children can then go on to be randomised in the second stage intervention of Tocilizumab or no additional treatment if they do not improve.

The RECOVERY trial is now also open for children with PIMS-TS. There are two tiers of randomisation. The first allows the comparison of high dose steroids to no additional treatment (in the presence and absence of IVIg) and IVIg to no additional treatment (in the presence and absence of steroids). This will enable investigators to use steroids or IVIg as standard care if necessary, but also recruit children with moderate disease who may not require additional treatment. The second tier of randomisation compares Tocilizumab to no additional treatment.
for children deemed eligible for biological therapy. As the trial is open label, children who do not receive Tocilizumab can be given another biological agent such as Anakinra or Infliximab.

**What studies are enrolling children currently to therapeutic trials?**

For any child either with PIMS-TS of COVID-19 infection causing more severe or critical illness ([RCPCH treatment criteria](https://www.rcpch.ac.uk/covid19-pimss)), please consider enrolment in the [RECOVERY trial](https://www.recoverytrial.co.uk/). This study is open at many sites including hospitals with and without on-site PICU, and from 11 May 2020 has included children down to those just born.

If you are considering entering a child to RECOVERY, we suggest you check with your Regional Infectious Disease team and watch the relevant video(s) and view the FAQs on the study website. Please note that there are separate training videos in respect to children and infants of less than 29 days of age. If you are still uncertain about eligibility, there is the possibility for you to contact an 'on-call' member of the study team to discuss further, but please only do this if you are particularly uncertain.

If you think entry into RECOVERY is indicated, it can take place in the hospital where the child is admitted - you don't have to wait for them to be transferred to a regional centre.

**Is it safe to give ibuprofen to a child who has tested positive for COVID-19 or is highly likely to be positive?**

There is currently insufficient evidence to establish a link between use of ibuprofen, or other non-steroidal anti-inflammatory drugs (NSAIDs), and contracting or worsening of COVID-19. Whilst an early report suggested ibuprofen was associated with poorer outcomes, subsequent work has not supported this. The RCPCH has made a statement about the use of ibuprofen in suspected/confirmed COVID-19. It remains a very powerful, safe and effective medicine for reducing fever and pain in infants, children and young people and adults.

**Is there an effective vaccine?**

Three vaccines have now been licenced for use. The majority of studies supporting their use have only been completed in adults. One vaccine (Pfizer-BioNTech OCID-19, mRNA Vaccine BNT162b2) is licensed for those 12 years and
over. It is recommended by the JCVI for children aged 12-15 years with severe neurodisabilities, Down’s syndrome, immunosuppression and multiple or severe learning difficulties. In addition, children aged 12-17 years should be offered the vaccine if they live with an immunosuppressed person and young people aged 16-17 with a condition that puts them at higher risk of serious COVID-19 should also be offered the vaccine. The JCVI advice on who should receive vaccinations is available here. Other countries including the USA and Israel have been vaccinating teenagers using the Pfizer-BioNTech vaccine. Reports of perimyocarditis in children receiving the vaccine are still under review but given that children in the vast majority suffer only mild disease after SARS-CoV-2 infection, consideration of the safety of the vaccine is imperative around decision making for vaccination of children. Clinical trials of vaccines for SARS-CoV-2 are currently being undertaken in children in the UK.

**Prognosis**

**What is the prognosis of a child who has had COVID-19?**

The short-term prognosis in those who recover appears to be good with both infants and children largely appearing to make a full recovery. There is growing evidence that children develop an antibody response to SARS-CoV-2 infection, even when mild, which persists up to six months after infection in the majority of children.

**Are there any long-term complications (in specific groups) such as reduced exercise tolerance, developmental delay, or worsening of cardiac function?**

A small publication of children without serological evidence of SARS-CoV-2 infection has suggested that some children may go on to have long-term effects after COVID-19. The research base on 'long COVID' in children is growing but not conclusive. A study of children admitted to hospital with SARS-CoV-2 has shown that children can complain of fatigue, sleep disturbance, sensory problems and GI disturbance after infection. However, without a control group it is difficult to draw conclusions on this. UK surveillance studies have demonstrated a higher prevalence of persistent symptoms up to a median of 46 days after infection with SARS-CoV-2, particularly fatigue, compared to those without.
Summary

In children, the evidence is now clear that COVID-19 is associated with a considerably lower burden of morbidity and mortality compared to that seen in the elderly. There is evidence of critical illness and death in children, but it is rare.

There is also some evidence that children may be less likely to acquire the infection. The role of children in transmission, once they have acquired the infection, is unclear, although there is no clear evidence that they are any more infectious than adults.

Symptoms are non-specific and most commonly cough and fever. Laboratory and radiological investigations may be normal or mildly altered.

There is some possible evidence of infection in newborns which could indicate vertical transmission, but it is not clear if this is intrauterine or perinatal. Early evidence suggests both infected mothers and newborns are not particularly more severely affected than other groups.

Children with co-morbidities, notably respiratory and complex neurodisability, appear more likely to suffer complications and need hospital +/- PICU admission, but not obviously more than would be expected from infection with other respiratory viruses.

Several reports document significant morbidity and mortality as a consequence of the pandemic; although this has not been universal.

Notable evidence


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A need of COVID19 vaccination for children aged <12 years: Comparative evidence from the clinical characteristics in patients during a recent Delta surge. (B.1.617.2). Hongru Li, Haibin Lin, Xiaoping Chen, Hang Li, Hong Li, Sheng Lin, Liping Huang, Haijian Tu, Xiaqin Li, Yuejiao Ji, Wen Zhong, Qing Li, Jiabin Fang, Quying Lin, Rongguo Yu, https://www.medrxiv.org/content/10.1101/2021.11.05.21265712v1


Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-


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