COVID-19 - research evidence summaries

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

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This summary is based on published and pre-print studies identified in our rapid review. As evidence is rapidly emerging the content of this page will be reviewed and updated regularly. Since 1 July 2020 we have refined our search process to update the summary with studies considered to be good quality or of high impact.

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.

This summary was last updated on 18 August 2020.

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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. 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).

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. Community surveillance systems suggest teenagers are more susceptible to COVID-19 disease than younger children.

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, 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 are significantly lower than in adults (16% vs 31%), displaying their reduced susceptibility to infection. It has been postulated that the difference in Angiotensin Converting Enzyme 2 Receptor is less commonly expressed and is less mature in children, giving a potential biological basis for this.

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).

Transmission

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

Emerging evidence suggests that children may be less likely to acquire the disease. This is supported in countries that have undertaken widespread community testing, where lower case numbers in children than adults have been found.

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, 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. Precise details regarding paediatric transmission cannot be confirmed without analysis of widespread sero-surveillance, but trends are emerging. 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. An epidemiological study where 1155 contacts of six COVID-19 positive cases in an Irish school were screened, there was no evidence of secondary transmission of COVID-19 from children to other children or adults, with the findings mirrored in a study from Singapore.

However, viable SARS-CoV-2 virus has been isolated from symptomatic children with COVID-19 and there is some evidence of asymptomatic transmission from children to others. Analysis of a large outbreak of COVID-19 disease in a summer camp was unable to differentiate between transmission from adults to children and between children themselves, but up to 50% of exposed children contracted the virus.

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. 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 was recommended.

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. 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.

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

The duration of viral shedding (in naso-pharyngeal or throat swabs) has been reported in children to range from 6-22 days, with mean reported at 12 days vs. median eight days.

**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, with stool shedding reported to be more than 30 days. 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.

Subsequent reports, however, indicate that there has been infectious virus in stool identified,
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.

**Clinical features and investigations**

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

Disease presentation can range from no symptoms (asymptomatic) 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 and ocular manifestations consistent with viral conjunctivitis. 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. There have not been any firm descriptions of wheeze with COVID-19 in the literature so far.

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, papularmacular 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 as well as the US and Luxembourg.

The RCPCH have produced a case definition for this 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 case definition.

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, macular papular 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, IVIg, 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.

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.

Further information can be found on the management of children presenting like this. 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.

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
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, it is uncertain what proportion of children do not have any symptoms or have sub-clinical symptoms. Testing of 120 asymptomatic cancer patients in a US cancer centre revealed 2.5% to be positive (vs. 14.7% of their care givers).

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, and raised liver transaminases. Lymphocytopenia is seen, but more children appear to have raised or normal lymphocyte counts.

Radiological investigations in infected children can be normal in up to 10%, and is associated with mild disease not requiring PICU. 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. These findings are non-specific and do not enable radiological differentiation between COVID-19 and other respiratory viruses, which have a similar picture.

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. CT changes have been reported in asymptomatic positive children.

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. 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.

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

There is some evidence reflecting a small increased risk of children with comorbidities needing hospitalisation or intensive care admission from COVID-19. A national Italian study of 3836 cases reports a mortality rate of 0.1% with all children who died having comorbidities. Reports of children with immunosuppression or cancer therapy have not shown it to be a significant risk factor for severe disease. 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. A case report of a child with cystic fibrosis who contracted COVID-19 from his grandfather, identified through contact tracing, also remained asymptomatic. There is a case report of COVID-19 pneumonia triggering acute chest syndrome in an adolescent with known sickle cell disease on daily hydroxyurea.

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.

CDC data from the USA reports that a high proportion of cases needing admission had at least one co-morbidity (most commonly respiratory). Further data from Italy and the US also finds that children with co-morbidities are over represented in those admitted to hospital, though most were reported to have mild illness. Notably there is no apparent difference in severity according to age in the Italian data, whereas CDC data noted increased hospitalisation in infants (under one year of age) and Dong et al noted higher rates of severe or critical illness infants under one year of age.

The RCPCH have provided guidance for the need for shielding in certain groups. 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.

Data on PICU admissions in Italy showed a higher proportion of those admitted to ITU had a co-morbidity (three out of four children needing ICU admission in this case series).
In a cross sectional study of 46 North American PICUs, 143 children were admitted to 14 PICUs, with a median age of 13 (4.2 to 16.6). Most presented with respiratory symptoms but there were other presentations, such as with vaso-occlusive crisis (sickle cell) and diabetic ketoacidosis. A total of 40 children (83%) had at least one pre-existing underlying medical condition. The most common comorbidity was medically complex, defined as children who had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic abnormalities. Of those, 20% (aged six years or older) had obesity, 38% required invasive ventilation. Extra corporeal membrane oxygenation was required for one patient (2%). Two children died, so the overall ICU mortality rate was <5% (vs. published mortalities of 50-62% in adults admitted to ICU). For those who had been discharged at the time of publication of the paper, the median (range) length of PICU stay was five days (three to nine days) and the mean hospital length of stay seven days (four to thirteen days).

The Spanish Paediatric Intensive Care Society published their findings of 50 children admitted to 47 PICUs in Spain (27 of which had suspected PIMS-TS). Overall, 12 (24%) had comorbidities and eight of these required mechanical ventilation (vs. six of those who did not have comorbidities).144

A large European study including 582 children admitted to hospital or cared for in the community with confirmed COVID-19 have found that age under one month, male sex, pre-existing co-morbidity, pyrexia, signs or symptoms of lower respiratory tract infection, radiological findings of pneumonia or acute respiratory distress syndrome and viral co-infection were correlated with ICU admission.25

A series of 11 patients admitted to ICU with COVID-19 from Great Ormond Street Hospital found that 64% of children were admitted for non-respiratory causes including status epilepticus, diabetic keto-acidosis, congenital heart disease and leukaemia.145

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.146 It is not clear if the SARS-CoV-2 infection was causal, contributary 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.147

**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.148 149 In general, neonates without comorbidities do not appear to be at an increased risk of severe disease.150 151 152

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.153
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 birth and signals of an increase in the rates of foetal loss/stillborn delivery.\textsuperscript{154, 155} Although significant, the magnitude of the increase is not likely to be meaningful.\textsuperscript{156}

Can the virus be transmitted vertically?

The vast majority of newborns have not acquired COVID-19 themselves or had adverse outcomes after maternal COVID-19.\textsuperscript{131, 132, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172} 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,\textsuperscript{173} suggesting that vertical transmission, whilst rare, can occur.\textsuperscript{174}

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.\textsuperscript{175, 176} There have also been cases of newborns and very young infants testing positive shortly after birth (including several\textsuperscript{154, 177} at or before 12 hours of age)\textsuperscript{2, 151, 178} 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.\textsuperscript{179}

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.\textsuperscript{3, 132, 152, 169, 180, 181}

There are a small number of reports of viral RNA being found in breast milk,\textsuperscript{182, 183} 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.\textsuperscript{184} Further large scale studies are needed to draw firm conclusions.

\textbf{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.

\textbf{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](https://www.rcpch.ac.uk/guidance-and-resources/guidance-views/clinical-management-children-admitted-hospital-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 those who develop more severe or critical illness ([RCPCH treatment criteria](https://www.rcpch.ac.uk/guidance-and-resources/guidance-views/clinical-management-children-admitted-hospital-suspected-covid-19)), please consider enrolment in the [RECOVERY trial](https://www.reakcovery.org). This study is open at many sites including hospitals with and without on-site PICU, and from 11 May will be including children down to those just born. It also includes those with PIMS-TS.

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](https://www.rcpch.ac.uk/guidance-and-resources/guidance-views/clinical-management-children-admitted-hospital-suspected-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?

Vaccines will hopefully provide protection against future outbreaks of COVID-19, though these are still early in the drug development pipeline and unlikely to be available this year.

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.

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

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

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.

Delayed access to care and late presentations, due to concerns over SARS-CoV-2 infection, have been observed in an Italian case series and a BPSU snap-shot survey. There is significant morbidity and mortality reported as a consequence of the pandemic.

Next steps
We will continue to collate and summarise the evidence around COVID-19 and children and young people as it emerges, in partnership with The Don’t Forget the Bubbles team. A comprehensive summary of all the papers identified on COVID-19 and children published to date is hosted by Don’t Forget the Bubbles.

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RCPCH COVID-19 Search Strategy - Phase 1 updated 22 May 122.14 KB
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