



**DFTB COVID-19
EVIDENCE REVIEW
22ND APRIL 2020**



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Introduction

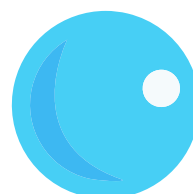
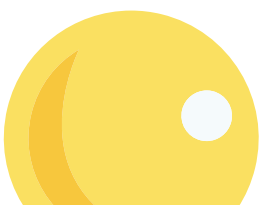
In order to help facilitate the best possible care for children with COVID-19, we sought to aggregate and rapidly review all of the original research being produced pertinent to children, making it available to everyone. Speed has been essential, and in order to keep pace with the rapid production of new evidence, we have proceeded with informal, rapid, evidence synthesis. There have been a handful of studies which were obtained and deemed not suitable for inclusion, due to poor quality or patient overlap. A list of studies not included is available.

Our evidence summaries have undergone internal peer review, as well as being open to external review from our readers. We would like to highlight that due to the speed with which the evidence has been produced, much is of low quality. Many studies include few patients. There are 3 other significant issues:

1. Heterogeneous denominators. There is a significant amount of heterogeneity in the way cohorts or cases have been collected, and many of these are not directly comparable.
2. Overlap. Much of the current evidence has come from a few regions in China. We have tried to identify where cases series were at risk of including the same patients multiple times, but this remains a risk.
3. Non-peer reviewed evidence. Many included papers have come from pre-print servers. Whilst they appear of sufficient quality to be useful, they require caution when interpreting.

We hope this evidence review proves useful in helping manage children with COVID-19

Contributors: The project was coordinated by Alasdair Munro. Reviews were conducted by Alasdair Munro, Alison Boast, Henry Goldstein, Dani Hall, and Grace Leo. Digital/technical support was provided by Tessa Davis.



Executive summary of evidence

Epidemiology

Following the initial epidemiological data released from China, it appeared children were significantly less affected by infection with SARS-CoV-2 than their adult counterparts. This was reflected both in total case numbers, but also severity, with very few cases in young children and no deaths in children under 10yrs in the initial report. This finding has been reproduced in subsequent data from other countries, most notably Italy, which showed much lower rates of infection in children and no deaths in those under 30 years of age. Low numbers of childhood cases have been seen in the rest of Europe, as well as the USA, where 1/3 of childhood cases are in late adolescence. Some concerns exist that low case rates reflect selective testing of only the most unwell, however data from South Korea and subsequently Iceland which have undertaken widespread community testing, have also demonstrated significantly lower case numbers in children. This has also been seen in the Italian town of Vo, which screening 70% of its population and found 0 children <10 years positive, despite a 2.6% positive rate in the general population.

More detailed information has emerged from China into childhood severity of COVID-19. A large number of children appear asymptomatic. Critical illness was very rare (0.6%) and concentrated in the youngest infants. It should be noted that large numbers of “suspected” cases in this group leave room for a significant number of illnesses to have been caused by other, familiar respiratory viruses. In the USA CDC data, infants appear most likely to be hospitalised, although rates of PICU admission do not appear to be significantly different as yet. To date, deaths remain extremely rare in children from COVID-19, with only a handful of reported cases.

Number of studies
included in this
report

78

To date, deaths remain extremely rare in children from COVID-19, with only a handful of cases reported.

Transmission

Precise details regarding paediatric transmission remain unclear. Low case numbers in children suggest a more limited role than was initially feared. Contact tracing data from Shenzhen in China demonstrated an equivalent attack rate in children as adults, however this has been contradicted by subsequent data in Japan which showed a significantly lower attack rate in children. This, coupled with low case numbers would suggest at least that children are less likely to acquire the disease. The role of children in passing the disease to others is unknown, in particular given large numbers of asymptomatic cases. Notably, the China/WHO joint commission could not recall episodes during contact tracing where transmission occurred from a child to an adult. A recent modelling study from the London School of Hygiene and Tropical Medicine (pre-print, not peer reviewed) however has suggested the most plausible explanation for low case rates was that children are more likely to be asymptomatic, rather than less likely to acquire the disease. Studies of multiple family clusters have revealed children were unlikely to be the index case, in Guanzhou, China, and internationally A SARS-CoV2 positive child in a cluster in the French alps did not transmit to anyone else, despite exposure to over 100 people.

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. This has raised the possibility of faecal-oral transmission. Research from Germany failed to find any live, culturable virus in stool despite viral RNA being detectable, suggesting this represents viral debris rather than active virus. Further studies will be needed to shed further light on this.

Clinical Features

A significant proportion of children with COVID-19 do not appear to develop any symptoms, or have subclinical symptoms. In the absence of widespread community or serological testing, it is uncertain what this proportion is. The most detailed paediatric population data from China showed 13% of confirmed cases had no symptoms (cases detected by contact tracing). Considering both confirmed and suspected cases, 32% of children aged 6-10yrs were asymptomatic.

Clinical features in symptomatic children are somewhat different to adults. Children tend to have more mild illness. The most common presenting features are cough and fever, occurring in over half of symptomatic patients. Upper respiratory tract symptoms such as rhinorrhoea and sore throat are also relatively common, occurring in 30-40% of patients. It is not uncommon for children to have diarrhoea and/or vomiting (around 10% of cases), even in some cases as their sole presenting features.

Blood tests also show slightly different features to adults. Lymphocytopenia is relatively rare in children, with the majority having normal or sometimes raised lymphocyte counts. Inflammatory markers such as CRP and Procalcitonin are often raised but only very mildly. Slight elevations in liver transaminases appears common.

Radiographic features in children are also somewhat different to their adult counterparts. Chest X-rays are often normal, and many CT chest scans are also normal. When present abnormalities are often less severe, however a reasonable number of children have bilateral pneumonia. Changes may be found on CT even in asymptomatic children. Common features in abnormal CT scans include mild, bilateral ground glass opacities, but with less peripheral predominance than is reportedly found in adults.

There appears to be little in the way of clinical signs in children to differentiate COVID-19 from other childhood respiratory virus infections.

Newborns

A number of case reports have been published looking at the outcomes of pregnant mothers with COVID-19 and their newborn babies, with nearly 50 cases of infants now reported. Mothers and their babies in general appear to do well. As yet, cord blood, amniotic fluid and placental swabs persistently testing negative for SARS-CoV-2. There has been a few cases of infants delivered to mothers with COVID-19, who had elevated SARS-CoV-2 IgM. This may indicate intrauterine transmission, however swab PCR from these children has been negative and false positives with IgM tests are not uncommon. The vast majority of newborns have not acquired COVID-19 themselves. There have been case reports of newborns and very young infants testing positive (one at 36hrs of age) however they have not suffered any complications of the disease and required minimal respiratory support. One case series has described 10 infants delivered prematurely via emergency caesarean section who had a more difficult neonatal course, including one death with disseminated intravascular coagulation. All of these infants tested negative for SARS-CoV-2, and the reason for their premature delivery is unclear from the report.

Children With Comorbidities

There is little clinical data to inform us on the effect of COVID-19 on children with other comorbidities. Some data has been published from a liver transplant unit in Lombardy, Italy, which had 3 cases of COVID-19 in post-transplant patients who all suffered very mild symptoms. A case series of 9 children with inflammatory bowel disease on immunosuppression all suffered a mild course, as did a series of 5 children being treated for malignancy. Of note, in USA CDC data a high proportion of cases needing admission had at least 1 co-morbidity (most commonly respiratory)

Conclusion

COVID-19 appears to affect children less often, and with less severity, including frequent asymptomatic or subclinical infection. There is evidence of critical illness, but it is rare. The role of children in transmission is unclear, but it seems likely they do not play a significant role. Changes in laboratory or radiographic parameters are slightly different to adults, and changes usually mild. There is no direct evidence of vertical transmission, and early evidence suggests both infected mothers and infants are no more severely affected than other groups. Early evidence suggests no significant increased risk for children with immunosuppression, but further data is needed.

Table of evidence

FIRST AUTHOR JOURNAL DATE OF PUBL. COUNTRY REGION N# CHILDREN STUDY TYPE PAPER LINK

Press the tabs below to read the detailed summary in the document or press See paper to check the external link

Neonatal

Yu, N Lancet: Infectious Diseases 24 Mar 2020 China Asia 7 Neonatal

Clinical

Top 10 Neonatal Papers



Zeng et al (Neonatal)

Zeng L, Xia S, Yuan W et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. JAMA Pediatr. Published online March 26, 2020. doi:10.1001/jamapediatrics.2020.0878

This is a cohort study following 33 neonates born to COVID-19 positive mothers, recruited Wuhan Children's Hospital, Hubei Province, China, between January 2020 and February 2020. The authors describe three cases of early-onset neonatal COVID-19, which they suggest implies vertical transmission. However, amniotic fluid, cord blood and maternal breast milk of the mothers of all 3 positive neonates were negative for SARS-CoV-2, therefore it is unclear whether the infection was transmitted vertically or environmentally.

Three of the 33 neonates tested positive for COVID-19 on day 2 of life (positive nasopharyngeal or anal swabs). All 3 were born by caesarean section, two at term and the third at 31+2 for premature rupture of membranes and foetal distress.

Clinical features: The two term COVID-19 positive neonates had fever. These two neonates were also lethargic, but neither had respiratory distress. Neonate 3 was the most unwell, although this may be due to prematurity, poor condition at birth and sepsis rather than COVID-19.

Bloods: Neonate 1 had normal bloods except raised procalcitonin (0.09 microgram/L). Neonate 2 had a leucocytosis, lymphocytopenia and elevated CK. Neonate 3 had leucocytosis, thrombocytopenia and coagulopathy with prolonged PT (21 sec) and APTT (81.9 sec).

Radiology: All 3 had radiological evidence of pneumonia on CXR.

Yu et al (Neonatal)

Yu, Nan et al, Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study, The Lancet Infectious Diseases, Volume 0, Issue 0, Published: March 24, 2020 DOI: [https://doi.org/10.1016/S1473-3099\(20\)30176-6](https://doi.org/10.1016/S1473-3099(20)30176-6)

This is a retrospective study of 7 pregnant mothers infected with COVID-19 between Jan 1st and Feb 8th at Tongji Hospital in Wuhan, China. They were all at term (range 37/40 – 41+2/40). The mothers were all symptomatic, mainly with fever, cough, shortness of breath and diarrhoea. They all delivered via emergency caesarian section. All mothers did well.

The babies were all born with normal apgars. Four babies were discharged home and not tested for SARS-CoV-2 and never developed symptoms (including at 28 days follow up phone call. Three children were tested, of which one was positive at age 36 hours (reported in separate study, Wang et.al Clinical infectious Diseases, but did well with no fever or cough and mild shortness of breath). The other two tested negative and were later discharged without complication.



Chen et al (Neonatal)

Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395 :809–15. doi:10.1016/S0140-6736(20)30360-3

This retrospective case series looks at 9 pregnant women who were positive for COVID19 in Wuhan University Hospital between Jan 20th and Jan 31st. They all underwent a caesarean section (between 36 and 39+4 gestation). All newborn babies were well with good APGARS and, importantly, tests from 6 (3 not tested) patients were negative for SARS-CoV-2 in all amniotic fluid, cord blood, neonatal throat swabs, and breastmilk samples. There was no evidence of vertical transmission.

Dong et al (Neonatal)

Dong L, Tian J, Songming H et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. JAMA. Published online March 26, 2020. doi:10.1001/jama.2020.4621

This is a case report that would suggest that vertical transmission of COVID-19 can occur. A 34+2 primiparous woman was diagnosed with COVID-19 (she was symptomatic with fever and respiratory difficulty and had classic CT chest findings and a positive nasopharyngeal swab for SARS-CoV-2). She was treated with antiviral medications, antibiotics and corticosteroids.

Her female infant was delivered by caesarean section 4 weeks after the onset of her mother's symptoms in good condition with Apgars of 9 and 10. Although the infant's nasopharyngeal swabs were negative, her IgM antibodies against SARS-CoV-2 were raised at 2 hours post delivery and cytokine levels were elevated. The risk of environmental infection was minimised: the caesarean was performed in a negative pressure room, the mother wore an N95 mask and did not hold her infant and the infant was immediately isolated in NICU. Maternal vaginal secretions were negative for SARS-CoV-2, which would also suggest the infection did not happen at birth. As IgM antibodies do not cross the placenta, the infant's elevated IgM antibody levels suggest that she was infected in utero. Moreover, IgM antibodies usually do not appear until 3 to 7 days after infection. The infant also had raised IgG antibodies, but IgG is transferred placentally so this may reflect maternal or infant infection. The mother's breast milk was negative for SARS-CoV-2 1 week following delivery.



Zeng et al (Neonatal)

Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA. Published online March 26, 2020. doi:10.1001/jama.2020.4861

This report outlines the course of 6 mothers who were symptomatic for COVID-19 in their last trimester, and gave birth to 6 liveborn infants. This study is notable for antibody testing of both mothers and infants. The accuracy of the antibody tests are suspiciously high given current struggles to produce adequate tests around the world, and should be treated with a high degree of caution.

All 6 infants were born in good condition, and all tested negative for SARS-CoV-2 viral throat swabs and blood PCR. Unsurprisingly all infants had elevated IgG or SARS-CoV-2 (as this crosses the placenta), but notably 2 infants had raised IgM (39.9AU/ml and 16.25AU/ml). This raises the possibility of intrauterine infection, similar to another case of an infant with raised IgM (Dong et al JAMA). Issues with cross reactivity of IgM are well described, and so whilst full validation of these tests is awaited internationally, this should be treated with caution.

Liu et al (Neonatal)

Liu, Yangli et al. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. Journal of Infection, Volume 0, Issue 0 <https://doi.org/10.1016/j.jinf.2020.02.028>

This is a small case series of 13 pregnant women with confirmed SARS-CoV-2 infection between December 8 2019 and February 25 2020, in China. Two women were <28 weeks at presentation, the remainder were in the third trimester. One infant was stillborn, the 12 remaining infants (92%) were well at birth with no complications. None were positive for SARS-CoV2 or had 'serological evidence' of vertical transmission. The method of testing neonates was not clearly defined. The stillborn neonate had a mother who was severely unwell on Extracorporeal Membrane Oxygenation (ECMO) at the time of delivery.

Five of the 10 patients (50%) were delivered by emergency cesarean section due to pregnancy complications including fetal distress (30%), premature rupture of the membrane (10%) and stillbirth (10%). Interestingly, six patients (46%) had preterm labour between 32- 36 weeks of gestation.





Han et al (Neonatal)

Han, M. S., M. W. Seong, E. Y. Heo, J. H. Park, N. Kim, S. Shin, S. I. Cho, S. S. Park and E. H. Choi (2020). "Sequential analysis of viral load in a neonate and her mother infected with SARS-CoV-2." Clin Infect Dis. <https://doi.org/10.1093/cid/ciaa447>

This is a case report of a 27 day-old female neonate with confirmed SARS-CoV-2 infection. Over the course of a short and reasonably mild illness, samples were tested from the nasopharynx, oropharynx, plasma, urine, stool and saliva. SARS-CoV-2 RNA was detected in all samples. Early in the infection, viral load was highest in the nasopharynx and oropharynx, decreasing to undetectable at day 17. Viral load in stool, however, remained high throughout, despite cessation of gastrointestinal symptoms. This was in contrast to the mother's stool sample in which viral load was undetectable earlier.

Zhu et al (Neonatal)

Zhu H, Wang L, Fang C, et al. *Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr* 2020;9:51–60. doi:10.21037/tp.2020.02.06

This is a retrospective series of 10 neonates (including a set of twins) born to 9 mothers in Hubei province who were confirmed to have COVID-19.

4 mothers had symptoms prior to delivery, 2 mothers on the day of delivery, and 3 mothers after delivery. 7 mothers delivered via caesarean section and 2 by vaginal delivery. There was intrauterine distress recorded in 6 cases.

Of the babies, 8 were male and 2 female, 4 born at term and 6 preterm (twins at 31/40, and 4 babies around 34 – 35/40). APGARS were good for all babies. 6/10 developed some respiratory symptoms, one had some vomiting and one developed shock with DIC and multiple organ failure, who later passed away. All neonates tested negative for SARS-CoV-2, as did placental swabs.

It is hard to know what to make of this study. There is little information about how/why babies were delivered prematurely, and it would seem most symptoms are related to their early arrival. None were positive for the virus, and there was no evidence of vertical transmission. It seems contradictory to other evidence of babies delivered to mothers with COVID-19 who did well. Interpret with great caution.





Li et al (Neonatal)

Li N, Han L, M, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. doi:10.1101/2020.03.10.20033605

A pre-print, the information should be treated with caution until it has undergone peer review.

This was a case-control study (Jan 24–Feb 29) in Wuhan, China. 16 women with confirmed COVID-19 pneumonia and 18 suspected cases (typical CT chest findings but PCR negative) were used as cases, and 121 women randomly selected from the same period were selected as controls, and a further 121 were selected from 2019 as controls to avoid the impact of mental stress from lockdown.

Complications in mother were found in 70% in COVID-19 cases – much higher than in controls. We will mainly focus on infants. 17 babies were delivered to the 16 mothers (15 singletons, one set of twins) with confirmed COVID-19. Preterm delivery was higher in the cases, with 23.5% of confirmed COVID-19 mothers birthing prematurely compared to 5% of controls. However, mean gestation was still 38+2 in the cases.

There was no difference in APGAR scores, no cases of vertical transmission and no neonatal complications.

Li et al (Neonatal)

Li, M., L. Chen, J. Zhang, C. Xiong and X. Li (2020). "The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study." *PLoS One* 15(4): e0230295. <https://doi.org/10.1371/journal.pone.0230295>

The study explores the presence of Angiotensin-converting enzyme 2 (ACE2) within the placenta and the developing baby. It demonstrates significant expression of RNA coding the for ACE2 protein at several points of the maternal-foetal interface, as well as variable expression in a number of foetal organs. This theoretically provides a potential route for vertical transmission, placental dysfunction and pregnancy complications. The authors call for further clinical analysis to establish this potential.



Top 10 Clinical Papers



Lu et al (Clinical)

Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020;:NEJMc2005073. doi:10.1056/NEJMc2005073

This retrospective study examines the clinical characteristics of children with confirmed COVID-19 diagnosed at Wuhan Children's hospital. There were 1391 children tested between Jan 28th and Feb 26th 2020 due to known contact with a case of COVID-19, of these 171 were confirmed to have SARS-CoV-2. Median age was 6.7yrs, and there was a relatively even spread amongst age groups. Children were predominantly male (104/171, 60.8%).

Clinical features: 83/171 had cough, 79/171 had pharyngeal inflammation (sore throat), 71/171 had fever. 15/171 had diarrhoea and 13/171 had rhinorrhoea. 49/171 were tachypnoeic on admission and 72/171 were tachycardia. Only 4/171 had Oxygen saturations <92% during hospitalisation. 0/31 infants <1yr were asymptomatic in this cohort, with rates of asymptomatic infection increasing with age. There were higher rates of pneumonia in infants (25/6), but the definition of this is unclear. We also have no information regarding co-infection with other viruses or bacteria. Radiology: Not delineated into CXR or CT, but descriptions sound like CT findings. The most common was bilateral ground glass opacity (56/171) followed by unilateral patchy shadowing (32/171) and bilateral patchy shadowing (21/171). There were several children with radiographic pneumonia who were asymptomatic. Bloods: The supplementary appendix contains lab results. Only 6/171 patients had lymphopaenia, the vast majority were in normal range (Med 2.9 \times 10⁹/L, IQR 2.2 – 4.4). CRP was elevated (>10mg/L) in 33/171 (Med 4, IQR 1.3 – 8) of which 27/33 had pneumonia.

Outcomes: 3 patients required ITU admission and intubation. All 3 had co-morbidities, including hydronephrosis, leukaemia and intussusception. The child with intussusception suffered multiorgan failure and died after 4 weeks. The cause of death is not clear from the report. As of writing 149 patients had been discharged with 21 stable in the general wards.

Qiu et al (Clinical)

Qiu, Haiyan et al, Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. The Lancet Infectious Diseases, Volume 0, Issue 0 DOI:[https://doi.org/10.1016/S1473-3099\(20\)30198-5](https://doi.org/10.1016/S1473-3099(20)30198-5)

Qui and colleagues retrospectively identified 36 children with an EMR diagnosis of COVID-19, during the period Jan 17 through March 1st, at three hospitals in Zhejiang, China, a province 900km to the east of Wuhan. Diagnosis was made by COVID-19 RT PCR for all patients presenting with fever, cough and radiographic presentation, or if there was a history of exposure to an infected individual.

The paper provides reasonably clear definitions of mild, moderate, severe and critical illness, with asymptomatic patients identifying as Mild. For this cohort, 28% of patients were asymptomatic, with Moderate cases more likely to have fever of 38degC or higher (47%), cough (24%), vomiting or diarrhoea (10%) or headache (10%). More than half (53%) of patients had ground-glass opacities on CT scan, meeting the case definition for Moderate illness.

Key laboratory values of note include lymphopaenia, leukocytopaenia and increased procalcitonin as all associated with moderate illness. No patients in this cohort were hypoxaemic as a result of their pneumonia. The authors further analyse their cohort as 1-5yo and 5-16yo, in general noting that the older children were more likely to be lymphopaenic and would shed virus for a longer period (11 vs 9 days).

The authors also draw comparisons between adults and children with COVID-19 (less severe illness, less likely to have abnormal investigations), as well as comparing the clinical features and severity of COVID-19 with SARS (milder symptoms and severity) and H1N1 influenza (fewer symptoms, more frequent pneumonia) in children.

Wisely, Qui & colleagues note the high rate of findings that are not clinically obvious, and the high proportion of asymptomatic cases make for very challenging case identification in the absence of clear epidemiologic information. "This finding suggests a dangerous situation if community-acquired infections occur."





Zheng et al (Clinical)

Zheng F, Liao C, Fan Q-H, et al. Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China. Curr Med Sci 2020;:1–6. doi:10.1007/s11596-020-2172-6

This is a retrospective case series of 25 children <14 years of age hospitalised with COVID-19 from 10 hospitals across the Hubei province between February 1st and February 10th 2020. It is unclear how the cases were ascertained. 14/25 were male (54%) and the median age was 3yrs (IQR 2-9yrs). Most patients were <3 years (40%). 2 patients had a background of repaired congenital heart disease (both infants), although we have no more detail than this. Both of these children went on to develop critical illness.

Clinical features: 13/25 (52%) had fever, 11/25 (44%) had cough, 3/25 (12%) had diarrhoea, and 2/25 (8%) had nasal congestion, vomiting, breathlessness or abdominal pain.

Bloods: Inflammatory markers were not particularly raised, with a median CRP of 14.5mg/L (IQR 0.93 - 25). 10/25 (40%) patients had lymphopenia.

Radiology: CT chest was normal in 8/24 (32%) with unilateral involvement in 5/24 (20%) and bilateral in 12/24 (48%). Changes typically showed patchy shadows. Younger children appeared more likely to have bilateral lung findings than older children.

Co-infection: Other organisms identified included *Mycoplasma pneumoniae* (3/25, 12%), Influenza B (2/25, 8%) and one of the 2 critically ill children had *Enterobacter aerogenes*.

Xu et al (Clinical)

Xu, Y., Li, X., Zhu, B. et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med (2020). <https://doi.org/10.1038/s41591-020-0817-4>

This study presents the results of widespread screening for COVID-19 in Guangzhou in China. 745 children were screened of which 10 were positive for COVID-19. Their ages ranged from 2 months to 15 years.

Clinical features: 6/10 had a fever over 38°C. 5/10 had a cough. 4/10 had a sore throat. 2/10 had rhinorrhoea and 2/10 had diarrhoea.

Radiography: 7/10 had coarse lung markings on CXR with no pneumonia, and 3/10 were normal. CT scans revealed ground glass or patchy opacities in 5/10.

Bloods: Basically normal in all cases

They made note that rectal swabs were frequently positive and that these swabs were positive for a longer duration than nasal swabs. The authors suggest on this basis that faecal-oral transmission may be possible, however this is very uncertain and will require further research to elucidate.





Chen et al (Clinical)

Chen C. Coronavirus Disease-19 Among Children outside Wuhan, China [Internet]. Lancet Child and Adolescent medicine; Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3546071

A pre-print, the information should be treated with caution until it has undergone peer review.

This is a prospective case series of 31 paediatric cases of COVID-19 diagnosed at the Shenzhen Third Peoples hospital between Jan 16th and Feb 19th 2020. This made up 7.9% of all cases diagnosed in Shenzhen. They were all confirmed by PCR. None had been exposed to the seafood market in WUhan. The patients received nebulised interferon and, IV ribavirin or oral lopinovir/ritonavir. The median age was 6.75, with most patients (41.9%) aged 5-9. Followed by 0-4yrs (32.2%) and 10-14yrs (19.4%). 41.9% were male.

Clinical features: 12/31 Children were asymptomatic. Fever was observed in 14/31, Cough in 13/41, Sore throat in 2/31, Rhinorrhoea in 22/31 and diarrhoea in 2/31. Median duration of fever was 2 days, with a range of 1 – 9 days. Bloods: Lymphopaenia was not observed. Lymphocytosis occurred in 17/31 patients. CRP was elevated in 4/31 patients.

Radiology: On admission 64.5% of CT were normal, with 25% having unilateral pneumonia and 9.7% having bilateral. During hospitalization one child developed a unilateral pneumonia whose radiography was initially normal.

Outcome: 23 children had been discharged at the time of writing, and the remainder were well and afebrile.

Xia et al (Clinical)

Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults [published online ahead of print, 2020 Mar 5]. Pediatr Pulmonol. 2020;10.1002/ppul.24718. doi:10.1002/ppul.24718

A case series of 20 paediatric patients with COVID-19 infection identified with COVID-19 NAT on pharyngeal swabs from Wuhan Children's Hospital. It reviews the clinical information and co-infections,

Clinical features: two thirds had a clear contact history. Incubation 24 hours-28 days of life. 13/20 had a cough, 12/20 had a fever

Bloods: 11/20 had (N) CRP i.e. less than 3 mg/L and 4/5 had PCT >0.05

Radiology: On CT:

- Subpleural findings were seen in all 20 patients
- 50% had bilateral findings, with a further 6/20 with unilateral findings.
- Consolidation with a halo in 50% of cases, considered as atypical signs in paediatric patient
- Chloral hydrate was the primary sedative for CTs

These were predominantly mild cases in the paediatric patients, with CXR adding little diagnostically. An early chest CT exam seemed to be necessary. 9/20 had coinfection, most commonly with mycoplasma (4/9) – although the 'flu B,'flu A or RSV accounted for almost all of the remainder. Despite this, the physical chest symptoms were mild, with retraction in one case, and another case with cyanosis.

The average length of stay 12.9 days. Some patients were managed on the basis of their CT alone. These are similar to those seen in adults.





Wei et al (Clinical)

Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang Z. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. Published online February 14, 2020. doi:10.1001/jama.2020.2131

This is a case series of, from Dec 8 2019 to Feb 6 2020, from China of 9 infants – all of whom had been hospitalised.

Clinical presentation: 4/9 fever, 2/9 mild URTI symptoms, 1/9 were asymptomatic. All had family members that were COVID-19 positive. There were no severe complications or ICU admissions.

Lazzerini et al (Clinical)

Lazzerini, Marzia et al, Delayed access or provision of care in Italy resulting from fear of COVID-19, The Lancet Child & Adolescent Health, Volume 0, Issue 0, Published April 9th 2020, [https://doi.org/10.1016/S2352-4642\(20\)30108-5](https://doi.org/10.1016/S2352-4642(20)30108-5)

This is a report of case studies during the COVID-19 pandemic in Italy of children whose presentations were thought to have been delayed due to parental fears of coming to the hospital. They report from 5 hospitals between March 1st and March 27th 2020, where paediatric presentations were reduced between 73–88%.

During this period, in the week of March 23rd to 27th 12 children are identified whose parents reported avoiding accessing hospital due to concerns over SARS-CoV-2 infection . 6 of these were admitted to PICU and there were 4 deaths. The cases include 2 children with DKA, 2 with acute leukaemia, 2 children with cerebral palsy and complex needs, 1 with pneumonia and febrile convulsions, 1 with pyelonephritis, 1 with pyloric stenosis, 1 with a Wilm's tumour, 1 with vomiting and hypoglycaemia and 1 with a congenital syndrome on dialysis.

This case series highlights the concerns of many paediatricians that more deaths will be seen in children from collateral damage born from the COVID-19 response, than will die of COVID-19. Delayed presentations is a major concern around the world currently, and whilst these cases certainly raise concerns, evidence is needed to ascertain the true presence and extent of this problem.





Turner et al (Clinical)

Turner D, Huang Y, Martin-de-Carpi J, et al. COVID-19 and Paediatric Inflammatory Bowel Diseases: Global Experience and Provisional Guidance (March 2020) from the Paediatric IBD Porto group of ESPGHAN [published online ahead of print, 2020 Mar 31]. J Pediatr Gastroenterol Nutr. 2020; doi:10.1097/MPG.0000000000002729

This article outlines the experience from Asia and Europe so far of children with inflammatory bowel disease given the COVID-19 pandemic. This is of particular interest because many of these children receive immunosuppression as part of their treatment, and so could be considered high risk for complications of the disease.

It appears to have been routine practice to suspend treatment for IBD during the outbreak of COVID-19, which resulted in a large number of relapses. No children with IBD contracted COVID-19 in China in the period covered by the survey.

In South Korea treatment for IBD was not suspended. They also have had no cases of COVID-19 in children with IBD.

In the PORTO IBD group of ESPGHAN (covering Europe, some centres in Canada and Israel) treatment was not suspended in 31/32 centres. 7 children with IBD, who were on immunosuppression, had COVID-19. They all suffered a mild illness with no flare of their IBD. There is an additional child case from an international IBD database identified who also experiences mild symptoms (no hospitalisation required).

This survey provides further reassurance that treatment with immunosuppression does not appear to significantly increase the risk of severe disease from COVID-19 in children.

Balduzzi et al (Clinical)

Balduzzi, A, Brivio, E, and Rovelli, A et al, Lessons After the Early Management of the COVID-19 Outbreak in a Pediatric Transplant and Hemato-Oncology Center Embedded within a COVID-19 Dedicated Hospital in Lombardia, Italy. Estote Parati. (Be Ready.) (3/19/2020). Available at SSRN: <https://ssrn.com/abstract=3559560> or <http://dx.doi.org/10.2139/ssrn.3559560>

This report from a paediatric haematology unit in Lombardia, Italy, includes the Italian experience of COVID-19 in children with malignancy so far. At their particular unit, they have had no children with malignancy test positive for COVID-19 (they admit this is dependent on testing criteria, requiring hospitalisation at their institute). They are aware of 5 cases of paediatric cancer patients who have had COVID-19 and have all suffered a mild course, with 3 managed at home and 2 in hospital.

This small case series provides further reassurance for at risk paediatric populations.

Top 10 Epidemiological Papers



Dong et al (Epidemiological)

Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics 2020:e20200702. doi:10.1542/peds.2020-0702

This landmark paper is a retrospective epidemiological study of 2143 pediatric patients with suspected or confirmed COVID-19 (Jan 16 – Feb 8 2020) from in and around Hubei province in China.

Confirmed cases were diagnosed by PCR of NPA or blood or genetic sequencing from the respiratory tract or blood highly homologous with SARS-CoV-2.

To be a suspected case you needed to be high risk (based on community exposure) with any 2 of: fever, respiratory symptoms or diarrhoea/vomiting; normal or lower white cell count +/- raised CRP; abnormal CXR.

If you were medium/low risk for community exposure, you could still be a suspected case if you met any 2 of the above criteria and had other respiratory viruses excluded.

Patients were classed according to severity:

Asymptomatic: no symptoms at all

Mild: Primarily URTI symptoms with or without fever

Moderate: Pneumonia, frequent fever, and cough, +/- wheeze, but not hypoxaemic OR none of these but an abnormal CT (worth noting)

Severe: Above symptoms but more severe, usually with accompanying hypoxaemia

Critical: ARDS, shock, organ failure



Dong et al cont. (Epidemiological)

So what did they find? There were 731 (34.1%) laboratory-confirmed and 1412 (65.9%) suspected cases. The median age was 7 years. There were 94 (4.4%) asymptomatic, 1091 (50.9%) mild and 831 (38.8%) moderate, accounting for 94.1% of all cases. Of note, the youngest patients (under 1yr) had the highest proportion of severe and critical illness (10.6%). However, this group also had the highest proportion of “suspected” disease (293/379) – of which we do not know how many had an infection with RSV, HPMV or Flu. This was peak bronchiolitis season. There was one death in a 14yr old boy, for which there are no clinical details available. The highest proportion of asymptomatic cases was in the 6-10yr olds (31.9%), for whom there was no recorded critical illness. Critical illness was uncommon in general (0.6% of all cases). The median time from illness onset to diagnosis was 2 days. Chest imaging was emphasized in delineating the severity (CXR and CT). There are also some interesting epidemiology graphs which essentially map to the well-described adult prevalence of disease and demonstrate Hubei as the epicentre.

This large cohort study provides reassuring data about the severity of illness of COVID-19 in children. There is an indication that younger infants may be most likely to be affected most severely, however, this cohort is highly likely to contain children with normal, severe, winter viral infections such as bronchiolitis. Critical illness was extremely rare.

CDC (Epidemiological)

Coronavirus Disease 2019 in Children – United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep. ePub: 6 April 2020. DOI: <http://dx.doi.org/10.15585/mmwr.mm6914e4>

This is the first USA CDC report of COVID-19 looking specifically at children, examining confirmed cases nationally between February 12th and April 2nd. Due to the extremely disparate nature of public health reporting in the USA, the data quality and availability for this report is highly variable. There is no information as to the basis on which tests were performed, whether for presentation to hospital, symptomology or due to contact tracing. This cohort is therefore likely extremely heterogeneous. Of the nearly 150,000 confirmed cases in the US at this time, 2,572 (1.7%) were in children. New York City had 33% of paediatric cases. The median age was 11y and males account for 57%. Nearly 33% of cases were in children aged 15 – 17yrs, 15% in children <1y, 11% in children ages 1 – 4y and 15% in children 5 – 9y. 91% of cases had exposure to a known COVID-19 case.

Data on signs/symptoms was only available for 11% of cases. Fever, cough OR shortness of breath were present in 73% of cases, with fever in 56%, cough in 54%, shortness of breath in 13%, rhinorrhoea 7.2%, sore throat 24%, vomiting 11% and diarrhoea 13%. They have not reported on “asymptomatic” cases due to incomplete reporting on symptoms. PICU admission was documented for 2% of cases. Hospitalisation was most common in infants (62%), with little difference between other age groups in regards to hospitalisation or ICU admission. From low numbers infants did not appear significantly more likely to be admitted to ICU. Underlying conditions were present in 23% of cases, most commonly respiratory (such as asthma), followed by cardiac conditions and immunosuppression. There are 3 deaths reported, but review is ongoing to determine whether COVID-19 was the cause.

This patchy data from the US is useful as it closely resembles data from Chinese cohorts of children in regards to low frequency of severity and adverse outcomes. It confirms available data suggesting lower frequency of common symptoms in children as compared to adults.





Gudbjartsson et al (Epidemiological)

Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. N Engl J Med, Published April 14th 2020, doi:10.1056/NEJMoa2006100.

This study describes the entry and spread of SARS-CoV-2 through Iceland. Importantly, this is the first epidemiological report to include SARS-CoV-2 screening of the general population and likely represents the most complete national epidemiological data published to date.

Study design: This report includes all confirmed SARS-CoV-2 infections in Iceland identified through either: targeted testing (January 31st to March 31st 2020) – 9199 predominantly symptomatic patients with travel to a high risk country or contact with a confirmed case; population screening (March 13th to April 1st 2020) – 13080 volunteers screened from the general population (without high-risk travel or contact with a confirmed case). Most patients in the population screening cohort were asymptomatic, with a minority with predominantly mild URTI symptoms. A subsequent period of random population screening from April 1st-4th excluded children. SARS-CoV-2 real-time PCR was performed on combined oropharyngeal and nasopharyngeal samples. All confirmed cases were isolated and close contacts placed in quarantine for 14 days.

Key paediatric findings - there is comparative data provided on the 1412 children <10 years of age tested: of 564 children <10 years old tested in the targeted testing cohort, 6.7% (38) were positive – compared with 13.7% of persons >10 years old; of 848 children <10 years old tested in the population screening cohort, 0% (0) were positive – compared with 0.8% of persons >10 years old. Details on severity of infection, hospitalisation rates and age specific symptom profiles are not included.



Gudbjartsson et al cont. (Epidemiological)

Discussion: The first SARS-CoV-2 infection in Iceland was confirmed on 28th February 2020. The dynamics of new cases has transitioned from imported infections initially to ongoing community spread. To date just over 0.5% of the population have had confirmed infection. Whilst physical distancing measures have been put into place including limiting gatherings to a maximum of 20 people, elementary schools have remained open.

Iceland has amongst the highest national rates of SARS-CoV-2 testing per capita, with 6% of the population tested as described here. As a result this report provides the most accurate and complete national epidemiological data published to date. The lower rate of positive tests in children <10 yo adds support the hypothesis that children are less susceptible to SARS-CoV-2 infection compared to adults. Similarly the lack of positive tests amongst >800 children screened goes against the theory that the low reported rates of COVID-19 in children are due to a large number of undocumented / asymptomatic paediatric cases. This finding, particularly, has important implications in decision-making around patient flow and isolation in general paediatric care, suggesting that routine testing and isolation of asymptomatic children may be of low yield in similar settings.

Clearly a single PCR screening test at one time point has an insufficient negative predictive value to exclude infection. As such, serological studies will be important in providing a clearer picture of the extent of SARS-CoV-2 infection in children.

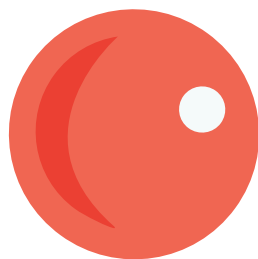
Conclusion: Children under 10 year old appear to be less likely to develop SARS-CoV-2 infection compared with people >10 yo. In settings with moderate levels of SARS-CoV-2 infection (0.5% population with confirmed infection in this setting), screening of asymptomatic children without overseas travel or contact with a known case is of very low yield.

Tagarro et al (Epidemiological)

Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. JAMA Pediatr. Published online April 08, 2020. doi:10.1001/jamapediatrics.2020.1346

This is a registry of confirmed COVID-19 cases in Madrid, Spain from March 2 to March 16 – the first 2 weeks of the epidemic in Spain. Children were screened according to recommendations at the time with PCR.

Of 365 children tested, 41 were positive (11.2%), out of the 4695 cases in the Madrid region (0.8%). 16 children (39%) with confirmed COVID had a known contact with a confirmed case. The median age of positive cases was 1 years. 60% required hospitalisation, 9.7% required PICU admission, and 9.7% required respiratory support beyond nasal prongs (including both non-invasive and invasive mechanical ventilation). Of those requiring ICU admission, only 1 (25%) had a comorbidity (recurrent wheeze). There were no deaths. Two patients (5%) had co-infection with influenza B, but it was not clear whether all patients were tested for co-infection.





Livingston et al (Epidemiological)

*Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA
Published Online First: 17 March 2020. doi:10.1001/jama.2020.4344*

This is a helpful one page summary of data around COVID-19 numbers in Italy as of 15th March 2020. Of note, there have been 22,512 cases of COVID-19 with 2026 (9%) being health care workers. There have been 1625 deaths (7.2%) of cases in Italy, which is a higher case fatality than rates from China and other countries so far. Below are two of the charts below which depict the age range and severity of COVID-19 infections. From a paediatric perspective, 1.2% of cases have been in patients <18 years old and remarkably there have been 0 deaths under 30yrs of age so far.

Mizumoto et al (Epidemiological)

*Mizumoto K, Omori R, Nishiura H. Age specificity of cases and attack rate of novel 1 coronavirus disease (COVID-19) 2. doi:10.1101/2020.03.09.20033142
A pre-print, the information should be treated with caution until it has undergone peer review.*

This is a series of the 313 domestically acquired cases of COVID-19, in Japan, up until March 7th 2020. It looks at the ages of patients who acquired the disease and compares this to those exposed (n=2496) to estimate attack rates.

Of note, there was a significantly lower attack rate in children (7.2% in males and 3.8% in females) than in the older populations (up to 22% in 50 – 59yr olds). This attack rate in children is similar to that observed in Shenzhen, but much lower than observed in older adults in Japan. This suggests children are much less likely to acquire the disease than adults if exposed. This is at odds with the findings from Shenzhen, and the reason for this disparity is unclear.





Lavezzo et al (Epidemiological)

Enrico Lavezzo, Elisa Franchin, Constanze Ciavarella, et. al, Suppression of COVID-19 outbreak in the municipality of Vo, Italy, medRxiv 2020.04.17.20 doi: <https://doi.org/10.1101/2020.04.17.20053157>

A pre-print, this article should be interpreted with caution until it has undergone peer review.

This paper outlines the strategy of a small town in Italy which immediately shutdown for 14 days following their first death from COVID-19 on Feb 21st 2020. They subsequently screened 86% of the population for SARS-CoV-2 using nasopharyngeal swabs, then screened again 2 weeks later (71.5% of the population). At the start of the lockdown 2.6% (95% CI 2.1 – 3.3%) of the population tested positive, but 0 of 217 children aged 0 – 10 tested positive (0%), and only 3/250 aged 11 – 20 (1.2%) tested positive. By the end of the lockdown, 0/157 (0%) children aged 0 – 10 tested positive, and 2/210 (1%) children aged 11- 20 tested positive. Many of the children aged 0 -10 lived with infected individuals. They also noted >40% of people who tested positive were asymptomatic. They note a significant number of infections appeared to have come from asymptomatic individuals during contact tracing. They also note these asymptomatic individuals never developed symptoms, and had similar viral loads to symptomatic patients (as determined by the cycle threshold from RT-PCR).

This study has relatively small numbers, but again appears to provide evidence for several important features of paediatric infection: primarily that children appear significantly less likely to become infected than adults. It presents evidence for asymptomatic transmission, and against the theory of viral load correlation with symptom burden.

Qin-Long et al (Epidemiological)

Qin-Long Jing, Ming-Jin Liu, Jun Yuan et al, Household Secondary Attack Rate of COVID-19 and Associated Determinants, medRxiv, 11th April 2020, <https://doi.org/10.1101/2020.04.11.20056010>

A pre-print, this article should be interpreted with caution until it has undergone peer review.

This is study from Guangzhou, China documenting the attack rate amongst 2075 close contacts of 212 confirmed COVID-19 cases from January 7th to February 17th 2020.

There were 97 non-primary cases amongst 770 household contacts giving an attack rate of 12.6% overall. Notably children (<20yo) had a lower non-primary household attack rate of 5.3%.

In statistical transmission modelling to estimate true secondary attack rates, children (<20yo) had a lower odds of infection compared with adults >60 years old (OR 0.27 for close contacts and OR 0.23 for household contacts). Only 10/217 (5%) of primary cases were children.

Although the criteria for testing contacts in this study are not entirely clear, the results suggests that children are less susceptible to SARS-CoV-2 infection compared with adults with similar exposure. This is in contrast to earlier data from Shenzhen, China suggesting similar attack rates in children, but is in keeping with more recent epidemiological data from Iceland and Italy.





Choe et al (Epidemiological)

COVID-19 National Emergency Response Center, Young June Choe. Coronavirus disease-19: The First 7,755 Cases in the Republic of Korea. medRxiv 2020.03.15.20036368; doi: <https://doi.org/10.1101/2020.03.15.20036368>

This is a report of the first 7755 patients with confirmed COVID-19 in Korea as of March 13th. It is notable as Korea undertook one of the worlds most intensive strategies to community testing, which may give a better understanding of the proportions of different groups affected who may have had mild or subclinical infection and might otherwise not have been tested.

The finding of significance is that children made up a very small proportion of total cases, with only 75 (1%) under 9 years of age, and 405 (5.2%) aged 10 – 19 years. There were no deaths in patients under 30 years of age. This suggests not just low severity of infection in children, but a low attack rate with such low cases numbers.

Kostas et al (Epidemiological)

Kostas Danis, Olivier Epaulard, Thomas Binet et al. Cluster of coronavirus disease 2019 (Covid-19) in the French Alps, 2020, Clinical Infectious Diseases, ciaa424, <https://doi.org/10.1093/cid/ciaa424>

This is a study of a cluster of COVID-19 cases in the French alps linked to a single index case. A child became infected and was symptomatic, but despite attending 3 schools during this time with exposure to 112 different school contacts the child did not transmit the infection to any other contacts.

Whilst a single case study, this evidence suggests different transmission dynamics from children, supporting other data which consistently demonstrates reduced infection and infectivity of children in the transmission chain.

