



**DFTB COVID-19
EVIDENCE REVIEW
3RD JUNE 2020**

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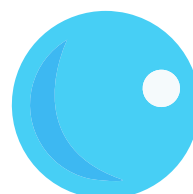
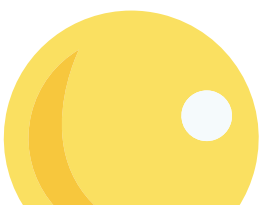
Introduction

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. Our team of reviewers includes Alasdair Munro, Alison Boast, Henry Goldstein, Grace Leo, Dani Hall, Daniel Yeoh, Tessa Davis, Melody Redman, Sarah Sloan, Tricia Barlow, Anna Bean, Maeve Kelleher, Victoria Dachtler, Irnthu Premadeva, Lilian Nyirongo, Esther Alderson, Sunil Bhopal, Aimee Donald and Rachel Harwood.



Executive summary of evidence

Epidemiology

Around the world, children make up a minority of confirmed cases of COVID-19, usually contributing to between 1 – 5% of total case numbers. 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 screened 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 into childhood severity of COVID-19. A large number of children appear asymptomatic. Critical illness appears very rare (~1%). In Chinese and 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

263

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

Transmission

Precise details regarding paediatric transmission cannot be confirmed without widespread sero-surveillance, however important trends are emerging. 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 4 subsequent studies in Japan, Guangzhou, Wuhan and Shanghai, and cities in close proximity to Wuhan. These have all demonstrated a significantly lower attack rate in children. This, coupled with low case numbers would suggest 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. Studies of multiple family clusters have revealed children were unlikely to be the index case, in Guangzhou, 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 6-10 years were asymptomatic. Data from Italian emergency departments found 21% of SARS-CoV-2 positive children to be 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. Several case series of rashes resembling chilblains (often occurring on feet/toes) have been reported from Europe, contemporaneously associated with the COVID-19 outbreak but with few cases simultaneously confirmed to be infected.

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 appear to be 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.

More recently, a hyperinflammatory syndrome resembling Kawasaki shock, which appears to be a delayed immune response to COVID-19 has been described. Published reports from London, Italy and France in a cohort of children with evidence of past COVID-19 infection have presented with early symptom of abdominal pain, vomiting and diarrhoea, with persistent high-grade fever and commonly progression on to shock with cardiac involvement. High inflammatory markers, myocarditis, macularpapular rashes and non-suppurative conjunctivitis are common. Respiratory involvement is notably absent. Investigations are underway to ascertain a link and mechanism of disease.

Newborns

A large number of cases of infants born to mothers with COVID-19 have now been reported, including several hundreds from the UK. Mothers and their babies in general appear to do well. There is a small but notable increase in the rates of preterm birth, and signals of increase in rates of foetal loss/stillborn delivery. As yet, cord blood, amniotic fluid and placental swabs persistently testing negative for SARS-CoV-2. There have 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. When tested, breast milk has been negative for SARS-CoV-2 except for on a single occasion. It is unclear if this positive result reflects live, infectious virus, and whether the source was the mother or the infant who subsequently also tested positive for the virus. The vast majority of newborns have not acquired COVID-19 themselves. There have been case reports of newborns and very young infants testing positive including several within 12 hours of age, however they have mostly not suffered any complications of the disease and required minimal respiratory support.

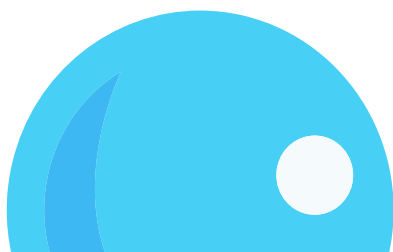
Children With Comorbidities

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. Studies from PICU admissions in the US and Italy found the majority have some comorbidities, most commonly respiratory or complex neurodisability – groups for whom there is a background increased risk of complications from all respiratory viruses. The rates of complications from SARS-CoV-2 infection do not appear disproportionate to those from other respiratory viruses from this early data.

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 consistent evidence is demonstrating a lower likelihood of acquiring infection, and lower rates of children bringing infections into households. Changes in laboratory or radiographic parameters are slightly different to adults, and changes usually mild. There is some evidence of vertical transmission to neonates, however it is unclear if this is perinatal or intrauterine. Evidence suggests both infected mothers and infants are no more severely affected than other groups. There does not appear to be significant increased risk for children with immunosuppression, but further data is needed. Children with respiratory and complex neurodisability appear more likely to suffer complications, however not obviously more than would be expected from infection with other respiratory viruses.

Please see the full article with a table of all the papers included here:



Top 10 Neonatal Papers



Knight et al (Neonatal)

Knight, K. Bunch, N. Vousden et al. Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV 2 infection in the UK: A national cohort study using UK obstetric surveillance system. Nuffield Department of Population Health, UKOSS Publications 11th May 2020, <https://doi.org/10.1101/2020.05.08.20089268>

As a pre print this study should be interpreted with caution until it has undergone peer review.

This is a prospective observational national cohort study carried out across all 194 consultant-led maternity units in the UK. It captured data from women admitted to hospital with confirmed SARS CoV 2 between 01/03/20 and 14/04/20, with tests having been carried out only if the woman was symptomatic. 427 women were studied and compared to a historical control sample of 694 women admitted between 01/11/17 – 31/10/18 (a historical sample was chosen to avoid confounding by including asymptomatic or minimally symptomatic carriers of COVID). The total number of maternities in the study period was 86293 and therefore the incidence of admission the SARS CoV 2 confirmed women was 4.9 per 1000 maternities. The median gestation at admission was 34 weeks (IQR 29-38 weeks), with 81% of admissions in the 3rd trimester. The results showed that there was a statistically significant risk of admission with SARS CoV 2 patients who had the following factors: From a Black and Minority Ethnicity group: adjusted OR 4.49 (3.37-6.00). Even after sensitivity analysis which excluded women from London, West Midlands and North West England which had high rates of general infection OR 3.67 (2.55-5.28).



Knight et al (cont)

Pre-existing medical condition (asthma, hypertension, cardiac disease or diabetes): adjusted OR 1.52 (1.12-2.06)

Maternal age >35: adjusted OR 1.35 (1.01-1.81)

Being a current smoker reduced the risk of admission, with adjusted OR 0.3 (0.17-0.51).

The odds ratio for each significant factor outlined above was adjusted for the other significant factors which became confounding variables. There were 40 admission to level 3 critical care with 4 requiring ECMO. There were 5 maternal deaths recorded, 3 of whom had been admitted to critical care. SARS CoV 2 associated maternal mortality was 5.6 (1.3-13.1) per 100,000. Only 9 women were treated with antivirals (oseltamivir, lopinavir/ritonavir and/or remdesivir). 61 women were given corticosteroids for the maturation of fetal lung.

247 women in this cohort gave birth (singleton/multip proportion not stated) to a live infant (n=243) or had a pregnancy loss (n=4). 59% of women gave birth via c-section with 20% under general anaesthetic compared to 29% of the control group with 7% of women delivering under GA. There were 63 (26%) preterm births (<37 weeks) and 29 of these were documented as being secondary to COVID 19 infection; the other reasons stated were iatrogenic, fetal compromise and other obstetric conditions. This is compared to 8.9% of births in the control group being born preterm. There were 5 neonatal deaths, including 3 stillbirth; in two of the cases of stillbirths, it is unclear whether COVID 19 infection contributed to death.



Knight et al (cont)

The rate of pregnancy loss, still birth, livebirth and neonatal death was not statistically different between the groups. The NICU admission rate was 26% (majority for prematurity) and 5% in the cohort and comparison groups, respectively. 12 infants tested positive for SARS CoV 2, with 6 being within the first 12 hours of life (early). 1 in the early positive and 5 in the later positive groups were admitted to NICU.

This is a national study reporting on the largest cohort of SARS CoV 2 positive pregnant women admitted to hospitals with symptoms. There is likely to be an underestimation of the true effect size presented in this report as analysis was carried out in only those patient in whom data was returned and not on the entire cohort of admissions in the specified time period. The results convincingly show important risk factors (maternal age, black and minority ethnicity, BMI, and pre-existing medical condition) for admission and thus confers the severe of infection in these risk groups. The black and minority ethnicity risk factor, which existed even after the sensitivity analysis, requires urgent further analysis and study as it was the biggest risk factor and one which has not been demonstrated to be the case in other coronavirus strains. The supposed protective factor of current smoker status is not explained in this report but could reflect lower current prevalence of smoking in pregnancy in general compared to the prevalence at the time of the historical sample. The report also highlights that most of the admission with SARS CoV 2 was in the second and third trimester thus providing weight for the precautions currently being taken in this group of women. However, they also correctly identify that there may be a sampling bias as those in the first trimester may be being admitted to hospital via routes other than the maternity services. There was a higher rate of preterm deliveries (statistical significance unknown) which is difficult to interpret but raises questions as to what extent the maternal infection may cause fetal compromise triggering preterm birth.



Knight et al (cont)

2% of babies tested positive for SARS CoV 2 suggesting a risk of vertical transmission, especially since 3 of the positive cases were pre-labour, c-section delivered babies. However, the IgG or IgM status of the infants is unknown and there were no placental, umbilical cord, etc samples taken/ reported. The discussion states that mothers and infants were kept together with infection control measures (surgical face masks) and the low rates of neonatal infection supports continuation of this practice. However, 6 of the 12 infants testing positive for SARS CoV2 required neonatal unit admission, majority of whom were classed as late infections as they tested positive after 12 hours of life. There is no information provided on the reason for these admissions and what support and/or treatment was required during this time. It is important to point out that the report does not specially say that all other infants born to this cohort of mothers were tested for SARS CoV 2 and found to be negative. Further questions are raised in the two cases of stillbirth which may have been caused by COVID 19. There is also no clarification on the characteristics of the cases of neonatal death (e.g. were they preterm, was mother critically ill in ITU, etc) which would have added greatly to the analysis of this report.

Although this study does not provide enough detail to draw firm conclusions, it provides an important basis for further avenues where research is needed.



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 Pediatrics. 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.



Zeng et al (cont)

The authors state that because strict infection control and infection prevention procedures were implemented during delivery, SARS-CoV-2 isolated from their upper respiratory tracts or anuses was therefore maternal in origin. However, although it is stated in the illustration that one neonate was immediately quarantined after birth, it's not clear whether this was the case for the other two babies. Plus, the negative amniotic fluid and cord blood does raise the question as to whether these neonates were truly infected in utero or not.

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.

Groß et al (Neonatal)

Groß, C. Conzelmann, J. A. Müller, S. Stenger, K. Steinhart, F. Kirchhoff and J. Munch. Detection of SARS-CoV-2 in human breastmilk. Lancet, May 21st 2020, [https://doi.org/10.1016/S0140-6736\(20\)31181-8](https://doi.org/10.1016/S0140-6736(20)31181-8)

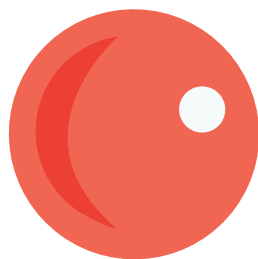
This report is presented as a letter.

The study primarily relates to the SARSCoV2 content of the breast milk of two “nursing mothers” who shared a room postnatally, with their babies, and who developed swab-positive mild Covid-19 infection after birth – three days and six days respectively. The gestation and birthweights of the babies are not reported but they seem to have been full term, well at birth and initially well for the first few days following delivery.

The babies developed abnormal respiratory signs, one with jaundice, at 8 days and 11 days respectively, both becoming swab positive for SARSCoV2 at about the same ages and both being admitted to a Neonatal Unit. One infant, who also tested positive for RSV, subsequently required mechanical ventilation. It is stated that one infant recovered but the outcome for the ventilated infant is not given.

The patient identification and recruitment processes are not described.

Breast milk was collected, after feeds and after nipple disinfection, from each mother starting at eight days and four days respectively after development of Covid-19 symptoms. Samples were collected on postnatal days 12-15 for the first mother and 10, 12, 13, 14 and 25 for the second. Testing for SARSCoV2 RNA was performed using RTqPCR. Information on the method of nipple disinfection is not provided.



Groß et al (continued)

A separate laboratory-based study investigated the effect of breast milk on viral recovery rates by “spiking” breast milk with serial dilutions of a SARSCoV2 stock.

The main findings of potential importance are:

-The breast milk of one of the mothers tested positive for SARSCoV2 RNA at 10-13 days after birth. Testing of breast milk from the other mother was negative.

-Quantification using Ct values corresponded to 1.32×10^5 copies per mL in whole milk and 9.48×10^4 copies per mL in skimmed milk.

-An 89.2% reduction in recovery rate in whole milk and 51.5% in skimmed milk, suggesting that the actual viral loads in whole milk of the mother could be even higher than detected.

This study provides the first report of the detection of viral RNA in human breast milk collected from a mother who had clinical signs of Covid-19 confirmed by PCR testing of swabs. This does not provide evidence that the RNA was indicative of infectious virus or that transmission of the virus to the baby occurred via breastmilk. Further studies will be necessary to attempt to culture virus from breast milk and assess risk of transmission, which to date has seemed low.



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.

Parri et al (Clinical)

Parri N, Lenge M, Buonsenso D; Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in Pediatric Emergency Departments in Italy [published online ahead of print, 2020 May 1]. N Engl J Med. doi:10.1056/NEJMc2007617

This report is of confirmed COVID-19 infections in children under 18 years of age who presented to a research collaboration of 17 paediatric emergency departments in Italy between March 3rd and March 27th. The median age was 3.3 years and 57/100 were male. Children under 1 year were over-represented (40%) followed by children >10 years (24%). Helpfully they categorise their patients according to criteria from Dong et. al (see review in Epidemiology top 10): Asymptomatic 21%, Mild 58%, Moderate 19%, Severe 1% and Critical 1%. Only 12% of patients appeared ill on assessment. Interestingly only 4% of patients had Oxygen saturations <94%. Only 38% of children needed admission for severity of illness. There were no deaths. The supplementary appendix includes a huge amount of detailed analysis of the cases, which are summarised below

Clinical features: Fever 54%, Cough 44%, Feeding difficulty 23%, Sore throat 4%, Rhinorrhoea 22%, Diarrhoea 9%, vomiting 10%.

Bloods: Largely unremarkable (although reports of lymphopenia unclear – state 14 patients lymphopenic but that this is 28%? – perhaps only 50 children had bloods, but this is not reported). Procalcitonin <0.5ng/L in 29/23 patients.

Radiology: Chest x-rays performed for 35 children, of which 14/35 had interstitial abnormalities, 6/35 consolidation and 1/35 pleural effusion: remaining 15/35 normal.

Comorbidities: There were 27/100 children with comorbidities – although it appears most had mild illness (did not require respiratory support). This included 6 with cystic fibrosis, 4 neurological, 4 haematological, 4 with a syndrome, 3 with prematurity, 2 with cardiac conditions, 2 immunological, 2 oncological and 1 metabolic disease.



Parri et al (continued)

Of the few patients who required respiratory support (9/100) a significant number had comorbidities (6/9), although the range was broad. This included 2 children with “epileptic encephalopathy”, one of whom also had CHARGE syndrome, a child with autism, a child with a VSD, a child with propionic acidemia, and a child with thrombocytopenia and frequent respiratory infections. One of the strengths of this study is comparisons across other studies of clinical features of COVID-19 in children. In comparison to Dong et al, CDC data and Lu et al, most features are broadly comparable. Some notable differences are a significantly larger number of infants in the Italian data (40% <1yr compared to 18% in Lu, 12% in Dong and 15.5% in CDC) and a slightly higher number of asymptomatic children (21% compared to 16% Lu, 13% Dong and 1.3% CDC). This most likely represents differences in which population cohorts presented for testing among the different studies – comparisons between cohorts is always difficult currently due to broad differences in the denominators used. Notably there is no apparent difference in severity according to age in this Italian data, whereas CDC noted increased hospitalisation in children <1 year and Don’t et al noted higher rates of severe or critical illness in infants <1 year.

Broadly speaking this study confirms findings from China and the USA regarding significantly milder illness in children than adults with COVID-19, including many asymptomatic children. Note is made of overrepresentation of children with comorbidities in this cohort (similar to CDC data), although most of these still had mild illness - it is unclear if these children become more unwell, or are more likely to present to be tested.





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."

Shekerdemian et al (Clinical)

Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. Published online May 11, 2020. doi:10.1001/jamapediatrics.2020.1948

This is a cross-sectional study of children admitted to 46 PICUs in North America. 48 children were admitted during the collection period (March 14 to April 3 2020). All had confirmed COVID-19 infection on PCR from a nasal swab.

Most patients presented with respiratory symptoms, but there were other presentations – three with DKA, and one with vaso-occlusive crisis (sickle cell). 86% of these patients had at least one comorbidity. 69% were severely or critically ill on admission, and 25% needed vasoactive drugs. 81% of patients needed respiratory support that exceeded their baseline.

61% had a range of therapies, including Hydroxychloroquine, Azithromycin, Remdisivir, and Tocilizumab. These were used as single agents or in combination with other therapies.

The overall mortality rate was 4.2% (both patients who died had pre-existing comorbidities and developed multisystem organ failure). 32% were still hospitalised at the time of publication (including one patient still receiving ECMO). 65% had been discharged.

This study reinforces what is known about the decreased burden of disease from COVID-19 in children compared with adults. Critically ill children had a less severe course of illness and better hospital outcomes than in adults. Children commonly had medically complex comorbidities. Overall the mortality is much lower in children (4.2%) than has been reported in adults (50-62%).





Riphagen et al (Clinical)

Riphagen, Shelley et al., Hyperinflammatory shock in children during COVID-19 pandemic, The Lancet, May 7th 2020, [https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1)

This is the first case series to describe a cluster of children presenting with hyperinflammatory shock during the COVID-19 pandemic. Eight children aged 4 to 14 years were identified by a paediatric retrieval service based in London in mid-April 2020. Interestingly, of the 8 children, 7 had weights >75th centile. Notably 6 were of Afro-Caribbean descent and 2 were Asian, with no Caucasian children in this cohort. 5/8 were boys. 4 children had exposure to family members with COVID-19.

The clinical presentation was similar to Kawasaki disease, with unrelenting fever, rash, conjunctivitis, peripheral oedema, and extremity pain, in addition to gastrointestinal symptoms. All children developed warm, vasoplegic shock and required inotropic support. Seven children required mechanical ventilation.

Small pleural, pericardial and ascitic effusions, also consistent with a diffuse inflammatory process were also observed. Vascular involvement was demonstrated with echo-bright coronary arteries seen in all children, with a giant coronary aneurysm in one patient. One child died from a large cerebrovascular infarct. Myocardial enzymes were significantly elevated. A range of investigations were done in all children, and despite this no causative pathogen was identified. Adenovirus and enterovirus were isolated in one child. Four children had known exposures to SARS-CoV-2 in family members, but only two tested positive for SARS-CoV-2 (1 was positive only postmortem).



Riphagen et al (cont)

In addition to other supportive therapies, all children received IVIG and broad-spectrum antibiotics (ceftriaxone, clindamycin). Six children have been given aspirin.

This clinical presentation may represent a new phenomenon associated with SARS-CoV-2 infection in children and has remarkable similarities to Kawasaki Disease. Following publication of this case series, Evelina London Children's Hospital has managed >20 similar cases in children. Ten of these children were SARS-CoV-2 antibody positive (unclear which antibody or which test was used).

These findings have garnered particular interest due to the fact that children have otherwise been relatively spared from severe disease due to COVID-19, and here both the temporal association and high proportion of children with seemingly positive serology suggests a possible association with this hyperinflammatory syndrome. Anecdotally, clusters have also been noted in the USA (particularly NYC) and some centres in Spain and Italy. Reports are conspicuously absent from Asia, most notable as Kawasaki disease is more common amongst this population normally. Even more striking is the gross overrepresentation of children with an Afro-Caribbean background, which given current investigations into the increased incidence of severe adult disease in these communities seems even more pertinent.



Riphagen et al (cont)

As so little is currently known about “garden variety” Kawasaki, it will make defining this disease and its associated with COVID-19 that bit more difficult, but studies are currently ongoing to assess the nature and mechanism of this disease (<https://www.diamonds2020.eu/>). Three points are worth noting at this stage:

-Kawasaki disease has been theorised to be triggered by viral infections. One could imagine if this is the case, then COVID-19 could also trigger a similar syndrome.

-It is well documented that some adults experience a systemic inflammatory response to COVID-19 (including cytokine storm) and whilst children generally suffer a much milder course, it seems within reason that a subset of children may develop a similar illness.

-Reports from a paper in 2005 suggested a link between human coronaviruses in Kawasaki disease. A case control study found significantly higher rates of coronavirus in children with Kawasaki (72.7%) than a matched control group without Kawasaki (4.2%).

For now, this cohort doesn't change the management of childhood COVID-19, nor does it change the management of hyperinflammatory shock or Kawasaki – although the RCPCH have produced excellent guidance for suggested investigations and processes to include these patients in ongoing research.

Toubiana et al (Clinical)

Julie Toubiana, Clement Poirault, Alice Corsia et al. Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France medRxiv 2020.05.10 doi: <https://doi.org/10.1101/2020.05.10.20097394>

As a pre print this study should be interpreted with caution until it has undergone peer review.

This retrospective cohort study looks at a cluster of patients diagnosed with Kawasaki disease at a hospital in Paris between April 27th and May 7th. During this time they admitted 17 children with a diagnosis of Kawasaki or incomplete Kawasaki, with a mean age of 7.5yr and 10/17 (59%) female.

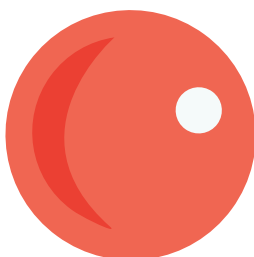
Clinical features: All children presented with persistent fever and with initial GI symptoms (vomiting and diarrhoea) with nearly half fulfilling complete KD criteria (8/17, 47%). The majority were irritable (11/17, 65%) and myocarditis was common (12/17, 71%). Coronary artery dilation was seen in 5/17 but no aneurysms seen. 6/14 who had chest imaging had lung changes. **Bloods:** Inflammatory markers were significantly raised, with a median CRP of 219, PCT 23.3 and IL-6 218. Interestingly mean platelet count was 432 (but up to 838). Median troponin 136 and D dimer 4762 (up to 19330). Ferritin not reported.

COVID-19 status: 7/17 tested positive on swab and 15/17 had positive serology

Treatment: All were given IVIg, following which 5/17 still had fever 36hrs afterwards. They were given a second dose of IVIg and steroids. 10/17 required inotropic support and the same number required intubation/ventilation.

Outcomes: Median length of stay was 8 days (range 5 – 17). There were no deaths.

Three subsequent studies have confirmed very similar presentations of this hyperinflammatory syndrome (PIMS-TS) in children, with initial abdominal pain, fever, diarrhoea and vomiting, progressing to a picture similar to Kawasaki disease but with a significant number developing shock and significant cardiac involvement.





Piccolo et al (Clinical)

Piccolo, V., I. Neri, C. Filippeschi, T et al (2020). "Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients." J Eur Acad Dermatol Venereol published online 24th April 2020 <https://doi.org/10.1111/jdv.16526>

This is a report of chilblain like lesions observed during the COVID-19 pandemic, collected through a survey issued to Italian dermatologists and Paediatricians. This is a preliminary report as data collection still ongoing. Importantly – very few patients in this cohort were tested for COVID-19 (11/63) and only 2 of these patients were positive. It is therefore difficult to extrapolate these findings to paediatric COVID-19 specifically, but is worth being aware of.

63 patients have been reported on with a median age of 14 years (IQR 12 – 16yrs) with feet alone being bar far the most commonly affected area (85/7%) followed by feet and hands together (7%). In uploaded pictures from 54 patients, erythematous-oedematous lesions were most common (31/54) followed by blistering lesions (23/54) and pain and itch were common, although a quarter of lesions were "asymptomatic". Median time of onset of rash to diagnosis was 10 days. The lesions were generally stable and no other cutaneous signs observed. GI symptoms were the most common co-existing (11.1%) with surprisingly low levels of respiratory symptoms (7.9%). This is basically a description of a common skin manifestation which coincided with COVID-19, and looked like it could be infectious in origin. Few patients tested, and even fewer positive. An interesting series worth bearing in mind given increasing reports of skin manifestation of COVID-19.

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.

Boulad et al (Clinical)

Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in Children With Cancer in New York City. JAMA Oncol. Published online May 13, 2020. doi:10.1001/jamaoncol.2020.2028

This research letter reports the results of SARS-CoV-2 screening of patients and caregivers from one of the largest paediatric cancer centres in the US (Memorial Sloan Kettering Cancer Center, New York) in a region with very high levels of community SARS-CoV-2 transmission.

From March 10th to April 12th 2020, inpatients and outpatients with either symptoms of or exposure to SARS-CoV-2 infection underwent RT-PCR testing. Asymptomatic patients were also tested prior to admission, deep sedation and or myelosuppressive chemotherapy, as were caregivers of children being admitted.

Overall 11% (20/178) of paediatric patients returned a positive SARS-CoV-2 result; including 29.3% in the symptomatic / exposed group and 2.5% in the asymptomatic group. In contrast 14.7% (10/76) of asymptomatic caregivers were positive. Despite close contact, 5 of the 10 children of caregivers with SARS-CoV-2 were uninfected.

Only 1 of the 20 paediatric patients required hospitalisation for COVID-19 symptoms, without need for critical care.

This data provides reassurance that children with cancer may not be more vulnerable to complications of SARS-CoV-2 infection compared to other children. The lack of specific clinical detail in this report limits the ability to draw more definitive conclusions regarding risk.

The lower rate of asymptomatic carriage in children relative to their caregivers provides further evidence that children, including paediatric cancer patients, may be less susceptible to SARS-CoV-2 infection compared with adults.

Clearly infection control strategies must consider the risk of nosocomial spread from infected caregivers as well as paediatric patients, particularly in areas with high levels of community transmission.

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.

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.





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.

Bi et al (Epidemiological)

Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study, Lancet Infectious Disease, April 27th 2020, [https://doi.org/10.1016/S1473-3099\(20\)30287-5](https://doi.org/10.1016/S1473-3099(20)30287-5)

This was a fairly impressive study looking at contact tracing of 1286 contacts of 391 patients with COVID-19. Only 20 (5.1%) of the initial 391 cases were children, of which 2/3 were asymptomatic. They discovered a secondary attack rate of 15% for household contacts and 9.6% overall. The most important finding is that the rate of infection in children <10 years (7.4%) was similar to the population average (7.9%). The findings of this study suggested that children were becoming infected at a similar rate to adults but were much less likely to be asymptomatic. As no repeat testing was performed, it is unclear if these children were truly asymptomatic, or presymptomatic. Subsequent studies have consistently shown lower attack rates in children, and the reason for this discrepancy is unknown.





Mizumoto et al (Epidemiological)

Mizumoto K, Omori R, Nishiura H. Age specificity of cases and attack rate of novel 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.

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.





Zhang et al (Epidemiological)

Zhang J, Litvinova M, Liang Y, et al, Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China, Science, 29th April 2020, DOI: 10.1126/science.abb8001

This fascinating study assesses contacts and infection risk in China (Wuhan and Shanghai) using 3 arms:

1. Surveys conducted within cities studying contacts between individuals, finding that during lockdown all contact except for those within households ceased – backing up evidence that about 90% of infections during this period occurred by household transmission
2. Most importantly for us – an age stratified model of susceptibility to acquiring infection was produced by assessing the data from the Hunan CDC, whereby every positive case found in Hunan had recent contacts placed under quarantine for 14 days and was tested for COVID-19. They estimated odds ratios for age groups to become infected, and performed statistical adjustment for clustering and correlation structures of contacts exposed to the same index case (generalized linear mixed model regression). Their finding was that susceptibility to infection increased with age, lowest in children 0-14 years (OR 0.34, 95% CI 0.24 – 0.49 – reference participants aged 15–64 years).
3. Finally using the above data they estimated the effects of non-pharmaceutical interventions on reducing spread of COVID-19. They found that closing schools was likely to significantly impact the R_0 but not enough to be a useful measure on its own. They describe social distancing as implemented in China, to be a sufficient measure to control COVID-19

This is the latest, and one of the most comprehensive of a number of studies to demonstrate significantly lower attack rate in children to adults, suggesting decreased susceptibility to infection.

Li et al (Epidemiological)

Li, W., B. Zhang, J. Lu, S. Liu, Z. Chang, P. Cao, X. Liu, P. Zhang, Y. Ling, K. Tao and J. Chen (2020). "The characteristics of household transmission of COVID-19." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 17. <https://doi.org/10.1093/cid/ciaa450>

This retrospective study calculated secondary attack rates of COVID-19 amongst 392 household contacts of 105 SARS-CoV-2 RT-PCR positive index cases hospitalised at Zaoyang First People's Hospital (250 km from Wuhan) and Chibi People's Hospital (150 km from Wuhan) between 1st January and 20th February 2020.

Study design: Households were eligible for the study if the index case was the only member of the household with a clear history of exposure to Wuhan, its residents or high-risk sites in the 14 days before onset of illness (the assumption then being that the only exposure of household contacts to SARS-CoV-2 was via the index case). Once index cases were confirmed, household contacts were quarantined for 14 days in local government sites and monitored daily, with at least 2 nasopharyngeal swabs (taken at the beginning and mid-point of quarantine). Variables analysed retrospectively in this study (using medical notes and telephone interviews) included household size, age/gender/symptoms of index cases and household contacts, time between onset of illness of the index case and hospitalisation (range 0-11 days) and spouse/non-spouse relationships.

Key paediatric findings: 100 of the 392 household contacts were under 18 years of age (median 6.5 yrs, IQR 4-11 yrs); of these, only 4 children became infected (all male, 1 aged 0-5 yrs, 3 aged 6-17 yrs). This secondary attack rate of 4% for children compares with 21% for the adult household contacts (60 out of 292 infected) and 16% overall (64 out of 392).



Li et al (cont.)

Li, W., B. Zhang, J. Lu, S. Liu, Z. Chang, P. Cao, X. Liu, P. Zhang, Y. Ling, K. Tao and J. Chen (2020). "The characteristics of household transmission of COVID-19." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 17. <https://doi.org/10.1093/cid/ciaa450>

Of interest: 14 of the 105 index cases self-quarantined within the home immediately after onset of symptoms before hospitalisation (wearing masks, eating and residing separately from the rest of the household); in these households there was a 0% secondary attack rate, versus 18% in those households where the index case didn't self-quarantine before hospitalisation. In households where the index case was afebrile, 13% of household contacts became infected, versus 19% where the index case had fever. In households where the index case had no cough, approximately the same proportion of household contacts became infected as in households where the index case had a cough (17% vs 16%). 9 of the infected household contacts were asymptomatic (14%), but this figure isn't broken down by age in the article. [Note: there are some discrepancies between calculations in the text and data tables; data from tables used here.]

This article provides further reassurance to the growing body of evidence of lower attack rates of COVID-19 in children as compared to adults, as well as a signal that symptomatic patients are higher risk of transmitting the virus than those who do not develop symptoms.

