An evidence summary of Paediatric COVID-19 literature

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Somekh, E., A. Gleyzer, E. Heller, M. Lopian, L. Kashani-Ligumski, S. Czeiger, Y. Schindler, J. B. Lessing and M. Stein (2020). “The Role of Children in the Dynamics of Intra Family Coronavirus 2019 Spread in Densely Populated Area.” Pediatr Infect Dis J. doi: 10.1097/INF.0000000000002783

This is a brief study of the transmission dynamics within households in Bnei Brak, an area of Isreal with high population density and high proportion of young people (almost 50% of its population are <18yrs). They assessed 13 family clusters and tested every member of their households by PCR, regardless of the presence or absence of symptoms. The index case was identified by date of onset of symptoms (this is standard practice but does leave open the possibility of misclassifying the index case if they were truly asymptomatic).

The results were as follows; Excluding index cases, 58.3% of adults tested positive, 32.5% of children aged 5 – 17 tested positive, and 11.8% of children aged <5yrs tested positive. In 12/13 families the index case was an adult. The other case was a 14yr old male.

This evidence is consistent with almost all other household contact tracing studies which have demonstrated a significantly lower secondary attack rate in children compared to adults. A strength is the clear documentation that all household members were tested regardless of symptoms, and for clarity the index case was not included in the rates of infection making secondary AR better defined.

Harman, K., A. Verma, J. Cook, T. Radia, M. Zuckerman, A. Deep, A. Dhawan and A. Gupta (2020). “Ethnicity and COVID-19 in children with comorbidities.” Lancet Child Adolesc Health, May 28th 2020, https://doi.org/10.1016/S2352-4642(20)30167-X

Date, patient identification and location. Between 25 February 2020 and 28 April 2020, 12h children aged 0 to 16 years with confirmed COVID-19 who required admission to hospital were prospectively identified at Kings College Hospital London. 5 of these had known comorbidities (identified here as Group A) and 7 had no known comorbidities (Group B).

Age: Median age of Group A was 7.1yrs (range 0.2-15.3 with 2 <1 yr) and Group B was 4.8yrs (range 0-15.4).

Gender: 40% (n=2) in Group A and 71% (n=5) in Group B are male gender.

Ethnicity: 80% (n=4) in Group A and 71% (n=5) in Group B were from a black, Asian and minority ethnic (BAME) group.

Comorbidities: In Group A pre-existing comorbidities included cerebral palsy, prematurity, Wilsons disease, and dilated cardiomyopathy.

Clinical features: Most common symptoms on admission in group A and B respectively were

fever (60%, n 3/5 and 86% n 6/7) and tachypnoea (60% n 3/5 and 71% n5/7). Liver dysfunction was observed in 4/5 patients in Group A but 2 had underlying liver conditions including one with Wilsons disease who has since had a liver transplant.

Radiology: In Group A radiological evidence of new infiltrates was seen in 50% (n2/4) of patients in Group A who had an x-ray because of clinical indication.

Bloods: In Group A 3 /5 patients had lymphopenia and thrombocytopenia, 3 /4 had raised CRP, 4/5 had liver dysfunction but 2 of these had underlying liver disease, 1/5 had renal dysfunction. None had symptoms that would be compatible with multisystem inflammatory syndrome. No blood data given for Group B.

Outcome: Median length of stay in hospital for Group A was 20 days (range 7-84 days) with 1child with liver transplant still an inpatient on 20th May 2020. For Group B the median stay was 3 days (range 1-8 days); 1 admitted to hospital for safeguarding concerns and another was a neonate with vertical transmission of Covid-19.

Other salient feature: During this period 2288 adults were admitted to Kings College Hospital so children only formed 0.5% of total admissions. in Group A all children received antibiotics, 1 remdesivir and 1 hydroxychloroquine.

This case study presents data on 12 children with COVID-19 (5 of whom had comorbidities) admitted to Kings College Hospital London during 25th Feb-28th April 2020.

It is noteworthy that 75% of the total children admitted with Covid-19 and 80% of 5 children who had comorbidities were from a black, Asian, and minority (BAME) communities. Even keeping in mind that in Inner London 39% of the population is BAME, this data suggests that ethnicity in children may be an independent risk factor for severe disease. Conclusion is that Children from BAME communities particularly if they have comorbidities, may be at greater risk of severe disease from COVID-19. This is particularly significant given the ongoing investigation into the increased rates of severe COVID-19 infection in adults from BAME backgrounds.

This is a relatively new observation in children and although the numbers are very small, justifies considering this paper to be important.

Parri, N., A. M. Magistà, F. Marchetti, et al, (2020). “Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks.” Eur J Pediatr: 1-9. https://doi.org/10.1007/s00431-020-03683-8

This study is published as a short communication describing the clinical presentations and outcomes in children with identified Covid-19 in 61 centres in Italy between 3rd and 26 March 2020.

Study Design: A retrospective study coordinated by the CONFIDENCE and COVID-19 Italian Paediatric Study Network’s involving 53(86.9%) hospitals and 8(13.1%) outpatient centres in 10 mainly northern regions. All children (0-18 years) diagnosed positive on screening and testing for Covid-19 by nasal/nasopharyngeal RT-PCR assay were entered into the study. Clinical, laboratory and imaging data was collected on standardised forms.

Study Population: 130 children and adolescents recruited (112 hospital;18 outpatient). <2

years 41 (31.5%), 2-9 years 35 (26.9%)'10-17 years 45 (34.6%). Male 73 (56.2%). Female 57(43.8%) p=0.47.

Comorbidities 34 (26.2%) most frequent cardiovascular, respiratory and neuromuscular. No information on ethnicity. One patients data unobtainable.

Disease Severity: The majority of subjects were categorised as being **asymptomatic** or having **mild** disease 98/130 (75.4%). 11 (8.5%) were **moderate** severity, 11 **severe** and 9 (6.9%).**critical**. 75 (57.7%)were hospitalised with 15.(11,5%)needing respiratory support (5 needing oxygen, 2 non invasive ventilation and 2 mechanical ventilation). 9 cases were admitted to ICU with 6 being less than 6 months. 3 of the latter were less than 2 months and did not require respiratory support. Children less than 6 months had an increased risk of **critical** disease than older children: 6/35 (17.1%) vs 3/86 (3.5%) p=0.34. OR 5.6 CI 1.3 to 29.1.

Symptoms: Common symptoms were fever 67(51.5%), dry cough 38(29.2%) and productive cough 16(12.3%). Other symptoms were rhinorrhoea25(19.2%), respiratory distress 17(13%), vomiting 15(11.5%);diarrhoea 10(7.6%); sore throat 9(6.9%). Thoracic pains (3%), somnolence, febrile convulsions (1.5%) and lower limb pains (1.5%) were reported as novel symptoms.

Oxygen saturation at presentation: 91-92% 1(0.8%). <90 1(0.8)

Radiology: 41 (31.5%) of children had CXRs. These were normal in 15 (36.6%). The commonest abnormalities were ground-glass opacities in 17 (41.5%). Focal consolidation was seen in 4 (9.8%).

Laboratory: 71 children were reported to have had laboratory tests. The authors report leukopenia (WCC %<5.5×109) and lymphopenia (<1.2×109) in 7/19 patients and 3/19 patients, respectively. They report elevation in aspartate transaminase >50U/l in 11/60 (18.3%) and alanine tranasaminase >45U/l in 8/68 (11.8%).

Outcomes: There were no deaths and all children were reported to have recovered.

Comment: The study obtained data on all but one child found Covid-19 positive in this largely hospital based population. The authors acknowledge that there is a bias toward more ill patients with their population than community studies and this may explain the 57.7% admission rate. Also this is reflected in the amount of comorbidity. However, the majority of patients were either asymptomatic or had mild disease and small numbers required respiratory support or ITU. The authors identify the increased likelihood of critical disease in those less than 6 months and their being the majority of ICU cases. They also comment on new presenting symptoms (thoracic pain, somnolence, febrile convulsions and lower limb pains).

Grimaud, M., J. Starck, M. Levy, C. et al "Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children." Ann Intensive Care **10**(1): 69. June 1st 2020 https://doi.org/10.1186/s13613-020-00690-8

This is a retrospective observational study of 20 children who were admitted to paediatric intensive care units across four academic tertiary centres in Paris, four weeks after the start of French lockdown. None of the children had existing co-morbidities nor a history of symptomatic COVID-19 infection.

All patients were less than 18 years old and presented with hypotensive shock and acute myocarditis.

All children had the same presenting complaint- severe abdominal pain, vomiting and fever, for an average of 6 days previously (1-10). On admission to PCIU all children had a raised CRP, (median 251) and procalcitonin, (median 46).

All children had myocarditis, defined as: elevated troponin, ST segment elevation or depression on ECG and regional wall motion abnormalities with decreased left ventricular function on ECHO. Pericardial effusion was found in four children. All children but one required inotropic support for a median of 3 days (1-7). Eight children required mechanical ventilation for 1-7 days.

Fourteen children had transient acute renal failure but none required renal replacement therapy.

SARS-CoV-2 PCR and serology were positive for 10 and 15 children respectively. One child had a negative PCR and serology but typical SARS-CoV-2 chest CT scan changes. No other bacterial or viral infections were identified.

All children had at least one feature of Kawasaki disease along with a fever, skin rash (10), conjunctivitis (6), cheilitis (5), adenitis (2).

All children received intravenous immunoglobulin within 48hrs of admission and 18 were afebrile thereafter. Two children also received corticosteroids, the reason for this additional therapy is not documented in the article.

All children survived and were afebrile with a full left ventricular function recovery at the time of discharge from PICU.

Ferrari, A., M. Zecca, C. Rizzari, F. et al (2020). “Children with cancer in the time of COVID-19: An 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy.” Pediatr Blood Cancer: e28410.

This Letter to the Editor describes the findings of 6 paediatric haematology and oncology centres in Lombardy during the 8 weeks after the COVID-19 pandemic began in Italy. Between 20th February 2020 and 15th April 2020 286 patients were tested for COVID-19 when accessing services at these centres: 74 were symptomatic, 25 had close contact with a diagnosed case and 187 were tested for screening purposes. Of these, 21 cases tested positive for COVID-19, with a median age of 6 years (range 1-17 years) and 48% were male.

Of the 21 cases 10 had leukaemia, 5 had soft tissue or bone sarcoma, 2 had lymphoma, two had hepatoblastoma, 1 had a CNS tumour and 1 had colon carcinoma. 15 patients were currently receiving treatment while 6 had completed treatment and were receiving follow up.

Clinical features: 1 patient (who had existing neurological respiratory impairment) developed aspiration pneumonia requiring respiratory support, and 1 developed atypical bilateral pneumonia with mild symptoms.

Outcomes: There were no deaths related to COVID-19 infection. Cancer treatment was modified in 10 cases (delaying chemotherapy, reducing drug doses and postponing surgery).

The authors observe that despite the overwhelming rate of COVID-19 in the general population in the region at the time, relatively few paediatric cancer patients were symptomatic, or tested positive for the virus, and that severe illness was rare. They suggest that these results may indicate that paediatric anti-cancer treatments could continue without major adjustments, especially as alterations may reduce their efficacy.

Of note, these centres experienced a reduction in newly diagnosed cancer cases to 55% of the expected rate, which may reflect delayed access to healthcare services.

Yan, J. Guo, C. Fan et al. Coronavirus Disease 2019 in pregnant women: a report based on 116 cases. American Journal of obstetrics and gynaecology. 23rd Apr 2020, https://doi.org/10.1016/j.ajog.2020.04.014

This is a retrospective cohort observational study of pregnant women with admissions to 25 different hospitals in China with a diagnosis of COVID pneumonia. A total of 116 women were captured during the study period of 30/01/20 – 24/03/20. 65 women had lab confirmed SARS COV2 on rt-PCR from pharyngeal swabs. 51 cases were clinically diagnosed based on the New coronavirus pneumonia prevention and control programme, published by the national health commission of China (all had abnormal CT chest findings on admission). The commonly reported symptoms were fever and cough, but in 23.3% of cases there were no symptoms. Mean maternal age at admission was 30.8 (SD +/- 3.8) There were 9 women with gestational diabetes and 5 women with hypertension, 4 of whom had pre-eclampsia. 8 women required ITU admission with 1 case requiring ECMO, 76 women had been discharged and there were no maternal deaths at the study end point. Below is the breakdown the women who presented before 37 weeks of gestation.

Gestation	No of cases	Salient findings
<24	8	1 case of missed spontaneous miscarriage, 4 had reached 20 weeks gestation with normal fetal growth and anatomy
24-33+6	10	1 term delivery, 2 preterm deliveries (28+1 for severe maternal pneumonia, 31+6 for twins), 7 ongoing pregnancy
34-36+6	22	2 term deliveries, 19 preterm deliveries (6 cases of spontaneous preterm rupture of membranes – 2 of whom had SVD), 1 ongoing pregnancy

A total of 99 women delivered 100 babies (x1 set of twins) with 85 women delivering via c-section. 86 neonates underwent pharyngeal swabs, 10 of whom had paired amniotic fluid and cord blood testing, with all samples being collected in the operating or delivery room. There was also 6 vaginal swab tests and 12 women had their breast milk tested. All tests were negative for SARS COV2. The rate of all- cause preterm birth was 21.2% (21/99). The rate of spontaneous preterm birth, where there was spontaneous preterm rupture of membranes, was 6.1% (6/99). There were 47 babies admitted to NICU for further management, with one neonatal death secondary to neonatal asphyxia following delivery at 35+2 due to severe maternal pneumonia (required ECMO).

This report provides a useful comparison to the national cohort report published by UKOSS. There are similar rates of maternal ITU admission, ECMO requirements and neonatal death rate being reported in the two studies. There is a 26% preterm delivery rate with UKOSS compared to the 21% reported in this study. There is a higher rate of c-section deliveries in this report compared to UKOSS (59%). Unlike the 2% of babies testing positive for SARS COV2 in UKOSS, there were no positive cases in this cohort. There are overlaps in the results from 4

other smaller case series already published, with 33 of the cases having already been reported on. The neonatal outcome data is incomplete with not all babies having been tested with nasopharyngeal swabs, no breakdown of reason for NICU admission and level of support required and important data on the specifics of the infection status of the neonatal death not reported. The authors accept that maternal infection with COVID does increase the rate of preterm births <37 weeks but report that there is no increase in the rate of spontaneous preterm births. There is no control group or national statistic given for this comparison statement. The report does not expand on what clinical criteria were met for 23.3% of women who had no symptoms to warrant a diagnosis of COVID pneumonia, i.e. did they undergo CT chest without the presence of any symptoms.

Lorenz, N., A. Treptow, S. Schmidt, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in a Newborn Presenting With Encephalitic Symptoms. The Pediatric infectious disease journal. May 12th 2020 doi: 10.1097/INF.0000000000002735

This is a letter describing a case of encephalitic and respiratory symptoms in a neonate with positive SARS-CoV-2 nasopharangeal and rectal swabs.

The mother was symptomatic (mild respiratory infection, loss of smell and taste, fever 38.1C) during delivery and confirmed SARS-CoV-2 positive after delivery.

The baby, born at 40+3 weeks gestation by vacuum extraction, developed lethargy and therapy refractory fever at 24 hours of life, progressing by 54 hours of life to symptoms described as encephalitic (lethargy with hyperexcitability, high pitched cry). Nasopharyngeal and rectal swabs were positive for SARS-CoV-2 (CSF was negative). No other viral or bacterial pathogens were isolated from blood/CSF/nasopharyngeal or faecal samples.

Respiratory symptoms developed from day 4 requiring oxygen and continuous positive airway pressure therapy, and a viral pneumonia was diagnosed on day 10. The baby recovered and was discharged on day 14 (SARS-CoV-2 swabs still positive at discharge).

Posfay-Barbe KM, Wagner N, Gauthey M, et al. COVID-19 in children and the dynamics of infection in families. *Pediatrics.* 2020; doi: 10.1542/peds.2020-1576

This is a report of the first 40 paediatric patients presenting to Geneva University Hospital's surveillance network (Switzerland). The aim of the study was to describe the clinical presentation of the patients and the dynamics of their familial clusters. Out of a total of 4310 SARS-CoV-2 cases, 40 (0.9%) were in children <16 years.

Clinical Presentation: Patients presented to medical care, and were confirmed via RT-PCR. Median age, years (IQR) 11.1 (5.7-14.5), 22/40 (56%) were female. The most common presentation was cough 32 (82%), Fever 26 (67%), nasal discharge 25 (64%). Most were previously healthy; with comorbidities reported in only 26% of patients; asthma (10%), diabetes (8%), obesity (5%), premature birth (5%) and hypertension (3%). Seven patients were admitted, none needed ICU care or Sars Cov2 specific therapy

Family Clusters: Family cluster evaluation was conducted by phone. 111 household contacts (HHC) were identified; 39 mothers, 32 fathers, 23 pediatric siblings, 8 adult siblings and 7 grandparents.

Family member was suspect if they had fever of acute respiratory symptoms. 61/111 had RT-PCR conducted. 77% (85/111) of household contacts (HHC) were symptomatic. Adult HHC were suspected or confirmed to have covid symptoms *before* the child 79% (31/39) of cases. In only 8% (3/39) of households did the study child develop symptoms first. 85% (75/88) of adult HHC developed symptoms at some point, compared to 43% (10/23) of pediatric HHC, which was statistically significant ($p<0.001$). Mothers were statistically more likely to develop symptoms than fathers (36/39 v 24/32, $p=0.04$). Due to the need for symptoms to qualify for testing, there is the possibility of undercounting paediatric infections due to their being more likely to have asymptomatic or oligosymptomatic infection.

The authors conclude that children are uncommonly the index case in family clusters of Sars CoV2. Household contacts who are children are less likely to be symptomatic than adult contacts. Children are most likely to be infected inside of family clusters, albeit at a time in Switzerland when creches and schools were closed.

Pandey U, Yee R, Precit M, et al Pediatric COVID-19 in Southern California: clinical features and viral genetic diversity, medRXiv, June 2nd 2020, https://doi.org/10.1101/2020.05.28.20104539

A study of 35 children age range 18 days to 18.5 years (median 12.5), 57% of whom were boys, seen over an 8 week period in Southern California. Patients were identified by nasopharyngeal swabs submitted to Los Angeles Children's Hospital between 11 March 2020 and 11 May 2020. 37% were hospitalised with a median inpatient stay of 4 days. Symptoms were diverse with fever and cough being the most common, 1/3 were symptomless. Whole genome sequencing was undertaken on Covid-19 samples. There was an association between disease severity and viral load. Children < 5 years age had a higher viral load and all were symptomatic. There was limited variation in the viral genome though a calculated evolutionary rate was like other RNA viruses. No correlation was identified between disease severity and genetic variation.

Yue Tao, Ruwen Yang, Chen Wen, Jue Fan, et al, SARS-CoV-2 entry related genes are comparably expressed in children's lung as adults, medRxiv May 25th 2020, doi: https://doi.org/10.1101/2020.05.25.20110890

As a pre print, this study should be interpreted with caution whilst awaiting peer review.

Question: do different expression levels of viral-entry associated genes in infection with SARS-CoV-2 in children compared to adults explain milder COVID-19 symptoms seen in children?

What was analysed? RNA and immunohistochemistry of Angiotensin converting enzyme 2 (ACE2), Transmembrane Protease Serine 2 (TMPRSS2). ACE2 interacts with the spike (S) protein of the virus which is then cleaved by TMPRSS2. They also looked at FURIN because a FURIN cleavage site has been identified in the S protein which may act as another pathway for the virus to gain entry.

Comparison: expression level of ACE2, TMPRSS2 AND FURIN in normal lung tissue derived from children and adults.

Methods: For scRNA-seq analysis for gene level expression lung tissue from:

Adults: 8 adult lung transplant donors, age range 20 to 69 years, 2 males and 6 females (5 African American, 1 Asian and 2 White)

Children: areas of normal lung tissue from 4 children requiring lobectomies, aged less than 1 year, 1 male and 3 females with congenital heart abnormalities (Ebstein Anomaly (EA), Tetralogy of Fallot (ToF), AVSD and VSD). Children with EA and ToF also had pulmonary hypoplasia, child with AVSD had pulmonary emphysema and child with VSD had a pulmonary cyst.

Results of scRNA-seq analysis: ACE2 mainly expressed in Alveolar type 2 (AT2) cells in adults and children. TMPRSS2 mainly expressed in AT2, AT1 and club cells in adults and children, FURIN in Endothelial Cells and monocytes in adults; in AT2 and club cells in children. No significant changes were observed in expression levels of ACE2, TMPRSS2 and FURIN between adults and children

For immunohistochemistry analysis for protein level expression lung tissue from: Adults: 10 adults with lung adenocarcinoma, aged between 40 and 79.

Children: 10 children aged between 1 and 15 years with various forms of cancer with lung metastasis.

Results of Immuno-histochemistry analysis: Overall expression levels of ACE2 similar in adults and children. TMPRSS2 and FURIN expression higher in children than in adults (although differences in FURIN not statistically significant

Interpretation: ACE2 receptors found mainly in AT2 cells, confirming that primary target of SARS-CoV-2 is the AT2 cell.

Partial discrepancy between results from scRNA-seq and IHC might be due to: complicated processes downstream of transcription, or semi-quantitative IHC and its limitations in identifying cell types

Conclusion: Comparable levels of expression of ACE2 and other genes in both children and adults suggests that different expression of these viral entry genes is unlikely to be the key reason for the milder symptoms of COVID-19 found in children.

Issitt R, Booth J, Bryant W, Spiridou A, Taylor A, DuPre P, Ramnarayan P, Hartley J, Borja MC, Moshal K, Dunn H. Coronavirus (COVID-19) infection in children at a specialist centre: outcome and implications of underlying high-risk comorbidities in a paediatric population. medRxiv. 2020 Jan 1. Doi https://doi.org/10.1101/2020.05.20.20107904

A retrospective cohort study published by Great Ormond Street Hospital (GOSH), London, UK suggested children who are defined as vulnerable in the COVID-19 pandemic era do not appear to be at significantly increased risk of being admitted to hospital with COVID-19. In addition, the vulnerable group have similar outcomes to those who are COVID-19 negative. However, the authors do identify children undergoing chemotherapy or radiotherapy are ‘over-represented’ in the vulnerable group.

Data was collected from the institution’s electronic health record system. The inclusion criteria were any patient admitted between 01/03/2020 and 15/05/2020 who was admitted with features suggestive of COVID-19 based on the attending clinician’s interpretation, of undefined grade,

including fever, cough and “systemic symptoms”. Children were defined as COVID-19 positive by a positive PCR test for nucleic acid in respiratory or blood specimens performed at the referring or presenting hospital or a documented positive familial test. Patients were classified as vulnerable if they fulfilled the high risk shielded list from NHS digital or the institutions local policy that was not provided. Due to the nature of the specialist paediatric services the population of children were highly selected.

166 children fulfilled the criteria; 65 (38.7%) were COVID positive and 101 (60.8%) were negative. The average age for COVID positive group was 9 years [IQR 0.9-14] with 38 (58.5%) males. This compared to the COVID-19 negative group with an average age of 1 year [0.1-5.75], 58 (55.4%) male. The COVID-19 positive patients were significantly older (p<0.001). Differences in ethnicity frequency was statistically significant for Asian ethnicity: 12 (8.5%) COVID-19 positive compared to 6 (5.9%) in the COVID-19 negative group (p=0.02).

The number of vulnerable children who were COVID-19 positive totalled 31 (47.7%) compared to 73 who were COVID-19 negative (72.3%), demonstrating a lower number of vulnerable children were positive for COVID-19, (p=0.002).

Clinical features: Breakdown of symptoms were not provided

Radiology: N/A

Bloods (For those COVID-19 positive): ALT 41.5 U/L [IQR 29-74], Albumin 32 g/L [IQR 27-36], AntiDNAse 310U/mL [80.8-402], AntiStreptolysin O 285 IU/mL [134-384], AST 70 U/L [43-100], CRP 28 mg/L [10-74], CK 63.5 U/L [35-214], Creatinine 23 umol/L [14-46], D-dimer 1876 ug/L [1043-3618], Ferritin 788 ug/L [445-1863], Fibrinogen 3.65 g/L [2.4-4.8], Interleukin-6 50 pg/ml [50-152], Interleukin-10 50pg/mL, LDH 848 U/L [654-1136], BNP 3550 pg/ml [626-6992], Lymphocytes 1.44 X10^9/L [0.64-2.49], Neutrophils 3.90X10^9/L [1.46-8.6], WBC 8X10^9/L [3.38-13.2], Troponin I 54 ng/L [13-157], Prothrombin time 12 seconds [11.3-13], bilirubin 6 umol/L [3-10], Triglycerides 2.48 mmol/L [1.65-3.56].

The results highlight the difference in results between the COVID positive and negative groups but do not define further differences between vulnerable and non-vulnerable groups. These include a statistically higher average CRP (p=0.002, fibrinogen (p<0.001), albumin (p0.02) neutrophil (p<0.001) and white blood cell count (p<0.001) and a lower LDH (p=0.002),

Treatments: Patient were treated following national or speciality specific guidance. No further information was provided.

Outcomes: Mortality for those who were COVID-19 was 1 (1.5%) who was in the vulnerable group. Additional comments described the primary focus of treatment was aspiration pneumonia. This compared to 4 (4%) in the non-COVID-9 group, all of whom were in the vulnerable group. The difference in mortality rates was not statistically significant.

There was no difference in the proportion of vulnerable patients based on their COVID-19 status: 61% of vulnerable patients who were COVID-19 positive compared to 64.3% who were negative, (p = 0.84). Overall, comparing all patients, a significantly lower proportion of COVID-19 positive patients required mechanical ventilation (27.7%) than COVID-19 negative patients (57.4%), (p<0.001). The individual number of patients were not provided.

The average ICU length of stay for those with COVID-19 was 4 days [2.4-10.6]. For those in the vulnerable subgroup the average was 11 days [3.7-15.1]. The significance of the difference between the vulnerable and non-vulnerable group was not described. However, vulnerable non-COVID-19 patients had a 6 [2.8-12.2] day stay in ICU. The difference between vulnerable COVID-19 positive and negative groups demonstrated no significance (p=0.3).

The average total hospital stay for vulnerable patients with COVID-19 was 16.2 days [3.8-20.8]. This compared to vulnerable COVID-19 negative patient were in hospital for 12.3 days [5.2-19.8]. The difference in duration was not significant (p=0.94).

Other salient features: Breaking down conditions that comprises vulnerable children there was a significant increased number of children with cancer undergoing active chemotherapy or radiotherapy who were admitted to hospital with symptoms and COVID-19 positive status compared to with symptoms but COVID-19 negative [7 VS 3 (p=0.01)]. There was no statistical differences between the COVID-19 positive and negative categories with on the national transplant, transplant medication, haematological cancer, respiratory and rare genetic, metabolic and autoimmune conditions lists or local severe respiratory conditions, rare diseases immunosuppressive therapies and other potential factors lists.

Zhao, W., Y. Wang, Y. Tang, W. Zhao, Y. Fan, G. Liu, R. Chen, R. Song, W. Zhou, Y. Liu and F. Zhang (2020). “Characteristics of Children With Reactivation of SARS-CoV-2 Infection After Hospital Discharge.” Clin Pediatr,May 28th https://doi.org/10.1177%2F0009922820928057

In this study from Beijing, China, serial nasopharyngeal swabs were performed on children discharged between January 21st and April 18th 2020 following hospital admission with confirmed SARS-CoV-2 infection. Criteria for hospital discharge included clinical improvement and 2 negative RT-PCR tests for SARS-CoV-2 on consecutive nasopharyngeal swabs. Follow up swabs were performed fortnightly following discharge; the authors report on children with subsequent positive RT-PCR on follow up.

In total 14 children were followed, 7 of whom had a subsequent positive SARS-CoV-2 PCR result, none of whom had significant symptoms at the time (one with a temperature of 37.5). There were no significant clinical or laboratory differences between the group with subsequent positive tests compared with those who remained negative.

The authors refer to those who have subsequent positive SARS-CoV-2 PCR as having “reactivation” of infection. This is a misnomer as the persistent shedding of viral RNA has been well recognised in adult studies. This includes a large cohort of over 200 patients from Korea with positive tests following negative PCR results, similar to the children in this study. Importantly no onward transmission from these “re-positive” cases was found amongst 790 contacts in the Korean cohort, suggesting the viral RNA detected in patients with prolonged shedding is not viable. Indeed in a recent in vitro study including 90 SARS-CoV-2 PCR positive samples, only samples taken within 8 days of symptoms onset were capable of infecting cells. This is in keeping with contact tracing data suggesting peak transmissibility occurs before and immediately after symptom onset with limited transmission beyond 5 days of symptom onset.

The likely explanation of the “reactivation” described here is prolonged shedding of non-viable viral RNA with an interim “false negative” samples prior to hospital discharge. Given the available data, it is unlikely that these “re-positive” discharged patients represent an infection risk to others

Wu, H., H. Zhu, C. Yuan, C. Yao, W. Luo, X. Shen, J. Wang, J. Shao and Y. Xiang (2020). "Clinical and Immune Features of Hospitalized Pediatric Patients With Coronavirus Disease 2019 (COVID-19) in Wuhan, China." JAMA Netw Open 3(6): e2010895. doi:10.1001/jamanetworkopen.2020.10895

In this retrospective case series from Wuhan, China, the clinical and immunological characteristics of children admitted to hospital with confirmed SARS-CoV-2 infection are examined. Details are provided for the 148 children with mild or moderate disease.

The median age was 84 months (IQR 18-123). Fever (40.5%) and cough (44.6%) and vomiting or diarrhoea (21.6%) were the most common symptoms. SARS-CoV-2 PCR became negative at a median of 7 days (IQR 4-11 days).
Lymphopenia was present in only 4.5% of patients; CD 4 lymphopenia in 1.9%. Elevation in CRP (32.4%) and procalcitonin (47.3% elevated; median 0.05 (IQR 0.04-0.08)) was observed in fewer than half of patients. Liver transaminases and LDH were significantly higher in moderate versus mild cases but the vast majority of levels fell within normal range.
Levels of inflammatory cytokines including IL2, IL6, TNG-a and IFN.y were largely normal; the authors note that one patient with severe disease had elevated IL-6 (3869 pg/mL). IL-10 was increased in 14%.
No deaths occurred amongst mild and moderate cases and all 148 patients were discharged.

In this large case series of children with mild or moderated SARS-CoV-2 infection, laboratory measures of inflammation were largely normal. Specifically the significant elevations in IL-6, D-dimer, and ferritin characteristic of severe COVID-19 in adults and also PIMS-TS / MIS-C in children were absent in these milder cases. The authors postulate that the relative preservation of CD4 T-cells and the higher levels of IL-10 compared with adults with severe COVID-19 may indicate these as important components of a protective immune response.
As yet our understanding of the drivers of variation in individual immune response to SARS-CoV-2 remains incomplete.

White A, Mukherjee P, Stremming J, et al. Neonates Hospitalized with Community-Acquired SARS-CoV-2 in a Colorado Neonatal Intensive Care Unit [published online ahead of print, 2020 Jun 4]. Neonatology. 2020;1-5. doi:10.1159/000508962

This Case Series of three infants with SARS-CoV-2 infection paper is published as a Brief Report.

The paper is a report of three full-term babies (39-41 weeks) who were admitted from home to the Neonatal Intensive Care Unit (NICU) at the Children's Hospital Colorado (CHCO) after presentation to the hospital's Emergency Department (ED) between March 28, 2020, and April 1, 2020. Ages at onset of "symptoms" were 16, 25 and 31 days and ages at admission were 17, 27 and 33 days respectively. Two were exclusively receiving breast milk at the time of admission; there are no details regarding feeding for the third infant. The mothers of two infants had a recent history of upper respiratory symptoms but there was no history of ill contacts for the third.

All of the babies had fever, rhinorrhea, and mild hypoxia with oxygen saturations in room air of 80–90%; the youngest infant also had tachycardia, systemic vasodilation, and bilateral conjunctivitis and received 20 mL/kg normal saline fluid resuscitation in the ED. There is no description of other abnormal respiratory signs such as cough or work of breathing. Blood

gases for all three infants were reported to be normal. All were treated with supplemental oxygen of 0.25 -1.0 l/min via nasal cannulae and with systemic antibiotics. Chest X-rays of all three showed low lung volumes with hazy opacities but no focal consolidation. Diagnosis The diagnosis was confirmed by real-time polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs for SARSCoV-2 which were taken in the ED; there was no repeat testing and no mention of antibody testing.

The youngest infant had initial lymphopenia, which resolved before discharge, subsequent neutropenia which ws ongoing at the time of discharge and a mildly elevated CRP (1.5mg/dL). CRPs in the other two infants were 1.1 and 1.2mg/dL and blood procalcitonin levels were within the normal range; liver function tests and other haematological tests were normal in all three and microbiology tests, including virology, were negative. The babies were discharged home when they had been afebrile for at least 24 hours, after stays of 77-81 hours. Details of follow-up are not given but two infants showed decreased absolute neutrophils at some point after discharge.

The paper provides details of three of the youngest patients reported to have developed community-acquired SARS-CoV-2. The authors state that the three infants (one was just outside the neonatal age range) met the diagnostic requirements proposed by Chinese researchers: (1) clinical symptoms including fever and the need for respiratory support, (2) abnormal chest radiographs, and (3) being at high risk for SARS-CoV-2 infection due to close contact with a person with symptoms consistent with SARS-CoV-2 or living in an area with widespread CA-SARS-CoV-2. All three had mild to moderate courses with short hospital stays, which is consistent with previous reports in the paediatric literature. The authors advise that caregivers of neonates should wear face masks and wash their hands before handling neonates in the community and that isolation from positive family members would be prudent.