SARS-CoV-2, SARS-CoV-1 and MERS-CoV: What do we know about children?
A narrative review using systematic review methodology

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Contributions

NM and EM wrote the paper. NM and WJ conducted the literature search, OMurphy coordinated the data extraction. NM, EM, CB, DE, CF, TF, CL and OMytton extracted data from included papers into a database.

Summary

There is currently a global epidemic of a novel coronavirus, named SARS-CoV-2. We urgently need to better understand the virus and the disease it causes in paediatric populations. We undertook a systematic review of all known literature relating to infection rates, clinical outcomes and transmissibility in paediatric populations affected by three novel coronaviruses, SARS-CoV, MERS-CoV and SARS-CoV-2. The main findings emerging from this review relating to SARS-CoV are: 1) SARS-CoV-1 caused severe disease, disproportionately in adults. There were 100 paediatric cases out of a global total of 8096 with no deaths in this group. 2) children under 12 generally had a milder course that resolved by day 7, and the symptoms in teenagers were more severe, and akin to those in adults; 3) There is little evidence relating to transmissibility from children to other children or adults. The evidence we do have suggests paediatric transmissibility was low, but as children were mostly strictly quarantined at home, we cannot be certain of this. Findings relating to MERS-CoV included: 1) The majority of documented cases were in adults with 31 paediatric cases out of a global total of 2449; 2) 42% were asymptomatic. There were 2 deaths in infants with comorbidities; 3) there is no evidence on transmissibility on MERS-CoV from children. With regard to SARS-CoV-2: 1) From large Chinese datasets children appear to be less affected by the current outbreak. (0-9 years - 0.9%, 10-19 years – 1.2% of cases in the largest study of 72,314 cases. A study followed 1286 close contacts of 391 cases and found children under 10 were just as likely to be infected as other age groups. This appears to be the first clear evidence that children are infected at the same rate as adults, but may be mild or asymptomatic. 2) Data regarding clinical outcomes is poor. Key emerging themes include family clustering, mild symptoms and several reports of asymptomatic cases; 3) There are no data relating to the transmissibility of SARS-CoV-2 and children. Overall, the quality of papers was low and we have a limited set of inconclusive data about COVID-19 in children.

Background

On 31 December 2019, the World Health Organization (WHO) was informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province, China. On 12 January 2020 it was announced that a novel coronavirus had been identified in samples obtained from cases and that initial analysis of virus genetic sequences suggested that this was the cause of the outbreak. This virus is referred to as SARS-CoV-2, and the associated disease as COVID-19. As of 3 March 2020, 90,961 cases have been diagnosed in 78 countries and areas (including mainland China), with a total of 3,100 fatalities. Over 10,000 cases and 131 deaths have been reported from countries outside mainland China. Within China, 84% of cases reported to date are in Hubei Province. On 5 March 2020, the total number of confirmed cases in the UK was 115 with one death.[1]

The scope of this review

Coronaviruses are large, lipid-enveloped, positive-sense, single-stranded RNA viruses found in avian and mammalian species. Human coronaviruses commonly cause mild upper respiratory tract infections, accounting for about 30% of common colds, although they can cause more severe disease in the elderly, children and immunocompromised hosts.[2] Three notable exceptions exist: SARS-CoV-1 (referred to in this paper as SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and SARS-CoV-2, which have produced epidemics of severe respiratory disease. The disease caused by SARS-CoV-2 has been named COVID-19.

The aim of this review is to summarise current understanding of the epidemiology and transmission dynamics of COVID-19 in children, in order to inform decision s regarding clinical and public health measures for children (eg school closures). We therefore undertook a rapid systematic review of all known literature relating to SARS-CoV-2, SARS-CoV and MERS-Cov in children, with a view to summarising what is known about the following clinical indicators and transmission dynamics in children:

1. Evidence of infection
2. Evidence for transmissibility
3. Severity of infection and clinical outcomes
4. Rating of the quality of evidence

Literature search methods

All searches were conducted on 28th February 2020 unless indicated otherwise. The timescale for production of the paper was one week. We assimilated information from the following sources:

1. A Medline search for abstracts (no date restrictions) using the following search terms: *coronavirus OR Severe acute respiratory syndrome OR covid-19 OR nCoV OR COVID OR SARS OR MERS OR middle east respiratory syndrome) AND (Child OR Children OR childhood OR preschool OR infant OR babies OR baby OR neonates OR paediatric OR paediatric OR pediatrics OR pediatric)*. This search yielded 1323 results, the abstracts of which were screened for potential relevance and from which 67 papers were requested for further analysis. This work was completed by one reviewer (NM).

2. A hand search and title screen of the WHO database of COVID-19 publications[3] using the following search terms: *child, children, childhood, infant, baby, babies, pediatric, paediatric*. This search yielded 15 papers, of which 7 were excluded due to English translations from Chinese not being available, leaving 8 included papers. This work was completed by one reviewer (WJ).

3. A hand search and title screen of the COVID-19 resource centres of major journals and publishers, recognising that many COVID-19 papers will not yet have been indexed into databases: This work was completed by one reviewer (WJ) Journals included: BMJ; Cambridge University Press; Elsevier; JAMA Network; The Lancet; New England Journal of Medicine; Oxford University Press; PLOS; Springer Nature; SSRN (reprints); Wiley. In addition, the pre-print server medRxiv was searched for all papers related to the term "coronavirus" and a title screen performed on the 212 results. These searches yielded 8 additional papers.

4. 4 studies with analysis of large numbers of cases (n>1000), which have emerged since the start of the COVID-19 epidemic were included for their sub-analyses which included paediatric groups. These papers were identified by one reviewer (WJ) from a database of daily summaries of key papers which are being collated by Public Health England, from which CMO's clinical team are extracting daily information relating to a range of clinical indicators and transmission dynamics.

5. We screened 5 further papers which were highlighted by reviewers and other colleagues of which 2 were not relevant to the scope of this paper, and 3 of which were included in the analysis.

6. After removing duplicates, excluding papers that were in Chinese with no English abstract (with the exception of one paper which was read by a Chinese speaking colleague as it related to inconsistent reports of SARS-CoV deaths), removing 1 important case series of 34 children infected with SARS-CoV-2 in Shenzhen that has unfortunately been retracted[4], and excluding papers that were not available for other reasons, a total of 66 papers were screened in detail and information relating to the four research questions was extracted into an online database.[5] 9 additional papers were included by the authors writing the draft, from snowballing references from included papers, and extracting relevant papers from PHE daily summaries of new SARS-CoV-2 / COVID literature. These papers were not included in the database.

7. Due to short timescales, the task of data extraction from included papers was split between 8 reviewers who were issued information in advance about the purpose and scope of the paper. They were also issued guidance on how to rate the quality of the papers as follows:

- Most papers will include small numbers of cases
- We are looking for careful and caveated analysis within these papers (please reflect in comments)
- Please grade papers as high / medium / poor / anecdotal
- The purpose of grading is to allow policy makers to understand the strength of the evidence upon which decisions will be taken

Results

SARS-CoV in Children

Infection rates

During the 2002-2003 SARS epidemic, 8096 cases and 774 SARS-CoV related deaths were reported from 29 countries and areas. A global case-fatality rate of 9.6% was recorded at the end of the outbreak.[6] The R0 of the disease was estimated at 2-4.[7] In the entire outbreak there were no deaths in the English literature reported in patients under 18 years of age. However Shen et al[8] report that there were deaths during the SARS epidemic, referencing 3 papers in Chinese. Two have English abstracts[9,10] (no deaths reported), and one paper in Chinese was read by a Chinese colleague who reports that this paper does not report any deaths.[11] There is only one published report of transmission of SARS-CoV from a paediatric patient.[12] There are conflicting reports in the literature about the total number of paediatric cases, with Denison reporting fewer than 100 cases of SARS-CoV in children reported around the world.[13] Stockman et al performed a literature search to identify reports of paediatric (<18yrs) patients meeting the WHO case definition for SARS and summarise 6 case series reporting 135 paediatric cases (80 laboratory-confirmed, 27 probable and 28 suspected) in patients younger than 18 years.[14] There are no reports suggesting higher numbers of children involved than this and the discrepancy may be due to Denison reporting only confirmed cases in 2004, and Stockman et al reporting confirmed, probable and suspected cases, and having searched the literature some years after the end of the outbreak. We could not find accessible figures from the WHO on this question.

In a low quality review,[15] Denison notes that there was less likely to be a positive test for SARS-CoV by reverse transcription(RT)-PCR or culture. He states that later studies showed evidence of serologic conversion and positive reverse transcription-PCR in many cases, suggesting that the early lack of positive tests may have been caused by a lack of developed assays. Neither of these assertions are referenced. We found one high quality prospective study in Pediatrics by Leung et al[16] who reported on the epidemiologic, clinical, laboratory, radiologic features and short to medium term outcomes for 44 lab confirmed cases. This is not directly relevant to infection rates but we have included it here as it may provide wider context. The authors report that all cases demonstrated SARS-CoV seroconversion >21 days after disease onset. Positive RT-PCR results for SARS-CoV in NPAs were documented for only 21 children (47.7%). For most children NPA specimens were obtained within 7 days after disease onset. Only 7 children (15.9%) demonstrated successful isolation of the virus from NPA cultures. Positive RT-PCR results for stool samples were noted for 17 children (38.6%), from as early as day 7 of the disease to as late as day 41. SARS-CoV was not isolated from stool samples from any of the children. RT-PCR and viral culture detection rates did not vary significantly with age and severity of illness.

Clinical Outcomes

In adults, SARS-CoV infection is characterized by fever, dyspnoea, lymphopoenia and rapidly progressive changes on radiography, resulting in ARDS and death.[17] Evidence for clinical outcomes for paediatric SARS-CoV is relatively consistent across several case series and epidemiological review papers, suggesting that young children (<12) generally had a much milder course which had resolved by day 7, and that symptoms in teenagers were more akin to those in adults.[18, 19,20, 21, 22,23,24]

In a small but detailed case series of 10 paediatric patients in the Lancet[25] the authors noted two distinct patterns of clinical presentation among children. Teenage patients presented with symptoms of malaise, myalgia, chills and rigor (similar to adults). The younger children presented mainly with cough and runny nose. None had chills, rigor or myalgia. The clinical course was much milder and shorter among younger patients and radiological changes were milder and generally resolved more quickly than in teenagers. 4/10 required supplemental oxygen, with two of these (both aged 15 years) requiring some ventilatory support (one BIPAP and one IPPV). In their review of all reported paediatric case-series, (135 confirmed, probable or suspected cases, Stockman et al[26] report that in children, among laboratory-confirmed and probable SARS cases, the most common symptoms included fever (98%), cough (60%) and nausea or vomiting (41%); 97% had radiographic abnormalities. The clinical presentation of SARS in patients older than 12 years of age was similar to that in adults. However, patients 12 years of age or younger had milder disease and were less likely than older children to be admitted to an intensive care unit, receive supplemental oxygen or be treated with methylprednisolone. Progression to ARDS was seen in a very small number of paediatric patients, predominantly adolescents.

Follow up papers consider longer term paediatric outcomes in more detail, as viral pneumonia has been reported to cause long term adverse sequelae including bronchiectasis and fibrosis in children.[27] In a retrospective review of clinical data and chest X-Rays of 67 children admitted to a SARS ward between March and May 2003, radiological abnormalities (which were non-specific and wide ranging) showed resolution at 1 month post discharge.[28] Li et al[29] examined the radiological (HRCT) and lung function outcomes of 47 SARS-CoV infected children (median age 13.6 years) in Hong Kong at 6 months from diagnosis. The median duration of fever for the course of illness in this group was 7 days and the median duration of hospital stay was 21.5 days. None of the patients were hypoxic on admission but 11 subsequently developed oxygen dependency during the course of illness. Five were admitted to ICU and two required mechanical ventilation (BIPAP and endo-tracheal intubation respectively). There was variation in the choice and duration of treatment with antibiotics

and second line steroid therapy between the five regional paediatric units that treated these children. At follow up all children were asymptomatic and had a normal clinical examination. However, mild pulmonary abnormalities were detected on HRCT in 16 (34%) of subjects (residual ground-glass opacification, air trapping and a combination of the two). The need for oxygen supplementation (p=0.02) and lymphopenia (p=0.012) during the course of the illness were significant risk factors in predicting abnormal HRCT. Four subjects had abnormal lung function (2 mild obstructive, 2 mild restrictive), but only one (restrictive) had a corresponding HRCT abnormality. Writing in Thorax, Yu et al[30] studied the aerobic capacity and lung function of 34 children 6 and (27 of these) 15 months after the diagnosis of SARS-CoV (mean age of study group 14.7, control group 14.0) They found that compared with normal controls, the patient group had significantly lower absolute and mass related peak oxygen consumption ($p<0.01$), higher ventilatory equivalent for oxygen ($p<0.01$) and a lower oxygen uptake efficiency slope ($p<0.01$) at 6 months. This impairment was out of proportion with the degree of lung function abnormality. Absolute and mass related peak VO2 in the patient group remained impaired at 15 months despite normalisation of lung function in all patients. The authors conclude that the mechanism for the reduced aerobic capacity in children following SARS-CoV is not fully understood but is probably a consequence of impaired perfusion to the lungs at peak exercise and deconditioning.

We do not know why SARS-CoV affects adults more severely than children. Yu et al[31] noted that serological analysis showed levels of antibodies against SARS-CoV were higher in children than adults, both in SARS-CoV infected and healthy children. By plating vaccine-antigens on ELISA plates to test for reactions against human pooled serum they tested the hypothesis that childhood vaccines may be a protective factor due to cross-immunity against SARS-CoV. No convincing evidence for any neutralising antibody was obtained towards SARS-CoV antigens. Van Bever et al summarise two other hypotheses: 1) The milder course in children with SARS-CoV is typical of other respiratory infections such as influenza, infections with m.pneumoniae or chlamydia pneumoniae and varicella. This may be explained by persisting cross immunity after recent exposures to other coronaviruses; 2) The strength of the specific immune response to SARS-CoV is known to vary with age. In adult patients with severe disease (20%), a biphasic clinical pattern was noted with a second more severe phase unrelated to viral replication. The second phase may be related to immunopathological damage and is characterised by ARDS and diarrhoea. In children the second phase was not seen, perhaps due to low immune response to the virus. The authors postulate that the difference in response could be related to differences in macrophage features between adults and children during infection with the virus. We were unable to find any scientific literature to support these hypotheses. Finally, the authors note that SARS infection did not appear to cause an increase in asthma exacerbations in children in Hong Kong or Singapore.[32]

Evidence for transmissibility

There is very little high-quality evidence relating to transmissibility from children to other children or to adults. We know from existing data that most, if not all, children with SARS were either in close contact with infected adults, as a household contact or in a healthcare setting.[33] Two papers which drew on the authors' experience of 64 cases of paediatric SARS in two hospitals in Hong Kong[34,35] suggested that symptomatic infection in children is less common than adults, but do not empirically support this statement. Similarly, it is suggested that there is no evidence of transmission from children to children or from children to adults, but again, there is no evidence to support this claim. In a retrospective study looking at triaging patients into 3 risk categories to minimise the risk of spread of SARS at the same hospital in Hong Kong[36], it was observed that children showed more 'typical' SARS symptoms earlier than adults (predominantly fever), which meant the disease was picked up more quickly in this group. 38 probable or suspected SARS cases were isolated in negative pressure rooms. The study noted there was no transmission of SARS to parents when an N95 mask

was used (it is not clear by whom), and there was no nosocomial spread or transmission of SARS from paediatric patients to healthcare workers.

In a state of the art review article[37] in Pediatric Pulmonology during the Hong Kong outbreak, Wong et al state that there had been no documented cases of spread from children to children or children to adults in the community, echoed by Li and Ng in their review in Archives of Disease in Childhood.[38] However, both papers note that the potential for this cannot be ruled out because all of the infected children were strictly isolated from the onset of the illness. Wong et al also note that many children in Hong Kong were attending schools until they were admitted with respiratory symptoms or fever, but there was not any spread in schools. The author notes that public awareness of infection was very high in the community. Parents were instructed to keep their child off school if they had fever or respiratory tract symptoms. This review also states that schools were closed for four weeks, but it is unclear as to whether this refers to all schools in Hong Kong or just schools affected by the 40 children who were infected as a result of leaky sewage pipes in the apartment complex of an infected adult patient (probably the latter).

Lee et al conducted a risk stratified seroprevalence study of SARS-CoV in children residing in a district with point source outbreak, compared to a low risk area.[39] The authors recruited 353 children living in a high risk area where large community outbreaks of SARS had occurred (infection rate >70/1000 persons) and 361 children in low risk areas (infection rate 0.1-0.4/1000 persons). Only two (0.6%) of 353 children from the high risk area were seropositive for SARS CoV antibody. Both had been asymptomatic of any SARS like illness. All 14 children in this area who had known SARS contact were seronegative for SARS-CoV antibody. Seroprevalence in the low risk area was 0%. The results of this study would suggest that positive serology for SARS-CoV in healthy asymptomatic children was very uncommon (0.57%), and that community transmissibility was low.

MERS-CoV in Children

Infection Rates

The WHO report 2449 laboratory confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection to June 2019, of which 84.0% were reported by the Kingdom of Saudi Arabia. Cases have been reported from 27 countries in the Middle East, North Africa, Europe, the United States of America, and Asia. Males above the age of 60 with an underlying medical condition, such as diabetes, hypertension and renal failure, are at a higher risk of severe disease, including death. To date, 845 individuals have died (crude CFR 34.5%).[40] The R0 of MERS was <1. [41]

There are reports of 31 cases of MERS amongst children (variously defined) in case series and reports from June 2012 to April 2016[42,43,44] 13/31(42%) were asymptomatic, identified through contact tracing. The male: female ratio was 1.7:1, mean age was 9.8 years and 25/31 children were from the Kingdom of Saudi Arabia. The most common source of infection, where identified, was household contact (10/15, 66%) and 5/15 (33%) patients acquired MERS within a healthcare facility.[45]

Clinical Features

Of the 31 children, 5 had co-morbidities. Two of these 5 children died. The first was 9 months old with a recent diagnosis of nephrotic syndrome treated with prednisolone. He initially presented with streptococcus pneumonia sepsis requiring intubation, ventilation and inotropes. After making a recovery, on day 8 of his admission he deteriorated and CXR showed a bilateral diffuse haziness.

Tracheal aspirate was found to be positive for MERS on RT-PCR. Renal failure developed and he died on day 12 after admission.[46]

The second infant who died was 2 years old had cystic fibrosis, initial presentation was with fever a respiratory distress and his sputum culture grew multi-resistant pseudomonas. He deteriorated rapidly and was intubated and ventilated, showed bilateral infiltrate. Nasopharyngeal swab CXR was positive for MERS CoV on RT PCR and also for H1N1. Thrombocytopaenia developed and he required peritoneal dialysis. Methylprednisolone therapy was used, however multi-organ failure developed and he died on day 60 after admission.[47]

Of the other children affected, 14/31 (45%) are reported as having symptoms (fever, mild respiratory symptoms or unspecified), 1 child with Down syndrome with pulmonary hypertension and on home oxygen recovered after treatment with supplemental oxygen, diuretics, imipenem and oseltamivir and the two children who died were treated on intensive care.[48]

Transmissibility

There is no information on transmissibility of MERs from children. MERS-CoV is viable in conditions with a temperature of 20°C and 40% relative humidity for 48 hours, this decreased to 8 hours at 30°C and 80% relative humidity.[49] MERS cases arise as sporadic infections in the community presumed to be due to animal exposure (camels), from family transmission and as hospital-acquired infection.[50]

There was concern in countries where MERS has been reported that it may be endemic, surveillance programmes were initiated to give further information. A centre in Jordan screened all children <2 years old admitted with acute respiratory symptoms for respiratory viruses. For 1005 samples where the standard screen was negative, MERS testing was carried out, yielding an initial 4 positive results which on 2 further assays were found to be negative.[51]

From October 2012, Saudi Arabia commenced screening for MERS in high risk individuals; 5065 individuals were screened for MERs over a 12 month period including hospitalised patients with suspected MERS (n=2908), healthcare worker contacts (n=1695) and family contacts of laboratory confirmed MERS cases (n=462). Of those children (<17 years) tested, 9/625 (1.4%) screened were positive for MERS.[52] Adults screened 99/4440 (2.2%) positive for MERS.

These surveillance data indicate that a low level of endemic MERS-CoV may be present in some populations.

SARS-CoV-2

Infection Rates

Data on infection rates of SARS-CoV-2 in children are still scarce. Early papers painted the picture whereby children appear to be less affected by the outbreak. However a MedRxvi pre-print paper[53] identified 391 confirmed cases and followed up 1286 close contacts, 95% for 12 days or longer. Attack rates were found to be similar across age categories, with some evidence of elevated attack rates in older groups. Notably, the rate of infection in children under 10 (7.4%) was similar to the population average (7.9%), indicating that the infection rate in children may be higher than those presenting with clinical symptoms.

The first 425 confirmed cases in Wuhan were analysed for demographics, exposure history and illness timelines There were no children (<15 years old) in this first cohort of cases. The mean (±SD)

serial interval distribution was estimated as 7.5±3.4 days. Up to January 4th, 2020, the epidemic growth rate was 0.10 per day (CI 0.050-0.16), the doubling time was 7.4 days (CI 4.2-14). Estimated R_0 was 2.2 (CI 1.4-3.9). [54]

The Chinese Centre for Disease Control and Prevention published the epidemiology of 72,314 cases in China, noting that this consisted of 61.8% confirmed cases, 22.4% suspected cases, 14.6% clinically diagnosed and 1.2% asymptomatic cases.[55] Children 0-9 years of age accounted for 0.9% of confirmed cases, 10-19 year olds for 1.2% of cases. There were no deaths in the 0-9 years of age group, one death was reported in the 10-19 years of age group, CFR 0.2%. The proportion of China's population aged 0-15 was 17.8% in 2018[56], suggesting that children are less likely to be diagnosed with COVID-19. This could be due a real difference in infection rate or generally asymptomatic or mild presentation which does not trigger diagnostic testing.

A smaller series of 1212 confirmed cases in Henan, China, reported a similarly low proportion of affected children; data on age was reported for 1156 cases, 24 (2.1%) in 0-10 years old and 31 cases (2.7%) in 11-20 years old.[57]

A population-level observational study identified 507 patients with COVID-19 both in and outside China, 13 (3%) of whom were younger than 15.[58] The authors adjusted for baseline demographics in the Chinese population and estimated a relative risk for COVID-19 infection of less than 0.5 in patients younger than 15 years.

Without better screening of populations, it is uncertain whether the observed paucity of COVID-19 cases in children is due to asymptomatic, mild or absence of infection in children.

Clinical Outcomes

Symptoms of COVID-19 are non-specific and disease presentation can range from asymptomatic to severe pneumonia and death.[59] The quality of the literature specifically describing disease in children is poor, consisting of small case series, individual case reports and unreferenced narrative reviews.[60] Unfortunately, one promising paper has been retracted without explanation and had to be excluded from the analysis.[61] The included literature has been described in more detail than would normally be the case as we wished to present as much evidence as possible, whilst acknowledging the overall deficit in quality, to inform urgent decisions relating to school closures.

Cai et al[62] report a case series of 10 paediatric patients with confirmed SARS-CoV-2 infection admitted to the Children's Hospital in Shanghai, Hainan, Hefei in Anhui province, and Qingdao in Shandong province in February 2020. The paper is convincing in its description of laboratory confirmation. Seven children were local residents, 2 were from Wuhan and 1 was from Xiaogan (an endemic area 50km away from Wuhan). 8 children had direct contact with adult patients with confirmed infection who had a history of travel to Wuhan or contact with persons from Wuhan. Exposure setting included household exposure in 7 patients, endemic area exposure in 2 patients, and bus travelling exposure in 1 patient who had contact with 2 adult travellers from Wuhan who already had mild respiratory symptoms during the bus journey and were confirmed with COVID-19 afterwards. Among seven children exposed to household adult cases, the number of secondary symptomatic cases including the child ranged from 1 to 4 (mean 2.43). The parents of a 3 month old infant looked after by her parents developed symptomatic COVID-19 7 days after they looked after her without protection measures. The interval between symptom onset and exposure to index symptomatic case ranged from 2 to 10 days (mean 6.5 days). The 10 patients were aged 3mths – 10 years (mean 6yrs), ratio M:F 1: 1.5. 8 patients had fever, 6 had cough, 4 had sore throat, 3 had nasal congestion and 2 had sneezing and rhinorrhoea. None of the patients had dyspnoea or diarrhoea

during the illness. Fever resolved after 24 hours with maximum temperature ranging from 37.7 – 39.2 degrees Celsius. Chest XR revelated unilateral patchy infiltrate in 4 of 10 patients. Lab findings are reported without reference ranges. None of the patients were positive for Influenza A or B. All patients received symptomatic treatment with no need for oxygen therapy and the patients with pneumonia received empirical antibiotics. At the time of publication all patients had been discharged when they recovered uneventfully with 2 consecutive respiratory samples tested negative for SARS-CoV-2. The virus was detected in NPA and throat swabs from all patients within 4-48 hours after symptom onset. It was undetectable in the same swabs within 6-22 days (mean 12) after illness onset. Six patients had faecal samples tested for SARS-CoV-2 RNA within 3-13 days after illness onset and 5 were positive. At the time of publication, the patients still have viral RNA detected in faeces within 18-30 days after symptom onset and are under close follow up. 5 patients had urine and serum samples tested for viral RNA within 2-3 days after symptom onset and all were negative.

Asymptomatic infection in a child was also reported in a Lancet paper describing a familial cluster of COVID-19 pneumonia, enrolled from January 2020, one of the first papers to report and scientifically prove person to person transmission for the virus in China.[63] The asymptomatic 10 year old boy, screened as part of the family cluster, and subjected to a CT scan at the request of his worried parents, was found to have radiological ground glass lung opacities on CT chest examination. It is worth noting that the other family members in the cluster were aged 65(F), 66(M), 37(F), 36(M) and 63(F). The three oldest patients in this family cluster (who had comorbidities) had more severe systemic symptoms of generalised weakness and dry cough and more abnormal blood chemistry. Their lung involvement was more diffuse and extensive than those of younger patients whose blood chemistry was largely normal.

Another asymptomatic child (3 year old, male) and his asymptomatic mother (age 33) was reported in a family cluster of three in China, in a report published in Lancet Infectious Diseases in Feb 2020.[64] Patient 1 (35 year old father) presented to the Third Affiliated Hospital of Guangzhou Medical University with a body temperature of 37.4 degrees Celsius which lasted for 2 days. On the second day he developed sore throat, arthralgia and myalgia. He had typical CT chest findings. His wife and son had no signs or symptoms during a three day observation period but two sets of NPA swab samples tested positive in these two individuals.

Writing in JAMA[65], Wei et al identified all hospitalised infants in China diagnosed with COVID-19 infection between Dec 8th 2019 and Feb 6th 2020. They identified the infants by screening the daily summary number and geographic location of new COVID-19 infections, released daily by the central government, and identified infants aged 28 days to 1 year old. Local hospitals were then asked to release demographic data, family clustering, linkage to Wuhan, clinical features, treatment, prognosis and discharge date. Nine infected infants were identified. All patients were hospitalised. The youngest was aged 1 month and the oldest 11 months. The patients were from seven separate locations in China. Clinical outcomes included: 1) Four patients had fever; 2) 2 patients had mild upper respiratory tract symptoms; 3) 1 had no symptoms but tested positive for COVID-19 during screening due to family exposure; 4) 2 had no information on symptoms available. None of the 9 infants required intensive care or mechanical ventilation or had any severe complications. The authors note that family clustering occurred for all the affected infants.

A further case report from Singapore relates to a well infant with COVID-19 with a high viral load, detected as part of the first local cluster suggestive of limited community transmission.[66] The 6 month old boy was referred to hospital in early February 2020 after his parents both tested positive for SARS-CoV-2 through occupational exposure to Chinese tourists. The infant was asymptomatic on arrival to hospital. He was afebrile with a normal respiratory rate. Oxygen saturation was 98% on

room air and his lungs were clear. No chest X-Ray was performed. A NP specimen tested by rRT-PCR confirmed the diagnosis of COVID-19. He tested negative for influenza A and B and 4 human coronaviruses. On day 2 of admission he was found to be viraemic with detection of SARS-CoV-2 in his blood sample via RT-PCR. Stool and urine from the same day were negative. During the viraemic phase he had 1 temperature of 38.5 which normalised within one hour. Otherwise he was afebrile and remained asymptomatic throughout the admission. Daily NP swabs became negative for the virus on day 17 of admission. On day 9 of admission his stool sample became positive for the virus, but his urine remained negative.

Asymptomatic cases are also reported in the English abstract of a paper in the Chinese Journal of Pediatrics.[67] The paper reports a retrospective analysis of clinical data and chest CT images of 15 children diagnosed with COVID-19 in the Third People's Hospital of Shenzhen from 16th January – 6th February 2020. The English translation from the Chinese into the abstract may render the radiology reporting in the abstract unreliable, but the clinical data appear not to have been lost in translation. As we only have the abstract in English we are unable to interrogate the data further than is reported here. The children were aged 4 to 14 years old. 5 of the children were febrile and 10 of the children were asymptomatic on first visit. The first nasal or pharyngeal swab samples in all the 15 cases were positive for SARS-CoV-2 nucleic acid. For the first chest CT, 6 patients had no lesions. 9 had 'pulmonary inflammation'. In 7 cases there were small nodular ground glass opacities and 2 cases of speckled ground glass opacities were found. After 3 to 5 days of treatment (it is unclear what), the paper reports that a second 'respiratory sample' was negative in 6 cases. The subsequent radiology reporting in the abstract is poor quality, but the authors conclude that 'the early chest CT images of children with 2019-nCoV infection are mostly small nodular ground glass opacities. The clinical symptoms..are non specific. Dynamic re-examination of chest CT and nucleic acid are important'.

Early reports on an infected 13 year old UK national diagnosed on 3rd March 2020, include that he has mild symptoms, has no underlying medical conditions, is clinically well and that there is no clear evidence at present that he transmitted the infection to anybody else, although contact tracing is not yet finished.[68]

We have included two papers of very poor quality simply because of the very limited data describing paediatric clinical outcomes, but both ought to be read with this in mind. Writing from the China National Clinical Research Centre for Respiratory Diseases in Beijing, Shen, K et al report 28 confirmed paediatric cases in a poorly referenced, data-light review in World Journal of Pediatrics.[69] The date range of included cases is not stated so it is unclear if any of these patients overlap with the case series from China already discussed. The authors report an age range of 1 month to 17 years. All were family clusters or had a close contact history. They report 'several' patients to be asymptomatic at diagnosis and further imaging suggesting pneumonia. Similarly, they also report 'several gradually presented with fever, fatigue, dry cough…nasal congestion, runny nose and seldom gastrointestinal symptoms'. They report blood chemistry was often normal and that lung imaging revealed mild increase of lung markings or ground glass opacity or pneumonia. 'Most' patients had mild symptoms, without fever or pneumonia

Our literature search also revealed papers containing unreferenced narrative about clinical signs of COVID-19 in children. For example, Chen et al[70] writing from the Children's Hospital, Zhejiang University School of Medicine, describe the onset of the disease as presenting with fever, fatigue and cough with nasal congestion, rhinorrhoea, expectoration, diarrhoea and headache. Fever is described in most as 'mild-moderate, even no fever'. The authors add that dyspnoea, cyanosis and 'other symptoms' can occur as the condition progresses after one week, with 'systemic toxic symptoms such as malaise, restlessness, poor feeding, bad appetite and less activity'. The authors

state that 'the condition of some children may progress rapidly and may develop into respiratory failure that cannot be corrected by oxygen supplementation within 1-3 days. In these severe cases, even septic shock, metabolic acidosis and irreversible bleeding and coagulation dysfunction may occur'. This is not referenced and no data is presented to support it. We have been unable to find any other reports in the literature suggesting such a severe course in children.

We found one well referenced paper attempting to explain the reasons that COVID-19 disease appears to be milder in children than adults.[71] The authors note that several infectious diseases are well known to be less severe in children than adults, including paralytic polio and rubella, in addition to SARS. Suggested reasons include children having a more active innate immune response, healthier respiratory tracts and fewer underlying disorders. As already discussed, a more vigorous immune response in adults may account for ARDS in adult COVID-19. Other possible explanations include a difference in the distribution, maturation and functioning of viral receptors. SARS-CoV, SARS-CoV-2 and HCoV-NL63 all use angiotensin-converting enzyme 2 (ACE-2) as the cell receptor in humans. ACE-2 expression in rat lung has been found to increase with age and studies show ACE-2 to be involved in protective mechanisms of the lung. Furthermore, previous studies have demonstrated that HCoV-NL63 infection is more common in adults than children, suggesting that there may be relative resistance to SARS-CoV-2 in children.

Evidence for Transmissibility

There are no clear data relating to transmissibility of SARS-CoV-2 and children. At present, we are only able to draw inferences from two papers.

The Report of the WHO-China Joint Mission on COVID-19 (published on 28th February 2020)[72] appears to have based its epidemiological data on the Chinese National Reporting System and China's National Infectious Disease Information System, which effectively makes COVID-19 a notifiable disease in China. It includes asymptomatic cases and data are uploaded in real time. We therefore assume that the following observations relating to transmission dynamics in paediatric populations are based on their analysis of these datasets, although their specific assertions later in the document are not actually referenced. The report concludes the following: 1) The data we have from China suggests a relatively low attack rate in children under the age of 18 (2.4% of all recorded cases); 2) Within Wuhan, based on influenza-like-illness samples, no children were positive in November and December of 2019 and in the first two weeks of January 2020; 3) From available data, and in the absence of serological studies, we cannot determine the extent of infection among children, what role children play in transmission, whether children are less susceptible or whether they simply present differently; 4) Infected children have largely been identified through contact tracing in households of adults; 5) None of the individuals interviewed by the Joint Mission Team could recall episodes in which transmission occurred from a child to an adult.

We have had advanced sight of a draft manuscript with the Lancet, in which Cowling et al conducted an observational impact assessment of non-pharmaceutical interventions and population behaviour change against COVID-19. They used influenza transmission as a proxy for SARS-CoV-2 transmission in Hong Kong, assuming that influenza and COVID-19 are likely transmitted in similar ways.[73] Given that the severe measures implemented in China may not be feasibly replicated elsewhere, the paper aims to assess the impact of more moderate measures (and accompanying behaviour change) that could plausibly be rolled out in similar settings. Hong Kong non-pharmaceutical interventions included school closures (with some teaching resuming via the internet). The authors measured changes in population behaviour through two telephone surveys in 20-23th January and 11-14th February, with over 2000 people in total, and weighted the results by age and sex to be representative of the Hong Kong population. They found significant rates of self-imposed population

behaviour change and social distancing measures including wearing masks, avoiding crowded places, increase in hand washing, using serving utensils while eating and staying home as much as possible. Tracking data on influenza activity based on the community ILI (influenza-like illness) proxy, they found them highly consistent with the rate of hospitalisation in children in Hong Kong. Influenza activity peaked in the second week of January and then declined to low levels by the second week of February, meaning that the Rt declined gradually from the second week of January to below 1 before Chinese New Year, rebounded to above 1 around Chinese New Year, and then declined again in early February. The estimated Rt was 1.28 (95%CI 1.26-1.30) before the start of the school holidays / closure, 0.72% (95% CI 0.70-0.74) during the holiday / closure weeks, corresponding to a 44% (95% CI 34-53%) reduction in transmissibility in the community and a 33% (95% CI 24%-43%) reduction in transmissibility based on paediatric hospitalisation rates.

Conclusion

From large datasets in China, it would appear that SARS-CoV-2 affects children and young people at a disproportionately low rate relative to the population. However new data suggests that children under 10 are infected at the same rates as adults, but may be asymptomatic or too mildly infected to come to medical attention. Emerging findings on infection rates do differ from what we know about SARS-CoV and MERS-CoV. Evidence suggests that the clinical course in COVID-19 in young children is milder, although we know relatively little about this and need more data on the clinical course in adolescents. There are several reports of asymptomatic infection in children, which would appear to be consistent with emerging data relating to infection rates. We have no data on transmissibility of SARS-CoV-2 from children to other children or children to adults, save one report of a 3 month old unwell infant whose parents became symptomatic days after caring for their child with no protective measures. The quality of the included papers was low and we require far more evidence on all aspects of COVID-19 in paediatric populations including seroprevalence studies when an assay is available.

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