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Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults

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60 References and 1 Table

Supplement: 1 (literature search)

ABBREVIATIONS

COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Abstract

Aim: The coronavirus disease 2019 (COVID-19) pandemic has affected hundreds of thousands of people. Data on symptoms and prognoses in children are rare.

Methods: A systematic literature review was carried out to identify papers on COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the Medline and EMBASE databases between 1 January and 18 March 2020.

Results: The search identified 45 relevant scientific papers and letters. The review showed that children have so far accounted for 1-5% of diagnosed COVID-19 cases, they often have milder disease than adults and deaths have been extremely rare. Diagnostic findings have been similar to adults, with fever and respiratory symptoms being prevalent, but fewer children seem to have developed severe pneumonia. Elevated inflammatory markers were less common in children and lymphocytopenia seemed rare. Newborn infants have developed symptomatic COVID-19, but evidence of vertical intrauterine transmission was scarce. Suggested treatment included providing oxygen, inhalations, nutritional support and maintaining fluids and electrolyte balances.

Conclusions: COVID-19 has occurred in children, but they seemed to have a milder disease course and better prognoses than adults. Deaths were extremely rare.

Key Words: Children, Coronavirus, COVID-19, 2019-nCoV, SARS-CoV2 , Newborn

KEY NOTES

- The coronavirus disease 2019 (COVID-19) pandemic has affected hundreds of thousands of people worldwide, but data on how it affects children are rare.
- A systematic literature review identified 45 papers and letters published up to 18 March and this showed that children have so far accounted for 1-5% of diagnosed cases.
- Children often have milder disease than adults, and deaths have been extremely rare.

INTRODUCTION

In December 2019, there was an outbreak of a new infectious disease in Wuhan in the Hubei province of China¹. Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was also previously known as 2019-nCoV. It is the seventh coronavirus.

On 11 March 2020, the World Health Organization (WHO) classified the outbreak as a pandemic. An interactive web-based real-time COVID-19 reporting system, known as a dashboard, has been set up by the Center for Systems Science and Engineering at Johns Hopkins University, Baltimore, Maryland, USA². By 18 March 2020, there had been more than 200,000 confirmed cases and more than 8,000 deaths due to COVID-19. This corresponds to a 4.0% case fatality rate.

A number of studies have reviewed symptoms and characteristics of adults with COVID-19. Although some of these studies have also included a smaller number of children^{3,4}, the aggregated data on children with COVID-19 are rare. This paper summarises the findings of a systematic literature review on the current knowledge of COVID-19 in children.

METHODS

Search process

The review was carried out at the Karolinska Institutet, Stockholm, Sweden, and the Medline

(used by PubMed) and EMBASE databases were searched for relevant terms related to COVID-19 and SARS-CoV2 in children. This search was carried out by two highly experienced librarians at the Institutet and the search algorithm is presented in Appendix S1. There were 89 papers published in Medline between 1 January and 18 March 2020 and eight publications in EMBASE during the same period. Of those, 44 were deemed relevant to this review⁵⁻⁴⁸. Also on March 18, but later during the day, the *New England Journal of Medicine* published a letter to the Editor describing 1,391 children assessed for SARS-CoV-2⁴⁹ (171 confirmed cases). That letter was also included in this review. The initial search was complemented by a further Medline search on 19 March 2020 by the author. This focused on 2019-nCoV, but this did not yield any additional studies (Appendix S1). This means that the current review was based on 45 scientific papers and letters. Most of the studies originated from China and it was notable that there were very few reports on children from Italy, Iran or South Korea, despite the large number of patients with diagnosed COVID-19 in those countries. There was no pre-specified protocol prior to the current review.

RESULTS

Background

The review with the largest number of positive COVID-19 cases was a Chinese paper by the *Chinese Novel Coronavirus Pneumonia Emergency Response Epidemiology Team* with 72,314 subjects and this found that about 2% of the 44,672 confirmed cases of COVID-19^{??} were children aged 0-19 years⁴⁹. Of these, 0.9% were under the age of 10 years at diagnosis⁴⁹. Italian data, published on 18 March 2020, reported that only 1.2% of 22,512 Italian cases with COVID-19 were children⁵⁰, with no deaths. In fact, no deaths had been recorded below the age of 30 years in Italy⁵⁰. Of 4,226 COVID-19 cases detected in the US until March 16, 2020, 5% were children⁵¹. Children constituted less than 1% of all US hospitalizations⁵¹.

In the early stages of the epidemic, many children with COVID-19 were part of family clusters with the disease^{18 45}. A large number of the cases described in this review originated from the

Chinese city of Wuhan, which has nine million inhabitants. Wuhan is situated 1,150 km south of Beijing and 840 km west of Shanghai and is the capital of the Hubei province, which has 58 million inhabitants.

The incubation period in children is usually about two days with a range of 2-10 days⁷.

Symptoms

The COVID-19 symptoms seem to be less severe in children than in adults¹⁴. One study by Dong *et al* examined 2,143 children who were identified through laboratory tests by a combination of clinical manifestations and exposure history. Of these 34.1% had laboratory-confirmed disease, while the remainder had clinically suspected disease¹⁴. Their symptoms were typical of acute respiratory infections and included fever, cough, a sore throat, sneezing, myalgia and fatigue. A number of children were wheezing. Another study from the Wuhan children's hospital⁵², which probably overlapped with the Dong *et al* study¹⁴, reviewed 171 children with confirmed disease and presented more detailed symptoms. The most common symptoms were cough (48.5%), pharyngeal erythema (46.2%) and a fever of at least 37.5 degrees C (41.5%)⁵². The authors reported that 32.1% of the children had fever above 38 degrees C and that most of these had 38.1-39.0 degrees C⁵². Other studies have suggested that fever in children is usually below 39 degrees C⁷.

Other symptoms⁵² were diarrhoea (8.8%), fatigue (7.6%), rhinorrhoea (7.6%) and vomiting (6.4%). Four out of 171 children (2.3%) had low oxygen saturations of less than 92%. It should be noted that some COVID-19 publications have defined low oxygen saturation as below 93% or 94%. A substantial proportion of children demonstrated tachypnea (28.7%) and tachycardia (42.1%) on hospital admission⁵². In a smaller case-series of 10 Chinese children diagnosed outside Wuhan, eight had fever and six had a cough⁷. In a study that has only been published in Chinese so far, but was referenced by Yang *et al*⁴⁵, 76.1% of 134 children with COVID-19 had fever.

Disease severity

In the largest child case series so far¹⁴, more than 90% of the 2,143 children diagnosed with laboratory-verified or clinically diagnosed COVID-19 had asymptomatic, mild or moderate

disease. Of the remainder, 5.2% had severe disease and 0.6% had critical disease¹⁴. According to the disease severity classification used by several Chinese publications, severe disease was defined as dyspnoea, central cyanosis and an oxygen saturation of less than 92%¹⁴. Critical disease required respiratory failure, sometimes with acute respiratory distress syndrome, shock and signs of multi-organ failure, such as encephalopathy, heart failure, abnormal coagulation and acute renal failure.

The prevalence of severe and critical disease was 10.6% in children aged <1 at diagnosis, 1-5 years (7.3%), 6-10 years (4.2%), 11-15 years (4.1%) and 16-17 years (3.0%)¹⁴. Half of the children with critical COVID-19 in this study were less than one year of age¹⁴ and a high prevalence of severe disease was seen in very young children also in another study¹³. Of 171 children treated at Wuhan Children's Hospital, three (1.8%) required intensive care and all of those had underlying diseases. There was one case of hydronephrosis, one child was undergoing chemotherapy for leukaemia and another had intussusception. Yang *et al* have noted that the child with hydronephrosis in question had bilateral hydronephrosis with renal calculus⁴⁵.

The percentage of 123 US children with COVID-19 in need of hospital admission was 1.6-2.5% with no child needing intensive care⁵¹.

Deaths

In a study of 44,672 confirmed COVID-19 cases up to 11 Feb 2020 (both adults and children), there were 965 deaths (2.2%). One child died in the 10-19 year age group⁴⁹ and no children aged 0-9 years died. No more information was given about the child who died and whether the test for COVID-19 was performed before or after death. The authors mentioned that some testing was carried out retrospectively, but they were not any more specific. The dead child was probably the 14-year-old boy described in the paper by Dong *et al*¹⁴. The two research groups seem to have used the same data source, from China's Infectious Disease Information System⁴⁹ and the Chinese Center for Disease Control and Prevention¹⁴, and they seemed to cover much of the same time period^{14 49}. Lu *et al* also reported the death of a 10-month-old child with intussusception and multi-organ failure⁵². None of the 123 US children with COVID-19 have died

so far⁵¹. This means that this review was able to identify two deaths in children with COVID-19 up to 18 March 2020.

Prognosis

One study reported that of 171 children diagnosed and admitted to hospital between 28 January and 26 February, 149 (87.1%) had been discharged by 8 March 2020⁵². In addition, a study by Cao *et al* of 398 paediatric cases outside the Hubei province claimed that most of the children recovered within 1-2 weeks⁸.

Signs

Early studies in adult populations found increased liver enzymes, anaemia, increased inflammatory markers, such as Erythrocyte sedimentation rate, C-reactive protein, procalcitonin and sometimes hyperglycaemia⁵³. Data on laboratory markers in children with COVID-19 were rare, according to this review. The exception was a study by Henry *et al* that summarised the findings from 12 different studies on 66 children¹⁷. The authors found that 69.2% of the children had normal leukocyte counts and that neutrophilia (4.6%) and neutropenia (6.0%) were rare. Only two children (3.0%) experienced lymphocytopenia¹⁷. C-reactive protein and procalcitonin were increased in 13.6% and 10.6% of cases, respectively¹⁷. In a separate study that was not reviewed by Henry *et al*, lymphocytopenia was seen in 3.5% children⁵².

The clinical spectrum of children with COVID-19 has often been similar to that of influenza. This was demonstrated by a Chinese study of 366 children up to the age of 16 years, who were hospitalised with respiratory symptoms in the early phase of the epidemic²⁵. Many of these children did not have COVID-19 but were instead diagnosed with the influenza A or B virus²⁵.

Computed chest tomography

Lu *et al* reported that ground glass opacity was seen in a third of 171 diagnosed children⁵². Local or bilateral patchy shadowing was seen in 18.7% and 12.3%, respectively. Overall, 15.8% of

children did not have symptoms of infections or radiological features of pneumonia⁵². A clinical diagnosis of pneumonia was made in 64.9% of the children⁵².

A second study reviewed five children²³ and reported that three had modest patchy ground-glass opacities on computed chest tomography. This was consistent with data reported by Liu *et al*²⁴. Finally Xia *et al* examined 20 children with computed tomography and found that 16 (80%) had some abnormalities, including halo signs, with ground-glass opacities seen in 12 patients (60%)⁴². Another Chinese report, cited in Yang *et al*⁴⁵, found viral pneumonia-like changes in 70.4% of 134 children undergoing chest imaging. It was unclear if this was carried out using X-rays or computed tomography.

Age

In the largest Chinese paediatric case series to date, of 2,143 subjects, the median age at paediatric diagnosis was seven years¹⁴. The median was 6.7 years (range 1 day to 15 years) in 171 patients from the Wuhan Children's Hospital, who were better characterised⁵². Children of all ages can be infected, including newborn infants and young children⁴¹.

Newborn infants with COVID-19

According to data from the National Health Commission of China, cited by Cai *et al*⁸, three neonatal cases were reported up to 20 February. At the same time, the total number of adult and paediatric cases in China was close to 80,000. The first neonate had fever and a cough for three days and the second had a runny nose and vomiting for one week. The youngest child, who was diagnosed at 30 hours of age, after being born to an infected mother, had respiratory distress, but no fever.

Schwartz reviewed five publications from China and was able to identify 38 pregnant women with 39 offspring³⁰: nine of the offspring were described in detail by Chen *et al*¹⁰ and another 10 by Zhu *et al*⁴⁸. Of the 39 offspring, 30 were tested for COVID-19 and all of them were negative.

Schwartz noted that none of the pregnant women had developed severe pneumonia or died. The relatively mild disease course in the 38 pregnant women was consistent with the conclusion of a

World Health Organization joint mission that investigated 149 pregnant women and found that pregnancy did not seem to be a risk factor for severe COVID-19 disease⁵⁴. However, having COVID-19 during pregnancy may still have an impact on fetal outcome, namely fetal distress, potential preterm birth and respiratory distress⁴⁸.

Sex

Dong *et al*¹⁴ reported that 56.6% of the 2,143 patients in their study were boys.

Comorbidities

A number of case reports have described comorbidities in children with COVID-19, but this review was unable to identify any study that quantified the prevalence of comorbidities in children. The section on disease severity in this paper notes that one study of 171 patients found that the three who required intensive care all had an underlying disease⁵².

Diagnosis

COVID-19 has mostly been diagnosed using nasal or pharyngeal swabs or blood specimens that were positive for 2019-nCoV nucleic acid using real-time, reverse transcriptase polymerase chain reaction assays. Alternative diagnostics have included genetic sequencing of specimens from the respiratory tract or blood consistent with SARS-CoV2.

Clinical diagnosis has been used for some cases, at least in China¹⁴. Diagnoses have been based on the presence of at least two symptoms (fever, respiratory symptoms, gastrointestinal symptoms or fatigue), combined with laboratory tests (normal or low white blood cell count, increased C-reactive protein) and an abnormal chest X-ray. Dong *et al* reported that other infectious diseases, such as influenza, were excluded before the patients were diagnosed with COVID-19, but no details were given¹⁴. This means that some of the cases reported in the Chinese papers did not have laboratory-verified diagnoses.

Management and treatment

This review was not able to identify any drug trials or testing that was specifically aimed at children. Most publications that commented on treatment mentioned supportive treatment, including oxygen therapy⁷ and antibiotics for bacterial superinfections⁷. Some^{40 32}, but not all researchers⁷, recommended antiviral treatment. Antiviral treatment was clearly used in severe cases, but data on its efficacy in children with COVID-19 are missing.

Chinese physicians have recommended that children diagnosed with COVID-19 to undergo a chest X-ray examination, preferably computed tomography³². A detailed epidemiological history should be taken. An extensive clinical examination should be performed and laboratory tests taken. Differential diagnoses include influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus and other known viral infections. They also include *mycoplasma pneumoniae* and chlamydia pneumonia and bacterial pneumonia³².

Recommended treatment is outlined in Table 1.

One Chinese consensus group recommended discharge from hospital when three criteria were satisfied. These were that the child's body temperature had been normal for three days, the respiratory symptoms had improved and the SARS-CoV2 tests were negative. This group also stressed the importance of blocking transmission routes³². The importance of potential faecal transmission remains unclear³⁵.

The secondary consequences of schools being closed and children being confined to their home were reviewed by Wang *et al.* The authors suggested that these measures may have negative effects on the children's physical and mental health. Such adverse effects included longer screen time, irregular sleep, less healthy diets that resulted in weight gain, and loss of cardiorespiratory fitness³⁷. In a study that was not related to the COVID-19 pandemic, Sprang *et al* reported that when children were quarantined and isolated after health-related disasters it could greatly increase the risk of post-traumatic stress disorder (data based on survey, focus groups, and interviews from 398 parents)⁵⁵.

Zhang and Liu reviewed the potential interventions for COVID-19, but these were primarily aimed at adult patients⁴⁶. In addition to nutritional support, the authors mention treatment with interferons, intravenous gamma globulin, thymosin alpha-1, thymopentin, levamisole,

cyclosporine A and traditional Chinese medicine⁴⁶. Of note one in three patients treated with intravenous gamma globulin during the SARS 2003 epidemic, developed venous thromboembolism⁴⁶.

DISCUSSION

This systematic review aimed to define the current evidence on COVID-19 in children. It identified 45 relevant publications, but I cannot rule out that there were other reports that my search algorithm may have missed. The literature search was carried out in English, but some identified papers presented results in Chinese but with English abstracts or summaries.

COVID-19 is either rare in children or it has not been diagnosed that often because this age group remain asymptomatic. One study suggested that 86% of all early COVID-19 infections in China remained undiagnosed⁵⁶. While undiagnosed (undocumented) cases may have a lower transmission rate, their greater number suggests that they may have been the source of 79% of all early cases⁵⁶. This may have implications if children with few symptoms are cared for by elderly people who constitute a risk group for COVID-19.

Children have represented some 2% of diagnosed cases in China⁴⁹, 1.2% of cases in Italy⁵⁰, and 5% of COVID-19 positive cases in the US⁵¹. These low figures were consistent with data from the SARS epidemic in 2003, when 6.9% of the positive cases were children, but none died. These data, from the e-SARS database in Hong Kong, were cited by Caselli *et al*⁹.

Earlier reports regarding adults with COVID-19 indicated a high prevalence of comorbidities⁵⁷. For example, comorbidities were reported in 26.0% of 44,672 confirmed cases recorded by the *Chinese Novel Coronavirus Pneumonia Emergency Response Epidemiology Team*⁴⁹. In adults, the most common comorbidities were hypertension, diabetes, cardiovascular disease and chronic respiratory disease. The report did not contain any information on the prevalence of these diseases in members of the general population who were a similar age. However, 67.2% of those who died from COVID-19 had a comorbidity and this higher prevalence⁴⁹ suggests that comorbidity is a risk factor for poor prognosis. This review only identifies case reports of children with COVID-19 and comorbidities. In adults, cancer does not seem to be a risk factor for severe disease. One of the 171 hospitalised children in the Lu *et al* study⁴⁴ had leukaemia and was receiving ongoing chemotherapy when being diagnosed with COVID-19. Recommendations for the management of sick children who are diagnosed with COVID-19 are appearing quickly⁴⁴.

While death is extremely rare in children with COVID-19, it can occur in patients who are already very sick.

COVID-19 seems to have a milder course in children than in adults and the obvious question is why? Several suggestions have been put forward. Children, especially smaller children, tend to have many viral infections. It is possible that repeated viral exposure supports the immune system when it responds to SARS-CoV-2. There have also been suggestions that the SARS-CoV-2 S protein binds to the angiotensin-converting enzyme (ACE) ²⁵⁸ and that children may be protected against SARS-CoV-2 because this enzyme is less mature at a younger age. The immune system undergoes substantial changes from birth to adulthood⁵⁹.

The proportion of children with COVID-19 with elevated inflammatory markers has reportedly been low¹⁷. Severe cases of COVID-19 have been linked to increased levels of pro-calcitonin.

Henry *et al* cited a Chinese paper that described how a young, very sick infant developed high interleukin-6 levels¹⁷ and trials of interleukin-6 inhibitors are on their way. Other trials underway are examining the efficacy of the drugs remdesivir and chloroquine.

It is worth noting that studies focusing on adults have reported very high rates of lymphocytopenia. For example Guan *et al* studied 1,099 subjects and found that the rate was 83.2% in adults. However, only nine of the subjects were children³. These adult data contrasted with data from a study of 171 children, where only 3.5% had lymphocytopenia⁵², and the 3.0% in the case series published by Henry *et al*¹⁷. Future studies on the severity of COVID-19 should focus on the role of lymphocytes and their interaction with SARS-COV2. In the 2003 SARS epidemic, a study cited by Henry *et al*¹⁷ reported that lymphocytopenia was seen in 46% of children and that neutropenia was seen in 52%.

Lack of smoking in children is unlikely to explain the lower prevalence of severe COVID-19 in paediatric patients. Smoking has not been a distinct feature in adults with COVID-19³.

It is important to note that a large share of the scientific evidence so far has originated from China and it is possible that country-specific factors there differ from children in some other countries. These include differences in day care and nutritional status and to what extent children come into contact with sick individuals.

An expert consensus statement published by *the World Journal of Pediatrics*³² in late January 2020 included a number of recommendations (**Table 1**). However, these were clearly based on findings from adults. More recent studies on children with COVID-19 are likely to have an impact on future recommendations. For instance, the current paediatric recommendations in China do not reflect the milder disease course and the different laboratory findings seen in children^{17 32}. It can therefore be questioned if children with mild COVID-19, normal inflammatory markers and normal oxygen levels should really undergo computed tomography or chest X-ray .

Although the data are scarce, there seems to be little, if any, vertical intrauterine transmission from pregnant mothers to newborn infants¹⁰. Cord blood and placental tissue in COVID-19 positive mothers have been negative for SARS-COV2¹⁶ and in a small series of 30 offspring none of the subjects developed COVID-19³⁰. However, it is worth noting that many of these children were delivered by Caesarean section. To what extent maternal hypoxaemia in delivering mothers can lead to intrauterine asphyxia and preterm birth in the offspring seems to be unknown.

There have been reports of newborn infants who have tested positive to COVID-19 after being born mothers who have also tested positive¹⁶. Chinese neonatologists and obstetricians have recently proposed how to prevent and control COVID-19 infections in newborns infants^{22 38 60}. Until now, there have been no reports of COVID-19 transmission within neonatal intensive care units, but although children seem to have less symptoms than adult patients also newborn infants can suffer from respiratory distress and are likely to transmit the disease if sick⁸ .

The main strength of this study was that it used well-established databases and wide-ranging search terms to pick up as many studies as possible up to 18 March 2020. The main limitation was that we were unable to read the full text of some of the identified Chinese studies but had to rely on English-language summaries, or publications that referenced papers published in Chinese.

CONCLUSION

In conclusion, this review identified 45 relevant studies on COVID-19 in children and the majority of the data were from China. Many of these studies seemed to overlap, with regards to the data they presented, and some of the children who were diagnosed with COVID-19 did not have their

diagnoses verified by laboratory tests. This has implications for prognoses. For example, Dong *et al* found that children with *suspected* COVID-19 had more severe disease than those with laboratory-confirmed disease. This suggests that a number of suspected COVID-19 cases may have been caused by other pathogens¹⁴, and it may still be too early to conclude that young children have a more severe COVID-19 than older children.

Our key findings were that the disease course in paediatric COVID-19 was milder than in adults, children had a better prognosis and deaths were extremely rare.

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FINANCE

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CONFLICTS OF INTEREST

The author is co-ordinating an unrelated study on behalf of the Swedish Inflammatory Bowel Disease Quality Register that has received funding from the Janssen Corporation.

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Table 1. Recommended treatment, after Shen *et al* ³².

Breathing and airway	Other support	Infectious disease	Experimental treatment*
Oxygen supply	Caloric intake (for a review of nutritional interventions see Zhang and Liu ⁴⁶)	Antibiotics when there are bacterial superinfections	interferon-alpha #
Inhalations	Water and electrolyte supply/balance		lopinavir/litonavir #
Keeping respiratory tract unobstructed	Anti-pyretics if high fever		interleukin-6 inhibitors #
Regular re-examination of airways			arbidol, oseltamivir, ribavirin and other anti-influenza drugs #
Non-invasive/invasive respiratory support/mechanical ventilation including ECMO			glucocorticoids
Fluid resuscitation, vasoactive drugs			immunoglobulin
			Traditional Chinese medicine

*Not yet supported by the literature

Suggested dosages and pharmacological aspects of antiviral treatment of COVID-19 in children have been reviewed by Wang and Zhu⁴⁰.

Accepted Article