JAMA Pediatrics | Review

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents
A Systematic Review

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IMPORTANCE The current rapid worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection justifies the global effort to identify effective preventive strategies and optimal medical management. While data are available for adult patients with coronavirus disease 2019 (COVID-19), limited reports have analyzed pediatric patients infected with SARS-CoV-2.

OBJECTIVE To evaluate currently reported pediatric cases of SARS-CoV-2 infection.

EVIDENCE REVIEW An extensive search strategy was designed to retrieve all articles published from December 1, 2019, to March 3, 2020, by combining the terms *coronavirus* and *coronavirus infection* in several electronic databases (PubMed, Cochrane Library, and CINAHL), and following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Retrospective cross-sectional and case-control studies, case series and case reports, bulletins, and national reports about the pediatric SARS-CoV-2 infection were included. The risk of bias for eligible observational studies was assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

FINDINGS A total of 815 articles were identified. Eighteen studies with 1065 participants (444 patients were younger than 10 years, and 553 were aged 10 to 19 years) with confirmed SARS-CoV-2 infection were included in the final analysis. All articles reflected research performed in China, except for 1 clinical case in Singapore. Children at any age were mostly reported to have mild respiratory symptoms, namely fever, dry cough, and fatigue, or were asymptomatic. Bronchial thickening and ground-glass opacities were the main radiologic features, and these findings were also reported in asymptomatic patients. Among the included articles, there was only 1 case of severe COVID-19 infection, which occurred in a 13-month-old infant. No deaths were reported in children aged 0 to 9 years. Available data about therapies were limited.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first systematic review that assesses and summarizes clinical features and management of children with SARS-CoV-2 infection. The rapid spread of COVID-19 across the globe and the lack of European and US data on pediatric patients require further epidemiologic and clinical studies to identify possible preventive and therapeutic strategies.

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JAMA Pediatr. doi:10.1001/jamapediatrics.2020.1467
Published online April 22, 2020.

In late December 2019, the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province in central China.[1] The causative pathogen has been identified as a novel enveloped RNA betacoronavirus.[2] Given the phylogenetic similarity to the previously isolated severe acute respiratory syndrome coronavirus (SARS-CoV), the new virus has been named SARS-CoV-2.[3]

The World Health Organization declared coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, a pandemic health emergency.[4] Person-to-person transmission of SARS-CoV-2 occurs primarily through close contact with an infected person, mainly via respiratory droplets and after touching contaminated objects. Additional routes of transmission are currently under investigation, including fecal viral shedding.[5] One of the putative mechanisms of viral entry depends on binding of the viral spike (S) proteins to angiotensin-converting enzyme 2 cellular receptors and on S protein priming by the host cellular serine protease TMPRSS2.[6] The understanding of the host-virus immunologic interaction is still incomplete.

The current rapid worldwide spread of SARS-CoV-2 infection and the severity of some cases of COVID-19 mimicking that of SARS justify the global effort to identify effective preventive strategies and optimal medical management, including the implementation of targeted therapies and vaccine development.

At present, defining the clinical characteristics and severity of the disease in large cohorts of patients is an urgent need. While data are available for adult patients with COVID-19, limited reports analyze pediatric patients infected with SARS-CoV-2. In this context, we performed the first systematic review, to our knowledge, of COVID-19 in children and adolescents to evaluate clinical features, diagnostic tests, current therapeutic management, and prognosis.

Key Points

Question What are the clinical features of pediatric patients with coronavirus disease 2019 (COVID-19)?

Findings In this systematic review of 18 studies with 1065 participants, most pediatric patients with SARS-CoV-2 infection presented with fever, dry cough, and fatigue or were asymptomatic; 1 infant presented with pneumonia, complicated by shock and kidney failure, and was successfully treated with intensive care. Most pediatric patients were hospitalized, and symptomatic children received mainly supportive care; no deaths were reported in the age range of 0 to 9 years.

Meaning Most children with COVID-19 presented with mild symptoms, if any, generally required supportive care only, and typically had a good prognosis and recovered within 1 to 2 weeks.

Methods

Outcome

The primary outcome of this study was the systematic evaluation and characterization of currently reported pediatric cases of SARS-CoV-2 infection. In particular, the primary analysis focused on age, clinical manifestations, diagnostic and therapeutic management, and prognosis of children with COVID-19.

Search Strategy

An extensive search strategy was designed to retrieve all articles published from December 1, 2019, to March 3, 2020, combining the generic terms *coronavirus* and *coronavirus infection* in key electronic bibliographic databases (PubMed, Cochrane Library, and CINAHL), following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[7] Search results were compiled using RefWorks software (ProQuest). In keeping with the quality standards for reporting systematic reviews and meta-analysis of observational studies,[8] 2 independent researchers (R.C. and M.V.) screened retrieved articles. The same investigators independently assessed full texts of records deemed eligible for inclusion. Any discrepancies were resolved by discussion and consensus. Authors of publications reporting unclear data were contacted by email for clarification.

Box. Inclusion and Exclusion Criteria

Inclusion criteria

1. Population: children and adolescents (age ≤19 y) with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
2. Study design: retrospective studies (cross-sectional studies, case-control studies, case series, and case reports), bulletins, and national reports
3. Outcome: evaluation of clinical symptoms of patients with coronavirus disease 2019 (COVID-19); description of the sources and the possible mechanisms of infection; description of diagnostic tests and therapeutic strategies; patients' prognosis

Exclusion criteria

1. Clinical guidelines, consensus documents, clinical trials, reviews, systematic reviews, and conference proceedings
2. Studies about other serotypes of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus infection

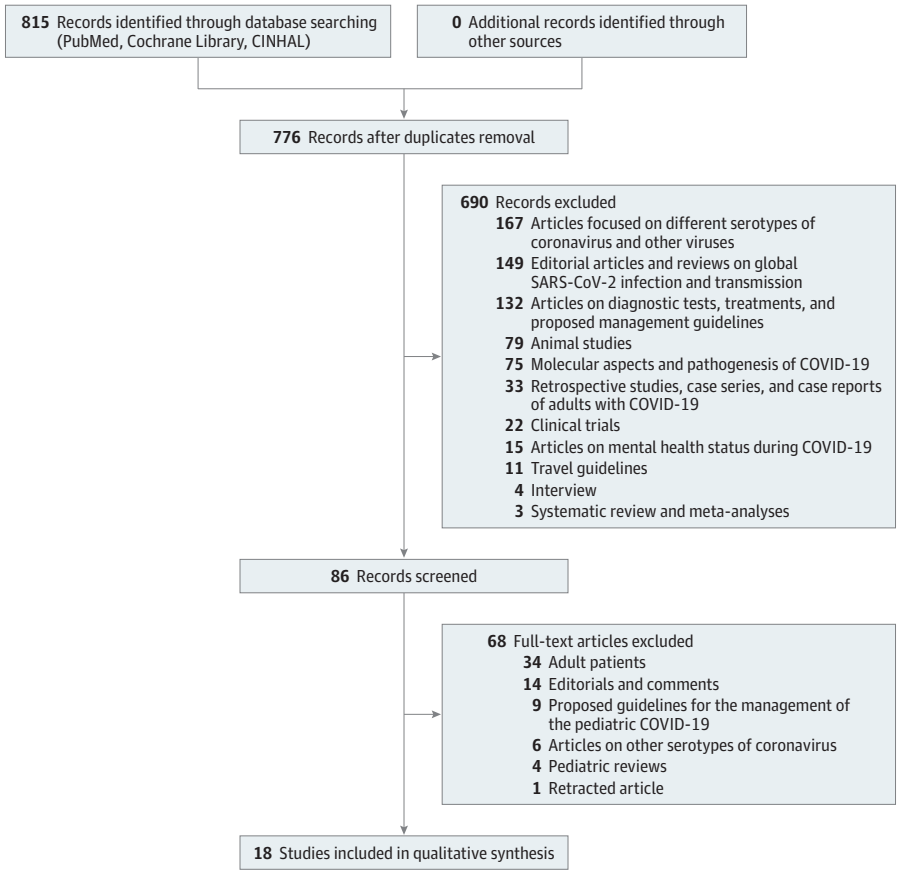
Study Selection and Risk of Bias Assessment

The risk of bias for eligible observational studies (cross-sectional and case-control) was assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[9] The risk was evaluated using a question tool explicitly designed for this review, which asked (1) Did the patients meet inclusion criteria (0- to 19-year-old participants affected by SARS-CoV-2)? (2) Were the diagnoses free from outcome misclassification? Two investigators (R.C. and M.V.) independently assigned an overall risk of bias to each eligible study, and if they disagreed, a third reviewer (A.L.) was consulted. Studies with risks of bias were excluded. Study inclusion and exclusion criteria are detailed in the **Box**.

Data Extraction

Two independent reviewers (R.C. and M.V.) extracted data from each eligible study using a standardized data extraction sheet and then proceeded to cross check the results. Disagreements between reviewers regarding extracted data were resolved through discussion and consensus of a third reviewer (A.L.). The following information was extracted: first author name, date of publication, country,

Figure. Flow Diagram of Study Selection



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

type of study (retrospective study, case report, case series), age (0-19 years) and sex of affected children, diagnostic tests (nasopharyngeal swab, chest radiograph, and lung computed tomography [CT]), clinical symptoms, therapies, and prognosis (hospitalization, intensive care unit admission, or death).

Results

The search found 815 articles. After removing 39 duplicates, 776 articles were reviewed based on the title and abstract, and of those, 690 articles were excluded. Eighty-six full texts were assessed for eligibility, with 68 excluded based on article type (reviews, systematic reviews, editorials, guidelines), topic (other viral agents), and population (adult patients with COVID-19). One of these 68 excluded articles was retracted. Eighteen articles met the inclusion criteria and were analyzed for the systematic review (**Figure**). Included cross-sectional studies showed low risk of bias.

Study Characteristics and Demographic Features

All the included articles were published in February 2020 except 1 article published in March 2020.[10] Seventeen studies were conducted in China[10-26] and 1 in Singapore.[27] We found a total of 1065 pediatric cases of SARS-CoV-2 infection. All included articles reported the age at onset of the infection. In particular, 444 were cases of children younger than 10 years,[11,14-19,22,24,26,27] and 553 were children ranging from age 10 to 19 years.[10,13,14,20,24] Two articles described the cases of 2 newborns,[15,22] and 5 other articles reported infant cases.[10,16-18,27] Twelve articles stated the sex of involved patients,[10,11,16-23,26,27] specifically, 24 children were boys, and 32 were girls. Seventeen articles reported that patients had a history of travel in Wuhan, China, or contact with affected family members (**Table**).[10-23,25-27]

Clinical Symptoms, Therapeutic Management, and Prognosis

Sixteen articles reported clinical symptoms.[10-12,14-23,25-27] Patients were symptomatic in 14 studies,[11,12,14-18,20-23,25-27] while 2 articles reported 3 clinical cases of asymptomatic children aged 12, 10, and 7 years.[10,19] Fever and cough were the main symptoms, with both reported in 6 of the included studies.[11,12,14,23,25,26] Also, fever was a symptom described in 12 articles.[11,12,14,16-18,20,21,23,25-27] When reported, respiratory symptoms appeared mild, except for 1 study of a severe SARS-CoV-2 infection in a 13-month-old infant.[17] This patient developed vomiting, diarrhea, fever, and pneumonia, complicated by shock with metabolic acidosis and kidney failure that required intensive care and assisted ventilation.[17] A history of gastrointestinal symptoms was described in 2 articles, with vomiting the primary clinical manifestation.[17,22] We found 2 articles that reported cases of neonatal COVID-19.[15,22] One article described a case

Table. Results of Systematic Review

Source	Publication date	Study type	Country	No.			Age	Sex	Symptoms (yes/no); type of symptoms	Radiologic		Therapy (yes/no); type of therapy
				Patients	Age <10 y	Age 10-19 y				Tests	Findings	
Cai et al[11]	February 4, 2020	Case report	China	1	1	0	7 y	M	Yes; the child presented with fever, cough, runny nose, dyspnea, nausea, and loss of appetite.	Chest radiograph and CT	Bronchial thickening	Yes; supportive care
Shen and Yang[12]	February 5, 2020	Case series	China	28	NA	NA	1 mo-17 y	NA	Yes; several patients gradually presented with fever, fatigue, and dry cough, accompanied by other upper respiratory symptoms including nasal congestion, runny nose, and seldom gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Most pediatric patients had mild symptoms, without fever or pneumonia. They had good prognosis and recovered within 1 to 2 wk after disease onset. Only a few patients had lower respiratory tract infections.	Yes	Lung imaging examination revealed mild increase of lung markings or ground-glass opacity or pneumonia.	NA
Song et al[13]	February 6, 2020	Retrospective study	China	1	0	1	16 y	NA	NA	Chest CT	NA	NA
Chang et al[14]	February 7, 2020	Case series	China	2	1	1	2-15 y	NA	Yes; the youngest patient (age 2 y) had intermittent fever for 1 wk and persistent cough for 13 d before COVID-19 diagnosis. No symptoms were reported for the other child.	Yes	NA	NA
Schwartz and Graham[15]	February 10, 2020	Case report with review of literature	China	1	1	0	30 h	NA	Yes; the infant developed shortness of breath and showed abnormalities of liver function.	Chest radiograph	Abnormal chest radiographs	NA
Zhang et al[16]	February 11, 2020	Case report	China	1	1	0	3 mo	F	Yes; the patient developed fever.	Chest radiograph and CT	Bronchial thickening	Yes; the patient required antiviral therapy, antibiotics (azithromycin and ceftazidime), aerosol therapy, and supportive care.
Chen et al[17]	February 11, 2020	Case report	China	1	1	0	13 mo	M	Yes; the patient developed vomiting and diarrhea 6 d before he showed fever, dyspnea, cyanosis, and hepatomegaly. The patient developed shock with metabolic acidosis that required intensive care and the administration of vasoactive drugs (dopamine), IV rehydration, and assisted ventilation. The patient also showed acute kidney failure that required the dialysis.	Chest radiograph and CT	Imaging showed different area of lung thickening, suggesting pneumonia.	Yes; shock required dopamine, IV rehydration, blood transfusion, and assisted ventilation. Also, the patient was treated with antibiotic therapy (meropenem and linezolid), oseltamivir, IVIG and steroids, nebulized interferon, and dialysis.
Wei et al[18]	February 14, 2020	Retrospective study	China	9	9	0	1-11 mo	2 M/7 F	Yes, but not all patients; 4 patients reported fever, 2 had mild upper respiratory tract symptoms, and 1 had no symptoms. For 2 patients, there were no available data on symptoms. None of the 9 infants required intensive care or mechanical ventilation or had any severe complications.	NA	NA	NA

(continued)

Table. Results of Systematic Review (continued)

Source	Publication date	Study type	Country	No.			Age	Sex	Symptoms (yes/no); type of symptoms	Radiologic		Therapy (yes/no); type of therapy
				Patients	Age <10 y	Age 10-19 y				Tests	Findings	
Chan et al[19]	February 15, 2020	Retrospective study	China	2	2	0	7 and 10 y	10-y-old M	No; patients were asymptomatic.	Chest CT	The 10-y-old patient showed ground-glass lung opacities.	NA
Zhang et al[20]	February 15, 2020	Retrospective study	China	1	0	1	15 y	M	Yes; the patient developed fever and fatigue.	Chest radiograph	NA	NA
Feng et al[21]	February 16, 2020	Retrospective study	China	15	NA	NA	4-14 y	5 M/10 F	Yes, not all patients; 5 children were febrile, and 10 were asymptomatic.	Chest CT	At chest CT images, 6 patients had no lesions, while 9 patients had pulmonary inflammation lesions. Seven cases of small nodular ground glass opacities and 2 cases of speckled ground glass opacities were found.	NA
Zeng et al[22]	February 17, 2020	Case report	China	1	1	0	17 d	M	Yes; the newborn had a history of rhinitis and vomiting.	Chest radiograph and CT	Imaging showed different area of lung thickening and enlargement of lung hila, suggesting pneumonia.	Yes; the newborn required IV rehydration and supportive care.
Pediatric Branch of Hubei Medical Association et al[23]	February 22, 2020	Case series	China	14	NA	NA	6 mo-14 y	6 M/8 F	Yes; fever, cough, fatigue, nausea, and vomiting were main symptoms.	NA	NA	NA
Wu and McGoogan[24]	February 24, 2020	Retrospective study	China	965	416	549	0-19 y	NA	NA	NA	NA	NA
Tian et al[25]	February 26, 2020	Retrospective study	China	11	NA	NA	0-12 y	NA	Yes; the most common symptoms of illness onset were fever, cough, fatigue, dyspnea, and headache. One severe case included dyspnea (patient age, <1 y).	NA	NA	NA
Kam et al[27]	February 28, 2020	Case report	Singapore	1	1	0	6 mo	M	Yes; the patient developed a transient temperature of 38.5 °C (1 episode).	NA	NA	No; no therapy
Cai et al[26]	February 28, 2020	Case series	China	10	10	0	3-131 mo	4 M/6 F	Yes; 8 patients (80%) had fever, 6 (60%) had cough, 4 (40%) had sore throat, 3 (30%) had stuffy nose, and 2 (20%) had sneezing and rhinorrhea. None of the patients had diarrhea or dyspnea during the course of illness. Fever resolved 24 h after fever onset with the peak of fever ranging from 37.7 °C to 39.2 °C.	Chest radiograph	Chest radiograph revealed unilateral patchy infiltrate in 4 of 10 patients (40%).	Yes; all patients received symptomatic treatment with no need of oxygen therapy, and a few patients with pneumonia received empirical antibiotic therapy.
Tong et al[10]	March 3, 2020	Case reports	China	1	0	1	12 y	M	No; the patient was asymptomatic.	NA	NA	No; NA

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; F, female; IV, intravenous; IVIG, intravenous immunoglobulin; M, male; NA, not available.

of a newborn aged 30 hours who acquired SARS-CoV-2 from the mother who had been infected, and the newborn developed mild respiratory distress with abnormal findings at chest radiography.[15] The other neonatal case was a 17-day-old infant who developed intermittent vomiting that required intravenous rehydration and supportive care.[22]

Patients (both symptomatic and asymptomatic children) were hospitalized.[11,12,14,16-23,25-27] Except for the single case of severe infection, none of the included patients required oxygen or assisted ventilation. Five articles reported the administration of treatments to 14 children.[11,16,17,22,26] The 3 asymptomatic patients did not require any therapy.[10,27] Most included patients needed supportive therapy. In 2 articles, children with pneumonia were treated with antibiotics.[16,26] The infant hospitalized in the pediatric intensive care unit for shock and acute kidney failure was successfully treated with an aggressive resuscitation therapy, assisted ventilation, intravenous dopamine, blood transfusion, dialysis, intravenous immunoglobulins, antibiotics (meropenem and linezolid), and oseltamivir.[17] In general, included patients had a good prognosis; however, 1 death was reported in the age range of 10 to 19 years.[24]

Diagnostic Tests

In all included studies, patients underwent the nasopharyngeal swab, which tested positive for SARS-CoV-2. The reason for performing the SARS-CoV-2 molecular test was reported in all articles and included a history of contact with infected parents or other family members and/or with people from Wuhan, China.[10-23,25-27]

Children underwent radiologic tests in 12 articles.[11-17,19-22,26] Three articles reported chest CT,[13,19,21] 3 articles mentioned chest radiographs,[15,20,26] and 4 articles reported both imaging tests.[11,16,17,22] Radiologic findings differed from article to article and were mainly characterized by bronchial thickening (described in 4 articles),[11,16,17,22] ground-glass opacities (reported in 3 articles),[12,19,21] or inflammatory lung lesions.[15,26]

Discussion

The current rapid worldwide spread of SARS-CoV-2 infection requires continual improvement of knowledge about the epidemiology and clinical characteristics of COVID-19. Since December 2019, when the disease was reported in Wuhan city and quickly spread throughout China, data on the clinical characteristics of the affected patients have been reported mainly from adult patients. At present, only limited reports analyze pediatric patients infected with SARS-CoV-2. In this context, we performed the first systematic review of COVID-19 in children and adolescents to evaluate clinical features, diagnostic tests, current therapeutic management, and prognosis, to our knowledge.

Seventeen articles reported studies performed in China, and 1 article reported a clinical case from Singapore, 1 of the countries with the highest number of confirmed COVID-19 cases in the Western Pacific Region after the Republic of Korea and Japan.[28] Although SARS-CoV-2 infection is currently spread throughout China and has widely diffused across other countries, complete reports on pediatric cases are still lacking. Generally, clinical data from affected Chinese adult patients have been available since January 2020, but pediatric retrospective studies and case reports were not published before February 2020, to our knowledge.

This systematic review of pediatric cases of COVID-19 shows that most children and adolescents who were infected by SARS-CoV-2 (ie, tested positive by nasopharyngeal swab) presented with mild symptoms.[29-31] Frequent clinical manifestations included fever, dry cough, and fatigue accompanied by other upper respiratory symptoms, such as nasal congestion and runny nose.[31] Moreover, the main gastrointestinal symptoms were nausea, vomiting, and diarrhea, which were reported in a few cases, particularly in a newborn and infants.[31] In our analysis, only 1 pediatric case presented with severe lower respiratory tract infection (COVID-19 pneumonia), complicated by shock and kidney failure, and fortunately, it was successfully treated with intensive care.[17] Unlike adults,[32-34] children do not seem to be at higher risk of severe illness based on age and sex. However, at present, no data are available on the role of comorbidities in the severity of pediatric COVID-19.

In general, pediatric patients with COVID-19 had a good prognosis and recovered within 1 to 2 weeks after disease onset, and cases of pediatric death from COVID-19 were not reported in the age range of 0 to 9 years. One death was reported in the age range of 10 to 19 years, but no more information was provided about this patient.[24,35] Our results confirmed the current knowledge about the disease severity of COVID-19 in children.[29-31,35]

It is worth noting that COVID-19 infection might affect newborns who acquired the infection from the mother, suggesting a possible perinatal-peripartum transmission.[15] However, Chen et al[36] recently reported 9 cases of pregnant women with COVID-19 who underwent cesarean delivery, without transmitting COVID-19 to their infants. In addition, viral infections might be acquired during vaginal delivery or through postpartum breastfeeding, but respiratory viruses, including Middle East respiratory syndrome coronavirus and SARS, did not show infection through vertical (intrauterine) and peripartum transmission or through breastfeeding.[15,37]

For COVID-19, there continue to be conflicting data as to the role of breastfeeding on transmitting neonatal-maternal infection. UNICEF recommends continuing with breastfeeding, while applying necessary precautions to prevent transmission of infection.[38] In contrast, the Chinese Working Group for the Prevention and Control of Neonatal SARS-CoV-2 Infection recommends milk formula for every child of a mother who has been infected.[39]

Our analysis showed that pediatric patients acquired infections mainly through close contact with their parents or other family members who lived in Wuhan, China, or had traveled there.[19,31] This finding aligns with results of a February 2020 report by Wang et al,[40] in which 31 patients, all pediatric, and all from provinces in Northern China, underwent nasopharyngeal swab to detect SARS-CoV-2 in respiratory secretions. Furthermore, the nasopharyngeal swab was performed in asymptomatic children with a history of contact with infected family members.[40] In our analysis, we included 3 cases of asymptomatic patients who tested positive for SARS-CoV-2 by nasopharyngeal swab, as part of an effort to perform a history of close contact with infected people.

Remarkably, in another recent article, Xu et al[5] reported that 8 pediatric patients tested positive on rectal swabs, even after nasopharyngeal testing was negative, suggesting viral shedding through gastrointestinal tract and the possibility of fecal-oral viral transmission. However, these preliminary results need to be confirmed by larger studies. Of note, no patients included in our analysis underwent rectal swab.

Recently, the group study at Johns Hopkins Bloomberg School of Public Health showed that children are at similar risk of infection as the general population, although they are less likely to have severe symptoms. This finding should be considered in analyses of transmission and control.[41] These preliminary data, coupled with our results, may suggest that children, even when presenting with mild symptoms or are asymptomatic, might be a source of viral transmission.[19,31] This underscores the importance of extensive preventive strategies that include quarantining and limitation of playing and school activities. Further studies focused on the pediatric population are needed to confirm this hypothesis.

Chen et al[31] report that the main radiologic features are bronchial thickening, ground-glass opacity, or inflammatory lung lesions, suggestive of pneumonia. These pulmonary findings were also found in patients with mild symptoms or who were asymptomatic, suggesting that COVID-19 induces a primary inflammation of lower respiratory tract airways.[29] Although mild respiratory symptoms were mainly reported, several patients underwent chest CT. Currently, there are no studies that compare the chest radiograph with CT or other radiologic tests (lung ultrasonography) to assess COVID-19 in children, to our knowledge.[31] Biologic effects of ionizing radiations are widely known; therefore, pediatricians should evaluate and choose the best radiologic options based on clinical conditions and possible adverse events.

Data about therapies were quite limited. Patients with mild respiratory symptoms, pneumonia, and fever were treated with antibiotics and supportive care. Except for the infant hospitalized in the pediatric intensive care unit, none of the patients required oxygen therapy. Currently, many therapeutic questions in children with COVID-19 remain unanswered, so in the interim, pediatric knowledge stems from the management of other respiratory infectious diseases.[31,42,43]

Limitations and Strengths

This study has several limitations. First, the research occurred over a brief 3-month period. Second, nearly all the articles came from Chinese reports, as European and US studies in children with COVID-19 were not available, to our knowledge, at the time this review was conducted. As a result, we could not assess possible clinical, diagnostic, and therapeutic differences, and compare pediatric results with data from adults with SARS-CoV-2 infection. Third, we were unable to evaluate any possible correlation between viral burden and clinical symptoms. Fourth, the included studies were observational designs, and many were simple case series or case reports.

A key strength of this systematic review is the absence of population bias (all patients tested positive for SARS-CoV-2). Also, to our knowledge, this is the first systematic review that summarized the current evidence on new SARS-CoV-2 infection in children, clarifying the clinical and therapeutic lack of knowledge.

Conclusions

This systematic review assesses and summarizes clinical features and management of children with COVID-19. Currently, the majority of evidence results from studies and clinical cases from China, where the outbreak of COVID-19 first started. Children mainly acquire SARS-CoV-2 infection from their family members but seem to experience less severe COVID-19 than adults, presenting mild symptoms, if any, good prognosis, and recovering within 1 to 2 weeks after disease onset. The quick worldwide spread of SARS-CoV-2 infection and the lack of European and US data on pediatric patients require further epidemiologic and clinical studies to identify possible preventive and therapeutic strategies.

ARTICLE INFORMATION

Accepted for Publication: April 6, 2020.

Published Online: April 22, 2020. doi:10.1001/jamapediatrics.2020.1467

Author Contributions: Dr Licari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Castagnoli and Votto contributed equally as co–first authors.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Castagnoli, Licari, Brambilla.
Drafting of the manuscript: Castagnoli, Votto, Licari, Brambilla, Bruno.
Critical revision of the manuscript for important intellectual content: Licari, Brambilla, Perlini, Rovida, Baldanti, Marseglia.
Statistical analysis: Castagnoli, Votto, Licari.
Administrative, technical, or material support: Perlini.
Supervision: Licari, Brambilla, Perlini, Baldanti, Marseglia.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. Published online February 28, 2020. doi:10.1056/NEJMoa2002032

2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565-574. doi:10.1016/S0140-6736(20)30251-8

3. Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017

4. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020. Published March 11, 2020. Accessed March 11, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

5. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med*. Published online March 13, 2020. doi:10.1038/s41591-020-0817-4

6. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. Published online March 4, 2020. doi:10.1016/j.cell.2020.02.052

7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097

8. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

9. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499. doi:10.1016/j.ijsu.2014.07.013

10. Tong ZD, Tang A, Li KF, et al. Potential presymptomatic transmission of SARS-CoV-2, Zhejiang province, China, 2020. *Emerg Infect Dis*. 2020;26(5). doi:10.3201/eid2605.200198

11. Cai JH, Wang XS, Ge YL, et al. [First case of 2019 novel coronavirus infection in children in Shanghai]. *Zhonghua Er Ke Za Zhi*. 2020;58(2):86-87. doi:10.3760/cma.j.issn.0578-1310.2020.02.002

12. Shen KL, Yang YH. Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. *World J Pediatr*. Published online February 5, 2020. doi:10.1007/s12519-020-00344-6

13. Song F, Shi N, Shan F, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia.

Radiology. 2020;295(1):210-217. doi:10.1148/radiol.2020200274

14. Chang D, Lin M, Wei L, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *JAMA*. Published online February 7, 2020. doi:10.1001/jama.2020.1623

15. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. *Viruses*. 2020;12(2):e194. doi:10.3390/v12020194

16. Zhang YH, Lin DJ, Xiao MF, et al. [2019-novel coronavirus infection in a three-month-old baby]. *Zhonghua Er Ke Za Zhi*. 2020;58(0):e006. doi:10.3760/cma.j.issn.0578-1310.2020.0006

17. Chen F, Liu ZS, Zhang FR, et al. [First case of severe childhood novel coronavirus pneumonia in China]. *Zhonghua Er Ke Za Zhi*. 2020;58(3):179-182. doi:10.3760/cma.j.issn.0578-1310.2020.03.003

18. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. Published online February 7, 2020. doi:10.1001/jama.2020.2131

19. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395(10223):514-523. doi:10.1016/S0140-6736(20)30154-9

20. Zhang MQ, Wang XH, Chen YL, et al. [Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing]. *Zhonghua Jie He Hu Xi Za Zhi*. 2020;43(0):E013. doi:10.3760/cma.j.issn.1001-0939.2020.0013

21. Feng K, Yun YX, Wang XF, et al. [Analysis of CT features of 15 children with 2019 novel coronavirus infection]. *Zhonghua Er Ke Za Zhi*. 2020;58(0):E007. doi:10.3760/cma.j.issn.0578-1310.2020.0007

22. Zeng LK, Tao XW, Yuan WH, Wang J, Liu X, Liu ZS. [First case of neonate infected with novel coronavirus pneumonia in China]. *Zhonghua Er Ke Za Zhi*. 2020;58(0):E009. doi:10.3760/cma.j.issn.0578-1310.2020.0009

23. Pediatric Branch of Hubei Medical Association; Pediatric Branch of Wuhan Medical Association; Pediatric Medical Quality Control Center of Hubei. [Recommendation for the diagnosis and treatment of novel coronavirus infection in children in Hubei (trial version 1)]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(2):96-99.

24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. Published online February 24, 2020. doi:10.1001/jama.2020.2648

25. Tian S, Hu N, Lou J, et al Characteristics of COVID-19 infection in Beijing. *J Infect*. 2020;80(4):401-406. doi:10.1016/j.jinf.2020.02.018

26. Cai J, Xu J, Lin D, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. Published online February 28, 2020. doi:10.1093/cid/ciaa198

27. Kam KQ, Yung CF, Cui L, et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. [published online February 27, 2020]. *Clin Infect Dis*. 2020;ciaa201. doi:10.1093/cid/ciaa201

28. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report 45. Published March 5, 2020. Accessed March 5, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200305-sitrep-45-covid-19.pdf?sfvrsn=ed2ba78b_4

29. Han Q, Lin Q, Jin S, You L. Coronavirus 2019-nCoV: a brief perspective from the front line. *J Infect*. 2020;80(4):373-377. doi:10.1016/j.jinf.2020.02.010

30. Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. *J Med Virol*. Published online February 25, 2020. doi:10.1002/jmv.25722

31. Chen ZM, Fu JF, Shu Q, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. [published online February 25, 2020]. *World J Pediatr*. 2020. doi:10.1007/s12519-020-00345-5

32. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. Published online March 23, 2020. doi:10.1001/jama.2020.4683

33. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. doi:10.1136/bmj.m1091

34. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

35. Rasmussen SA, Thompson LA. Coronavirus disease 2019 and children: what pediatric health care clinicians need to know. *JAMA Pediatr*. Published online April 3, 2020. doi:10.1001/jamapediatrics.2020.1224

36. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. doi:10.1016/S0140-6736(20)30360-3

37. Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: what neonatologist need to know. *J Med Virol*. Published online February 25, 2020. doi:10.1002/jmv.25740

38. UNICEF. Coronavirus disease (COVID-19): What parents should know. Accessed March 3, 2020. https://www.unicef.org/stories/novel-coronavirus-outbreak-what-parents-should-know

39. Working Group for the Prevention and Control of Neonatal 2019-nCoV Infection in the Perinatal Period of the Editorial Committee of Chinese Journal of Contemporary Pediatrics. [Perinatal and neonatal management plan for prevention and control of 2019 novel coronavirus infection (1st Edition)]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(2):87-90.

40. Wang D, Ju XL, Xie F, et al. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. *Zhonghua Er Ke Za Zhi*. 2020;58(4):e011. doi:10.3760/cma.j.cn112140-20200225-00138

41. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in Shenzhen China: analysis of 391 cases and 1,286 of their close contacts. Preprint. Posted online March 27, 2020. medRxiv. doi:10.1101/2020.03.03.20028423

42. Arabi YM, Mandourah Y, Al-Hameed F, et al; Saudi Critical Care Trial Group. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. doi:10.1164/rccm.201706-1172OC

43. Behzadi MA, Leyva-Grado VH. Overview of current therapeutics and novel candidates against influenza, respiratory syncytial virus, and Middle East respiratory syndrome coronavirus infections. *Front Microbiol*. 2019;10:1327. doi:10.3389/fmicb.2019.01327