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

The World Health Organization declared coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, a pandemic health emergency.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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.

## 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.<sup>7</sup> Search results were compiled using RefWorks software (ProQuest). In keeping with the quality standards for reporting systematic reviews and meta-analysis of observational studies,<sup>8</sup> 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.

## 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.

## Box. Inclusion and Exclusion Criteria

### Inclusion criteria

1. Population: children and adolescents (age  $\leq 19$  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

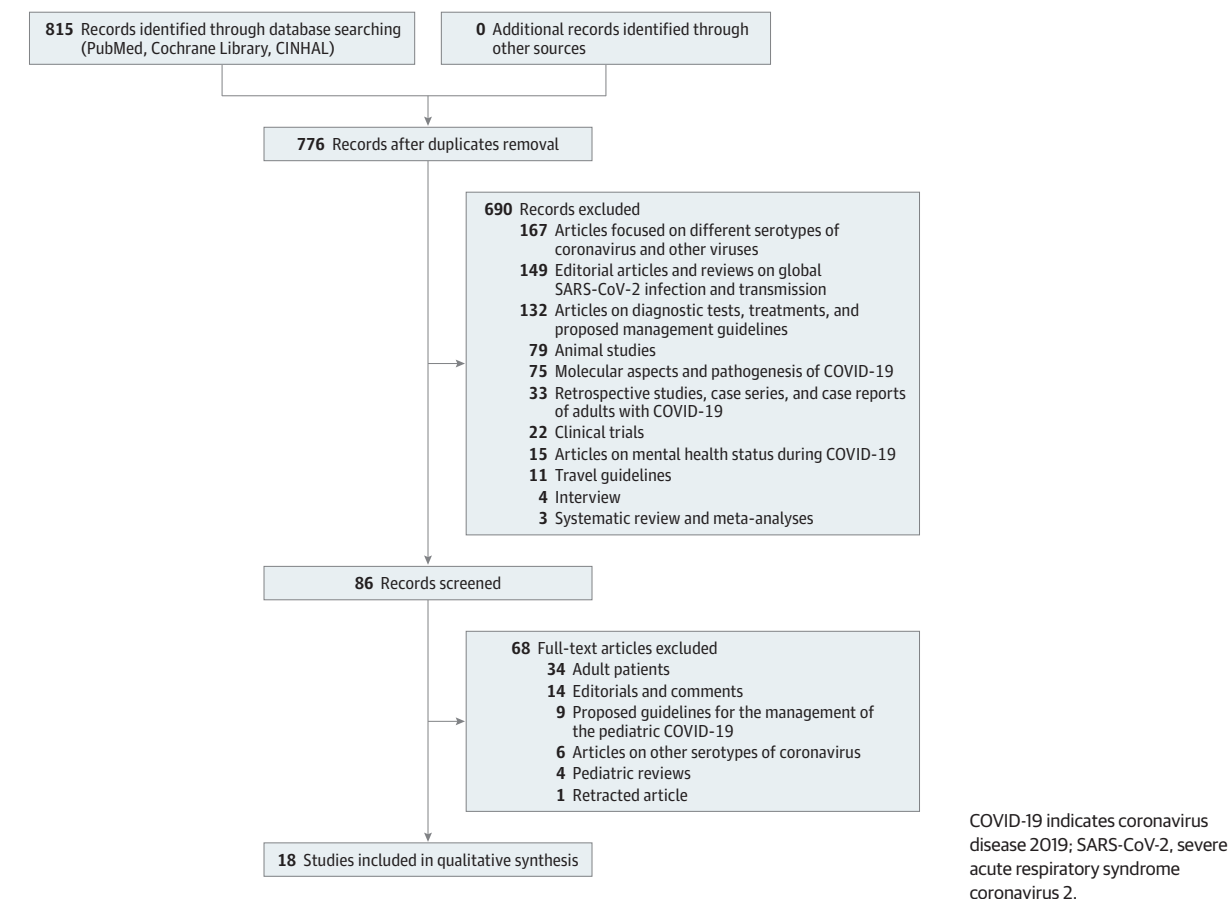
## Study Selection and Risk of Bias Assessment

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.<sup>9</sup> 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



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.<sup>10</sup> Seventeen studies were conducted in China<sup>10-26</sup> and 1 in Singapore.<sup>27</sup> 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,<sup>11,14-19,22,24,26,27</sup> and 553 were children ranging from age 10 to 19 years.<sup>10,13,14,20,24</sup> Two articles described the cases of 2 newborns,<sup>15,22</sup> and 5 other articles reported infant cases.<sup>10,16-18,27</sup> Twelve articles stated the sex of involved patients,<sup>10,11,16-23,26,27</sup> 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).<sup>10-23,25-27</sup>

### Clinical Symptoms, Therapeutic Management, and Prognosis

Sixteen articles reported clinical symptoms.<sup>10-12,14-23,25-27</sup> Patients were symptomatic in 14 studies,<sup>11,12,14-18,20-23,25-27</sup> while 2 articles reported 3 clinical cases of asymptomatic children aged 12, 10, and 7 years.<sup>10,19</sup> Fever and cough were the main symptoms, with both reported in 6 of the included studies.<sup>11,12,14,23,25,26</sup> Also, fever was a symptom described in 12 articles.<sup>11,12,14,16-18,20,21,23,25-27</sup> When reported, respiratory symptoms appeared mild, except for 1 study of a severe SARS-CoV-2 infection in a 13-month-old infant.<sup>17</sup> This patient developed vomiting, diarrhea, fever, and pneumonia, complicated by shock with metabolic acidosis and kidney failure that required intensive care and assisted ventilation.<sup>17</sup> A history of gastrointestinal symptoms was described in 2 articles, with vomiting the primary clinical manifestation.<sup>17,22</sup> We found 2 articles that reported cases of neonatal COVID-19.<sup>15,22</sup> 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 |     |         |   | Tests                   | Findings   |   |
| Cai et al <sup>11</sup>           | February 4, 2020  | Case report                           | China   | 1        | 1         | 0   | 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 <sup>12</sup>       | February 5, 2020  | Case series                           | China   | 28       | NA        | NA  | 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 <sup>13</sup>          | February 6, 2020  | Retrospective study                   | China   | 1        | 0         | 1   | NA      | NA  | Chest CT                | NA   | NA  |
| Chang et al <sup>14</sup>         | February 7, 2020  | Case series                           | China   | 2        | 1         | 1   | 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 <sup>15</sup> | February 10, 2020 | Case report with review of literature | China   | 1        | 1         | 0   | NA      | Yes; the infant developed shortness of breath and showed abnormalities of liver function.   | Chest radiograph        | Abnormal chest radiographs   | NA  |
| Zhang et al <sup>16</sup>         | February 11, 2020 | Case report                           | China   | 1        | 1         | 0   | 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 <sup>17</sup>          | February 11, 2020 | Case report                           | China   | 1        | 1         | 0   | 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 <sup>18</sup>           | February 14, 2020 | Retrospective study                   | China   | 9        | 9         | 0   | 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 | Age        | Sex        | Symptoms (yes/no); type of symptoms   | Radiologic              |  | Therapy (yes/no); type of therapy   |
|---|-------------------|---------------------|-----------|----------|-----------|-----|------------|------------|---|-------------------------|--|---|
|   |                   |                     |           | Patients | Age <10 y |     |            |            |   | Tests                   | Findings   |   |
| Chan et al <sup>19</sup>  | 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 <sup>20</sup>   | 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 <sup>21</sup>  | 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 inflammatory lesions. Seven cases of small nodular ground glass opacities and 2 cases of speckled ground glass opacities were found. | NA  |
| Zeng et al <sup>22</sup>  | 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 <sup>23</sup> | 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 <sup>24</sup>                                     | February 24, 2020 | Retrospective study | China     | 965      | 416       | 549 | 0-19 y     | NA         | NA  | NA                      | NA   | NA  |
| Tian et al <sup>25</sup>  | 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 <sup>27</sup>   | 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 <sup>26</sup>   | 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 <sup>10</sup>  | 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; I/VG, 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.<sup>15</sup> The other neonatal case was a 17-day-old infant who developed intermittent vomiting that required intravenous rehydration and supportive care.<sup>22</sup>

Patients (both symptomatic and asymptomatic children) were hospitalized.<sup>11,12,14,16-23,25-27</sup> 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.<sup>11,16,17,22,26</sup> The 3 asymptomatic patients did not require any therapy.<sup>10,27</sup> Most included patients needed supportive therapy. In 2 articles, children with pneumonia were treated with antibiotics.<sup>16,26</sup> 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.<sup>17</sup> In general, included patients had a good prognosis; however, 1 death was reported in the age range of 10 to 19 years.<sup>24</sup>

### 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.<sup>10-23,25-27</sup>

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

## 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.<sup>28</sup> 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.<sup>29-31</sup> Frequent clinical manifestations included fever, dry cough, and fatigue accompanied by other upper respiratory symptoms, such as nasal congestion and runny nose.<sup>31</sup> Moreover, the main gastrointestinal symptoms were nausea, vomiting, and diarrhea, which were reported in a few cases, particularly in a newborn and infants.<sup>31</sup> 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.<sup>17</sup> Unlike adults,<sup>32-34</sup> 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.<sup>24,35</sup> Our results confirmed the current knowledge about the disease severity of COVID-19 in children.<sup>29-31,35</sup>

It is worth noting that COVID-19 infection might affect newborns who acquired the infection from the mother, suggesting a possible perinatal-peripartum transmission.<sup>15</sup> However, Chen et al<sup>36</sup> 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.<sup>15,37</sup>

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.<sup>38</sup> 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.<sup>39</sup>

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.<sup>19,31</sup> This finding aligns with results of a February 2020 report by Wang et al,<sup>40</sup> 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.<sup>40</sup> 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<sup>5</sup> 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.<sup>41</sup> 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.<sup>19,31</sup> 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<sup>31</sup> 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.<sup>29</sup> 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.<sup>31</sup> 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.<sup>31,42,43</sup>

## 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

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**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.

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