

Epidemiology, Clinical Characteristics, and Treatment of SARS-CoV-2 Infection in Children: A Narrative Review

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Abstract

SARS-CoV-2 has infected millions of people around the world, with most cases recorded among adults. The cases reported among children have been acknowledged to be minimal in comparison to adults. Nevertheless, COVID-19 has been reported to affect children at all ages, including newborns. The symptoms among children have also been identified to be similar to those observed among adults, although pediatric patients have been noted to display spectrum of clinical features ranging from asymptomatic through mild to moderate symptoms. Despite ample publications on the ongoing pandemic, the literature is only replete with guidelines on treating SARS-CoV-2 infection among older people. In this narrative review, comprehensive updates on the infection in children have been discussed. The latest information on the spread of the disease among children around the world, the clinical features observed among the pediatric population, as well as recommended pharmaceutical treatments of COVID-19 among this special group of patients have been covered. Further, expert consensus statements regarding the management of this highly contagious disease among pregnant women and neonates have been discussed. It is believed that this comprehensive review will provide updated information on the epidemiology and clinical features of the ongoing pandemic among pediatric patients. Additionally, the guidelines for handling SARS-CoV-2 among pregnant women and children, as reviewed in this article, are anticipated to be useful to frontline clinicians battling this fatal disease around the globe.

Research Methods

- Published articles were searched from April 1, 2020, through April 21, 2020 using trusted databases such as PubMed, PubMed Central, Cochrane Library, and Google Scholar.
- Search terms such as 2019-nCoV, COVID-19, 2019 novel coronavirus, SARS-CoV-2, along with epidemiology, clinical features, pediatric, pediatric patients, children, child, infants, neonates, or newborns, were included in the search.
- Articles were thoroughly screened for similarities in information, common clinical presentations, and dates of data compilation to select the most up-to-date and relevant literature.

Keywords: SARS-CoV-2; COVID-19; Children; Pediatrics; Clinical Features; Epidemiological Characteristics

1. Introduction

The ongoing novel coronavirus pandemic was initially detected in the Hubei Province, located in Central China. Early etiological and epidemiological findings posit that the virus has a zoonotic origin, and might have spilled over from a bat to an intermediate host in the Huanan Seafood and Wet Animal Wholesale

Market, and subsequently spread to humans in Wuhan, the capital city of the Hubei Province, before spreading widely beyond the borders of the People's Republic of China (PRC). According to Chinese health officials, the virus was discovered in December of 2019, with a cluster of infections originally emerging in Wuhan.¹⁻⁵

Due to the heightening concerns about this cluster of pneumonia-like respiratory ailments with inexplicable causes at Wuhan in late December 2019, the Chinese Center for Disease Control and Prevention (CDC-China) deployed a team on 31 December to work with officials of the Hubei provincial Health Commission to investigate the causes of the strange illness.⁶ In early January 2020, the virus causing the new disease was isolated from samples of bronchoalveolar lavage fluid from a patient in Wuhan, and subsequently detected as a novel beta-coronavirus, using deep genome sequencing analyses.⁷⁻⁹ The World Health Organization (WHO) then named the pathogen the 2019 novel coronavirus (2019-nCoV) in January, and subsequently called the illness associated with the virus as the 2019 coronavirus disease (COVID-19) on February 11, 2020. On the same day, the International Committee on Taxonomy of Viruses (ICTV) classified the new coronavirus as "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) because of its close relations with the 2003 SARS-CoV. That notwithstanding, the genetic characteristics of SARS-CoV-2 are noticed by scientists to be distinctly different from those of SARS-CoV.¹⁰⁻¹²

Owing to the fast transmission nature of COVID-19, and its widespread across the whole world, the WHO declared the outbreak as a public health emergency of international concern (PHEIC), and later announced that the infection has attained a pandemic status in early March, 2020.^{12,13} Presently, the outbreak has spread to over 200 nations and territories in 6 continents across the world, in exception of Antarctica. Table 1 shows the number of confirmed cases, deaths and case-fatality rates in the top-ranked 23 nations across the world, all of which have over 10,000 cases as of April 16, 2020. Globally, the total number of confirmed cases has surpassed 2 million patients, with approximately 135,000 deaths.^{14,15} The high fatality rates in some countries have resulted in more deaths than in countries where the number of cases is much higher. This could be seen in the case of Belgium. Even though the number of confirmed cases in this country is much lesser than the cases in Germany, China, and Turkey, the fatalities recorded in Belgium is higher than in these nations.

****Table 1****

Considering the increasing trends of daily new cases and deaths globally since the beginning of March, as represented in Figure 1, health experts opined that the fatal COVID-19 could persist for another 12 months; following the typical nature of similar past pandemics which have all lasted between 12 to 36 months.^{16,17}

****Figure 1****

During the early days of the outbreak, COVID-19 was predominantly reported among adults of age 15 years and above, with the proportion of cases recorded among pediatric patients being comparatively trivial.¹⁰ Nevertheless, as noted by Wei et al.,¹⁸ the number of cases began to increase among children, especially in infants, in late January. This observation was made for PRC, and was believed to be spurred by the fact that younger children were unable to observe the control and preventive measures instituted, including the wearing of nose masks. This discovery prompted the health officials and authorities of China to issue a notice in early February regarding the control and prevention of SARS-CoV-2 infections in infants and pregnant women. The new notice clearly indicated that children are vulnerable to the novel coronavirus contagion due to the immaturity of their immune systems. Also included in the latest procedures is the fact that all populations, regardless of age, were vulnerable to the novel disease. Additionally, as children were recognized to have difficulties with recounting their health status and trace their contact history, it was obvious that the challenges in protecting, diagnosing, and treating this age group could be critical.¹⁰

More recently, the widespread outbreak has been reported to infect children not only in PRC, but globally. Although many of the cases have been reported as mild, there are equally severe cases recorded, and deaths as well. As updated information on the characteristics of the ongoing pandemic in this special population is scarce in literature, this article conducts comprehensive reviews of the latest information on the clinical

and epidemiological features of SARS-CoV-2 infections in pediatric patients around the world. The article also covers the expert consensus for managing and treating the infection in pregnant women, neonates, and children in general.

2. Research Methods

We searched published articles through PubMed, PubMed Central, Cochrane Library, and Google Scholar with search terms such as 2019-nCoV, COVID-19, 2019 novel coronavirus, SARS-CoV-2, along with epidemiology, epidemiological features, clinical features, clinical characteristics, treatment, pediatric, pediatric patients, children, child, infants, neonates, or newborns. Supplemental data were also obtained from websites with dedicated COVID-19 databases with similar search terms. These websites include <https://www.statista.com/search/?q=COVID-19>, <https://www.cdc.gov/coronavirus>, <https://www.worldometers.info/corona> and <https://coronavirus.jhu.edu/>. Articles were searched from April 1, 2020, through April 21, 2020. A total of 58 studies were retrieved. Articles were thoroughly screened for similarities in information, common clinical presentations, and dates of data compilation to select the most up-to-date and relevant literature. The state-of-the-art information compiled from these studies have been discussed comprehensively below.

3. Etiology and Bioinformatics of SARS-CoV-2

The results of several analyses on the genomic characteristics of SARS-CoV-2 have shown that the new virus is over 85% homologous to two bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, collected in 2018 in Zhoushan, eastern China, but were more distant from SARS-CoV and MERS-CoV.^{8,19} Detailed phylogenetic analyses revealed that the novel virus belongs to the Beta (β)-coronavirus genus, in the subgenus Sarbecovirus. The analyses also disclosed that the 2019-nCoV has a relatively long branch length to its closest relatives bat-SL-CoVZC45 and bat-SL-CoVZXC21, and was genetically distinct from SARS-CoV. Despite amino acid variations at some key residues, homology modellings showed that the 2019-nCoV had a similar receptor-binding domain structure to that of SARS-CoV. Based on these findings, scientists have concluded that, although the 2019-nCoV is similar to SARS-CoV, it is sufficiently different to be considered a new human-infecting β -coronavirus. They also suggest that bats might be the origin of this new virus, with the possibility of an animal sold at the Huanan Wet Seafood Market in Wuhan serving as the intermediate host that facilitated the eventual emergence of the virus in humans.^{8,10,20,21}

In a more recent research conducted by the Wuhan Institute of Virology (WIV), the virologists have reported that they have obtained sufficient evidence to conclude that SARS-CoV-2 has originated from bats. They also concluded that SARS-CoV-2 enters cells by binding to the angiotensin converting enzyme 2 (ACE-2) cell receptor, similar to SARS-CoV.¹⁰ Later publications also indicate that pangolins could be the possible intermediate hosts for this novel pathogen. Some these authors observe that the new pathogen share about 98% amino acid homology with Malay pangolin, and about 89% similarity for the same receptor binding motif fragment.²²⁻²⁴ Another study which analysed the genomic evolution of over 100 2019-nCoVs discovered that the pathogen has evolved into two subtypes, namely L and S. The authors also found that the virus strain has roughly 149 mutation points, which raises fears that SARS-CoV-2 could be more infectious and spread wider than SARS-CoV.²⁵ These fears have become realities around the whole world as scientists continue to unveil more strains of the novel coronavirus every day. One recent findings believe that there could be up to 49 new strains of the virus, with one of the strains referred to as the ZJ01 having preference of binding to the Furin cleavage site, rather than ACE-2. Other latest findings also observe that SARS-CoV-2 has at least four modes of binding to human host cells.²⁶

4. Spread and Transmission Modes of SARS-CoV-2

COVID-19 has been declared by the WHO to have attained a global pandemic status. This raises the question about what the difference between the disease being an outbreak, an epidemic, and a pandemic is. In line with the definitions of the CDC-US, there are distinct differences between the three stages of an infection. When a disease suddenly infects more people than expected in a certain geographical location, it is termed an outbreak. On the other hand, when the degree of infection extends to a larger region, then it is acknowledged to have attained an epidemic status. When this epidemic spreads across the borders of several

countries and territories, infecting a large number of people across different continents, then a pandemic status has been attained. It is vital to note that these three stages of the contagion do not say anything about how severe it is, but rather how widely it has transmitted, and what percent of the population it has infected.²⁷

As it is the case with most respiratory viral diseases, the transmission of COVID-19 is believed to be mainly via direct or indirect contact, droplet spray in short range transmission, and aerosol in long-range transmission. With regards to person-to-person spread of the disease, CDC-US reported that the virus can spread between people who are in close contact with one another, approximately 6 feet close. It could also be transmitted through respiratory droplets produced when an infected person coughs, sneezes or talks. Scientists noted that this mode of transmission is mostly possible when this respiratory droplets, which are >5-10 μm in diameter, land in the mouths, nose, or eyes (conjunctiva) of another person. In addition, the pathogen can equally spread through an airborne transmission mode when a person inhales the respiratory droplets of an infected person into his/her lungs. Some other researchers also disclosed that transmission could occur through fomites in the immediate environment around an infected person. Thus, the COVID-19 pathogen is widely noted to be transmitted through direct contact with an infected person, indirect contact with the aerosol from an infected person, and indirect contact with surfaces, objects, or materials which have been contaminated in the close environment of an infected person.²⁸⁻³¹ As there are evidences of asymptomatic carrier transmissions of COVID-19, the WHO has described four levels of transmission of the viral disease. These include: 1. No cases reported, 2. Sporadic cases, 3. Clusters of cases, and 4. Community transmission.^{32,33} That notwithstanding, the primary transmission route of COVID-19 has been identified to be direct contact with infected persons in a cluster scenario.

5. Epidemiological and Clinical Features of SARS-CoV-2 in Pediatric Patients

In a letter published by Raj Bhopal,³⁴ emeritus professor of public health, the expert expressed concerns over the need to precisely stratify infected SARS-CoV-2 patients by age group and sex nationwide. He noted that such data are required in handling the ongoing pandemic as the disease is highly variable by age and sex, requiring the need to examine age and sex specific mortality rates.³⁴ This letter accentuates the necessity to review the epidemiology and demographic data on 2019-nCoV infected patients, including children.

Even though the tally of infections among age groups lesser than 18 years are relatively small, as compared to the confirmed cases among adults, the spread of COVID-19 among children have been reported worldwide. Current data from the US Centers for Disease Control and Prevention (CDC-US), as obtained from the US public health jurisdictions and the National Notifiable Diseases Surveillance System (NNDSS), disclosed that children <18 years old account for approximately 1.75% of the total number of infected cases. This represents 8,171 infected children under 18 years old out of the 465,995 total confirmed cases as of April 15, 2020, at 4:00 pm Eastern Time (ET). This information is shown in Figure 2. It is obvious from the same Figure that the tally increases sharply among age groups from 18 years to 64 years, before decreasing again.

****Figure 2****

Nonetheless, CDC-US noted that the rates of hospitalization for COVID-19 patients in the US increases with age, with children under 18 accounting for the least rates.³⁵ According to the data released by the New York City (NYC) Health Department on April 14, 2020 at 6:00 pm ET, the total number of death reported among children [?]17 years old is 3, all of which have underlying conditions. These underlying illnesses include diabetes, lung disease, cancer, immunodeficiency, heart disease, hypertension, asthma, kidney disease, and GI/Liver disease.³⁶ In an updated information released by CDC-US on April 16, 2020, the death toll among children [?] 14 years old was 3. The recorded death among age group 15 – 24 years however amounted to 10 as per records on the same date.³⁷ Apart from the US and China, Germany, Italy, and Canada are among the nations with high records of pediatric patients who are 19 years old and below. This tally could be observed in Table 2, which shows the distribution of COVID-19 infection among children in 20 nations around the world, as adapted from www.statista.com at 3:30 am ET on April 21, 2020.

****Table 2****

In Moscow, Russia, children aged 0-17 years were reported to account for 10.9% of the confirmed new cases on April 1, 2020. Since then, at least 3% of the daily new cases have been reported among the same age group. Until April 20, an average of 5% of the daily new cases were recorded among the same age group of children.³⁸

In China, where the outbreak initially started, initial cases of pediatric patients were reported in a 3 months old female infant in Xiaogan (Hubei province),³⁹ in a 7 years old boy at Shanghai,⁴⁰ in a 10 years old boy at Shenzhen,⁴¹ and later in 9 infants¹⁸ and 3 newborns⁴² across different provinces nationwide. Subsequently, a number of literature publications have described the characteristics of SARS-CoV-2 among children in Mainland China. One of the largest studies undertaken in China on the age distribution of COVID-19 patients involved 72,314 patients, out of which 44,672 cases were classified as confirmed cases. Children under 9 years old accounted for 0.9% of the 44,672 confirmed cases studied as of February 11, 2020. Children from 10 to 19 years of age accounted for 1.2% of the same group. This same publication found that the fatality rate rises gradually with increasing age. Among children of age 9 years and less, no fatalities were recorded, while the rate among children from 10 to 19 years was 0.2%.⁴³⁻⁴⁵ As one of the most important laboratory findings observed in SARS-CoV-2 infected pediatric patients, Xia et al.⁴⁶ noted that procalcitonin (PCT) elevation was common among children, although it was rare in adults.

Depending on exposure history and symptomatology, Dong et al.⁴⁷ conducted a nationwide case study on 2143 children [?]17 years old who were reported to the CDC-China from January 16 to February 8, 2020. This research was meant to understand the epidemiology and transmission patterns of SARS-CoV-2 among pediatric patients in China. Out of the 2143 children, 731 (34.1%) were laboratory-confirmed to have COVID-19 while 1412 (65.9%) were suspected cases. The median age of the whole group was 7 years, out of which 56.6% were boys. Among the 731 confirmed cases, the average age was 10 years, out of which boys accounted for 57.5%. More than 90% of the patients were reported to be asymptomatic, mild, or moderate cases. Among these, about 13% were asymptomatic, 43.1% had mild symptoms of respiratory tract infection, and 41% reported moderate symptoms such as fever, pneumonia, and cough without hypoxia. 18 children however experienced severe infection of hypoxia, and 3 of the children were in critical conditions such as respiratory failure and a combination of systemic dysfunctions in the form of shock, heart failure, encephalopathy, myocardial injury, acute kidney injury, or coagulation disorder. Whereas the duration from the onset of illness to diagnoses ranges from 0 to 42 days, the median time was determined to be 2 days. Based on these results, the authors concluded that, although young children, especially infants are more susceptible to contagion, children at all ages are vulnerable to SARS-CoV-2 infection, without any significant gender biases. They also noted that the clinical features of this fatal disease in children appeared to be generally less severe than those observed in adults.^{47,48}

Another studies completed by Lu et al.⁴⁹ investigated the infection of SARS-CoV-2 in a total of 1,391 children under 16 years in the Wuhan Children's Hospital from January 28 through February 26, 2020. Throat or nasopharyngeal swabs were obtained for the detection of 2019-nCoV, and the clinical outcomes were monitored until March 8, 2020. Out of the 1,391 children, 12.3% (171) were confirmed to have been infected by the novel virus. 154 of them were infected through a family cluster transmission, 2 were believed to have had contact with other suspected cases, and 15 had an unidentified source of infection. The demographic data and clinical features indicated that the median age of the infected children was 6.7 years. 31 of them were less than a year old, 40 were 1-5 years old, 58 were 6-10 years old, and 42 were 11-15 years old. Among them, 104 were boys, representing 60.8% of the infected group. 27 of the infected children were observed to be asymptomatic, 12 of which had radiologic features of pneumonia even though they had no symptoms of infection. Cough, pharyngeal erythema, tachycardia on admission, fever, and tachypnea on admission were among the most common signs and symptoms, and were present in 83, 79, 72, 71, 49 of them respectively. Other less common symptoms were diarrhea (8.8%), fatigue (7.6%), rhinorrhea (7.6%), vomiting (6.4%), nasal congestion (5.3%), and oxygen saturation (2.3%). The computed tomography of their chests shows abnormalities such as ground-glass opacity (32.7%), local patchy shadowing (18.7%), bilateral patchy shadowing (12.3%), and interstitial abnormalities (1.2%). Based on these outcomes, the authors concluded that most infected children appear to experience milder clinical course in contrast to

adult patients. Asymptomatic infections were also observed to be common among these pediatric patients, requiring further research to determine the transmission potential of these asymptomatic individuals in order to guide the development of control measures of the disease.^{48,49}

In a critical review and meta-analysis published by Chang et al.,⁵⁰ the authors reviewed data on 93 COVID-19 pediatric patients of age 1 day to 17 years (48 of which were male) in China, from January to February 2020. The last update of this review was completed on March 15, 2020. The analyses revealed that 75% of the children had household contact history with an infected person. Majority of the patients, 98% of them, were reported to exhibit clinical spectrum ranging from asymptomatic to moderate cases, with 26% of the children being asymptomatic, and 2% experiencing severe symptoms that had to be treated in intensive care units (ICUs). The most common symptoms observed were fever and cough, which were observed in 59% and 46% of the patients respectively. 12% of the patients were also reported to show gastrointestinal symptoms, whereas glass opacities were detected to be the most prevalent radiographic findings in 48% of the patients. This study also reviewed the demographics and outcomes of 19 neonates born to SARS-CoV-2 infected mothers. Although 10 of the neonates were born prematurely, and 16 were delivered through cesarean-section, none of the newborns tested positive for COVID-19. Based on these findings, Chang et al. concluded that the disease severity in children is generally mild, with no evidence of vertical transmission from infected mothers to neonates.⁵⁰

The clinical analysis of 10 neonatal children (8 singletons and 2 twins) born to 9 SARS-CoV-2 infected pregnant women in 5 different hospitals in China, were published by Zhu et al.⁵¹ in journal of Translational Pediatrics in February. Among the 9 2019-nCoV pneumonia infected mothers, 4 of them had clinical symptoms before delivery, 2 of them showed symptoms on the day of delivery, while the remaining 3 only showed symptoms after delivery. The most common symptoms were observed to be fever and cough, but one patient experienced diarrhea. 8 of the neonates were male; 6 were born preterm; 2 were observed to be small-for-gestational (SGA) infants while 1 was large-for-gestational (LGA) infant; 6 had a Pediatric Critical Illness Score (PCIS) less than 90. The initial symptoms displayed by the newborns were shortness of breath (n=6), thrombocytopenia with abnormal liver function (n=2), fever (n=2), rapid heart rate (n=1), pneumothorax (n=1), and vomiting (n=1). One of the neonates was reported dead. The pharyngeal swab specimens collected from the remaining 9 within 1 to 9 days after birth were analyzed for COVID-19 infection, but all the results turned out negative. Base on the results of these analyses, Zhu et al. concluded that perinatal SARS-CoV-2 contagion could have adverse impacts on neonates, and is likely to result in premature labor, fetal distress, respiratory distress, thrombocytopenia with abnormal liver function, and even death. Nevertheless, the authors noted that there was no proof for vertical transmission of SARS-CoV-2 pneumonia from the mothers to the newborns.⁵¹

A review paper by Duan et al.⁵² surveyed 8 different publications which reported on the chest computed tomography (CT) scans of 238 pediatric patients infected with COVID-19 pneumonia in China. The key findings of this review indicated that children have fewer severe cases, shorter course of the disease, and slighter clinical symptoms, including lighter lung abnormalities. The chest CT scans of these pediatric patients were observed to be atypical, with lower ground glass opacity (GGO), more localized GGO extent, and relatively scarce interlobular septal thickening. Conclusively, the authors maintained that most pediatric cases demonstrate mild symptoms, and requires a good balance between the necessity for a chest CT scan and the risk of radiation. Consequently, they recommended a low-dose CT scan to be more appropriate for the pediatric population.⁵²

6. Expert Consensus for Managing Pediatric Patients and Pregnant Women with COVID-19

In a letter to the editor of *Acta Paediatrica* by Devi Dayal,⁵³ a pediatrician from the Postgraduate Institute of Medical Education and Research (PIMER), Chandigarh, India, the scientist noted that children have been suggested to have a relative protection from the ongoing pandemic due to their less mature ACE-2, which the SARS-CoV-2 protein binds to for pathogenic effects. That notwithstanding, the author raised the concern over an increased risk of critical disease and fatality rate in infants and young children, which could partly be associated with their less efficient immune system response to infections. Due to this concern, Dr. Dayal

expressed the urgent need for guidelines to manage the highly-infectious COVID-19 in children, especially in those with comorbidities.⁵³

In another article commentary published in *Clinical Pediatrics*, the authors reviewed the epidemiology, clinical features, diagnosis, treatment and mortality rates among 2019-nCoV infected pediatric patients. It was recognized that pediatric patients were spared from symptoms such as headache, lethargy, altered mental status, and myalgia, which are common in COVID-19 infected adults. Fatality in children was also described as an extremely rare occurrence. Diagnosis in pediatric patients was also noticed to be mainly through throat swab with reverse transcription-polymerase chain reaction. Nonetheless, there were reported cases of rectal swab which turned positive for children whose throat swab tested negative. Although majority of children who tested positive for SARS-CoV-2 infection were recorded to test negative for other common respiratory viruses, there was a study which observed that 40% of COVID-19 pediatric patients had also tested positive for mycoplasma, respiratory syncytial virus, cytomegalovirus, or influenza A/B. With regards to treatment in pediatric patients, the asymptomatic children were usually kept in quarantine without any special treatment, while symptomatic patients received supportive care. Children who showed mild symptoms received oxygen therapy, while moderate cases were treated with empiric antibiotics. The few severe cases were recorded to have received invasive mechanical ventilation.⁴⁸

In a different article published in *The Lancet Infectious Diseases*, Alyson et al.⁵⁴ observed that all COVID-19 infected pediatric patients were aggressively treated with aerosolized interferon alfa, with 39% of them receiving lopinavir-ritonavir syrup twice a day for 2 weeks, and 17% of them supported with supplemental oxygen.⁵⁴

A publication on a SARS-CoV-2 infected neonate in the US was reported by Paul Patek and his colleagues⁵⁵ from the Beaumont Hospital, Royal Oak, Michigan State. This article reported on the clinical features and treatment of the disease in a fortnight old male child with neutropenia. It was not clear what the route of transmission was, and the mother was only reported positive for Group B Streptococcus (GBS), not for SARS-CoV-2. The patient was recognized to have fever and fussiness upon admission, and was also observed by mother to have shown a progressively worsening erythema of the right thumb and fourth digit within the previous 3 days prior to hospitalization. On day 1 of admission the SARS-CoV-2 polymerase chain reaction returned positive for the patient's throat swab. During admission, the rectal temperature reading of the infant was recorded to be 38 °C, and the chest radiograph was notable for bilateral perihilar streaking without focal consolidation. The patient was admitted to the pediatric ICU due to hypoxic respiratory failure, and was treated with empiric antibiotic therapy as well as acyclovir, given his high count of liver enzymes and suspicious finger lesions. The patient was also supplied with a modest nasal cannula oxygen support within the first day of admission, and was gradually weaned to room air without need for therapy escalation. Series of blood count later revealed improvement from 0.3 bil/L to 0.7 bil/L in neutrophils, and the patient was discharged on day 4 of hospitalization with oral antibiotics to treat soft tissue infections. Based on this study, Patek et al. recommended that neonatal SARS-CoV-2 infected patients should be quarantined in wards to limit further transmission while more research is conducted to develop management and treatment guidelines in this special population of patients as they are at higher risk of morbidity and fatality.⁵⁵

Wang et al.⁵⁶ recommended 5 antiviral drugs including interferon- α (IFN- α), lopinavir/ritonavir (LPVr), ribavirin, chloroquine diphosphate (CD), and arbidol for treating COVID-19 in children. Table 3 presents a summary of their pharmaceutical care recommendations. IFN- α has been recommended clearly by experts for treating SARS-CoV-2 infection in pediatric patients. Being a broad-spectrum antiviral medicine, this drug is used to treat diverse diseases in children, including herpes angina, bronchiolitis, and hand-foot-mouth disease (HFMD). A combination of IFN- α and ribavirin was observed to inhibit viral replication and improve clinical results in a Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infected rhesus macaques.

****Table 3****

IFN- α is however contraindicated in children with abnormal liver function, history of mental illness, aplastic anemia, severe or unstable heart disease, and prohibited in children with creatinine clearance lower than

50 mL/min. Mainly used for the treatment of Human Immunodeficiency Virus (HIV), LPVr has been proposed to treat COVID-19 based on clinical experiences in using this drug to treat SARS-CoV and MERS-CoV, which are close relatives to SARS-CoV-2. Intravenous injection of ribavirin, another broad-spectrum antiviral drug, at a dose of 10 mg/kg (maximum of 500 mg every time) for 2–3 times daily, has also been recommended for treating children with SARS-CoV-2. Aside these drugs, the authors equally proposed the use of chloroquine diphosphate arbidol, also known as umifenovir, to inhibit the replication of the SARS-CoV-2 RNA virus in children.⁵⁶

An Iranian Expert’s Consensus Statement also proposed some antiviral treatments for COVID-19 infected pediatric patients based on their clinical characteristics. Based on their algorithmic approach to treating this special population of patients, the experts recommended the use of four antiviral drugs including oseltamivir, hydroxychloroquine, Kaletra (lopinavir + ritonavir), and ribavirin. These drugs could be used with antibiotics depending on the patient’s condition. In patients with mild pneumonia with risk factor, the scientists recommended the use of oseltamivir in combination with hydroxychloroquine. In patients with mild pneumonia without risk factor, oseltamivir is recommended with or without hydroxychloroquine. Patients with moderate to severe pneumonia were recommended to take oseltamivir in combination with hydroxychloroquine and Kaletra. Ribavirin could also be included for patients under ICU. The authors however noted that Kaletra should not be administered to neonates before gestational age of 42 weeks and postnatal age of at least 14 days.⁵⁷ The recommended dosages of the four different antiviral drugs for varying age groups, as listed by these Iranian medical experts, are shown in Table 4.

Table 4

Table 5

In another article published by Chen et al.⁵⁸ in International Journal of Gynecology & Obstetrics, the authors provided ten key guidelines for handling pregnant women and newborns of mothers with suspected or confirmed SARS-CoV-2 infection. These recommendations are presented in Table 5. The quality and importance attached to the different recommendations were noted to have been adapted from the quality and importance of evidence criteria in the Canadian Task Force on Prevention Health Care. The authors however maintained that there is no exact evidence regarding optimal delivery timing, the safety of vaginal delivery, or whether cesarean delivery prevents vertical transmission at the time of delivery. Hence, the timing and route of delivery should be managed on individual basis depending on obstetrical indications and maternal-fetal status.⁵⁸

7. Conclusions

The comprehensive review conducted in this article reveals that children at all ages are susceptible to SARS-CoV-2 infection. Although the cases in this age group are few across the world, nations such as the US, China, Germany, Italy, and Canada have recorded high number of cases in children 19 years old and below. That notwithstanding, fatality in this population is extremely rare, with almost all the cases succumbing to the disease being reported to have comorbidities. In general, COVID-19 is less severe in children as most of the spectrum of clinical features indicate that pediatric patients only show mild to moderate symptoms, with some patients remaining asymptomatic throughout the duration of illness. Among other symptoms, fever and cough were noted to be the most common among pediatric patients. The epidemiological studies conducted on the infection among children show that most of the transmissions happen in familial cluster situations, with only few cases contracting the disease from other sources. Regarding the treatment of COVID-19 pneumonia in pediatric patients, expert consensus statements suggest that combinations of antiviral drugs such as interferon- α , lopinavir/ritonavir, ribavirin, chloroquine, arbidol, and oseltamivir could be used to treat the infection. Depending on the clinical features of the patient, antibiotics are also proposed to be used in conjunction with these antiviral medicines. The information reviewed on SARS-CoV-2 infection among pregnant women and their neonates recognized that there is no evidence of vertical transmission of the pathogen from mothers to their newborns. Nonetheless, adequate care should be taken to prevent infecting neonates from external sources as they are equally vulnerable to the highly contagious disease.

Conflict of Interest

The authors declare none.

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List of Figures

Figure 1. Daily new cases and deaths¹⁴

Figure 2. Demographic characteristics of COVID-19 cases in US as of April 15, 2020, at 4pm ET (n=465,995)³⁵

List of Tables

Table 1. Number of confirmed cases and deaths in 23 top-ranked nations^{14,15}

Table 2. Distribution of COVID-19 in children around the world³⁸

Table 3. Dosage regimen and precaution of antiviral drugs in children⁵⁶

Table 4. Recommended drug dosages for COVID-19 infected children⁵⁷

Table 5. Expert consensus for managing suspected or confirmed COVID-19 infected pregnant women and their neonates⁵⁸

Table 1. Number of confirmed cases and deaths in 23 top-ranked nations^{14,15}

Number	Country	Cases	Deaths	Fatality Rate, %
1	US	644,089	28,529	4.5
2	Spain	180,659	18,812	10.5
3	Italy	165,155	21,645	13.1
4	France	147,863	17,167	12.8
5	Germany	134,753	3,804	2.8
6	UK	99,489	12,868	13.0
7	China	83,392	3,342	4.0
8	Iran	76,389	4,777	6.3
9	Turkey	69,392	1,518	2.2
10	Belgium	33,573	4,440	13.2
11	Brazil	28,912	1,760	6.1
12	Canada	28,379	1,010	3.6
13	Netherlands	28,253	3,134	11.1
14	Switzerland	26,336	1,239	4.7
15	Russia	24,490	198	0.8
16	Portugal	18,091	599	3.3
17	Austria	14,350	393	2.7
18	Ireland	12,547	444	3.5
19	Israel	12,501	130	1.0
20	India	12,370	422	3.3
21	Sweden	11,927	1,203	10.1
22	Peru	11,475	254	2.2
23	South Korea	10,613	229	2.1

Table 2. Distribution of COVID-19 in children around the world³⁸

Country	Date Recorded	Confirmed Cases in Children by Age, years	Country	Date Recorded	Confirmed Cases in Children by Age, years
Germany	Apr 20	0-5 = 1,115 5-14 = 2,779	South Korea	Apr 19	Under 10 = 138 10-19 = 578
Philippines	Apr 2	0-9 = 8 10-19 = 17	Japan	Apr 19	0-9 = 159 10-19 = 245
Finland	Apr 19	0-9 = 69 10-19 = 191	Australia	Apr 20	Under 10 = 74 10-19 = 195
Romania	Apr 20	0-9 = 226 10-19 = 284	Latvia	Apr 20	0-9 = 17 10-19 = 25
India	Apr 20	0-10 = 62 11-20 = 137	Czech Republic	Apr 20	0-14 = 378 15-24 = 668
Italy	Apr 17	0-18 [?] 2,930	Sweden	Apr 20	0-9 = 74 10-19 = 192
Austria	Apr 17	Under 5 = 74 5-14 = 321 15-24 = 1,355	Iceland	Apr 19	0-5 = 11 6-12 = 13 13-17 = 14

Country	Date Recorded	Confirmed Cases in Children by Age, years	Country	Date Recorded	Confirmed Cases in Children by Age, years
Canada	Apr 19	0-19 [?] 1,700	Denmark	Apr 19	0-9 = 84 10-19 = 215
Switzerland	Apr 16	Hospitalized cases 0-9 = 24 10-19 = 27	Slovenia	Apr 19	0-4 = 6 5-14 = 22 15-24 = 90
Norway	Apr 20	0-9 = 87 10-19 = 311	New Zealand	Apr 20	0-9 = 34 10-19 = 114

Table 3. Dosage regimen and precaution of antiviral drugs in children⁵⁶

Drugs	Age available	Dosage regimen of COVID-19 in children	Precaution/contraindication
IFN- α	Nebulization: using with caution in neonates and infants younger than 2 months	Nebulization: 200,000–400,000 IU/kg or 2–4 μ g/kg in 2 mL sterile water, twice daily for 5–7 days Spray: 1–2 sprays on each nostril and 8–10 sprays on the oropharynx, once every 1–2 h, 8–10 sprays/day for 5–7 days	Contraindication: abnormal liver function; CrCl < 50 mL/min; histories of mental illness, severe or unstable heart disease, or aplastic anemia
LPVr	China: OS [?] 6 months, T [?] 2 years USA: OS [?] 14 days, T [?] 6 months	Based on body weight (kg): 7–15: 12 mg/3 mg/kg/time, twice daily for 1–2 weeks 15–40: 10 mg/2.5 mg/kg/time, twice daily for 1–2 weeks > 40: 400 mg/100 mg/time, twice daily for 1–2 weeks	Contraindication: patients with severe hepatic insufficiency Not recommended for children with jaundice
Ribavirin	China: oral dosage forms [?] 6 years USA and Europe: oral dosage forms [?] 3 years	Intravenous infusion at a dose of 10 mg/kg every time (maximum 500 mg every time), 2–3 times daily	Not recommended: CrCl < 50 mL/min Should be discontinued: SCr > 2 mg/dL Warning: hemolytic anemia
CD	Using with caution	No recommendation	Acute poisoning is usually fatal with a dose of 50 mg/kg

Drugs	Age available	Dosage regimen of COVID-19 in children	Precaution/contraindication
Arbidol	[?] 2 years for influenza in Russia	No recommendation	Use with caution in patients with liver dysfunction

CrCl: creatinine clearance, *SCr*: serum creatinine, *OS*: oral solutions, *T*: tablets

Table 4. Recommended drug dosages for COVID-19 infected children⁵⁷

Oseltamivir doses for at least 5 days

* Preterm infants should consult a Pediatric Infectious Diseases Specialist. * Term infants 0 - 12 month, 3 mg/kg/dose, twice daily

Hydroxychloroquine doses

Infants and children: Intravenous (IV) fluid therapy * Hydroxychloroquine sulfate: 3 - 5 mg/kg/day (max dose 400 mg), twice daily

Kaletra (Lopinavir + Ritonavir) doses for 5 - 14 days, based on physician's judgment

14 days to 12 months: 16 mg/kg/dose or 300 mg/m²/dose (lopinavir component) orally twice a day * 12 months to 18 years: 400 mg/kg/day

Ribavirin (Oral) doses for up to 14 days, depending on patient's response

For children over 3 years old: * < 47 kg: 15 mg/kg/day-BID * 47 - 59: 400 mg-BID

Table 5. Expert consensus for managing suspected or confirmed COVID-19 infected pregnant women and their neonates⁵⁸

No.	Recommendations
1	Medical centers should standardize screening, admission, and management of all pregnant women infected with COVID-19. Management should be coordinated in accordance with local, federal, and international guidelines; the public should be informed about the risks of adverse pregnancy outcomes Quality: Moderate Importance: Critical
2	All pregnant women should be asked whether they have a history of travel to endemic areas or contact with others confirmed to have COVID-19 and should be screened for clinical manifestations of COVID-19 pneumonia Quality: High Importance: Critical
3	Pregnant women with suspected COVID-19 infection should undergo lung imaging examinations (CXR, CT) and diagnostic testing for COVID-19 as soon as possible Quality: High Importance: Critical

No.	Recommendations
4	<p>Pregnant women who have a suspected or confirmed COVID-19 infection should be encouraged to report symptoms immediately. They should be screened promptly by qualified medical personnel and directed to present to the appropriate hospital if clinically required.</p>
5	<p>Hospitals with isolation rooms or negative pressure wards should preferentially admit these patients into those units rather than have the patient triaged and transferred between multiple clinics and facilities Quality: High Importance: Critical</p> <p>For pregnant women with confirmed COVID-19 infection, routine antenatal examination delivery should be carried out in a negative pressure isolation ward whenever possible, and the medical staff who take care of these women should wear protective clothing, N95 masks, goggles, and gloves before contact with the patients Quality: Low Importance: Critical</p>
6	<p>The timing of childbirth should be individualized. Timing should be based on maternal and fetal well-being, gestational age, and other concomitant conditions, not solely because the pregnant patient is infected. The mode of delivery should be based on routine obstetrical indications, allowing vaginal delivery when possible and reserving cesarean delivery for when obstetrically necessary Quality: Low Importance: Important</p>
7	<p>In pregnant women with COVID-19 infection who need a cesarean delivery, it is reasonable to consider regional analgesia. If the maternal respiratory condition appears to be rapidly deteriorating, general endotracheal anesthesia may be safer; multidisciplinary planning with the anesthesiology team is recommended Quality: Very low Importance: Important</p>

No.	Recommendations
8	It is currently uncertain whether there is vertical transmission from mother to fetus, but limited cases have shown no evidence of vertical transmission in patients with COVID-19 infection in late-trimester pregnancy. Neonates should be isolated for at least 14 d. During this period, direct breastfeeding is not recommended. It is recommended that mothers pump milk regularly to ensure lactation. Breastfeeding may not be safe until COVID-19 is ruled out or until both mother and neonate clear the virus. Multidisciplinary team management with neonatologists is recommended for newborns of mothers with COVID-19 pneumonia Quality: Low Importance: Important
9	It is recommended that obstetricians, neonatologists, anesthesiologists, critical care medical specialists, and other medical professionals jointly manage pregnant women with COVID-19 pneumonia and strictly prevent cross-infection. Medical staff caring for these patients must monitor themselves daily for clinical manifestations such as fever and cough. If COVID-19 infection pneumonia occurs, medical staff should also be treated in isolation wards Quality: Low Importance: Important
10	All staff engaged in obstetrics should receive training for COVID-19 infection control Quality: High Importance: Critical



