Received: 21 April 2020 | Revised: 8 December 2020 | Accepted: 19 November 2021

DOI: 10.1111/ijcp.15012

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

NON-SYSTEMATIC REVIEW

Infectious disease

Epidemiology, clinical characteristics and treatment of SARS-CoV-2 infection in children: A narrative review

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Abstract

Severe acute respiratory syndrome coronavirus 2 (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, coronavirus disease 2019 (COVID-19) has been reported to affect children of all ages, including newborns. The symptoms among children have also been identified to be similar to those observed among adults, although paediatric patients have been noted to display a spectrum of clinical features ranging from asymptomatic 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 paediatric 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 paediatric 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.

1 | INTRODUCTION

The ongoing 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]

As a result of the heightening concerns about this cluster of pneumonia-like respiratory ailments with inexplicable causes in Wuhan in late December 2019, the Chinese Center for Disease Control and Prevention (CDC-China) deployed a team on 31 December 2019, 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) shortly thereafter and subsequently called the illness associated with the virus as the COVID-19 on 11 February 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 patients, deaths and case-fatality rates in the top-ranked 23 nations across the world, all of which have over 10,000 patients as of 16 April 2020. Globally, the total number of confirmed patients has surpassed 2 million patients, with ~135,000 deaths.[14,15] The high fatality rates in some countries have resulted in more deaths than in countries where the number of patients is much higher. This could be seen in the case of Belgium. Even though the number of confirmed patients in this country is less than the patients in Germany, China, and Turkey, the fatalities recorded in Belgium is higher than in these nations.

Considering the increasing trends of new patients and deaths globally, 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 and 36 months.[16,17]

During the early days of the outbreak, COVID-19 was predominantly reported among adults of age 15 years and above, with the proportion of patients recorded among paediatric 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 by PRC and was believed to be spurred by the fact that younger children were unable to observe the control and preventive measures instituted, such as wearing face masks. This discovery prompted the health officials and authorities in PRC 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 because of 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 recognised 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 the literature, this article conducts comprehensive reviews of the latest information on the clinical and epidemiological features of SARS-CoV-2 infections in paediatric patients around the world. This article also covers the expert consensus for managing and treating the infection in pregnant women, neonates, and children in general.

Review criteria

- Published articles were searched from 1 April 2020, through 21 April 2020 using 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, paediatric, paediatric patients, children, child, infants, neonates, or newborns.
- 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.

Message for the clinic

- In general, COVID-19 is less severe in children as most of the spectrum of clinical features indicate that paediatric patients only show mild to moderate symptoms.
- Fever and cough were noted to be the most common among paediatric patients, with most transmissions happening in familial cluster situations.
- 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.
- 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.

2 | RESEARCH METHODS

Published articles were searched 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, paediatric, paediatric 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, but are not limited to:

- https://www.statista.com/search/?q=COVID-19
- https://www.cdc.gov/coronavirus
- https://www.worldometers.info/coronavirus/
- https://coronavirus.jhu.edu/.

TABLE 1 Number of confirmed patients and deaths in 23 top-ranked nations[14,15]

Number	Country	Patients	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	3804	2.8
6	UK	99,489	12,868	13.0
7	China	83,392	3342	4.0
8	Iran	76,389	4777	6.3
9	Turkey	69,392	1518	2.2
10	Belgium	33,573	4440	13.2
11	Brazil	28,912	1760	6.1
12	Canada	28,379	1010	3.6
13	Netherlands	28,253	3134	11.1
14	Switzerland	26,336	1239	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	1203	10.1
22	Peru	11,475	254	2.2
23	South Korea	10,613	229	2.1

Articles were searched from 1 April 2020, through 21 April 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 has been discussed comprehensively below.

3 | AETIOLOGY 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 modelling 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

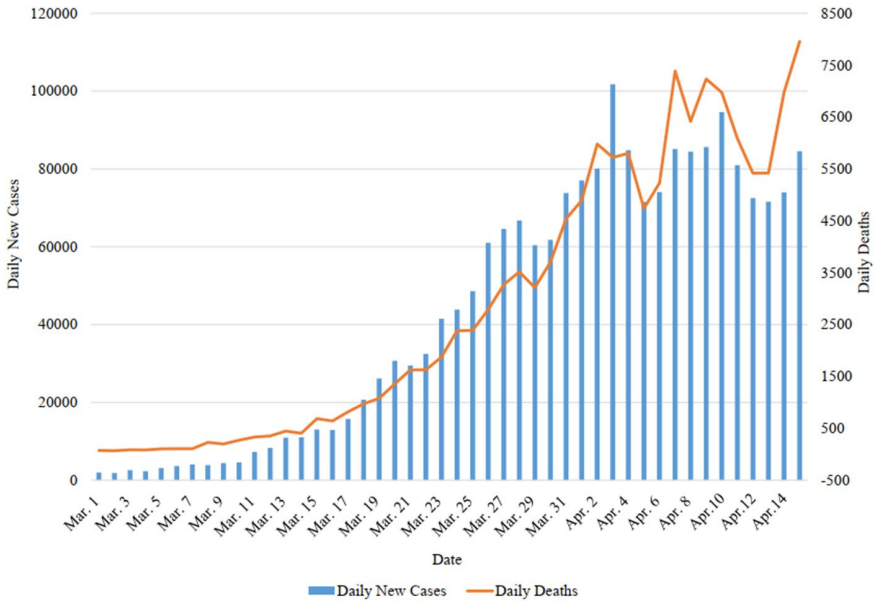

FIGURE 1 Daily new patients and deaths[14]

pangolins could be the possible intermediate hosts for this novel pathogen. Some of 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 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 a 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

Coronavirus disease 2019 (COVID-19) has been declared by the WHO to have attained 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 US Center of Disease Control (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 contrary, 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 per cent 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 regard to the 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, within ~6 feet. 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 these 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 patients reported, 2. Sporadic patients, 3. Clusters of patients, 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 PAEDIATRIC PATIENTS

In a letter published by 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] The 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 less than 18 years is relatively small, as compared with the confirmed cases among adults, the spread of COVID-19 among children has been reported worldwide. Current data from the 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 ~1.75% of the total number of infected patients in the United States. This represents 8171 infected children under 18 years old out of the 465,995 total confirmed patients as of 15 April 2020, at 4:00 PM Eastern Time (ET). This information is shown in Figure 2.

Nonetheless, CDC-US noted that the rates of hospitalisation 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 14 April 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 updated information released by CDC-US on 16 April 2020, the death toll among children ≤14 years old was 3. The recorded death among the age group 15–24 years, however, amounted to 10 as per records on the same date.[37] Apart from the United States and China, Germany, Italy and Canada are among the nations with high records of paediatric patients who are 19 years old and below. This tally could be observed in Table 2, which shows

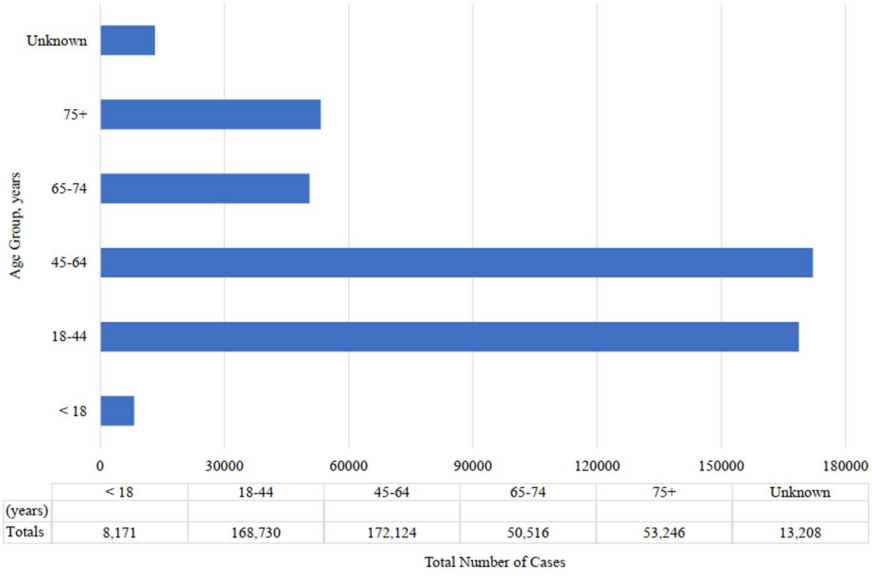

FIGURE 2 Demographic characteristics of COVID-19 patients in the United States as of 15 April 2020, at 4:00 PM ET (n = 465,995)[35]

TABLE 2 Distribution of COVID-19 in children around the world[38]

Country	Date recorded	Confirmed patients in children by age, years	Country	Date recorded	Confirmed patients in children by age, years
Germany	Apr 20	0–5 = 1115 5–14 = 2779	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 ≈ 2930	Sweden	Apr 20	0–9 = 74 10–19 = 192
Austria	Apr 17	Under 5 = 74 5–14 = 321 15–24 = 1355	Iceland	Apr 19	0–5 = 11 6–12 = 13 13–17 = 14
Canada	Apr 19	0–19 = 1700	Denmark	Apr 19	0–9 = 84 10–19 = 215
Switzerland	Apr 16	Hospitalised patients 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

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 21 April 21 2020.

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

In PRC, where the outbreak initially started, initial cases of paediatric patients were reported in a 3 months old female infant in Xiaogan (Hubei province),[39] in a 7 years old boy in Shanghai,[40] in a 10 years old boy in Shenzhen,[41] and later in 9 infants[18] and 3 newborns[42] across different provinces nationwide. Subsequently, a number of literature publications have described the characteristics of SARS-CoV-2 among children in Mainland PRC. One of the largest studies undertaken in PRC on the age distribution of COVID-19 patients involved 72,314 patients, out of which 44,672 patients

were classified as confirmed patients. Children under 9 years old accounted for 0.9% of the 44,672 confirmed patients studied as of 11 February 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, whilst 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 paediatric 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 16 January to 8 February 2020. This research was meant to understand the epidemiology and transmission patterns of SARS-CoV-2 among paediatric patients in China. Out of the 2143 children, 731 (34.1%) were laboratory-confirmed to have COVID-19 whilst 1412 (65.9%) were suspected patients. The median age of the whole group was 7 years, out of which 56.6% were boys. Among the 731 confirmed patients, 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 patients. 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. However, 18 children experienced severe infection of hypoxia, and 3 of these 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. The duration from the onset of illness to diagnoses ranges from 0 to 42 days, whereas 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 study completed by Lu et al.[49] investigated the infection of SARS-CoV-2 in a total of 1391 children under 16 years in the Wuhan Children's Hospital from 28 January through 26 February 2020. Throat or nasopharyngeal swabs were obtained for the detection of 2019-nCoV, and the clinical outcomes were monitored until 8 March 2020. Out of the 1391 children, 12.3% (171) were confirmed to have been infected by the novel virus. One hundred and fifty-four of them were infected through a family cluster transmission, 2 were believed to have had contact with other suspected patients, 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. Thirty-one 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. Twenty-seven 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 diarrhoea (8.8%), fatigue (7.6%), rhinorrhoea (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 courses in contrast to adult patients. Asymptomatic infections were also observed to be common among these paediatric 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 paediatric 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 15 March 2020. The analyses revealed that 75% of the children had a household contact history with an infected person. The majority of the patients (98%), were reported to exhibit clinical spectrum ranging from asymptomatic to moderate patients, 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. Twelve per cent 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 caesarean section, none of the newborns tested positive for COVID-19. Based on these findings, Chang et al[50] concluded that the disease severity in children is generally mild, with no evidence of vertical transmission from infected mothers to neonates.

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 the 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, and the remaining 3 only showed symptoms after delivery. The most common symptoms were observed to be fever and cough, but one patient experienced diarrhoea. Eight of the neonates were male; 6 were born preterm; 2 were observed to be small-for-gestational (SGA) infants whilst 1 was a large-for-gestational (LGA) infant; 6 had a paediatric 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 analysed 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 labour, foetal 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 paediatric patients infected with COVID-19 pneumonia in China. The key findings of this review indicated that children have fewer severe patients, a shorter course of the disease, and slighter clinical symptoms, including lighter lung abnormalities. The chest CT scans of these paediatric patients were observed to be atypical, with lower ground-glass opacity (GGO), more localised GGO extent, and relatively scarce interlobular septal thickening. Conclusively, the authors maintained that most paediatric patients demonstrate mild symptoms, and require 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 paediatric population.[52]

6 | EXPERT CONSENSUS FOR MANAGING PAEDIATRIC PATIENTS AND PREGNANT WOMEN WITH COVID-19

In a letter to the editor of Acta Paediatricia by Dayal,[53] a paediatrician from the Postgraduate Institute of Medical Education and Research (PIMER), Chandigarh, India, the scientist noted that children have been suggested to have relative protection from the ongoing pandemic because of 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. As a result of 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 Paediatrics, the authors reviewed the epidemiology, clinical features, diagnosis, treatment and mortality rates among 2019-nCoV infected paediatric patients.[48] It was recognised that paediatric 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 paediatric patients was also noticed to be mainly through throat swabs with a reverse transcription-polymerase chain reaction. Nonetheless, there were reported patients of the rectal swabs which turned positive for children whose throat swab tested negative. Although the 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 paediatric patients had also tested positive for mycoplasma, respiratory syncytial virus, cytomegalovirus or influenza A/B. With regard to treatment in paediatric patients, the asymptomatic children were usually kept in quarantine without any special treatment, whilst symptomatic patients received supportive care. Children who showed mild symptoms received oxygen therapy, whilst moderate patients were treated with empiric antibiotics. The few severe patients were recorded to have received invasive mechanical ventilation.

In a different article published in The Lancet Infectious Diseases, Kelvin et al[54] observed that all COVID-19 infected paediatric patients were aggressively treated with aerosolised 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 United States was reported by Paul Patek and his colleagues[55] 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 recognised to have fever and fussiness upon admission and was also observed by the mother to have shown a progressively worsening erythema of the right thumb and fourth digit within the previous 3 days prior to hospitalisation. On day 1 of admission, the SARS-CoV-2 polymerase chain reaction (PCR) returned positive for the patient's throat swab. During admission, the rectal temperature reading of the infant was recorded to be 38 °C (100.4 °F), and the chest radiograph was notable for bilateral perihilar streaking without focal consolidation. The patient was admitted to the paediatric ICU because of 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 the need for therapy escalation. Series of blood counts later revealed improvement from 0.3 to 0.7 bil/L in neutrophils, and the patient was discharged on day 4 of hospitalisation with oral antibiotics to treat soft tissue infections. Based on this study, Patek et al.[55] recommended that neonatal SARS-CoV-2 infected patients should be quarantined inwards to limit further transmission whilst 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.

Wang and Zhu[56] recommended five 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 paediatric patients. Being

TABLE 3 Dosage regimen and precaution of antiviral drugs in children[56]

Drugs	Age available	Dosage regimen of COVID-19 in children	Precaution/contraindication
IFN-α	Nebulisation: using with caution in neonates and infants younger than 2 months.	Nebulisation: 200,000–400,000 IU/kg or 2–4 μg/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 anaemia.
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: haemolytic anaemia
CD	Using with caution	No recommendation	Acute poisoning is usually fatal with a dose of 50 mg/kg
Arbidol	≥2 years for influenza in Russia	No recommendation	Use with caution in patients with liver dysfunction

Note: Abbreviations: CrCl, creatinine clearance; OS, oral solutions;SCr, serum creatinine; T, tablets.

TABLE 4 Recommended drug dosages for COVID-19-infected children[57]

Oseltamivir doses for at least 5 days

- Preterm infants should consult a Paediatric Infectious Diseases Specialist
- Term infants 0–12 months, 3 mg/kg/dose, twice daily
- Children ≥12 months by body weight
  - ≤5 kg: 30 mg, twice daily (BID)
  - >15–23 kg: 45 mg, BID
  - >23–40 kg: 60 mg, BID
  - >40 kg: 75 mg, BID
  - Adults 75 mg, BID

Hydroxychloroquine doses

- Infants and children: Intravenous (IV) fluid therapy
- Hydroxychloroquine sulphate: 3–5 mg/kg/day (max dose 400 mg), twice daily for 5 days
- Prolonged QT interval, Torsades de Pointes (TdP) and ventricular arrhythmias were reported with chloroquine, especially in concurrent use with Kaletra
- Risk is greater if chloroquine is administered at high doses
- Use with caution in patients with cardiac disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesemia or bradycardia (<50 bpm)
- Can also be used as a single dose in high-risk patients
- ECG (electrocardiogram) prior to starting chloroquine and after the onset of the drug, cardiac monitoring is recommended

Kaletra (Lopinavir +Ritonavir) doses for 5–14 days, based on the physician's judgement

- 14 days to 12 months: 16 mg/kg/dose or 300 mg/m^2/dose (lopinavir component) orally twice a day
- 12 months to 18 years: Based on body surface area (BSA): 230 mg/m^2/dose (lopinavir component) orally twice a day (maximum dose: lopinavir 400 mg), ritonavir 100 mg/dose, orally twice a day

  Based on weight:
  - Less than 15 kg: 12 mg/kg/dose (lopinavir component) orally twice a day
  - 15–40 kg: 10 mg/kg/dose (lopinavir component) orally twice a day
  - Greater than 40 kg/dose: Lopinavir/ritonavir 2 × 200/50 mg tablet, orally twice a 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
- 60–73: 400 mg in the morning, 600 mg in the evening
- >73: 600 mg-BID

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.

IFN-α is, however, contraindicated in children with abnormal liver function, history of mental illness, aplastic anaemia, 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) 2–3 times daily, has also been recommended for treating children with SARS-CoV-2. Aside from 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 paediatric 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 a risk factor,

TABLE 5 Expert consensus for managing suspected or confirmed COVID-19-infected pregnant women and their neonates[58]

No.	Recommendations
1	Medical centres should standardise 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
4	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. 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
5	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
6	The timing of childbirth should be individualised. Timing should be based on maternal and foetal 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 caesarean delivery for when obstetrically necessary. Quality: Low Importance: Important
7	In pregnant women with COVID-19 infection who need a caesarean delivery, it is reasonable to consider regional analgesia. If the maternal respiratory condition appears to be rapidly deteriorating, general endotracheal anaesthesia may be safer; multidisciplinary planning with the anaesthesiology team is recommended Quality: Very low Importance: Important
8	It is currently uncertain whether there is vertical transmission from mother to foetus, but limited patients 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 days. 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

the scientists recommended the use of oseltamivir in combination with hydroxychloroquine. In patients with mild pneumonia without risk factors, 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 the 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.

In another article published by Chen et al.[58] in the International Journal of Gynecology & Obstetrics, the authors provided 10 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 caesarean delivery prevents vertical transmission at the time of delivery. Hence, the timing and route of delivery should be managed on an individual basis depending on obstetrical indications and maternal-foetal status.[58]

7 | CONCLUSIONS

The comprehensive review conducted in this article reveals that children of all ages are susceptible to SARS-CoV-2 infection. Although the patients in this age group are few across the world, nations such as the United States, China, Germany, Italy and Canada have recorded high numbers of patients in children 19 years old and below. That notwithstanding, the fatality rate among paediatric patients is extremely low, with almost all the patients which succumbed 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 paediatric 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 paediatric patients. The epidemiological studies conducted on the infection among children show that most of the transmissions happen in familial cluster situations, with only a few patients contracting the disease from other sources. Regarding the treatment of COVID-19 pneumonia in paediatric 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 recognised 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.

ACKNOWLEDGMENTS

The first author would like to acknowledge the Research Support Program (RSP) from Curtin University, Australia, which provides funding for this Short-Term Postdoctoral Fellowship. Curtin Malaysia Research Institute (CMRI) is also acknowledged for additional research supports. The contributions of Associate Professor Agus Saptoro (Curtin University Malaysia) during the final editing of this article are equally acknowledged.

DISCLOSURES

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data underlying this article are incorporated into the article.

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How to cite this article: Ayittey FK, Chiwero NB, Dhar BK, Tettey EL, Saptoro A. Epidemiology, clinical characteristics and treatment of SARS-CoV-2 infection in children: A narrative review. *Int J Clin Pract*. 2021;75:e15012. doi:10.1111/ijcp.15012