



# COVID-19 in Children: A Narrative Review

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## Abstract

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**BACKGROUND:** In December 2019, coronavirus (CoV) disease 2019 (COVID-19) was detected in Wuhan, China, which is known as severe acute respiratory syndrome CoV 2 (Severe acute respiratory syndrome [SARS]-CoV-2).

**AIM:** This study attempted a narrative review of the researches about COVID-19 in children.

**METHODS:** We searched all articles between 2000 and April 2020 in PubMed, Scopus, and ScienceDirect related to COVID-19 in children, using the following terms: "COVID-19," "coronavirus," "SARS-CoV-2" in combination with "pediatrics," or "children."

**RESULTS:** The most common method of transmitting the disease to children was through close contact with family members through respiratory droplets. Coinfection is common in pediatric with COVID-19 infection. One of the most important transmission routes is oral feces. The severity of the disease was mild or asymptomatic in most children. The most common clinical symptoms were fever and cough, and gastrointestinal symptoms were more common in children than in adults. Infants and preschoolers had more severe clinical symptoms than older children. The most common radiographic findings from the lungs were bilateral ground-glass opacity. Increased procalcitonin and lactate dehydrogenase should be considered in children. The use of intravenous immunoglobulin, lopinavir/ritonavir, and oseltamivir, along with oxygen therapy, had the greatest effect on improving children's conditions.

**CONCLUSIONS:** The most important way to prevent this disease in children is to follow the health tips of family members. Although the number of children with the disease is low, children are vulnerable to infection. Antiviral medications along with the use of muscle relaxants and oxygen therapy have a great impact on children's condition.

## Introduction

Coronaviruses (CoV) were discovered in 1965 and continued to be studied until the mid-1980s. Corona's history of human viruses began in 1965 when Tyrrell and Bynoe discovered that they could pass a virus called B814. The virus was found in the human embryonic trachea that was obtained from the respiratory tract of an adult with a cold. In the late 1960s, Tyrrell, along with a team of virologists working on human and animal strains of many viruses, found that a group of viruses, including infectious bronchitis virus, mouse hepatitis virus, and transmissible gastroenteritis virus of swine, they are similar in morphology. This new group of viruses was called CoV (the crown because of the crown-like appearance on the surface) and was later formally accepted as the new genus of viruses [1]. CoVs are a large family of viruses and a subset of the coronaviridae belonging to the nidovirales order in the realm riboviria that range from the common cold virus to the more severe causes of diseases such as severe acute respiratory syndrome CoV (severe acute respiratory syndrome [SARS]), middle east respiratory

syndrome (MERS), and CoV disease 2019 (COVID19). CoVs are a group of viruses that cause diseases in mammals and birds. In December 2019, COVID-19 was detected in Wuhan, China. It has a very high transmission capacity and is known as severe acute respiratory syndrome CoV 2 (SARS-CoV-2) [2], [3].

## Search Strategy

This is a narrative review. According to its nature as "narrative," we did not graduate the articles, but we chose the most relevant contributions to the matter. This article is a narrative review study and an attempt to gather information on all aspects of COVID-19 in children. These aspects include virology and genetics, physiopathology, epidemiology, clinical manifestations, diagnosis, and treatment. The search was conducted using five keywords "COVID-19," "coronavirus," "SARS-CoV-2" in combination with "pediatrics," or "children" in PubMed, Scopus, and ScienceDirect among articles between 2000 and April 2020. We focused on

publications post-year 2000, with emphasis on the past 10 years, but we did not exclude commonly referenced, relevant, and influential older publications. The clinical trial, case–control, review, and a meta-analysis study of 20 years; 2000–2020 articles, case series, cohort, and cross-sectional studies were reviewed. We also reviewed the references of each article to include further other studies or reports not identified by the search. We excluded articles considering the expert viewpoints and letters to the editor, which was only one article. A total of 85 articles were obtained that resulted in a decrease of 64 in the selection of English articles and articles on human research.

## Virology

All viruses in the *Nidovirales* order are ribonucleic acid (RNA) viruses which are enveloped, non-segmented positive-sense RNA viruses. These viruses have very large genomes for RNA viruses, and Coronavirinae is the largest known RNA genome and contains approximately 30 kb genomes [2]. The genome of these viruses includes a 5' cap structure with a 3' poly (A) tail, authorizing it to act as messenger RNA (mRNA) to translate replicase polyproteins. The replicase gene that encodes nonstructural proteins, unlike structural and accessory proteins, which make up only about 10 kb of the viral genome, makes up two-thirds of the genome, about 20 kb [4]. The CoV is specified by club-like spikes from its surface [5]. Proteins that contribute to the overall structure of all CoVs are the spike (S), envelope (E), membrane (M), and nucleocapsid (N), all of which are encoded within the 3' end of the viral genome. In the specific case of the SARS CoV, a defined receptor-binding domain on S mediates the attachment of the virus to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) [6]. Some CoVs (specifically the members of beta-CoV subgroup A) also have a shorter spike-like protein called hemagglutinin esterase (HE) [7]. CoVs can be divided into four genera: Alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans [8]. So far seven types of CoV have been found in humans: HCoV-229E, human CoV OC43 (HCoV-OC43), HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV, and the SARS-CoV-2 or novel CoV (2019-nCoV) [9]. SARS-CoV-2 belongs to the CoV strain associated with severe acute respiratory syndrome (SARS-CoV) and from the genus beta-CoV [10]. Recent studies have shown that SARS-CoV-2, known as a novel virus, can share 79.5% of its genetic sequence with SARS-CoV and 96.2% is homologous to bat CoV genome named RaTG13. Still, the synonymous mutation also results in increased T: C transition. This mutation may be due to the loss of RNA 3'-to-5' exonuclease function. 2019-nCoV

shares an ACE2-like entry cell receptor with SARS-CoV-2, which indicates that SARS-CoV-2 may be more infectious to humans than SARS-CoV [11], [12].

## Physiopathology

Epithelial cells are the first cells of the human body to be infected by CoVs. *In vitro* studies show that CoVs spread from a particular part of these polar cells, and this polar spread may be important for the spread of infection *in vivo*. In epithelial cells, CoVs are located between the rough endoplasmic reticulum and the Golgi body. After the replication of viral particles with inverse genetic systems, viruses are transmitted to the plasma membrane through the secretory pathway and released by exocytosis [13]. As mentioned, CoVs can use a number of factors to promote pathogenesis. The CoV has four major structural proteins that are: Spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. S glycoprotein is a Class I fusion protein that mediates binding to the host epithelial cell receptor. M protein enhances membrane curvature and attaches to the nucleocapsid and determines the shape of the virus. E protein facilitates virus assembly and release but has other functions such as ion channel activity in the SARS-CoV E protein for pathogenesis. N protein helps to bind the viral genome to the replicase-transcription complex and wraps the encapsulated genome into the viral particles. HE binds sialic acid to surface glycoproteins with its acetylesterase activity. These activities are thought to increase the entry of S protein into the cell and the virus to enter the mucosa [2], [14]. It is possible that SARS-CoV-2 is entered to host cells through the binding of spike glycoprotein to the enzyme two ACE2, sialic acid receptor, transmembrane 2 serine proteinase (TMPRSS2), and extracellular slow cell matrix metalloproteinase (CD147). This condition which causes endothelial dysfunction is exacerbated by hypoxia and causes thrombosis by increasing blood viscosity as well as the signaling pathway associated with the hypoxia transcription factor [15].

## Epidemiology

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province, China. This virus was referred to as SARS-CoV-2 and the associated disease as COVID-19. As of January 5, 2020, 9692 cases were identified in China, of which 213 died. Most children with COVID-19 have a mild clinical presentation. Few

may progress to the lower respiratory infections [16]. The incidence of this disease in patients under 18 is low (2.4% of total reported) [17]. Since the first report of COVID-19 cases from Wuhan to the end of February 2020, 87,137 people have been diagnosed with the disease [18]. The disease is highly contagious, with the pandemic reported in the 51<sup>st</sup> WHO Status Report on March 11, 2020 [19]. On April 3, the WHO announced that 972,303 people had contracted the disease and 50,321 had died from the disease [20]. In the first major report from China Centers for Disease Control and Prevention, which approved 44,672 COVID-19 cases, only one death occurred in people under 19 and about 80% of deaths in adults over 60 years of age [21]. The first report of United States results among patients with COVID-19 shows that 80% of deaths occur in adults over the age of 65, with the highest percentage of severe consequences among people aged 85 and no casualties observed in people under 19 [22]. In Italy, only 1.1% of reported primary deaths occurred in people <50 years of age, none of whom were children [23].

Current calculations show the incubation period of COVID-19 ranging from 1 to 14 days with an average of 5–6 days. However, some studies suggest that incubation may take up to 24 days, which is higher than the WHO statistics. The number of reproductions ( $R_0$ ) for SARS-CoV-2 is estimated by current studies between 2 and 3, indicating that the epidemic potential of this disease is higher than SARS with  $R_0 = 0.8$  and MERS with  $R_0 = 0.69$  [24], [25], [26]. Recent data suggest that COVID-19 has a mortality rate of between 2.3 and 3 [18], [27]. We need to be careful in calculating the case fatality rate of COVID-19 (currently at a global rate of up to 5%), authenticating that these rates will be lower after setting the denominator to reflect the exact number of individuals who acquired the infection [26].

### **Infection sources**

The CoV reservoir is different for its variants. For SARS, cats were the reservoir of infection, for MERS camels, but COVID-19 is still unclear [11]. Given that human SARS-CoV-2 has a unique retinoic acid receptor recognize motif in S protein, the idea that human SARS-CoV-2 is directly from pangolins is partially rejected [28]. Some recent studies have suggested that pangolins and snakes are likely to host SARS-CoV-2 mediators [29], [30].

### **Transmission route**

It is thought that CoVs are transmitted from person to person by sneezing and coughing through airborne droplets to the nasal mucosa [31], [32]. So far, no evidence has been found that COVID-19 is transmitted through the air. Still, it has shown that respiratory droplets containing the virus, which disperse on surfaces, may be responsible for transmitting the

virus. These surfaces can be as small as the vents [33]. In a study by Seyedi *et al.*, it was suggested that the virus might also be transmitted through the oral-fecal route [34]. Due to the presence of the virus in the feces, there is particular concern about the transmission of fecal-oral feces, especially for infants and children who are not trained in the toilet. Prolonged ejaculation of nasal and fecal secretions has important implications for community development in childcare centers, schools, and homes [35].

In Qiu *et al.*'s study, which conducted on 36 children infected with COVID-19, the transmission route was through close contact with family members (32 [89%]) and a history of exposure to the epidemic zone (12 [%33]). Eight cases (22%) both had exposure [36]. In a study by Chang *et al.*, according to the data collected, most infected children (75%) had a home contact history [37]. In Xia *et al.* study, 13 patients in children (13.20%, 65%) had a history of close contact with family members with COVID-19. Given that most reports of the disease have been passed onto children through close contact at home with family members, it is recommended that family members, especially parents, follow the health tips. Coinfection (8/20, 40%) is common in pediatric with COVID-19 infection [38]. At present, there is no evidence of vertical transmission in infants born to mothers with COVID-19 [37], [39] but some previous reports have also shown that babies are infected in the first few hours after birth [40], [41], [42].

## **Clinical Characteristics**

### **Clinical presentations**

At present, COVID-19 is classified according to symptom severity into four levels: Mild, moderate, severe, and critical. Mild patients have mild symptoms, no symptoms, and no clear radiographic features. Patients with severe symptoms have one of three criteria: (1) Shortness of breath, respiratory rate (RR) >30 times per minute, (2) oxygen saturation <93% in ambient air, and (3) partial pressure of oxygen/fractional inspired oxygen <300 mmHg. Critically, ill patients have one of three criteria: (1) Respiratory failure, (2) septic shock, and (3) multiple organ failure [28]. Most children with COVID-19 infection are asymptomatic or have mild symptoms, no fever, or pneumonia [43], [44]. The range of manifestations described in 171 children (1 day–15 years) infected with SARS-CoV-2 treated at Wuhan Children's Hospital showed that the most common symptoms included cough (in 48.5% of cases), pharyngeal erythema (46.2%), and fever (41.5%). Less common symptoms were present in <10% of children: Diarrhea, fatigue, rhinorrhea, and nasal congestion. It was observed in 28.7% of children with tachypnea and in 2.2% of children with hypoxemia (oxygen saturation



<92% during hospitalization) [45]. In a study of 2214 children suspected of COVID-19, Dong *et al.*, of which 731 children were diagnosed with the disease, 94 (12.9%), 315 (43.1%), and 300 (41%). They were placed in asymptomatic, mild, or moderate cases, respectively, accounting for 97% of the confirmed cases. The proportions of children classified as severe and critical were 2.5% and 0.6%, respectively, significantly lower than those observed in adults with COVID-19. The point of this study was that infants and preschoolers had more severe clinical symptoms than older children [46]. In a study by Chang *et al.*, the severity of the disease was mostly mild to moderate (98%). Only two children (2%) received intensive care. Fever occurred in 59% of patients with cough in 46%. Gastrointestinal symptoms (12%) were not common. About 26% of children are asymptomatic [37]. In a study by Qiu *et al.*, 19 (53%) infected children had a moderate clinical type with pneumonia; 17 (47%) had a mild clinical type, and either was asymptomatic (ten [28%]) or had acute upper respiratory symptoms (seven [19%]). Common symptoms on admission were fever (13 [36%]) and dry cough (seven [19%]). Of those with fever, four (11%) had a body temperature of 38.5°C or higher, and nine (25%) had a body temperature of 37.5–38.5°C [36]. Dong *et al.* study showed the intensity of illness by age, and it disclosed that young children, particularly infants, were vulnerable to 2019-nCoV infection. The content of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age group of <1, 1–5, 6–10, 11–15, and ≥16 years, respectively [46]. In Ludvigsson's study, studies have shown that children have so far accounted for 1–5% of COVID-19 cases, which are often milder than in adults, and that mortality is very rare among them. Diagnostic findings are similar to those of adults, and fever and respiratory symptoms are common, but fewer children appear to have severe pneumonia [39]. In Xia *et al.*'s study, fever (12/20, 60%) and cough (13/20, 65%) were the most common symptoms [38].

In another study, children with COVID-19 usually develop fever, fatigue, and cough at the onset of the disease, which may be accompanied by nasal congestion, runny nose, expectoration, diarrhea, headache, and so on. Most children had low to moderate fever and no fever. Dyspnea of breath, cyanosis, and other symptoms was concomitant with systemic toxic symptoms, such as weakness or restlessness, malnutrition, poor appetite, and less activity after 1 week and may develop to respiratory failure. Septic shock, metabolic acidosis, and irreversible bleeding and coagulation dysfunction may occur in these severe cases. Characteristics and features of rapid RR for the diagnosis of pneumonia in children are 60 times per minute for <2 months; 50 times per minute for 2–12 months, 40 times per minute for 5 years, 30 times/min for >5 years (after dismissing the effects of fever and crying) [47]. According to recent reports, children usually have a good prognosis for the disease

and improve after 1–2 weeks after the onset of mild symptoms. The reason for this can be attributed to the decrease in ACE2 expression in the lung with increasing age. ACE2 plays a role in lung-protective mechanisms [48], but it is not clear why children with COVID-19 have a milder condition. Adults may be more sensitive to conditions such as high blood pressure, diabetes, heart disease, or smoking, which can reduce their ability to prevent infections. Adults may also be more likely to develop an immune overdrive that leads to acute respiratory distress syndrome (ARDS). Mild or asymptomatic presentation in children may be effective in controlling the infection because it can be eliminated with existing monitoring.

### Laboratory examination

Laboratory samples were taken from nasopharyngeal in children with COVID-19 demonstrated lymphopenia, leukopenia, and decreased hepatic and myoglobin enzymes in the first phase. Thrombocytopenia may occur [49]. It has been shown that lactate dehydrogenase and C-reactive protein (CRP) levels increase and decrease in children more than adults, respectively, especially in severe cases [44], [49]. Elevated erythrocyte sedimentation rate and CRP in the second phase, and increased dimerization and severe lymphopenia in children with severe symptoms can be seen. Procalcitonin (PCT) is normal in most cases (PCT<0.5) [16], [47]. In a study by Qiu *et al.*, common abnormal laboratory findings in children were an increase in creatine kinase MB (11 [31%]), decreased lymphocytes (11 [31%]), leukopenia (seven [19%]), and elevated PCT (six [17%]). The variables that were significantly associated with COVID-19 intensity were decreased lymphocytes, elevated body temperature, and high levels of PCT, D-dimer, and creatine kinase MB [36]. In Ludvigsson's study, high inflammatory markers were less common in children, and lymphocytopenia was rare. Newborn babies have developed COVID-19 [39]. In a study by Xia *et al.*, it was suggested that laboratory findings in children should be noted for an increase in PCT (16/20, 80%), which is not common in adults [38].

### Imaging features

Chest X-ray (CXR) can also be used to diagnose the disease. The most common findings for CXR were bilateral ground-glass opacities with or without consolidation in the lung periphery. In children with severe infection, there have been numerous lobar lesions in both lungs [16]. In a study by Li *et al.*, it was reported that children had similar but fewer pulmonary abnormalities in computed tomography (CT) than adults [50]. In a study by Lu *et al.*, the most common radiological finding was bilateral ground-glass opacity, which was observed in one-third of cases [45]. In

another study, the most common radiographic findings were ground-glass opacities (48%) [37]. In the study by Xia *et al.* had a total of six patients with unilateral lung lesions (6/20, 30%), ten people with bilateral lung lesions (10/20, 50%), and four cases with no chest CT abnormality (4/20, 20%). Consolidation with surrounding halo sign was observed in ten patients (10/20, 50%), ground-glass opacities were observed in 12 patients (12/20, 60%), fine mesh shadow was observed in four patients (4/20, 20%), and tiny nodules were observed in three patients (3/20, 15%) [38].

## Diagnosis

For those who are suspected of having COVID-19 disease, we must review the epidemiological and clinical criteria. Epidemiological criteria are based on the presence of the person in the areas infected with the virus and clinical criteria are based on clinical symptoms, laboratory findings, and radiography [47]. To diagnose COVID-19 infection in infants, all of the following criteria must be met: (1) At least one of the clinical symptoms, including unstable body temperature, low activity or poor nutrition, or dyspnea, (2) visualization of abnormality in chest radiography including bilateral ground-glass opacities, (3) diagnosis of infection in the patient's family or companions, and (4) close contact with people who may have or definitively have the disease, patients with pneumonia without any specific cause or close contact with wild animals [41]. Types of samples include upper airway specimens (pharynx, nasal swabs, and nasopharyngeal secretions), inferior airway specimens (sputum, air ducts, and bronchoalveolar lavage fluid), blood, stool, urine, and conjunctival secretions. Sputum and other lower respiratory tract specimens are highly positive for nucleic acids and should preferably be collected from them. Combined testing with respiratory, fecal, blood, and other specimens is useful to improve the diagnostic sensitivity of suspected cases, monitor the effectiveness of treatment, and manage post-discharge isolation measures [35]. Gene sequencing is one way to survey and diagnose COVID-19. RT-PCR, based on the S and N genes, is now used to detect viral RNA and is known as the gold standard [10], [28], [51], [52].

## Treatment

There is no specific antiviral treatment recommended for children with COVID-19, but general treatment strategies for children include bed rest and supportive therapies. Affected children should get

enough calories and water. Preservation of water and electrolytes, homeostasis, and strengthening of psychotherapy in older children should be performed if necessary [43], [39]. In one study of serine protease TMPRSS2, which is required for protein S priming, it was suggested that camostat mesylate as a protease serase inhibitor could prevent COVID-19 from entering the lung cell [53]. Children with COVID-19 who breathe through a ventilator often need sedatives, painkillers, and even muscle relaxants to prevent lung damage caused by the ventilator. Note that, antibiotics and corticosteroids should be avoided except in some cases. Corticosteroids can be used in limited cases, such as the occurrence of ARDS on CXR, septic shock, encephalopathy, and hemophagocytic syndrome. Some studies recommended drug and dose is intravenous methylprednisolone (1–2 mg/kg/day) for only 3–5 days [16], [47]. In the study of Shen ibuprofen was used orally at a dose of 5–10 mg/kg and acetaminophen orally at a dose of 10–15 mg/kg [16]. In Ludvigsson's study, the proposed treatment included oxygen supply, inhalation, nutritional support, and fluid retention, and electrolyte balance [39].

## Therapeutics and drugs

### Antiviral therapy

Numerous studies have been conducted on drugs that affect the treatment of COVID-19 in children, but so far, no antiviral drug has led to definitive treatment. In a study by Chen *et al.* as well as Shen and Yang study, some effective antiviral drugs to improve the condition of children with the disease include interferon- $\alpha$ 2b nebulization 100,000–200,000 IU/kg for mild cases, and 200,000–400,000 IU/kg for severe cases, 2 times/day for 5–7 days [16], [47]. Lopinavir/ritonavir (200 mg/50 mg), the recommended doses: Weight 7–15 kg, 12 mg/3 mg/kg; weight 15–40 kg, 10 mg/2.5 mg/kg; and weight >40 kg, 400 mg/100 mg as an adult each time, twice a day for 1–2 weeks [47], [54]. In Wang *et al.* study, food and drug administration-approved antiviral drugs *in vitro*, especially remdesivir and chloroquine, have been effective in controlling COVID-19 infection *in vitro* [55]. In Tang *et al.* study, medicines for treating infected children include oseltamivir, ribavirin, interferon, Kaletra, and traditional Chinese medicine [56]. In the study by See *et al.*, none of the children needed antiviral therapy [57]. In the study of Liu *et al.*, in six children, ribavirin was used in two patients and oseltamivir in six children [44]. In a study of nine children by Rahimzadeh *et al.*, oseltamivir, lopinavir, and ritonavir were used for treatment, with the role of oseltamivir being very pronounced. However, there was no use of ribavirin [17]. In the study of Shen *et al.*, arbidol and oseltamivir were used [16]. In Qiu *et al.* study, all children received interferon alpha twice daily by aerosolization and 14 (39%) infected children

received twice daily lopinavir-ritonavir syrup [36]. In another study, double-stranded RNA activated caspase oligomerizer (DRACO) and immucillin-A, which inhibit RNA synthesis, have been suggested as antiviral drugs for the treatment of this disease (Table 1) [49].

### Antibody therapy

Intravenous immunoglobulin can be used in severe cases, but the effect should be further investigated. The recommended dose is 1.0 g/kg for 2 days or 400 mg/kg for 5 days [14], [16], [17], [44], [56]. It has been shown that monoclonal antibodies (from human brain plasma, animal, or manufactured plasma) affect glycoprotein S, inhibiting the penetration of CoVs into human cells and reducing mortality in patients infected with SARS-CoV-2 (Table 1) [58].

### Antibacterial therapy

In Rahimzadeh *et al.* study, meropenem, vancomycin, and chloroquine were used as an antibacterial therapy [17]. In the Lu *et al.* study, the combination of sirolimus plus dactinomycin in pediatric treatment has been suggested [40]. In a study by Zimmermann and Curtis, it was noted that the use of chloroquine *in vitro* is effective against SARS-CoV-2, but further studies have been recommended *in vivo* (Table 1) [58].

### Other drugs

In Lu *et al.* study, two-drug combinations (mercaptapurine plus melatonin, and toremifene plus emodin) are the drugs suggested for pediatric treatment [40]. Scutellariae Radix, Armeniaca Semen and Coicis Semen have been suggested in a study examining herbal medicines used to treat COVID-19 in children (Table 1) [59].

### Oxygen therapy

In hypoxia in children, an oxygen mask or nasal catheter should be used immediately to adjust the oxygen concentration. In many studies, using oxygen therapy or mechanical ventilators have been effective in improving patients' well-being [16], [17], [36], [44], [47]. In Lu *et al.* study, infants with ARDS, high-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane lung may be highly recommended (Table 1) [40].

### Plasma therapy

Studies that show that serums from COVID-19 improved patients may be useful for the treatment of COVID-19 infection [40].

## Conclusions

The current prevalence of COVID-19 is widespread in the world and the WHO has identified it as one of the public health concerns. The disease is highly contagious because most children with COVID-19 have close contact with family members, including their parents, increasing public health information and following these tips can have a significant impact on reducing children's susceptibility to the disease. Although the number of children with the disease is low, children are vulnerable to infection. Antiviral medications for the treatment of children Along with the use of pain relievers, muscle relaxants, and oxygen therapy have a great impact on children's condition. The role of serum therapy should also be taken seriously in future COVID-19 treatment.

**Table 1: Different types of treatments of children with COVID-19 according to various studies**

Studies	Antibacterial therapy	Antiviral therapy	Antibody therapy	Oxygen therapy	Plasma therapy	Other medications
Shen <i>et al.</i> [16]	No	Arbidol, oseltamivir, interferon- $\alpha$ nebulization, interferon- $\alpha$ 2b nebulization	Yes (Intravenous immunoglobulin)	Yes	No	Ibuprofen, acetaminophen, intravenous methylprednisolone
Rahimzadeh <i>et al.</i> [17]	Meropenem, vancomycin, chloroquine	Lopinavir, oseltamivir, ritonavir	No	Yes	No	No
Liu <i>et al.</i> [44]	Yes	Ribavirin, oseltamivir	Yes (Intravenous immunoglobulin)	Yes	No	Glucocorticoids
Chen <i>et al.</i> [47]	No	Interferon- $\alpha$ 2b nebulization, lopinavir/ritonavir	Yes (Intravenous immunoglobulin)	Yes	No	Intravenous methylprednisolone
Zimmermann and Curtis [49]	Chloroquine	Lopinavir/ritonavir, DRACO, and immucillin-A	Yes (Intravenous immunoglobulin)	Yes	Yes	No
Tang <i>et al.</i> [56]	No	Ribavirin, oseltamivir, interferon- $\alpha$ 2b nebulization, lopinavir/ritonavir	No	No	No	Traditional Chinese medicines
Lu and Shi [40]	Combination of sirolimus and dactinomycin	No	Yes	Yes	Yes	Mercaptopurine plus melatonin, toremifene plus emodin, and inhaled nitric oxide
Qiu <i>et al.</i> [36]	No	Interferon alpha twice daily by aerosolization and twice-daily lopinavir-ritonavir syrup	No	Yes	No	No
Ang <i>et al.</i> [59]	No	No	No	No	No	Scutellariae Radix, Armeniaca Semen and Coicis Semen

COVID-2019: Coronavirus disease 2019.



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## Author's contributions

AR analyzed the data and were a major contributor in writing the manuscript. HJ and LS searched and collected data. LD and AR designed the review and were responsible for communicating the work. All authors read and approved the final manuscript.

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