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## Covid-19 in Children: A Review of the Manifestations and Treatment Options

Olayinka Rasheed Ibrahim,<sup>1</sup> Yetunde T Olasinde<sup>2</sup>

<sup>1</sup>Department of Paediatrics, Federal Medical Centre, Katsina, Nigeria

<sup>2</sup>Department of Paediatrics, Bowen University, Iwo and Bowen University Teaching Hospital, Ogbomoso, Nigeria

### ABSTRACT

The global spread of severe acute respiratory syndrome coronavirus 2, the causative agent of coronavirus disease 2019 with more than a million cases and more than 50,000 deaths as of 4<sup>th</sup> April 2020 remains a source of concern to humans. The initial impression that children have been less susceptible to the virus when compared with adults has changed recently, with an increasing number of paediatric data becoming more available. The paediatric data have shown a very low mortality rate among the children. The studies in children from China showed the predominance of respiratory and gastrointestinal symptoms; however, few studies outside China reported the absence of gastrointestinal symptoms. Also, the guidelines on the use of specific antiviral and other therapeutic agents in children are limited to few drugs with the use of some of them on compassionate ground. Thus, we have summarized the various clinical manifestations and treatment options of the Covid-19 in childhood since the current outbreak started. This may be of benefits to clinicians and policymakers. Finally, we have also reviewed the various studies on COVID-19 concerning their strength and weakness.

**Keywords:** Children; signs and symptoms; therapeutics.



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#### Address for correspondence:

Dr. Olayinka Rasheed Ibrahim.  
Department of Paediatrics,  
Federal Medical Centre, Katsina,  
Nigeria

Phone: +2348066188403

E-mail: ibroplus@gmail.com

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### INTRODUCTION

The whole world is battling with the containment of the spread of severe acute coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (Covid-19).<sup>[1,2]</sup> The World Health Organization (WHO) declared Covid-19 a pandemic on the 11<sup>th</sup> of March 2020.<sup>[1,3,4]</sup> The situation report by the WHO on the 4<sup>th</sup> April 2020 indicated a total 1,051,635 confirmed cases of the Covid-19 with 56,985 deaths giving a case fatality of 5.4% since the outbreak in Wuhan, China.<sup>[5,6]</sup>

The SARS-CoV-2 believed to have originated from bats (as the virus genome sequence shared about 96% similarity with the genome of bats coronavirus) belongs to a beta group of coronavirus, a group the virus shares with SARS-CoV and Middle East respiratory syndrome coronavirus.<sup>[7–9]</sup> SARS-CoV-2 is a large envelope positive-stranded RNA virus that spreads via respiratory droplets, contact with contaminated surfaces and possibly a faecal-oral route.<sup>[10]</sup> The virus uses angiotensin-converting enzyme 2 receptor found in the respiratory system as the port of entry into the human system by binding to these receptors.<sup>[9]</sup> Hence, the predominance of respiratory symptoms and signs in those infected.<sup>[11]</sup> The diagnosis of Covid-19 in children is usually confirmed by demonstration of SARS-CoV-2 from the nasopharyngeal swab, oropharyngeal swab, bronchoalveolar lavage, saliva, stool samples and blood of infected children through real-time polymerase chain reaction.<sup>[12,13]</sup>

The past few months (from January 2020) have witnessed an increase in the number of publications and sharing of data on Covid-19, which seems to have improved the case management. However, most of the published works focused on the adult population, which gave an initial erroneous belief that children may not be susceptible.<sup>[7]</sup> Indeed, the first two studies describing the epidemiology of Covid-19 from China reported no child among those that were infected.<sup>[14,15]</sup> The follow-up works from China also had a few paediatric data.<sup>[16,17]</sup> Thus, clinical manifestations in children remain mostly unclear. Furthermore, the guidelines on the use of specific antiviral drugs and other therapeutic agents in children are limited to few drugs. Thus, we have carried out a literature search on Covid-19 in childhood since the current outbreak started in the last three months (1<sup>st</sup> January to 2<sup>nd</sup> April 2020) with a view to summarize the various manifestations and treatment options that may benefit clinicians and policymakers. Finally, we have also reviewed the various studies concerning their strengths and weaknesses.

### Manifestations of Covid-19 in Children

The available literature indicates that most children tend to be asymptomatic and are unlikely to spread the disease.<sup>[17,18]</sup> The symptoms in children range from the predominance of respiratory symptoms or gastrointestinal symptoms to non-specific symptoms in the neonatal age group.<sup>[19]</sup> A case series that included two children out of 62 infected people reported the common symptoms as fever (77%), cough (81%), expectoration (56%) myalgia or fatigue (52%), diarrhoea (8%) and haemoptysis (3%).<sup>[17]</sup> Unfortunately, the two children did not have the clinical features described separately. Similarly, Guhan et al. in China described the clinical features of Covid-19 among 1099 patients, including nine children and observed fever in 43.8%, cough in 67.8%, and nausea or vomiting or diarrhoea in 5%.<sup>[16]</sup> Although their study included nine children aged 1-14 years, the lack of separate analysis of children's clinical features makes it difficult to delineate the features in them, bearing in mind that children are not small adults. One of the earliest studies that focused on children in China was the work of Wei et al., that described the clinical features in a group of nine infants aged one to eleven months.<sup>[20]</sup> Although limited by small sample size, their study observed a female preponderance (seven out of nine) in contrast to male preponderance in the adults. The study reported that four out of nine children had a fever, one had a runny nose with cough, and one had a productive cough with sputum. All the nine infants were in contact with family members with confirmed Covid-19, re-enforcing the findings in some studies that children tend to acquire their infection from older family members.<sup>[21]</sup> A

similar study which involved a slightly higher number of children in Hubei reported the clinical features of the fever (60%), cough (65%), diarrhoea (15%), nasal discharge (15%), sore throat (5%), vomiting (10%), tachypnoea (10%) diarrhoea (15%), and nasal discharge (15%).<sup>[22]</sup> While the study observed that 65% of the children had a history of contact with households with Covid-19, 35% with uncertainty in their mode of acquisition was of concern.<sup>[22]</sup> A large cohort in Wuhan that involved 171 children with confirmed Covid-19 showed that fever occurred in 41.5%, cough in 48.5%, pharyngeal erythema in 46.2%. diarrhoea in 8.8%, fatigue in 7.6%, rhinorrhea in 7.6% and vomiting in 6.4%.<sup>[23]</sup> Furthermore, the study found that out of the 171 confirmed cases of Covid-19 in the children, 27(15.8%) were asymptomatic, 33(19.3%) had upper respiratory tract infections, and 111(64.9%) had pneumonia.<sup>[23]</sup> A study in Wuhan that involved eight children who were severe or critically ill showed polypnea, fever and cough.<sup>[24]</sup> The findings probably suggest a higher frequency of respiratory symptoms may point towards a severe form of the disease in the children.

A study with 36 children with Covid-19 disease in Zhejiang province in China showed a fewer frequency of the common symptoms of respiratory tract and fever compared with some of the earlier studies in adults in China.<sup>[25]</sup> The study found that among the 36 children with Covid-19, had a dry cough (19%), dyspnoea/tachypnoea (3%), pharyngeal congestion (3%), sore throat (6%), vomiting/diarrhoea (6%), fever (36%) and headache (8%). The largest cohort in China that involved 2143 paediatric patients with 731 (34.1%) laboratory-confirmed cases did not give a detailed report of the clinical features of Covid-19 in the children.<sup>[26]</sup> However, the study did not find any differences in the gender occurrence of the disease and reported a median age of all patients of seven years. The study found that young children, particularly infants, were vulnerable to SARS-CoV-2 infection.

Studies among children in China indicated a predominance of respiratory symptoms and gastrointestinal tract though of lesser frequency compared with adults.<sup>[22]</sup> A recent case series from Iran that involved nine children studied had fever, cough and tachypnoea.<sup>[26]</sup> None of the children had diarrhoea, and runny nose or vomiting. Also, a case report of a three-months-old infant in Vietnam showed that he presented with rhinorrhoea and nasal congestion, but there was no cough, fever, vomiting, diarrhoea, wheezing, or dyspnoea.<sup>[27]</sup> Another case report of a 10-year-old girl in Korea reported that she had mild pneumonia with mild fever and a small quantity of sputum production and there were no gastrointestinal symptoms.<sup>[28]</sup>

The neonatal manifestations of Covid-19 may occur within hours of birth and maybe delay up to a few days after birth.<sup>[29,30]</sup> The possibility of a vertical route of transmission of Covid-19 is still yet to be fully elucidated.<sup>[29]</sup> The manifestations tend to be non-specific but usually with a positive history of Covid-19 in the mother during pregnancy.<sup>[30]</sup> Wang et al. in Wuhan reported a neonate with Covid-19 disease who presented with vomiting within half an hour after birth and confirmed to be positive for SARS-CoV-2 at 36 hours of life.<sup>[29]</sup> Zeng et al. in China demonstrated in a follow up of 33 new-borns delivered to mothers with Covid-19 disease a low infection rate in the neonates.<sup>[31]</sup> The study found that only three out of 33 Newborns eventually developed Covid-19. The clinical features in the neonates with confirmed Covid-19 have included fever (67%), pneumonia (100%), the shortness of breath (33%), cyanosis (33%) and feeding intolerance (33%). Similarly, a review of 10 neonates born to mothers with Covid-19 pneumonia in China found that the common symptoms in the neonates were shortness of breath, fever, thrombocytopenia accompanied by abnormal liver function, rapid heart rate, vomiting, and pneumothorax.<sup>[32]</sup> Besides, gastrointestinal symptoms, such as feeding intolerance, bloating, refusing milk, and gastric bleeding, occurred in four out of the ten patients. Chest radiography abnormalities also occurred in seven neonates.<sup>[32]</sup>

The laboratory changes in children with mild to moderate illnesses tend to be less in severity compared with adults and the haematological changes showed less of leukopenia and lymphopenia.<sup>[22,25]</sup> However, children with severe to critical illnesses may have cytokines storm and may experience worse laboratory indices.<sup>[24]</sup> The X-ray findings

may be normal in children with mild diseases; however, the computed tomography scan abnormalities were present in most children with Covid-19, including the asymptomatic cases. The chest imaging abnormalities found in children with Covid-19 could be unilateral or bilateral consolidation, ground-glass opacities, fine mess shadow and tiny nodules.<sup>[25]</sup>

The import of the various clinical features in children is the need for the clinicians managing children to be aware that the symptoms may not be typical in children, but instead, there may be mild gastrointestinal or respiratory symptoms, especially where there is an outbreak or presence of a confirmed case of Covid-19 in the family.

### Treatment Options in the Paediatric Age Group

There is little information on drug usage in children with Covid-19 disease because only few publications on Covid-19 in children mentioned drugs therapy. Generally, for mild to moderate disease, the use of supportive management has been advocated.<sup>[33,34]</sup> However, for children with severe to critical illness, some antiviral therapies have been reportedly used, mostly on compassionate ground. Most of the drugs work by blocking a specific stage of viral replication, including the enzymes involved in the viral replications or prevent entry into the host cells or works as an immunomodulator (Table 1).<sup>[35]</sup> One of the most commonly used drugs in children with Covid-19 is the interferon-alpha, which is administered via the inhalational route.<sup>[36]</sup> Interferon-alpha is a broad-spectrum antiviral drug that inhibits the synthesis of viral RNA. Other drugs that are used in the paediatric age group include ribavirin, arbidol, oseltamivir, glucocorticoids, chloroquine and azithromycin.<sup>[35]</sup>

**Table 1.** Summary of the treatment options for the children with Covid-19

Drug	Mechanism of action	Dosage
Interferon-alpha <sup>[24,33]</sup>	Inhibits the synthesis of viral RNA	200.000–400.000 IU/kg or 2–4µg/kg in 2 mL sterile water
Ribavirin <sup>[34]</sup>	Broad-spectrum activity against both RNA and DNA viruses	47 kg: 15mg/kg/day-BID, 47–59 kg: 400 mg-BID
Oseltamivir <sup>[24,26,34]</sup>	A neuraminidase inhibitor	<12 months (3 mg/kg/dose), ≥12 month (≤15 kg: 30 mg, 15-23 kg: 45 mg, >23-40 kg: 60 mg, >40 kg: 75 mg, all given BID)
Lopinavir/ritonavir <sup>[25,26,33,34]</sup>	Protease inhibitor/ the inhibition of SARS main protease enzyme	Lopinavir/Ritonavir: <15 kg: 12 mg/kg/dose (lopinavir component), 15 to 40 kg: 10 mg/kg/dose (lopinavir component), > 40 kg/ 2x200/50 mg tablet
Chloroquine <sup>[34]</sup>	Inhibits a pre-entry step of the viral cycle	3- 5 mg/kg/day (max dose 400 mg)
Corticosteroids <sup>[33]</sup>	Dampen the inflammatory	1-2 mg/kg/day
Immunoglobulins	viral neutralization	
Azithromycin <sup>[27,33,34]</sup>	Immunomodulatory	5-10 mg/Kg

Ribavirin is a guanosine analogue with broad-spectrum activity against both RNA and DNA viruses.<sup>[37]</sup> Oseltamivir is a neuraminidase inhibitor, although the enzyme is not present in SARS-CoV-2, whose effectiveness against the influenza virus prompts its usage in children with Covid-19.<sup>[37]</sup> Hence, more data are needed to evaluate its efficacy in Covid-19. Lopinavir/ritonavir is an anti-retroviral drug that is protease inhibitor and its proposed mechanism of the action in Covid-19 involves the inhibition of Severe Acute Respiratory Syndrome main protease enzyme.<sup>[38]</sup> Chloroquine is an anti-malarial, anti-inflammatory and immunomodulatory with a potential for causing cardiotoxicity in people who take it. Chloroquine inhibits a pre-entry step of the viral cycle by interfering with viral particles binding to their cellular cell surface receptor and possibly interfere with sialic acid biosynthesis (human coronavirus HCoV-O43 and the orthomyxoviruses use sialic acid moieties as receptors).<sup>[39]</sup> Corticosteroids tend to dampen the inflammatory cascades that occur in the severe and critical form of the disease.

The Chinese experts' consensus statement on the diagnosis, treatment and prevention of the 2019 novel coronavirus infection in children recommends interferon-alpha, lopinavir/ritonavir-boosted, immunoglobulins, and glucocorticoid in some cases for children with Covid-19.<sup>[33]</sup> The Iranian experts' consensus on the approach to diagnosis and treatment of Covid-19 in children recommends the use of oseltamivir, hydroxychloroquine, lopinavir/ritonavir and ribavirin.<sup>[34]</sup>

The use of antibiotics is advocated if there is a possibility of bacteria super-imposed infection, or there is laboratory evidence of bacterial infection, such as elevated procalcitonin. The antibiotics use should be broad-spectrum and should be adjusted appropriately once culture results are available.

The eight critically ill children in Wuhan, China, received antiviral treatments (Ribavirin, oseltamivir and interferon), and these appeared well-tolerated.<sup>[24]</sup> Although not a randomised trial, there was no report of the increase in case fatality. In Iran, the nine children admitted with the diagnosis of Covid-19 received a combination of chloroquine and oseltamivir.<sup>[26]</sup> Besides, two of the children received additional lopinavir/ritonavir-boosted without significant adverse events.<sup>[26]</sup> All the children were successfully discharged home.<sup>[26]</sup> The 36 children in Zhejiang province in China received interferon alfa by aerosolisation twice a day, 14 (39%) received lopinavir-ritonavir syrup twice a day, and 6 (17%) needed oxygen inhalation, and all patients cured.<sup>[25]</sup> In the case report in Vietnam, the infant received azithromycin at a dose of 10 mg/kg per day orally for five days and later discharged from the hospital.<sup>[27]</sup>

## CONCLUSION

Children are susceptible to SARS-CoV-2 infection although their disease appeared to have less severity when compared with adults. A large number of children remains asymptomatic; their role in the epidemiological spread of the disease is yet to be proven. The manifestations of Covid-19 in children are predominantly respiratory, with a few presenting with a few of them presenting with gastrointestinal symptoms. There is few antivirals usage in children that include interferon-alpha, oseltamivir, lopinavir/ritonavir and ribavirin. Also, chloroquine and azithromycin are being used in children.

## Disclosures

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**Conflict of Interest:** None declared.

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