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# COVID-19 INCIDENCES AND SYMPTOMS AMONG CHILDREN

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## ABSTRACT

COVID-19 is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to beta-coronaviruses. SARS-CoV-2 has caused a pandemic since it was reported in December 2019 in Wuhan, China. The data about the severity of this viral infection in children increased gradually with the appearance of the new variants, but they are still limited compared to the data of adults. Generally, Children with COVID-19 are asymptomatic or have mild symptoms. The most common symptoms include fever, headache, cough, rhinorrhea, sore throat, myalgias, fatigue and gastrointestinal manifestations.

**KEYWORDS:** Children, IL-6, Pandemic, SARS-COV-2, Variant.

## INTRODUCTION

Coronaviruses (CoVs) belong to a large family of enveloped, positive single-stranded RNA viruses. They have the ability to infect a vast group of organisms, including humans, rodents, birds, chiropters, carnivores and other mammals.[1,2] They are divided into four subfamilies: alpha-, beta-, gamma- and delta-coronavirus.[3] Alpha- and beta-coronaviruses arise from mammals, principally bats, causing more severe and fatal diseases to humans, whereas gamma- and delta-coronaviruses mainly arise from birds and pigs causing asymptomatic or mild disease to humans.[4,5]

CoVs have been known for many years as viral sources responsible for respiratory diseases. Until recently, HCoV-229E, HCoV-OC43, HCoV-HKU1, HCoV-NL63, MERS-COV, SARS-CoV are recognized as human coronaviruses; four of them (HCoV-229E, HCoV-HKU1, HCoV-NL63) caused mild infections. They caught the attention of the entire world again in December 2019, when acute respiratory syndrome coronavirus 2 (SARS-COV-2) was reported in Wuhan, China.[1,3,6-9]

By time, SARS-CoV-2 spread to all continents of the world, which forced WHO to declare the pandemic state on March 11$^{th}$.[4,10] To date, more than 204 million cases have been reported and almost 4.3 million deaths.[11] Pandemic COVID-19 is easily transmissible between humans through respiratory droplets (reproduction number R0: 2–3, which means one sick person could infect three), and may spread through asymptomatic or minimally symptomatic individuals. It has a mean incubation period of five-to-six days and the period of infectivity extend from two days before symptom appear to 15 days after disease onset in severe cases.[12,13] Of note, this virus could be transmitted through fecaloral route mainly in infants and children who are not trained to use toilet.[13]

### The Structure of Sars-COV-2

CoVs possess the largest genomes (26–32 kb) among all RNA virus families.[14] SARS-CoV-2 is one of the Orthocoronavirinae subfamily`s viruses with the "crown-like" spikes on their surfaces.[15] It shares approximately 75–80% of its viral genome with SARS-CoV.[4]

SARS-CoV-2 virion has a spherical form, with some exceptions for pleomorphic and oval ones.[14] It contains four structural proteins (spike (S), membrane (M), envelope (E) and nucleocapsid (N)) and sixteen nonstructural proteins (nsp1−16) (Fig. 1). S protein (S1 and S2 subunits) interacts with angiotensin-converting enzyme 2 (ACE2) receptor on the host cell and mediates the viral entry in it. The most abundant membrane protein in SARS-CoV-2 is M protein, while the smallest one is protein E. Protein M alongside with E protein are responsible for the formation of the virus envelope. As for N protein, it combines with the genome RNA to form the helical nucleocapsid and contribute in the increasing transcription assembly of the virus. On the other hand, the nonstructural proteins usually interfere with the host innate immune response.[4,10,16-21]

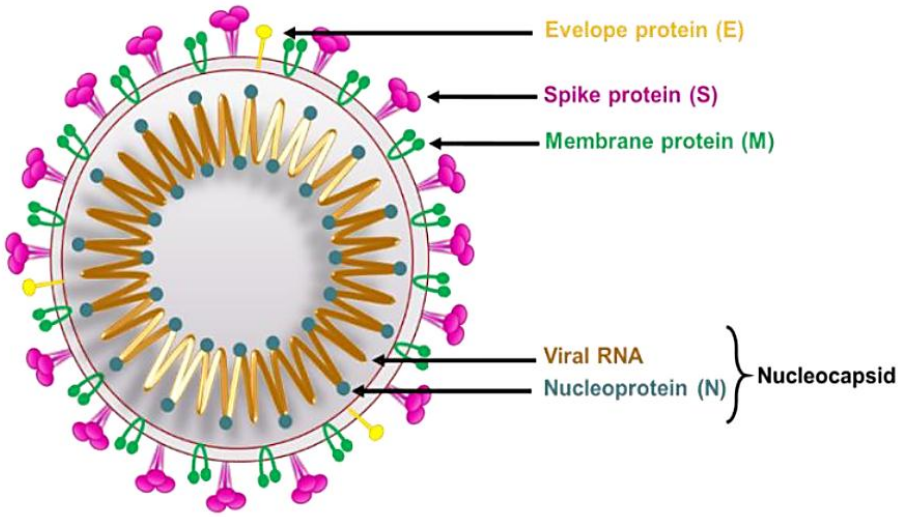


**Fig. 1: SARS-CoV-2 structure.[19]**

**Sars-Cov-2 Replication and Variants**

After cell entry, the viral RNA is released into the host cell cytoplasm and undergoes translation and replication to form progeny genomes and sub-genomic mRNAs. mRNAs translates into S, M, E ,N and other proteins. Then, mediated by endoplasmic reticulum and Golgi apparatus of the host cell, newly comprised proteins assemble and form virus particles. Finally, the virus is transported to the plasma membrane and released out of the host cell through exocytosis.[4,22,23]

Taking into account that SARS-CoV-2 is an RNA virus, so it has high mutation rates, which are related with enhanced virulence and evolvability.[24] In fact, recent studies identified several SARS-CoV-2 variants, which carry deleterious mutations in the S protein, S1 unit in particular, which include the receptor-binding domain (RBD) which bind to ACE2 receptor. It is also the principal target of neutralizing antibodies (Ab) against SARSCoV-2. Thus, S1 is considered a hotspot for mutations that are predicted or known to avoid host immune recognition, diagnostic or therapeutic escape causing the aggravation of pathogenicity and transmissibility of COVID-19, including.[9,20,25-27]

- Variants of concern (VoC): They are associated with an increase in transmissibility or virulence, or a decline in vaccines and/or therapeutics effectiveness:
  - Alpha (B.1.1.7) was first reported in the United Kingdom in Sep. 2020
  - Beta (B.1.351, B.1.351.2, B.1.351.3) was first reported in South Africa in May 2020.
  - Gamma (P1, P1.1, P1.2) was first documented in Brazil in Nov. 2020.
  - Delta (B.1.617.2, AY.1, AY.2, AY.3) was first reported in India in Oct. 2020.
- Variants of Interest (VoI): They are important but don`t meet the criteria for VoC:
  - Eta (B.1.525) was first reported in multiple countries in Dec. 2020
  - Iota (B.1.526) was first reported in the USA in Nov. 2020
  - Kappa (B.1.617.1) was first reported in India in Oct. 2020
  - Lambda (C.37) was first reported in Peru in Dec. 2020

Up to date, Alpha variant was reported in 185 countries, Beta variant was documented in 136 countries, Gamma variant is reported in 81 countries, while Delta variant is reported in 142 countries.[28] The S1 mutations markedly increases the binding affinity to ACE2 while lowers the affinity to neutralizing antibodies.[20,29-31] suggesting a possible explanation for their higher transmissibility and virulence even among children.[20]

In addition to the features of variants mentioned above, Delta variant is twice contagious and has a potentially higher rate of transmission compared to other variants. It is characterized by increased secondary attack rate and hospitalization risk and similar transmissibility between vaccinated and unvaccinated individuals, although the latter pose a greater concern.[28,32,33]

**Sars-Cov-2 Infections Among Children**

The real burden of paediatric SARS-CoV-2 infection is still unclear, but the undoubtable thing is that children can be infected with this virus and transmit it to others. The data about the pathogenesis and severity of this viral infection in children increased in the last year but are still limited compared to the data in adults.[13,27]

Since the pandemic began, children represented 14.3% of total cumulated cases in the USA. Of them, 0.1-1.9% of the cases that needed hospitalization and 0.00- 0.26% of total deaths in the USA.[34]

In general, children have the same risk of SARS-CoV-2 infection as the general population, with the most severe cases among newborns.[7,35-38] However, since the

outbreak of COVID-19, it was reported that children had a milder infection than adults had, in the absence of concomitant diseases, and rarely required hospitalization.[27,38- 40] This could be a result to the loss of immune protection due to aging, causing cellular and molecular dysregulation of the innate immune system. Besides, it was confirmed that the number and function of ACE2 receptors are less in children compared to adults, having less ACE2 receptors in nasal and bronchial epithelial cells.[38,41] This expression increases from the age of 40, with a peak between 60–80.[38]

The majority of children with SARS-CoV-2 will not need any specific therapy, with the exception of those who have a history of medical complexity. Children patients with obesity, developmental delays, neurologic impairment, genetic syndromes (such as trisomy 21), chronic cardiopulmonary disease, or who are immunocompromised may be at increased risk for severe disease.[27]

**Symptoms of Sars-Cov-2 Among Children**

It`s worth noting that signs and symptoms of COVID-19 may overlap markedly with those of other viral infections like influenza.[27] Normally, children infected with SARS-CoV-2 are asymptomatic or have mild symptoms.[13,27,42] The most common symptoms are fever, headache, cough (mostly dry cough, followed by productive cough), myalgias, fatigue, shock, hypoxia, tachypnea, shortness of breath, rhinorrhea, sore throat and gastrointestinal manifestations, such as nausea, vomiting and diarrhea.[13,27,35,43,44] In addition, the radiologic test in infected young patients show a bilateral ground glass opacity.[37]

As for some children with severe cases, they show lower absolute neutrophil count (ANC), higher level of D-dimer and cytokine (particularly IL-6, IL-10, and TNFα), hypoxia, shock and some of them may need a mechanical ventilation.[13,37]

SARS-CoV-2 infection normally causes extrapulmonary manifestations in children, such as multisystem inflammatory syndrome (MIS-C), cardiovascular and hematological manifestations. Hence, it is important to consider the extrapulmonary manifestations a differential diagnosis of the infection of SARS-CoV-2 in paediatric patients. Therefore, to prevent poor prognosis serum levels of creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), inflammatory markers and myocardial enzymes should be used to identify any nonpulmonary manifestations of this viral infection, especially in critically ill children.[13]

## CONCLUSION

Previous COVID-19 infections included high rates of adults, with no clear risk factors or significant incidences among children, as they were limited to mild infections in general. Now, with the emergence of virus variants, especially the delta variant, the COVID-19 prevalence and incidences rates has increased a lot among children, alongside with the increments of symptoms`s severity and deaths rates. Fever, Upper respiratory and gastrointestinal symptoms are the most frequent in children. Despite the fact that children have a milder infection compared to adults, and rarely require hospitalization, some children experience severe cases of COVID -19. They experience a decline in absolute neutrophil count, increments in D-dimer and cytokines, hypoxia, shock and may need a mechanical ventilation.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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