



## COVID-19: UNFOLDING REASONS FOR LOW PREVALENCE AND Milder CLINICAL PRESENTATION OF SARS-COV-2 INFECTION IN CHILDREN

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**ABSTRACT** Coronavirus disease 2019 (COVID-19) first reported in Wuhan, China has rapidly spread globally to become a pandemic. As on 30 August, 2021, it has affected almost 216,303,376 individuals with no available effective drug against it. Though the disease affects individuals of all age groups and both sexes, it is observed to have low prevalence, milder manifestations and better prognosis in children when compared to adult population. A number of asymptomatic cases have also been reported in children, which possess a great threat to community spread of this highly infectious disease. This literature summarizes various hypotheses postulated for unfolding the reasons for low prevalence and milder clinical presentation of COVID-19 in children.

**KEYWORDS :** COVID-19; coronavirus; prevalence; SARS-CoV-2

### INTRODUCTION

In December 2019, in Wuhan China a new disease, Coronavirus disease 2019 (COVID-19) was first identified to be caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1, 2, 3]. In a short span of time, the disease has spread rapidly across almost 221 countries, with 216,303,376 confirmed cases and 4,498,451 deaths, reported by World Health Organisation (WHO) as on 30 August, 2021 [4]. WHO has declared it a pandemic and a Public Health Emergency of International Concern (PHEIC) [3, 5]. Though the disease is found to affect children of all age groups and both sexes, the number of cases reported in children remains remarkably low [6]. Data with respect to COVID-19 in children including epidemiology, risk factors, clinical presentation and clinical outcomes is poorly documented in the literature due to low prevalence of the disease in children. Many explanations have been illustrated, but the exact reason for low prevalence of the disease is still unknown. This review attempts to summarise a comprehensive overview of various theories for unfolding the reasons for low prevalence and milder clinical presentation of COVID-19 among children.

### SARS-CoV-2

SARS-CoV-2 belongs to the family of virus, named Coronaviridae [7]. It is a large pleomorphic spherical enveloped positive sense single stranded RNA (+ssRNA) virus [8]. It is formed by four structural proteins namely Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N) protein. The S, M and E protein together form the viral envelope whereas the N protein integrates the viral genome. This S protein present on the envelope is responsible for binding to the Angiotensin Converting Enzyme-2 (ACE2) cellular receptors of the host cells [9]. In the past, six different strains of coronaviruses have been reported to infect human population namely 229E, NL63, OC43, HKU1, MERS-CoV and SARS-CoV. SARS-CoV-2 is the seventh reported coronavirus to infect human beings [10].

### Epidemiology of previous coronavirus outbreaks in children

In the recent past, two major coronavirus outbreaks have been reported namely Severe Acute Respiratory Syndrome (SARS) and Middle Acute Respiratory Syndrome (MERS) outbreaks. An epidemic of SARS caused by SARS coronavirus (SARS-CoV) occurred in 2003, which affected almost 26 countries and population more than 8,000 was infected [11]. Stockman et al collected data of pediatric cases of SARS from various countries and reported that the clinical course was milder and prognosis seen was better in children as compared to the adult cases. Only 6.9% cases were reported in children aged below 18 years. They also reported nil fatal case in children or adolescent due to SARS [12]. In 2012, Middle Acute Respiratory Syndrome (MERS) outbreak caused by MERS coronavirus (MERS-CoV) was first reported in Saudi Arabia with a case fatality rate of approximately 35% [13]. Azhar et al reported that out of total 552 MERS cases reported in the Kingdom of Saudi Arabia, only 09 (1.6%) cases were reported in children. It was concluded that children younger than 2 years of age have less severe clinical manifestation than adults [14].

### Epidemiology of COVID-19 in children

The low prevalence of disease in children as noted in previous outbreaks of SARS and MERS is a consistent finding in the current

pandemic of COVID-19 also. Report of WHO-China Joint Mission on Coronavirus 2019 (COVID-19) reported a relatively lower attack rate of COVID-19 among individuals younger than 18 years of age accounting to only 2.4% of all the reported cases. The Joint Mission also reported that the relative risk of acquiring the disease in the age group of 0-19 years is rare and only few of this age group developed severe (2.5%) or critical (0.2%) disease [15]. A descriptive analytical study by Zhonghua Liu Xing Bing Xue Za Zhivol reported that out of 44,672 confirmed COVID-19 cases, individuals below 20 years of age were only 2.1% and the number of asymptomatic cases reported were 1.2% [16]. As on March 15, 2020, in Italy among 22,512 confirmed cases of COVID-19, 1.2% cases were among individual aged 0-18 years as reported by Livingston et al [17]. As per Morbidity and Mortality Weekly Report (MMWR) dated 26 March 2020, 4,226 COVID-19 cases were reported in the United States till 16 March 2020, out of which only 5% of cases were observed in 0-19 years of age group. Among persons in 0-19 years of age group, hospitalization was 1%, whereas no Intensive Care Unit admission or death was reported in this age group in United States [18].

### Clinical characteristic of COVID-19 in children

Children are infected by human to human transmission via respiratory droplets from cough and sneezes of infected closed contacts [19]. The incubation period in children is approximately 2-10 days [20]. COVID-19 presents in children with a wide range of clinical manifestations, affecting children of all age groups and both sexes [19]. The most common presentation is with fever (41.5%), cough and pharyngeal erythema, other manifestations being diarrhoea, vomiting, rhinorrhoea and nasal congestion. It was observed that the severity of symptoms and signs present in children was lesser when compared to adults [21] Prognosis in children was also observed to be better than adults. The recovery from COVID-19 in children was reported to be approximately within 1 to 2 weeks after the onset of disease [22].

### Theories for low prevalence and milder clinical presentation in children

The epidemiological variations of COVID-19 observed in children in terms of prevalence, severity of symptoms and signs, and prognosis may be attributed to various host factors, viral exposure and environmental conditions. Firstly, the fear of such a pandemic disease makes caretakers overprotective towards their children. They are taken care at home in safe environment with relatively lesser outdoor activities and travel to expose them to infected persons. Also, the respiratory tract of children is much healthier as compared to adults because of less exposure to air pollutants, absence of active smoking and lesser association with underlying co-morbidities. One of the main reasons for the lower number of reported cases is that a large number of cases remain asymptomatic in children [23]. Xiaoxia Lu reported that around 15.8% of pediatric cases were asymptomatic and without any radiological evidence of pneumonia [21]. Furthermore, maternal antibodies acquired during the first few months of life have been suggested to provide some protective effects against various infections infecting children [24]. Though the presence of maternal antibodies against coronavirus such as SARS-CoV-2 has not been demonstrated

till date. Moreover, one of the basic differences lies in the immune system development from infancy to adulthood both in terms of their composition and functional responsiveness [25, 26]. It is experimentally shown that the initial process in SARS-CoV-2 infection is the binding of Spike protein of virus envelope to the Angiotensin Converting Enzyme-2 (ACE2) cellular receptors of the host cell membrane. Age related difference in the distribution, function and expression of these cellular receptors in children may be one of the possible explanations for the variation in the clinical presentation [27–30]. In addition, it is well known that acute respiratory tract infections are commonly seen during childhood. Most of these infections are caused by viruses such as Rhinovirus, respiratory syncytial virus (RSV), Influenza virus, parainfluenza virus etc [31].

Cross reactivity due to innate immune evasion from exposure to previous RNA viruses may be a possible explanation for protective actions against coronavirus infection [32]. One more study on coronaviruses has shown that children infected with coronaviruses have been found to be co-infected with other viruses is around two third of cases [33]. It is suggested that concurrent presence of other viruses in the respiratory tract will eventually affect the growth of SARS-CoV-2 by direct interactivity and competition between these viruses [34]. Also, in various retrospective studies it has been observed that C-reactive protein levels were moderately elevated in less number of infected children. It can be inferred that these cases had milder immune response which in turn is related to lesser immune damage occurring in children [35].

## DISCUSSION

The reported asymptomatic pediatric cases represent the tip of the iceberg with a much higher expected number of true asymptomatic cases concealed in the population. These undiagnosed asymptomatic cases possess a great threat for human to human transmission of this infectious disease. Hence, we recommend screening of all asymptomatic children, who are in close contacts with confirmed COVID-19 cases, to facilitate early detection of infection and restriction of community spread by these asymptomatic children. Also, it is suggested that low prevalence and milder clinical presentation should not bring reluctance in the precautionary measures and care to be given to children.

Multiple theories have been cited here for the plausible explanations for epidemiological variations in prevalence and clinical manifestation in children. We recommend further studies may be done to find out the exact underlying mechanism which could accord path towards the management of COVID-19 outbreak.

## Abbreviations

COVID-19	Coronavirus disease 2019
MERS-CoV	Middle East Respiratory Syndrome coronavirus
PHEIC	Public Health Emergency of International Concern
SARS-CoV	Sever Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Sever Acute Respiratory Syndrome Coronavirus 2

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## Conflict of interest

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