

REVIEW ARTICLE

Coronaviruses in children: A review of potential mechanisms of childhood protection

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Abstract

Aim: The 2019 coronavirus disease (COVID-19) has spread worldwide and the number of cases continues to rise exponentially. Epidemiologic reports indicate that severity of illness increases with age. However, the reasons behind the relative protection of children and infants are unclear. Whether the rationale is host-related or virus dependent is important to determine since the latter could change with viral mutations. We review factors that could affect the susceptibility of children to the novel coronavirus.

Methods: We search publications indexed on PUBMED.

Results: Descriptions of the pathophysiology of current and previous coronavirus infections suggest several viral targets and immunomodulatory pathways affecting the severity of illness. There is limited evidence to suggest age-variability of viral cell receptors and transmembrane co-factors required for coronavirus entry and replication. However, the ensuing cytokine storm and the effect of higher melatonin in children are age-dependent and could explain decreased disease variability in children.

Conclusion: We believe that current evidence suggests host factors can play a role in disease severity in children and thus may remain protective despite potential virus mutation in the future. However, we recognise and discuss avenues of future research that can further illuminate the reasons children are protected from severe COVID-19 illness.

KEYWORDS

SARS, COVID-19, pediatric, protection, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is currently causing a devastating global pandemic, threatening to overburden health-care facilities worldwide. Initial impressions indicate the likelihood of paediatric infection is significantly less than the age distribution would suggest, and conjecture is that children younger than 10 years

old have some physiologic or inherent resistance. Understanding the apparent paediatric resistance to COVID-19 could predict whether it will change with future SARS-CoV-2 mutations.

The global prevalence of COVID-19 in children remains unknown. The lack of estimates for paediatric COVID-19 diagnosis can be largely attributed to the unprecedented global health challenge that has limited the universal availability of testing to diagnose

Abbreviations: ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; CoV, coronavirus; COVID-19, coronavirus disease of 2019; HCoV, human coronavirus; MERS, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; TMPRSS2, type 2 transmembrane serine protease.

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asymptomatic carriers. The age distribution of COVID-19 cases in South Korea, one of the first countries to implement mass testing, shows that only 8.0% of patients were below 19 years of age, and the main risk factor for severe illness and death was increased age.¹

While it remains to be seen if children are as vulnerable to SARS-CoV-2 infection as adults, the disease appears to be less severe in the paediatric and neonatal age group.^{1,2} We review the clinical presentation of COVID-19 in the paediatric age group and search for possible reasons behind the decreased severity in children and neonates.

2 | BACKGROUND

Coronaviruses (CoVs) are zoonotic positive-strand RNA viruses that are subclassified into four genera: alpha and beta CoVs (most likely from bats and rodents), and delta and gamma CoVs (most likely from avian species).³ Due to their propensity for rapid mutation and recombination, crossover infection from natural hosts to humans is possible. Seven human CoVs (HCoVs) have been identified to date—four of which cause usually mild, upper respiratory symptoms and three responsible for acute respiratory distress syndrome (ARDS) pandemics with high morbidity and mortality.

2.1 | Mild human coronaviruses

In 1965, alpha HCoV-229E and beta HCoV-OC43 were isolated from adults with common colds.⁴ These viruses were considered to play a negligible role in paediatrics since they appeared to cause only mild upper respiratory symptoms in children, unless they infected premature infants or children with chronic underlying disease in whom they could cause severe lower respiratory tract illness.⁴ HCoV-OC43 and HCoV-229E are considered inconsequential pathogens that are endemic globally and are responsible for ~1.5% and ~0.5%, respectively, of respiratory illnesses requiring hospitalisation, generally causing respiratory distress only when there is a coinfection with another virus.⁴

In 2004, HCoV-NL63 was isolated from a seven-month-old infant with bronchiolitis.⁵ In studies of children hospitalised with respiratory tract infections, HCoV-NL63 has been reported to cause between 1.2% and 9.3% of respiratory disease in children, with the variability attributed to severity of illness in the study population, or the collection season of respiratory specimens.⁶

In 2005, a 71-year-old man presented in Hong Kong with pneumonia after returning from Shenzhen, China. After testing negative for influenza and other known coronaviruses at the time, he was eventually diagnosed with a new coronavirus, termed HCoV-HKU1.⁷ In one study of 11,399 hospitalised paediatric patients aged 14 years and younger, HCoV-HKU1 was detected in 38 (0.3%), half of which were co-infected with another pathogen, such as influenza A, *Mycoplasma pneumoniae*, or respiratory syncytial virus.⁸

Key Notes

- We attempt to understand why children are either less susceptible to infection with the 2019 novel coronavirus, or less likely to develop severe disease (or both).
- We found several possible mechanisms to explain the apparent age-based protection.
- Further research is necessary to qualitatively assess each proposed mechanism of childhood protection as this may help in slowing the growing impact of disease.

Prill et al⁹ showed that the four strains of HCoV were detected equally in inpatient children and control (asymptomatic) children and those who had been admitted were more likely to have been co-infected with other viruses. Symptomatic children whose only detectable respiratory virus is a CoV were more likely to be under the age of 3, have underlying heart disease, or other chronic illness.^{10,11} These results suggest that these four HCoVs are endemic in paediatrics.

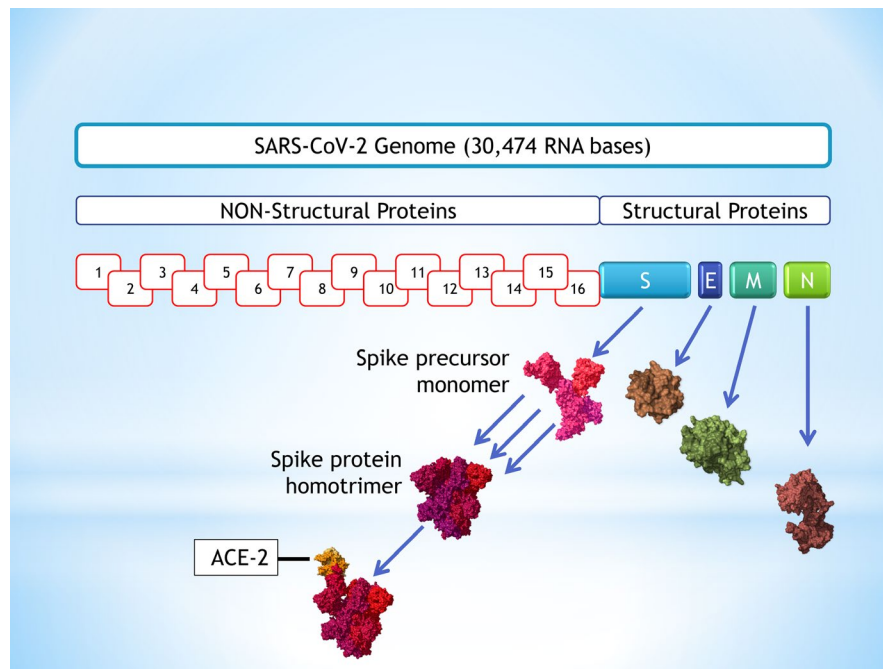
2.2 | Pandemic human coronaviruses

Three other HCoVs have been responsible for three large scale epidemics with alarming morbidity and mortality: severe acute respiratory syndrome coronavirus (SARS-CoV-1), the Middle East respiratory syndrome coronavirus (MERS-CoV) and, most recently, SARS-CoV-2 that is responsible for COVID-19.³

In 2002, SARS-CoV-1 was identified as the causative agent behind a life-threatening pneumonia and respiratory failure outbreak that was—until then—the most pathogenic human coronavirus identified.¹² A highly contagious CoV, it had a high mortality rate in the adult population (9.6 to 16.7%) but children younger than 12 years old ran a less aggressive clinical course and no deaths were reported in children and adolescents.¹³ Whereas adults followed a 'triphasic' clinical course, the majority of paediatric patients appeared to follow a 'biphasic' pattern.¹³ The viral replication phase (phase 1) presents with fever and other systemic symptoms. A few days later, the development of hypoxia and progression of pneumonia (phase 2) are likely mediated by the exaggerated host immunologic reaction. Young children (<12 years) often developed only mild symptoms and for shorter clinical course and recovered without incident, and older patients were more likely to progress to ARDS (phase 3). Swift containment strategies worldwide limited the impact of SARS, and the last reported SARS-CoV-1 infections were laboratory-acquired in 2004 and have not been isolated from humans since.¹⁴

MERS-CoV was first identified in a patient who was hospitalised in Saudi Arabia in June 2012.¹⁵ Over the next 6 years, MERS would be diagnosed in 2182 people from 27 countries, causing 779 deaths (35.7%).¹⁶ However, children under 20 years of age are rarely reported to be positive for MERS-CoV, comprising only 1.1 to 4.2%

FIGURE 1 The RNA genome of SARS-CoV-2 contains 30,474 nucleotides and codes for at least four main structural proteins: envelope (E), membrane, nucleocapsid and spike (S) proteins which facilitate entry into cells. The spike protein precursor is a monomer that consists of S1 and S2 subunits. Three monomers combine to form the complete spike protein, a homotrimer. The S1 subunit binds to ACE-2 receptors, and S2 subunit facilitates membrane fusion



of total reported cases, the majority of whom were household contacts of adult cases.¹⁷ Most paediatric cases were either asymptomatic or had mild respiratory symptoms. Paediatric deaths usually had comorbidities, such as infantile nephrotic syndrome and cystic fibrosis.¹⁷

In late 2019, SARS-CoV-2 was first isolated from a cluster of pneumonia cases in Wuhan City, initiating a pandemic that, as of October 28, 2020 (date of this writing), has been diagnosed in every country in the world, infected more than 44 million of people with a case fatality rate as high as ~2.6% with no signs of slowed spread.¹⁸ By far the largest coronavirus pandemic to date, it has overwhelmed healthcare facilities and, in some cases, patients died from ARDS simply due to a shortage in respiratory support devices.¹⁹ Lacking any effective treatments for COVID-19, the threat to global health security has necessitated the implementation of drastic quarantine measures in multiple countries: the Tokyo 2020 Olympics were delayed for the first time since World War 2; Saudi Arabia has banned international visitors from making the annual religious pilgrimage (Hajj) of over 2 million Muslims for the first time since the 1918 Spanish flu pandemic; and international travel was essentially brought to a halt.²⁰⁻²²

The homological characterisation of the receptor-restricting area of SARS-CoV-2 has been shown to be similar to that of SARS-CoV-1, suggesting that the pathogenesis of COVID-19 infection may be comparable to that of SARS.³ Despite similarities between SARS-CoV-1 and SARS-CoV-2, the latter is causing a pandemic of a much greater proportion mainly due to two reasons. First, asymptomatic transmission occurs with SARS-CoV-2 whereas there have been no reported instances of transmission of SARS-CoV-1 before the onset of symptoms. Second, a much larger proportion of SARS-CoV-2 patients have relatively mild disease, increasing the difficulty of proactive containment.

While it is currently too early to accurately determine, the case fatality rate of COVID-19 is between 0.3% and 11.4%.²³ However, despite the rapid spread of the disease, COVID-19 remains relatively mild in children, with a hospitalisation rate per 100,000 of 8.0 in children younger than 18 years versus 164.5 in adults.²⁴ The reason for the decreased severity of CoV infections in children as compared to adults remains unknown. Unlike other viruses such as influenza, it appears that younger children are more likely to recover from SARS-CoV-1 and -2 and MERS.² It is noteworthy that younger children are often more prone to severe respiratory infections caused by almost all other respiratory viruses.

3 | PATHOGENESIS OF COVID-19

The RNA genome of SARS-CoV-2 contains ~30,000 nucleotides and codes for at least four main structural proteins: envelope (E), membrane, nucleocapsid and spike (S) proteins which facilitate entry into cells (Figure 1).²⁵ CoV E protein is critical in the life cycle, and CoVs lacking E protein could be vaccine candidates.²⁶ The S proteins, or peplomers, act as the ligand for human ACE-2 receptors, infecting cells with a high concentration of ACE-2 receptors, facilitating viral entry and replication within the cytoplasm, similar to the process for SARS-CoV-1. ACE-2 counterbalances the vasoconstriction, aldosterone stimulation and stimulation of myocardium effects of ACE-1. The balance between ACE-1 and ACE-2 levels has been implicated in several diseases including cardiovascular disease, diabetes, hypertension and acute respiratory distress syndrome.²⁷

The ACE-2 protein is expressed in many tissues but primarily on the surface of type 2 alveolar epithelial cells in normal lungs.²⁸ These cells produce surfactant which prevents alveolar collapse

and, hence, are critical to the gas exchange function of the lungs. Overexpression of human ACE-2 has been shown to enhance disease severity in mice infected with SARS-CoV-1, demonstrating that ACE-2-dependant viral entry is critical for disease process.²⁹ ACE-2 receptors are also present, to a lower extent, in nasopharyngeal mucosa, arterial and venous endothelial cells. The localisation of ACE-2 expression can theoretically identify routes of infection for CoVs and may explain the extrapulmonary manifestations of COVID-19.

Upon inhalation of SARS-CoV-2, the S-protein binds to ACE-2 and creates a S-protein-ACE-2 complex (Figure 2A). The affinity with which SARS-CoV-2 binds to ACE-2 is even higher than that of SARS-CoV-1.³⁰ The S-protein-ACE-2 complex is then proteolytically processed by type 2 transmembrane serine protease (TMPRSS2) leading to cleavage of ACE-2 and activation of the spike protein (Figure 2B),²⁷ similar to the mechanism employed by influenza and

human metapneumovirus, thus facilitating viral entry, through endocytosis, into the target cell. It has been suggested that cells in which ACE-2 and TMPRSS2 are simultaneously present are most susceptible to entry by SARS-CoV.³¹

The endocytosed viral particles are actively maintained in an acidic environment, and the endosomal pH plays a key role in SARS-CoV-2 processing and replication. Hydroxychloroquine, an antimalaria drug, has the ability to increase endosomal pH and was postulated as a potential prophylactic medication to prevent SARS-CoV-2 infection. However, recent studies have shown that there is no clinical benefit of hydroxychloroquine in the prevention or treatment of COVID-19.³²

Viral entry initiates the self-replication of the SARS-CoV-2 RNA and the virus spreads, presumably in the mucosal epithelium of the upper respiratory tract initially. Further multiplication occurs in the lower respiratory tract due to the abundance of expression of ACE-2 in type 2 alveolar cells.³³ When the majority of these cells are infected by SARS-CoV-2, a number of pathological processes occur that define ARDS. Pneumocyte destruction, decreased surfactant production, viremia-induced cytokine storm and impaired vascular permeability lead to diffuse alveolar damage and ineffective gas exchange.³⁴ In addition, destruction of ACE-2 causes a dysfunction of the renin-angiotensin system, further exacerbating the pulmonary oedema and hypoxemia.³⁵

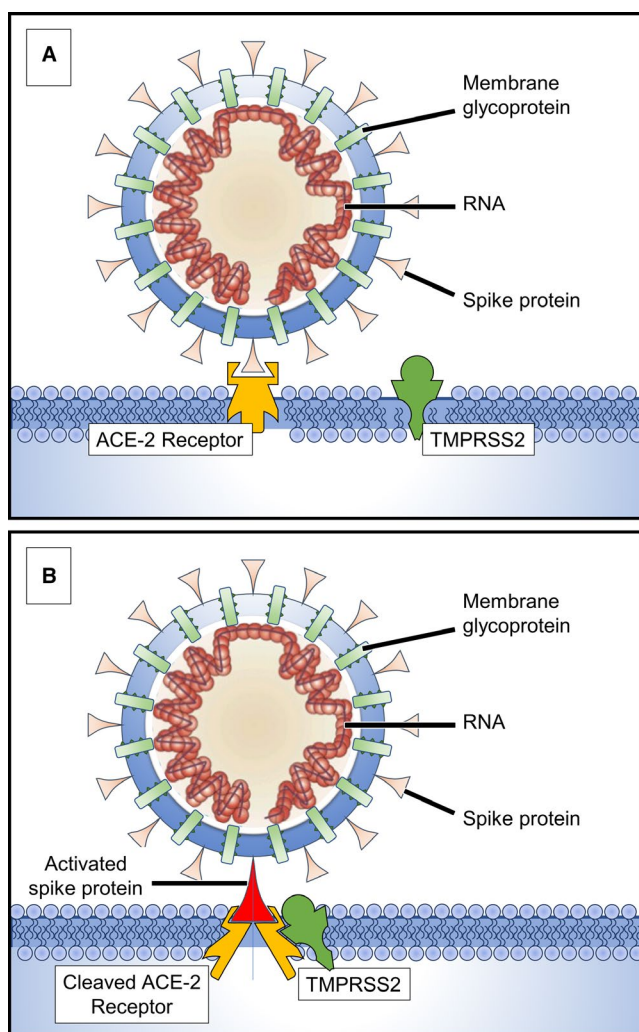


FIGURE 2 The S-protein binds to host ACE-2 receptors and creates a S-protein-ACE-2 complex (2A). The S-protein-ACE-2 complex is then proteolytically processed by type 2 transmembrane protease (TMPRSS2) leading to cleavage of ACE-2 and activation of the spike protein (2B). Images previously published by our group in March 2020³

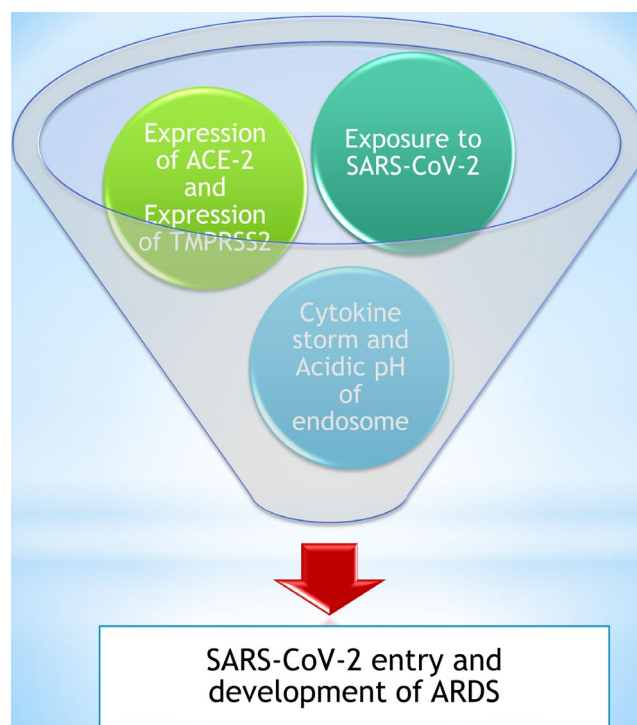


FIGURE 3 Several elements of the pathogenesis of COVID-19 can alter the severity of illness. Exposure to SARS-CoV-2, presence of ACE-2 receptor and TMPRSS2, and activation of cytokine storm. The age-dependence of any of these factors may help explain the decreased clinical severity seen in children with COVID-19

It is apparent that several elements of the pathogenesis of COVID-19 can alter the severity of illness (Figure 3). The age-dependence of any of these factors may help explain the decreased clinical severity seen in children with COVID-19.

4 | POTENTIAL FACTORS PROTECTING CHILDREN

There are many ways by which the paediatric immune system differs from that of adults. A discussion of the general decline of immune function known to be associated with ageing, immunosenescence is beyond the scope of this paper and has been reviewed well by Aiello et al³⁶ Adults are more likely to have co-morbid conditions that weaken their immune system such as diabetes, hypertension or cardiovascular conditions. In addition, adults are more likely to have a hyper-immune response that may cause destruction of healthy cells alongside the infected cells. The known factors necessary for SARS-CoV-2 infection and development of ARDS are reviewed below.

4.1 | Exposure to SARS-CoV-2

Children tend to have fewer outdoor activities, particularly in the winter months. SARS-CoV-1 and SARS-CoV-2 both started in China in the winter seasons of 2002 and 2019, respectively. In addition, children undertake less international travel, further decreasing their exposure risk, hence the fact that most children diagnosed with SARS, MERS and COVID-19 were household contacts of adult cases.^{37,38} If this was the primary factor leading to decreased severity of CoVs in children, then one would expect other winter respiratory diseases to similarly spare children. However, we see quite the opposite for influenza, for example, where the highest burden of hospitalisation is in the 5 to 17-year age group.³⁹ Moreover, as the SARS-CoV-2 pandemic continued into the spring and summer months of 2020, it became apparent that the rate of infection in children is similar to that in adults.³⁸

4.2 | Expression and maturity of ACE-2

ACE-2 is the receptor for SARS-CoV-1, HCoV-NL63 and SARS-CoV-2. Expression of ACE-2 in the airway epithelium is dynamic and correlated with cellular differentiation.³³ The factors modifying the expression of ACE-2 are unknown to date. Studies have shown either no age-dependent differences in ACE-2 levels in alveolar fluid of patients with ARDS,³⁴ or decreased ACE-2 expression with age.^{27,40} In one study assessing ACE-2 receptor expression in tissues of 224 patients with lung cancer, there were no significant disparities in ACE-2 gene expression between racial groups (Asian vs. Caucasian), age groups (older or younger than 60 years old) or gender groups (male vs females).⁴¹ However, smoking and angiotensin-receptor blockers (ARBs) have both been shown to upregulate ACE-2 gene

expression.⁴² Since children are less likely to have either exposure that could at least partially explain the COVID-19 age discrepancy. Further epidemiologic data are required to determine whether nonsmoking adults not taking ARBs are as equally protected from COVID-19.

Muus et al⁴³ analysed the expression of ACE-2 in 164 donors. Although the number of children was small, the authors did note that ACE-2 expression in children was lower than that in adults.⁴³ It would be reasonable to surmise that if ACE-2 expression is reduced in children, then SARS-CoV-2 would be less likely to cause infection at any given viral load.

4.3 | Expression of TMPRSS2

The TMPRSS2 gene, located at human chromosome 21q22.3, encodes an androgen-regulated type II transmembrane serine protease that is expressed in many tissues, including the prostate and lungs.⁴⁴ The physiologic role of TMPRSS2 is currently unknown and TMPRSS2 null mice have no reported abnormalities, but it has been implicated in prostate carcinogenesis.^{45,46} However, studies have shown that the interaction of TMPRSS2 with the S-protein-ACE-2 complex is essential for the spread of several viruses, including coronaviruses.⁴⁷⁻⁴⁹ Since it appears that TMPRSS2 is dispensable for normal physiology, it thus constitutes an attractive antiviral target. Camostat mesylate, a drug approved for pancreatitis in Japan, is a TMPRSS2 inhibitor that blocks SARS-CoV-2 cell entry in vitro.⁴⁹ Clinical trials as a therapeutic agent for COVID-19 are underway.⁵⁰

If ACE-2 receptor expression is not age-dependent, then TMPRSS2 expression may explain the paediatric reduced susceptibility to COVID-19. Cells expressing both ACE-2 and TMPRSS2 appear to rare in children,⁴³ although this study had a limited number of children. However, a PubMed search for 'TMPRSS2' and 'children' or 'age' showed no other relevant results, and this avenue of research may be ripe for exploration.

4.4 | Cytokine storm

In the early stages of CoV infection, neutrophils and activated epithelial and dendritic cells express a cluster of pro-inflammatory cytokines and other proteins such as IL-1 β , IL-2R, IL-6, IL-8, IL-10, TNF α , C-reactive protein, ferritin, D-dimer and procalcitonin.⁵¹ This suggests that the overproduction of cytokines and chemokines ('cytokine storm') is associated with disease severity. Previous animal studies on SARS-CoV-1 showed that peak disease severity coincided with maximal immune dysregulation rather than levels of peak viremia, indicating that the cytokine storm was more responsible for disease severity than the virus itself.⁵² The cytokine storm in neonates is blunted since neonates are known to have reduced neutrophil number and function and have been shown to have lower production of pulmonary inflammatory mediators during ARDS.⁵³ While neonatal neutropenia can predispose

neonates to increased infection, the development of ARDS may be diminished, and there is clinical evidence that mortality from ARDS increases with age.⁵³

4.5 | Melatonin

Melatonin is a hormone produced by the pineal gland that has gained acceptance as a natural sleep aid in adults, but also has a variety of favourable biological and therapeutic activities. Melatonin exerts immunomodulatory effects through various pathways.⁵⁴ It inhibits nuclear factor kappa-B (NF- κ B) activation, which plays a role in the activation of ARDS. It also stimulates nuclear factor erythroid 2-related factor 2 (Nrf2) which plays a role in the protection of various organs during oxidative stress. Melatonin also upregulates superoxide dismutase and downregulates nitric oxide synthase, exerting an anti-oxidative effect that may help attenuate the damage from high-oxygen therapy in those with severe ARDS. In addition, melatonin stimulates the production of natural killer cells and T and B lymphocytes, and animal studies have shown it augments the antigen-presenting function of macrophages. There are no reports yet of the use of melatonin in the treatment of COVID-19, but it has been proposed as a potential adjuvant medication and theoretically show promise.⁵⁴

All mammals, including humans, produce melatonin from serotonin in response to retinal light-dark perception cycles and play an important role in sleep organisation.⁵⁵ Neonates develop photorhythmic production of melatonin by 9 weeks of age, and infants and children with a well-developed sleep cycle have a higher amplitude melatonin production cycle.⁵⁶ In fact, neonatal exposure to irregular light patterns can impair melatonin production in premature infants or infants who required neonatal intensive care, such as those with congenital heart disease, has been associated with poor outcome including sudden infant death syndrome.⁵⁷ The production of melatonin is known to decline with age due to a variety of reasons, and melatonin supplementation has been suggested to boost immune function in the elderly.⁵⁸

Melatonin deficiency is related to suppressed immunocompetence and the increased levels of melatonin in children compared to adults may explain the age discrepancy seen in oxidative stress seen in ARDS.^{59,60}

5 | DISCUSSION

Several explanations have been proposed for why children differ from adults in SARS-CoV-2 infection rate and COVID-19 clinical severity, including potential protective factors in children or exacerbating factors in adults. We provide the first review of the main mechanisms of coronavirus infection and the age variability of various components of SARS-CoV-2 infection and clinical severity. Reduced likelihood of exposure to SARS-CoV-2 was a preliminary theory but developing epidemiologic data suggests that children are

at least as likely as adults to contract the virus. Reduced quantity or maturity of ACE-2 receptors or TMPRSS2 in children has been postulated, but current data are insufficient to support this theory. However, reduced cytokine storms in children and protection afforded by greater levels of immunomodulatory melatonin in the young can help explain the reduced COVID-19 severity.

Based on currently published data, we cannot conclusively determine that the childhood protection seen in COVID-19 is exclusively host dependent and future viral mutations may change the current age distribution of clinical severity. It is possible that children are simply less likely to develop severe coronavirus infection than adults due to biological factors that we described, or others that are yet to be defined. We believe there are multiple avenues to be explored to further explain the protective features of young age.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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