REVIEW ARTICLE

Why COVID-19 is less frequent and severe in children: a narrative review

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Abstract

Background Despite the streaks of severity, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is, in general, less frequent and severe in children than in adults. We searched for causal evidence of this mystery.

Data sources An extensive search strategy was designed to identify papers on coronavirus disease 2019 (COVID-19). We searched Ovid MEDLINE, PubMed, EMBASE databases, and Cochrane library and carried out a review on the causes of this dilemma.

Results Our searches produced 81 relevant articles. The review showed that children accounted for a lower percentage of reported cases, and they also experienced less severe illness courses. Some potential explanations, including the tendency to engage the upper airway, the different expression in both receptors of angiotensin-converting enzyme and renin–angiotensin system, a less vigorous immune response, the lower levels of interleukin (IL)-6, IL-10, myeloperoxidase, and P-selectin and a higher intracellular adhesion molecule-1, a potential protective role of lymphocytes, and also lung infiltrations might have protective roles in the immune system–respiratory tract interactions. Finally, what have shed light on this under representation comes from two studies that revealed high-titer immunoglobulin-G antibodies against respiratory syncytial virus and mycoplasma pneumonia, may carry out cross-protection against SARS-CoV-2 infection, just like what suggested about the vaccines.

Conclusions These results require an in-depth look. Properties of the immune system including a less vigorous adaptive system beside a preliminary potent innate response and a trained immunity alongside a healthier respiratory system, and their interactions, might protect children against SARS-CoV-2 infection. However, further studies are needed to explore other possible causes of this enigma.

Keywords Children · Coronavirus disease 2019 · Severe acute respiratory syndrome-coronavirus 2

Introduction

The novel coronavirus infection spread rapidly, so that the World Health Organization (WHO) declared this epidemic as a pandemic on March 11, 2020 [1]. According to the preliminary data, the overall case fatality rate is about 2.3% and is significantly higher in older patients [2]. Also, hospitalization rate increases with age, given the increased risk of nasal colonization and secondary infections [3, 4]. Limited initial data exist on the burden of coronavirus disease 2019 (COVID-19) in children [5]. Thus far, only a small number of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection have involved children, so that they have accounted for only 1–5% of total patients [2, 6–10]. However, doubt has existed as to whether COVID-19 is really less common in children, and some have believed that children are as likely as adults to become infected, but are less likely to be symptomatic or to develop severe symptoms [11]. Some have attributed this to a lack of real epidemiological studies in children. However, the recent epidemiological studies have shown that although children are more likely to be affected than those

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reported previously, children are still less likely to be affected than adults. In Iceland, researchers screened 6% of country's population and found that children under 10 years of age had a lower incidence of SARS-CoV-2 infection than adults [12]. Although similar epidemiological results, especially those from serological investigations, are emerging in other countries, such as the Netherlands, Australia, and China, researchers in China found that children were less likely to catch the COVID-19 within households from an affected family member [13]. Similarly, of 806 close contacts in 15 schools in Australia, only two students have been identified as secondary cases [14]. However, these are three ways that researchers have gauged whether children are less frequently infected by SARS-CoV-2 infection. The available data also suggest that SARS-CoV-2 is less severe in children. In a report, among 149,082 cases reported in the United States through April 2, 2020, children experienced less severe symptoms. Fever, cough, or shortness of breath were in 73% of children compared to 93% of adults. Also, myalgia, sore throat, headache, and diarrhea were less commonly reported by pediatric patients. Three deaths were noted among the pediatric patients in this analysis. However, children aged less than 1 year accounted for the highest hospitalization [15]. Dong et al. investigated epidemiological characteristics of 2143 suspected pediatric patients. Infection was confirmed in 34% of these patients, whereas 94.1% of them were asymptomatic, or had mild to moderate courses, and 4.4% were asymptomatic [16]. These data were similar to previous findings that children with COVID-19 may not have reported fever, cough, or sore throat as often as adults [17]. Also, Dong et al. revealed that the prevalence of severe and critical disease was 10.6% in children aged less than 1 year, 7.3% in those aged 1–5 years, 4.2% in those aged 6–10 years, 4.1% in those aged 11–15 years, and 3% in those aged 16–17 years [16]. However, some patients experienced severe courses of illness. Severe SARS-CoV-2 infection is characterized by a hyper-proinflammatory response or cytokine storm state that results to acute respiratory distress syndrome (ARDS) and multisystem inflammatory syndrome (MIS). ARDS is characterized by hypoxemic respiratory failure with bilateral lung infiltrates often necessitating invasive respiratory support. In contrast, this situation occurs less frequently in pediatric patients [18, 19]. In a systematic review of 7480 pediatric patients with confirmed COVID-19, only 2% were severe (e.g., dyspnea, central cyanosis, and hypoxemia), and 0.7% were critical (e.g., ARDS, respiratory failure, and shock) [20]. Unexpectedly, there is now a growing cognizance of small reports of pediatric patients with a hyper inflammatory response termed as MIS-C or Kawasaki-like disease [21, 22]. Nevertheless, these two entities are not so common, and the most children experience milder illness. For the first time, we reported two pediatric patients with reactive arthritis who presented with limping following SARS-CoV-2 infection [23]. The data on laboratory markers in children also revealed lower lymphocytopenia

(3–3.5%) than adults (63%) in several studies. Also, children generally had lower increased C-reactive protein and procalcitonin levels. Thus, the overall prognosis of the disease in children is relatively good [15, 17, 24–26]. Unfortunately, due to the high percentage of missing data, a real statistical evaluation and comparison could not be conducted [27]. However, it seems that symptoms in children are both less frequent and less severe. In this review, we comprehensively investigated the most likely causes of this enigmatic topic, although all the actual causes remain unclear.

Search strategies

An extensive search strategy was designed to identify all relevant papers from beginning to August 23, 2020. We used Ovid MEDLINE, PubMed, EMBASE, and Cochrane library and carried out a review on the causes of the lower prevalence and less severity of COVID-19 in pediatric patients. The search strategy was constructed based on searching terms 2019 novel coronavirus, COVID-19, SARS-CoV-2 with using and/or, also the terms of child, pediatric, newborn, infant, adolescence, adult, age, age groups, severity, epidemiology, prevalence, difference, immune system, etiology, reasons in title, abstract, and key words.

The data were screened and extracted independently by two investigators (the first and corresponding authors) and by one highly experienced librarian; then we proceeded to cross check the results. In addition, we increased the references by using an additional snowballing method. After discussion and consensus, the article was written. The inclusion criteria were: (1) children and adolescents < 19 years of age; (2) all scientific papers and letters, about COVID-19; and (3) description of the possible causes of lower prevalence and less severity of diseases. The exclusion criterion is that of ≥ 19 years of age.

The search found 994 papers. After removing the duplications and less relevant papers, 81 scientific papers and letters (5–19, 24–69, 84–103) were included. However, several speculations were derived from pathophysiology of disease and defensive mechanisms. The results were categorized into two main groups of causes (immunological and non-immunological considerations), and each group included the six subsets described below. All causes are involved in the less severity of illness, but some (as *) include the simultaneous and parallel causes of less frequency.

Immunological considerations

Children have a less vigorous immune response

The first results stem from some considerations that children have a less vigorous immune response to the virus than adults

because the cytokine storm is thought to be important in the pathogenesis of severe SARS-CoV-2 infections [28]. These results have been suggested from several studies in which elevated inflammatory markers are less common in children, so they experience milder disease than adults [29].

Children have a more active innate immune response[*]

Of course, this is not in conflict with another hypothesis that children have a more active innate immune response that can be one of the early stages of defense [11]. This can be attributed to the fact that children had more recurrences of recent viral infections [30]. However, if the disease went further extension, a less vigorous immune response may prevent them from the cytokine storm and help to reduce the severity.

The immunosenescence phenomenon[*]

Jeljeli et al. studied the ontogeny of cytokine production in the response of phytohemagglutinin by aging and found a rapid shift from enhanced interleukin (IL)-10 secretion capacity at birth toward balanced IL-10/T helper (Th) 1/Th2/Th17 cytokine levels early in life. This change appears to be an essential precondition to fight pathogens and also avoids overwhelming inflammatory reactions [31]. Schouten et al. discovered an age-dependent difference in levels of biomarkers in the lungs of ARDS patients. Levels of IL-6, IL-10, myeloperoxidase, and P-selectin were higher by aging; whereas intercellular adhesion molecule-1 was higher in neonates [32]. However, immunosenescence also may be explain COVID-19 age variability. It refers to the gradual deterioration of the immune system (especially adaptive type) brought on by natural age advancement [33, 34]. Some studies revealed that with aging, there is a gradual decrease of naïve T cell numbers related to the thymic changes, shrinkage in the collection of T cell clones generated in the thymus, and loss of costimulatory receptor CD28. All these factors may impair the immunological responses with age [35–37]. Shortening of telomeres, especially T cells with cell divisions, might be associated with impaired immune response to new antigens along with increasing the production of proinflammatory cytokines [38, 39]. Zhu et al. revealed that among 667 adolescents, the African and the girls had longer telomeres [40]. These findings along with those of other studies can justify the severity of COVID-19 in males and also by aging [41].

The higher lymphocyte and natural killer cell counts in children[*]

Some have suggested that the constitutional higher percentage of lymphocytes and natural killers (NK) in children may have a defensive role in COVID-19 [42]. Indeed, increasing proinflammatory cytokines associated with neutrophil function with age, associated with severity of ARDS and may explain, to some extent, the age-dependent difference [43]. In adult patients lymphocytopenia (especially CD4 + and CD8 + T lymphocytes) has been associated with increased severity or worse outcomes [44]. Total leukocyte and neutrophil counts and the neutrophil/lymphocyte ratio can be used as follow-up parameters in COVID-19 [45]. At least in three cohorts, the majority of pediatric patients had normal leukocytes and lymphocytopenia accounted for only 3–3.5% of cases [17, 24, 25]. Given the central role of lymphocytes and monocytes in the induction of immune responses, their frequency in peripheral blood might be expected to reflect the state of an individual's immune response to infection [46]. In addition, since T cells are required for controlling exuberant innate immune responses, the absence of a potent antivirus T cell response in aged hosts could lead to an exuberant response and damage, which is not seen in children [47, 48]. Wynn and colleagues found that 2360 genes in neutrophils, 965 in monocytes, and 109 genes in lymphocytes were up- or down-regulated in pediatric septic shock, referring the data that circulatory lymphocytes are not the main leukocytes population with altered gene profiles during septic shock [49].

Children have more trained immunity after previous infections[*]

Other results for a milder disease in children are linked to a trained immunity that represents an immune memory after antigen exposure [26]. Interestingly, what have shed light on this under representation comes from two studies that revealed multiple high-titer antibodies against respiratory syncytial virus (RSV) and *Mycoplasma pneumoniae* (MP) in the blood of children appears to offer cross protection against SARS-CoV-2 infection [50, 51]. Several studies have shown that children are more susceptible than adults to infection by RSV and MP [52–55]. MP has been reported in 10–40% of community-acquired pneumonia cases, and children with 5–15 years age are the most susceptible groups. Although, this was documented in children under 4 years by the report of 2010–2011 of European epidemic data [54]. Also, RSV is more prevalent in infancy. The WHO has reported RSV as a causative pathogen for over 30 million new cases of lower respiratory infection episodes, including acute bronchitis in children less than 5 years age [52]. Older siblings are a greater source of spreading infection than adults because they spend significant time in nurseries and schools [55]. These events can train the immunity of children so that neutralizing cross-reactive antibodies of MP and RSV may be more common in children than in adults. In a retrospective review of all COVID-19 patients treated at Wuhan union

hospital until March 20, 2020, Mi et al. evaluated the correlation between prior exposures to MP and better clinical response in COVID-19 patients. The immunoglobulin G (IgG) positive patients had a higher lymphocyte, monocyte and eosinophil counts and percentages ($P < 0.05$) than COVID-19 patients without MP IgG. In addition, thrombin time and lactate dehydrogenases were better in this group. Furthermore, requirement and use of nasal catheter oxygen mask was significantly lower in COVID-19 patients with MP IgG positivity ($P = 0.029$). Their findings indicate that MP IgG positivity is a potential protective factor for SARS-CoV-2 infection [51]. Orange et al. showed that the intravenous immunoglobulin (IVIG) manufactured from a plasma pool derived from high-titer, anti-RSV plasma donors contains high titers of antibodies to several common respiratory viruses (influenza A, B, human metapneumovirus, parainfluenza 1, 2, and 3, CoVOC42 and V299E); this study found a direct correlation between antibody responder status of donors to RSV and their responder status to other viruses ($P < 0.05$). Although, there are, however, a number of considerations, this could be due to higher humoral immune responders in general or especially against intercellular antigens, to diversity in major histocompatibility complex alleles, and finally to donors that might have experienced a greater diversity of viral infection. This can be generalized to the more infections in children and the potential protection effect that results from these infections [50].

A trained immunity after previous vaccines*

Cao and colleagues emphasized the role of trained immunity as a new immune model that represents a cross protection against various pathogens. It can be activated also by some vaccines, such as Bacille Calmette-Guerin (BCG), by generation of immune memory just like what is seen in MP [26]. Miller and colleagues found that countries without universal policies of BCG vaccination (e.g., USA, Italy) have been affected more severely as compared to countries with universal and long-standing BCG policies. Also, countries that have a late start of universal BCG policy (e.g., Iran in 1984) had a high mortality, consistent with the idea that BCG protects the vaccinated elderly population. In addition, they found that BCG vaccination reduced the number of reported COVID-19 cases in the country. The combination of reduced mortality and morbidity makes BCG vaccine a potential new tool in the fight against COVID-19 [56]. However, this cross-protection has been considered, and what argues against this anecdotal assumption is the higher mortality of COVID-19 in countries where BCG vaccine is compulsory [47]. Myśliwska et al. investigated the relationship between NK activity in the vaccinated population and specific immune protection against influenza virus. They concluded that NK cells activation, which was still significantly

elevated after 1 month of vaccination, may allow protection against influenza and other respiratory viral infections [57]. Indirect epidemiological analyses also have suggested a protective role of the Measles, Mumps, and Rubella vaccine against COVID-19 [58]. Because the majority of vaccinated individuals had not protective IgG titer against measles after 10 years, Hanker et al. hypothesized that age-dependent decline in immunogenicity against measles vaccine could be an explanation for the higher occurrence of COVID-19 in adults [59].

Non-immunological considerations*

There are several issues at this setting. The results show at least six other considerations including some constitutional and behavioral reasons: (1) available data suggest that children may have more upper respiratory tract involvement than the lower. Thereafter, viral interference in young children leads to a lower viral load [16]. However, several speculations have emerged at this setting. Young children generally, have a healthier respiratory machinery due to their lower exposure to harmful environmental factors. In addition, children have fewer underlying chronic diseases, than what seen in adults [11]; (2) possible reasons for the disparity in severity between adults and children may be related to the difference in distribution, maturation, and functioning of receptors of renin angiotensin system (RAS), angiotensin-converting enzyme 2 (ACE-2), and altered inflammatory response to virus [60]. Zhu et al. have looked for reasons of this disparity in severity [61]. ACE-2 is the receptor of viral endocytosis and also alters the RAS activity from proinflammatory to anti-inflammatory response [62]. The ACE levels may be altered by several underlying diseases [63] and by age [64] in a murine model, although Schouten and colleagues found that there is no marked difference in ACE and ACE-2 among age groups [32]. However, this speculation should be investigated; (3) Xie et al. believe that children are less likely to be exposed to the virus. This may be due to fewer outdoor activities and to less international travel. Also, Xie et al. considered an under-diagnosis of children that might have resulted from their milder symptoms and therefore yielded fewer laboratory tests [27]; (4) in Attili and colleague's investigation, age-stratified odds ratios showed that the nasal carriage was higher in adult rabbits [65]. This result suggested that the presence of the respiratory nasal bacterial colonization might have more impact in the adult population [49]. In contrast, it is possible that the presence of other viruses in the respiratory tract of young children limits the SARS-CoV-2 development by direct virus–virus interactions [66]. This hypothesis stems from the greater frequency of viral infection in children and also provides a link between the viral load and COVID-19 severity [52–55, 67];

(5) in total, some results suggest that children have specific mechanisms that regulate the interaction between their immunological and respiratory systems, which could be contributing to milder disease. As a result, lymphocytes have participated in the inducible bronchus associated lymphoid structure after that respiratory insult has happened [68]; (6) it was suggested that maturational changes in the axonal transport system may explain the relative resistance to immature mice to poliovirus induced paralysis [69]. This can be generalized to the issue as a complementary reason.

Some exceptions and especial issues

Neonatal period and vertical transmission

Knowledge about neonatal outcomes of SARS-CoV-2 infection is relatively limited. Immaturity of both innate and adaptive immune systems make this group highly vulnerable to infection [70]. Interestingly, the majority of neonates born to mother with COVID-19 were not infected, and to date few reports have suggested that neonates have been affected by COVID-19. The possible reasons might be related to surgical delivery and to rapid separation of neonate [71]. Levy found that neonatal antigen presenting cells and plasmacytoid dendritic cells have impaired production of interferon-γ and present a bias against the production of Th1 cytokines [72]. However, the levels of IL-6, IL-10, myeloperoxidase, and P-selectin are higher by aging, whereas intercellular adhesion molecule-1 is higher in neonates [32]. Therefore, unlike the infants under 1 year that are at higher risk of infection and hospitalization (17.6% of pediatric cases and 10.6% of critical cases) [16], neonates are less likely to be infected. In contrast, two known ACE-2 and transmembrane protease serine-2 receptors are widely spread in specific cell types of maternal–fetal interface and might be vulnerable to the neonate affecting by SARS-CoV-2 infection. However, on March 2020, the first case report of possible vertical transmission of SARS-CoV-2 infection was published [73]. Dong et al. speculated the possibility of maternal fetal transmission of virus by demonstrating a higher IgM level and abnormal cytokines 2 hours after birth [74]. However, two independent manuscripts described elevated SARS-CoV-2 specific IgM and IgG antibodies in the blood of newborns of affected mothers. To date, while maternal infections were observed in the late phase of pregnancy, there may not have been sufficient time for the generation of antibodies. Thus, serological investigation for the diagnosis of neonate is still controversial. Nevertheless, increased level of IgG could be explained by trans-placental transferring from infected mother, while IgM strongly indicates a self-immune response of newborns [74, 75]. Thus, the elevated IgM might suggest that neonate was infected in utero. In

any case, the possibility of vertical transmission has been raised. After birth, the neonates might be involved. Zeng et al. reported a series of 33 infants from mothers with COVID-19, while three of whom were symptomatic, with a radiological picture of pneumonia. The 31 weeks neonate developed coagulopathy, associated with sepsis. None of the newborns died. The clinical features of infected newborns might be nonspecific and include acute respiratory distress syndrome, temperature instability, gastrointestinal, and cardiovascular dysfunction [76]. However, the age-dependent pattern of immune reactions and other physiological elements may influence the response to SARS-CoV-2 in the neonatal subpopulation [73].

Some exceptions of severity

Although COVID-19 in children appears largely to present with mild features, a very small percentage of children with SARS-CoV-2 infection experience MIS-C weeks later. However, the MIS-C cases usually do not primarily affect the lungs [77].

Multisystem inflammatory syndrome and Kawasaki-like disease

The recent reports from European countries and the US followed by growing universal reports support the emergence of this novel phenomenon [18]. The clinical presentations of this entity are variable and include persistent fever, severe illness, and involvement of two or more organ systems, in combination with laboratory evidence of both inflammation and SARS-CoV-2 infection. However, some presentations of MIS-C resemble Kawasaki disease (KD), toxic shock syndrome, and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome [18, 19]. Of the 191 potential cases reported across 191 hospitals in New York State, 95 patients were classified as confirmed MIS-C. The peak in the number of MIS-C cases followed the peak in the number of cases of laboratory-confirmed SARS-CoV-2 infection by 31 days. The researchers stated that based on molecular and serological results, MIS-C is probably a post-infectious, inflammatory process related to COVID-19 [78]. Also, because the majority of patients have had positive serological results for SARS-CoV-2, with a lesser number of positive RT-PCR tests, this condition may be more a postinfection entity rather than one related to acute early infection state. This hypothesis seems to have emerged for two reasons. First, MIS-C cases lagged in time compared with the peak of SARS-CoV-2 infection. Second, children who were involved in MIS-C, more often have IgG than positive molecular tests. However, MIS-C is a delayed immunological response associated with inflammation characterized by elevated levels of proinflammatory cytokines

including IL-6, IL-1β, IL-17, TNF-α, and granulocyte colony-stimulating factor. As a hypothesis, because the younger patients have increased number of naïve T cells in different sites to respond to new pathogens [43], this may prevent severe respiratory disease in children. Thus, a low-level, persistent infection in other sites may accumulate over time in some children, resulting in MIS-C [19].

One compelling alternative hypothesis for this entity stems from the ability of coronaviruses to block type I and III of interferon responses, that can result from delayed hyper-inflammatory response in whom that have a high viral load or cannot to control the infection [79, 80].

A mapping systemic inflammation and antibody (Ab) responses in MIS-C was conducted. They documented that all MIS-C patients had IgG against SARS-CoV-2 infection. They identified elevated signatures of inflammation (IL-18, IL-6), lymphocytic and myeloid chemotaxis and activation (CCL3, CCL4, and CUB domain-containing protein-1), and mucosal immune dysregulation (IL-17A, CCL20, CCL28). Also, a reduction in m-Dendritic cells, NK cells, and T cells in blood were seen, suggesting extravasation to affected tissues. Also, some disease-associated autoantibodies (anti-La) were seen. These results suggest that autoreactivity secondary to SARS-CoV-2 infection and the inflammatory innate immune response may be crucial to the pathogenesis of MIS-C [81]. Interestingly, Diorio et al. based on the clinical phenotype, hypothesized that children with MIS-C are presenting with a syndrome that is distinct from both KD and severe COVID-19 infection. The researchers found that the patients with MIS-C had elevated levels of TNF-α and IL-10, whereas patients with severe or mild COVID-19 had no or minimally elevated levels of these cytokines. This profile for MIS-C is distinct from what happens in KD, which is associated with mild elevations of other cytokines (IL-1, IL-2, and IL-6) and not IL-10. TNF-α appears to play key role in the pathogenesis of both MIS-C and KD. Viral cycle thresholds (Cts) and burr cells on blood smears also differentiated between patients with severe COVID-19 and MIS-C. The high Cts associated with MIS-C support a postinfectious etiology phenomenon that has previously been postulated but not demonstrated [18, 82]. However, children with MIS-C have no higher IL-10 level, and this may be due to their higher lymphocyte counts hypothetically. In addition, they showed distinct Ab responses as compared to adults with severe COVID-19 causing ARDS, and to those who recovered from mild disease. Patients with MIS-C, often generate IgG Abs specific for spike (S) protein, while adults with COVID-19 showed anti-S, IgM, and IgA Abs, as well as anti-N IgG Abs. Moreover, MIS-C patients had reduced neutralizing activity compared COVID-19 cohorts, indicating a reduced protective serological response [19]. These results suggest a distinct infection course and immune response in children and adults with severe disease.

Children appear to have a less severe pulmonary manifestation due to all previous reasons, especially a lower gene expression of the ACE-2 receptor. In contrast, adults with severe respiratory failure syndrome due to SARS-CoV-2 infection, who typically deteriorate near one week later of illness onset, have a dysregulation of immune system as opposed to direct cellular injury from viral infection. The immune dysregulation in adults that experienced respiratory distress is characterized by lymphopenia and a sustained production of proinflammatory cytokines, such as TNF-α and IL-6 [83], giving the basis of immunomodulatory therapies like IL-6 blockade at this situation. Although, some suggest more conservative treatments, such as IVIG or even corticosteroids for MIS-C cases, empirical treatment with immunomodulators, such as anakinra or tocilizumab, as a substituted agent in refractory cases are promising [75, 81].

Acute respiratory distress syndrome as another severe presentation

ARDS is the most severe manifestation of COVID-19 in adults. The survival rate of COVID-19 patients with ARDS who are admitted to an intensive care unit (ICU) is approximately 25% [18]. In contrast, this situation is uncommon among pediatric patients and is called PARDS [18, 19].

Why some children experience more severe illness?

The reasons that children may experience a severe course have not yet been elucidated. Here, we summarize some possible causes of this discrepancy.

Underlying conditions

There are some suggestions that several conditions increase the risk of severe disease in children and include hospitalization, mechanical ventilation, congenital heart disease, neurologic, genetic and metabolic conditions [84–86]. Other conditions are related to all ages and include: diabetes mellitus I and II, immunocompromised due to solid organ transplant and other conditions, cerebrovascular accidents, chronic pulmonary disease (e.g., cystic fibrosis, moderate to severe asthma), chronic kidney disease, liver disease, pregnancy, obesity, smoking, sickle cell disease, thalassemia, and hypertension [87]. In two multicenter studies of children admitted to PICU, 40 of 48 and 12 of 17 had an underlying condition [80, 81]. In a systematic review of 587 confirmed pediatric patients, 22% had an underlying condition. Most of them were chronic pulmonary disease (45%), congenital heart disease (23%), immune suppression (12%), and hematological and oncological conditions (6%) [20].

Immunodeficiency

It has an important role in development and worse outcome of severity, in both pediatric and adult patients. In the largest ARDS epidemiologic study of adults, 20.8% and in the pediatric acute respiratory distress syndrome incidence and epidemiology study, 13% of ARDS cases, had immunosuppression [88, 89].

Weight extremes

The higher body mass index has been shown to be an independent factor associated with increased risk of ARDS development. As a paradox, the underweight patients with ARDS have higher mortality [90].

Environmental factors

In adult population, cigarette smoking is associated with ARDS in patients with sepsis [91]. This can be generalized to pediatrics as both active and passive smokers.

Age

It seems that infants aged less than 1 year are at higher risk of infection and severity [15]. In the largest pediatric population-based study to date with 2143 patients, the proportion of severe and critical cases was 10.6% under 1 year, suggesting the higher risk of severe respiratory failure in infants. In addition to smaller airways, both immaturity of respiratory tract and immune system, alongside with relatively lower trained immunity might contributed to this severity [16, 68, 92].

Race and ethnicity

Pediatric studies have not always observed a marked association between ARDS and both race and ethnicity, perhaps due to limited sample size. However, African and Hispanic ethnicity appears to be major risks in MIS-C patients [81].

Genetic factors

Genetic factors associated to acute respiratory distress syndrome

To date, several single-nucleotide polymorphisms have been identified by the increased risk of ARDS. The most significant variants are surfactant protein-B, ACE, angiotensin-2, and IL-1R antagonist [93]. The endothelial protein C receptor and thrombomodulin genes were independent factors associated with mortality [94]. IL-1 pathway cytokines are associated with ARDS risk, although this association has not been found in PARDS studies [95]. The regulatory gene arylsulfatase-D was linked in 22 and 4% of ARDS cases and controls, respectively. Also, XK Kell blood group complex membr-3 was present in a minor allele frequency of 37 and 4% of ARDS cases and controls, respectively [96]. It has been shown that there are five variants of cystic fibrosis transmembrane conductance regulator splicing factor gens that independently are associated with PARDS in African American children without cystic fibrosis. Another variant also was identified in Caucasian children with cystic fibrosis, without higher risk of ARDS development [97].

Genetic factors associated to other severe types and multisystem inflammatory syndrome

Interestingly, the cluster of MIS-C patients in some countries after the peak incidence of coronavirus infection among adults by approximately one month and in contrast no statistically significant difference in Japan and Korea, suggest a genetic and ethnicity background for these severe cases [22]. However, at this time the extent to which genetics impacts the development of MIS-C is unclear. Considering the implications of host genes in the cell entry and replication of SARS-CoV-2 and in mounting the immune system response, it appears that several genes might be involved. The variations within *ACE-2* gene, the human leukocyte antigen locus, and the genes regulating Toll-like receptor and complement pathways seem to influence susceptibility and subsequently the severity of COVID-19 [98]. In addition to possible involvement of several other genes (e.g., ABO blood type and Mediterranean fever gene) [99], genetic variations in these gateways might be influenced by the societies geographically. Using a combinational analysis approach, Taylor and colleagues identified 68 protein-coding genes that were highly associated with severe COVID-19 [100]. Ouyang et al. revealed that the number of differentially expressed genes (*DEGs*) increased by disease progression and decreased after initial treatment. All down-regulated *DEGs* in severe cases mainly involved Th17 activation [101].

Blood group

Researchers identified the 3p21.31 gene cluster as a genetic susceptibility locus in severe COVID-19 patients with respiratory failures. The results from comparing 1900 severe COVID-19 patients and 1200 healthy blood donors indicated that people with blood group A had a 45% higher risk of infection than others. Similarly, they found blood group O was associated with a lower risk of acquiring COVID-19 [102].

Other reasons

Unexpectedly, some children may have more viral loads without any other reasons. The higher exposure with or without high-risk behavior, alongside the more expression of ACE-2 receptors due to the less immaturity, a less previous exposure to coronavirus, influenza and other viruses, not getting the flu vaccine and some other vaccines, a less simultaneous presence of other viruses in body, and a more bacterial nasal colonization, all can be generalized as involved factors at this setting. In addition, some children may have a weaker innate response; while the strong innate response can be due to more exposure to previous viruses and many other reasons. They also, may have a relatively greater adaptive response alongside memory cells like adults [30, 90].

Conclusions

There are several potential reasons that children have relatively milder illness. In addition to a fewer outdoor activity, children have a number of characteristics that protect them against SARS-CoV-2 infection. They have a healthier respiratory machinery alongside a different expression of receptors in the lower respiratory tract. Also, we believe that the collection of immune system specifications including a less vigorous adaptive system beside a preliminary potent innate response, the constitutional higher level of lymphocyte counts, the trained immunity with cross-reactive neutralizing antibodies, the lack effects of aging, and the interaction between the immune system and respiratory tract might be protecting children against SARS-CoV-2 infection. Although, these findings suggest that COVID-19 is less common and somewhat milder in children compared to adults, there are now some reports of children presenting with severe types of infection such as MIS-C. The exact incidence of MIS-C following an asymptomatic or even a mildly symptomatic infection with SARS-CoV-2 is unclear. However, further investigations are needed to explore other possible causes of less severity of SARS-CoV-2 infection in the pediatric population.

Compliance with ethical standards

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