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Variability of severe acute respiratory syndrome coronavirus 2 infection in children and adults

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Dear Editor,

The novel coronavirus disease-2019 (COVID-19) has taken the whole world by storm. It has not only challenged the scientific community and medical services in terms of treatment and vaccination but also raised a lot of questions. One such question that needs to be addressed is its lesser infection rate in children (age: 0–13) compared to adults. Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is novel, no one has pre-existing immunity to it. A peculiar trend of SARS-CoV-2 infection has been observed in adults or patients with a weak or compromised immune system, leading to influenza-like symptoms, namely cough, fever, myalgia or fatigue[1,2], and death in severe cases (like acute respiratory distress syndrome, pneumonia) around the globe[3]. To everyone's surprise, no such severe symptoms or need of hospitalization has been reported in children although children under 5 years of age have a less-developed immune system compared to adults and are more vulnerable to diseases like influenza or common cold. It is significant to highlight that fatality rates differ significantly between nations, possibly because of factors like starvation, the availability of healthcare, misdiagnosis, and a decline in the detection of patients with no symptoms. In low-income nations, these elements have a key role in determining the course of the COVID-19 illness[4].

Previous data have also revealed that the number of children infected with SARS-CoV and middle east respiratory syndrome coronavirus were also meagre compared to adults[5]. The fact that children have an underdeveloped and immature immune system might be one of the reasons, which is thought to be a blessing in disguise. During the first year of life, children do not have a strong acquired immunity because their immune systems are not primed to elicit an influential immune response unlike adults. At birth and the early years of childhood, the immune system is harbored with a large number of T cells, which help in building a robust adaptive immune system to encounter different pathogens with increasing age. The immune system of the adults also relies on the memory cells, which retain the memory of the previous encounter and generate sufficient immune responses. Hence, the immune system of children behaves differently compared to adults. It is interesting to consider that the previous and more frequent common coronavirus infections in adults may cause immunological memory that hinders rather than strengthens the immune response to an antigen-specific neoantigen like SARS-CoV-2[6]. Furthermore, immunological responses to SARS-CoV-2 may be further hampered by immune senescence, which affects thymic output and T-cell receptor repertoire in the elderly and has an influence on the innate immune response[4,7]. Children infected with SARS-CoV-2 have shown significantly lower SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell responses and reduced $CD4^+$ T-cell effector memory compared to SARS-CoV-2-infected adults[8].

Additionally, the innate immune response in children, particularly in the upper respiratory tract, has been associated with increased resistance to the SARS-CoV-2 infection. This stronger immune response can be associated with vaccinations such as the BCG vaccine. The administration of BCG and other live vaccines in children has been thought to confer protection from COVID-19[9]. These vaccines exert immunomodulatory effect to neutralize the off-target viruses like SARS-CoV-2. Children usually get these vaccinations in their early childhood and have a trained immunity with higher number of natural killer cells, that is, required to clear viral infections. Moreover, children are less likely to have a compromised immune system or diseases like diabetes, cardiovascular conditions, pulmonary hypertension or lung diseases, which might be another reason for the milder COVID-19 pathogenesis.

Additionally, the role of the angiotensin-converting enzyme 2 (ACE 2) receptor in facilitating the entry of SARS-CoV-2 is well established[10]. The ACE 2 receptor in children has less affinity for SARS-CoV-2, due to which the entry of virus into the body becomes difficult[11]. This could be another reason for children not contacting the COVID-19 disease often. Additional ACE 2 expression studies need to be conducted in children of different ages to explore the possibilities of SARS-CoV-2 transmission.

It is interesting to mention that no transmission of SARS-CoV-2 infection has been observed in the fetus or neonates born from COVID-19-positive women who developed pneumonia in late pregnancy[12]. Surprisingly, immunoglobulin G and

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immunoglobulin G antibodies specific to SARS-CoV-2 have been observed in newborns from COVID-19 pneumonia-affected mothers[13], suggesting the transfer of antibodies via placenta from mother to child and thus protecting the newborns from the infection. However, it would be exciting to know the reason behind the transfer of antibodies but not the SARS-CoV-2 infection through the placenta.

A study conducted by Dugas *et al.*[14] has shown that prior exposure to betacoronaviruses facilitates T-cell-based immune response to SARS-CoV-2, and children are very much prone to common cold infections in their early ages, which are also caused by different seasonal betacoronaviruses; therefore, it might be possible that antibodies to common cold prevailing in the immune system may provide cross-immunity against SARS-CoV-2, hence affecting disease severity. Children infected with SARS-CoV-2 have shown lower levels of antibodies to β-coronaviruses[8]. It should be noted that these pre-existing cross-reactive antibodies do not prevent infection from SARS-CoV-2[15] but may affect the severity of the disease. Therefore, there remains a possibility of a large proportion of asymptomatic SARS-CoV-2 infection in children[8].

Another factor to be considered is the administration of supplements like vitamin D. The immunomodulatory effects of vitamin D on innate and adaptive immune responses are well established[16] and children are usually given vitamin D in their early years of life. Children are also exposed to the natural source of this vitamin, that is, sunlight, while playing or doing other forms of activities. This also might be a reason in protecting children from COVID-19.

The other possibility might be the less exposure of children to the outside world and the extra precautions, namely washing hands, healthy food, and the use of masks, taken by the parents and the family when it comes to their child. Since the beginning of COVID-19, lockdown came into effect and the children were not even allowed to go to schools in India and many other parts of the world, hence minimizing the chances of getting infected compared to adults who need to travel for different reasons.

Contrary to the facts discussed above, it might be possible that children are developing mild symptoms or are asymptomatic, and are hence not showing up for COVID-19 testing like adults. Therefore, COVID-19 testing data are needed to have a clear picture on this scenario. The majority of the current knowledge on COVID-19 immunological response, diagnosis, and therapy comes from adults. The complexity of COVID-19's downstream manifestations, such as long COVID-19, is not well understood, considering the fact that acute lung injury in children is often moderate[4]. Hence, a better understanding of the immune system of children is needed to decipher the role of their immunity, if any, against SARS-CoV-2. Extensive studies emphasizing on shedding of the infectious virus via children need to be conducted. A comprehensive and detailed research is needed in this field to reach any conclusion. Importantly, children need to be prioritized in future research efforts given the clinical manifestations and impacts are so distinct in the paediatric setting compared to adult populations. Many scientists have claimed that children and teenagers should get the COVID-19 vaccine to protect them against the disease, but immunization is also advised to help all age groups establish herd immunity[17]. Along with the clinical features, the extra indirect effects of the pandemic on children's mental health, well-being, and educational achievement must be taken into account[4].

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G.V. made significant contributions to the conception, design, writing, and revision of the manuscript critically for important intellectual content. M.D. contributed to the writing, review, and editing. A.A.S. contributed to the writing, review, and editing. R.K. contributed to the review and editing, R.P.N.M. contributed to the critical revision of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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The author declare that they have no financial conflicts of interest with regard to the consent of this report.

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Data statement

The current manuscript does not have any research data.

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