

# Higher prevalence of asymptomatic or mild COVID-19 in children, claims and clues

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## 1 | INTRODUCTION

The current pandemic of COVID-19 has generated many challenging questions for the scientific community, ranging from queries about the origin of the virus to its pathogenesis and clinical management. Addressing these questions may help in controlling the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2 or 2019-nCoV) and in reducing its mortality rate, which is substantially higher than that of H1N1 influenza, as reported by World Health Organization. Interestingly, while children of different age groups are vulnerable to SARS-CoV2 infection, they mostly experience either an asymptomatic or a mild form of the disease compared with adults.<sup>1</sup> This observation has attracted the attention of biomedical scientists and a plausible explanation is sought for this phenomenon. Considering that this phenomenon bears both pathogenic and therapeutic significance, here we discuss potential mechanisms that might underlie this peculiar aspect of SARS-CoV2 infection.

## 2 | DOES THE LEVEL OF ACE2 IN CHILDREN MATTER?

Similar to the more widely studied SARS-CoV, newly discovered SARS-CoV2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor for cell entry. The role of ACE2 as a receptor for the virus raises the possibility that a lower level of ACE2 expression would likely be associated with decreased viral entry and hence less severe clinical disease.

Nonetheless, evidence regarding the expression of ACE2 in various age groups or in people with lung disease indicates that ACE2-SARS-CoV2 relation may be more complicated. Animal studies have shown that there is a negative correlation between aging and ACE2 expression in the lung tissue of rats.<sup>2</sup> That said, a study on patients suffering from acute respiratory distress syndrome ranging from less than 28 days to more than 65 years has shown that there is no difference in ACE2 enzyme activity between different age groups in humans.<sup>3</sup> In the context of viral infections, a 2010 study has shown that SARS and NL63 coronaviruses' spike proteins can downregulate the expression of ACE2 in the lung.<sup>4</sup> A preprint study has also reported lower levels of ACE2 in senescent COVID-19 patients associated with decreased levels of sex hormones.<sup>5</sup> ACE2 has been reported to exert a protective role in the context of infection with viral respiratory pathogens.<sup>6</sup> Overall, current evidence with regard to the role of ACE2 expression in COVID-19 severity is fragmentary at best. Based on limited available data, it seems that while ACE2 acts as a viral entry receptor, its higher expression levels may be associated with a less severe disease in the younger population.

## 3 | CHILDHOOD VACCINATION, THE POTENTIAL FOR CROSS-PROTECTION AGAINST COVID-19

Vaccination stimulates adaptive immune responses against infectious agents, and these responses might provide cross-protection against

phylogenetically-related pathogens or unrelated pathogens containing similar antigenic structures. It is conceivable that the immunity generated by childhood vaccination against other viruses (eg, measles, mumps, and rubella or polio vaccines) might be associated with a degree of cross-protection against coronaviruses. Exploring this possibility in the context of SARS-CoV, Yu et al<sup>7</sup> reported that there was no meaningful cross-reactivity between the immunization with routine childhood vaccines and immune responses against SARS-CoV in mice. However, as mentioned by the authors, there might be differences between immune responses of mice and humans upon receiving live attenuated vaccines. While the main outcome of vaccination is the stimulation of pathogen-specific immune responses, some vaccines are known to lead to an altered immune status, partly at the level of innate immune system and likely by influencing leukocyte (eg, monocytes and natural killer cells) differentiation. In theory, this might lead to protection against unrelated pathogens. Bacillus Calmette-Guérin (BCG) vaccine vaccination provides an example for this nonspecific type of immunity. Various studies have shown that BCG vaccination might provide cross-protection against viral infections.<sup>8</sup> Studies have shown the BCG vaccination can lead to histone methylation and genome-wide epigenetic changes in innate immune cells, a phenomenon referred to as “trained immunity.”<sup>9</sup> These alterations might influence antiviral responses independent of adaptive immunity, or get translated to altered differentiation and response at the level of adaptive immune cells (ie, Th cells). Considering that BCG vaccination is not performed in all countries, pediatric immune responses against COVID-19 cannot be entirely attributed to the BCG training of immune system. However, the possibility remains that other globally administered vaccines might also lead to similar epigenetic alterations in immune cells, giving rise to similar phenomena. Further analysis of innate (and adaptive) immune cells following childhood vaccination might provide evidence for or against these “trained immunity” hypotheses.

#### 4 | THE DIFFERENCE IN INNATE AND ADAPTIVE IMMUNITY BETWEEN CHILDREN AND ADULTS

Different lines of evidence point to pathological immune activation/response in COVID-19 patients. Initial laboratory findings have demonstrated lymphopenia and an increase in neutrophil:lymphocyte ratio in COVID-19 patients. More detailed immunological studies have shown decreases in CD4<sup>+</sup> and regulatory T cells and enhanced levels of proinflammatory cytokines and chemokines, especially in more severe COVID-19 cases.<sup>10</sup> Results of clinical trials with immunomodulatory agents have indicated that these immunological alterations are not just consequences but important pathogenic players in COVID-19 disease.<sup>11,12</sup>

Immune system of children is on the path of maturation and it might respond differently to invading pathogens compared with the adult immune system. The overall innate immune response in children, especially upon the birth, is weaker than adults, however, this might be

helpful in the context of a viral infection whose pathogenesis is precipitated upon a severe inflammatory response.<sup>13</sup> Adaptive immune responses are also different in children. At the organ level, thymus has a bigger size and higher level of activity in children. Thymus regresses by age and as a consequence, production of naïve T cells, their diversity and perhaps more importantly, production of regulatory T cells (Tregs) decline in older ages. Tregs play a key regulatory role in maintaining the homeostasis of the immune system, controlling both the adaptive and innate immune responses. Hence, they might be crucial in controlling adverse immune reactions and cytokine storms during infections.<sup>14,15</sup>

Another relevant concept is immuno-senescence, that is, changes in immune system that occur as a part of normal aging. Changes related to immuno-senescence are more obvious in adaptive immunity and are more prominent in the elderly.<sup>16</sup> An immune system that has undergone senescence might be less dynamic in the production of sufficient protective antibodies and/or virus-specific CD8<sup>+</sup> T cells and thereby may be unable to provide appropriate defending responses against infection.<sup>14</sup>

Another mechanism that might explain the difference in prevalence and severity of COVID-19 in different age groups is the increase in the frequency of underlying diseases (ie, hypertension, diabetes, etc) with age. These underlying conditions have the potential to affect COVID-19 disease severity through alterations in various hemostatic mechanisms. That said, these conditions are all known to influence protective immune responses and immune regulation, leading to exacerbated immuno-senescence.<sup>16</sup>

#### 5 | CONCLUSION

Epidemiological data and clinical observations have pointed to lower prevalence of COVID-19 as well as higher likelihood of mild/asymptomatic COVID-19 among younger individuals, especially in children. Here, we reviewed available data that might explain this phenomenon and proposed some mechanisms. Basic and clinical investigations are required to provide evidence for or against the proposed explanations.

#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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