

## Nasal ACE2 Levels and COVID-19 in Children

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**Coronavirus disease 2019 (COVID-19)** has disproportionately affected certain vulnerable populations. Studies noted higher rates of certain comorbidities such as hypertension, diabetes mellitus, and chronic obstructive pulmonary disease in patients infected with COVID-19 with severe disease.<sup>1</sup> Additionally, areas with more racial/ethnic minorities and higher rates of poverty have been shown to have higher rates of COVID-19 hospitalization and death.<sup>2</sup> After adjustment for comorbidities, age has been independently associated with increased mortality due to COVID-19.<sup>3</sup> However, limited attention has been given to children, who appear to have lower risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and mortality.

In this issue of *JAMA*, Bunyavanich et al<sup>4</sup> identify a possible factor that may be related to lower rates of SARS-CoV-2 infection in children. The authors evaluated gene expression in nasal epithelial samples collected as part of a study involving patients with asthma from 2015 to 2018. The nasal epithelium is one of the first sites of infection with SARS-CoV-2, and the investigators probed for the expression of the cell surface enzyme angiotensin-converting enzyme 2 (ACE2), which has been proven to bind to SARS-CoV-2 spike protein and promote internalization of the virus into human cells.<sup>5</sup> Among a cohort of 305 patients aged 4 to 60 years, older children (10-17 years old; n = 185), young adults (18-24 years old; n = 46), and adults (≥25 years old; n = 29) all had higher expression of ACE2 in the nasal epithelium compared with younger children (4-9 years old; n = 45), and ACE2 expression was higher with each subsequent age group after adjusting for sex and asthma.

Numerous studies have highlighted the low rates of SARS-CoV-2 infection in children compared with adults. Children have been shown to have fewer and less severe symptoms compared with adults.<sup>6,7</sup> This leads to the question of whether low rates of SARS-CoV-2 infection in children are due to low rates of testing in children, or if children are less susceptible to infection. An evaluation of 1286 close contacts of index cases in China found that infection rates in children were comparable with or slightly higher than in younger adults (aged 30-49 years) but were significantly lower than in older patients (aged ≥60 years).<sup>8</sup> This finding suggests that children seem to have similar rates of becoming infected compared with middle-aged adults following close contact with a person infected with SARS-CoV-2. In contrast, a targeted screening approach in Iceland found SARS-CoV-2 in 6.7% of children younger than 10 years old (n = 564) compared with in 13.7% of people aged 10 years or older (n = 8635). A population-wide screening approach not

restricted to people at risk of disease in the same study found no positive cases of SARS-CoV-2 among children under 10 years old, whereas 0.8% of people older than 10 years were positive for SARS-CoV-2.<sup>9</sup> Although the true rate of acquiring SARS-CoV-2 infection among children of different age groups in the United States remains unclear, initial studies have suggested a lower incidence of SARS-CoV-2 infection in US children.<sup>7</sup>

While ACE2 binds to the receptor binding domain of SARS-CoV-2, a serine protease, TMPRSS2, is shown to cleave SARS-CoV-2 S protein, allowing for cell membrane fusion and endocytosis of the virus and subsequent viral replication. To better understand expression of these 2 key proteins, a number of single-cell RNA sequencing experiments have mapped them to various human cell types. One study using human and nonhuman primate tissue found ACE2 expression in the secretory cells of the nasal epithelia (upper respiratory tract) and in the type II pneumocytes of the lower respiratory tract.<sup>10</sup> In fibrotic human lung tissue, only 1.4% of type II pneumocytes expressed ACE2, and 0.8% of type II pneumocytes expressed both ACE2 and TMPRSS2. In human ethmoid sinus surgical specimens representing upper respiratory epithelia, 1.3% of all secretory cells expressed ACE2 while 0.3% expressed both ACE2 and TMPRSS2 but were further enriched in secretory goblet cells.<sup>11</sup> The spatial resolution offered by single-cell RNA sequencing highlights the limited number of cells in the respiratory tract that express ACE2. Further evaluation of ACE2 expression at the single-cell level in children could help explain whether a lower percentage of ACE2-expressing cells or a decrease in expression in ACE2 expression per cell is related to lower ACE2 expression in nasal epithelium, as noted in children identified by Bunyavanich et al.<sup>4</sup>

ACE2 has an important role in counterbalancing the effects of ACE. Angiotensin II, a product of ACE cleaving angiotensin I, can cause vasoconstriction, inflammation, and fibrosis by signaling through angiotensin II type 1 receptors. ACE2 can cleave angiotensin II to angiotensin 1-7, which can suppress inflammation and fibrosis and generate vasodilation by binding to the Mas receptor. Previous studies have found ACE2 to play a protective role in severe lung injury in ACE2 knockout mice.<sup>12</sup> If ACE2 can mitigate lung injury but serves as a receptor for viral entry, then is more ACE2 or less ACE2 expression protective for children? In the nasal epithelium of the upper airway, lower ACE2 expression could be helpful in decreasing acquisition of SARS-CoV-2 infection. However, in the lower respiratory tract, it appears that decreased ACE2 expression could portend a higher risk of developing severe acute respiratory distress and lung injury.

Bunyavanich et al<sup>4</sup> suggested that *ACE2* expression in the nasal epithelium in their cohort does not reflect *ACE2* expression in the pulmonary epithelium, and the expression of *ACE2* in the lower respiratory tract is under different regulation. This emphasizes the importance of understanding the distribution of *ACE2* in cells in different parts of the respiratory epithelium but also between cell-bound and plasma fractions. *ACE2* is cleaved from the cell membrane on binding with SARS-CoV-2, releasing *ACE2* into the plasma. The role of soluble *ACE2* in neutralizing SARS-CoV-2 virus has recently been shown in vitro,<sup>13</sup> but its activity in vivo is still to be determined. Ultimately, studying tissue expression of *ACE2* in the lower respiratory tract of children may be helpful

in understanding differences in the severity of COVID-19 among children compared with adults.

A new study called Human Epidemiology and Response to SARS-CoV-2 (HEROS), funded by the National Institute of Allergy and Infectious Diseases, is designed to prospectively follow 6000 children to determine risk factors for development of COVID-19.<sup>14</sup> Data from this study could help identify whether the lower *ACE2* expression identified by Bunyavanich et al<sup>4</sup> correlates with lower rates of SARS-CoV-2 infection, and could serve to support the possibility that decreasing *ACE2* expression in the nasal epithelium may be a potential therapeutic approach to mitigate transmission of COVID-19.

#### ARTICLE INFORMATION

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