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Less ACE2, better immune function may protect children from severe COVID-19

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A new perspective piece suggests differences in lung physiology and immune function as possible reasons why children are often spared from severe illness associated with SARS-CoV-2, the novel coronavirus that causes COVID-19. The article is published ahead of print in the *American Journal of Physiology-Lung Cellular and Molecular Physiology*.

The percentage of children under the age of 18 infected with SARS-CoV-2 has been considerably lower than expected compared to adults. Reports from China and Italy have shown that children who become infected with the virus show symptoms less often than adults and are less likely to develop respiratory symptoms such as a cough or shortness of breath when they are symptomatic. In most cases, the infected under-18 population does not become as severely ill as can happen among their older counterparts. The newly identified multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, though serious, is believed to affect only about 1% of young people exposed to SARS-CoV-2.

"These profoundly decreased rates of symptomatic infection, hospitalization and death are well beyond statistical significance, require further examination and may hold the key to identifying therapeutic agents," the authors wrote.

The way that SARS-CoV-2 virus enters the body and the state of the immune system itself are thought to be two primary differences in how children and adults become infected with coronavirus.

SARS-CoV-2 enters the body by binding to angiotensin converting enzyme-2 (ACE2), which is attached to the outer surface of cells in the lungs, arteries, heart and other organs. Studies have found that expression of ACE2 in the lungs increases with age. Infants and very young children have very low ACE2 expression, and older children have lower expression than adults. Research suggests that children may be protected from the serious respiratory components of COVID-19—including acute respiratory distress syndrome—due to their reduced ACE2 expression.

The immune system also plays a role in infection. Imbalance between mediators that increase versus suppress the inflammatory response plays a critical role in the clinical manifestations of this disease. Heightened immune response is often a factor in the inflammatory "cytokine storm" phase of COVID-19, in which the body attacks itself. Studies have shown that older mice had lower levels of the anti-inflammatory substances IL-10 and IL-13 and higher levels of pro-inflammatory chemicals in the lungs than younger animals. CD4 T-cells, which play an important role in controlling viral replication and disease severity, are markedly decreased in adults with severe COVID-19. In addition, lung tissue in children naturally has a higher concentration of regulator T-cells, which may protect against severe COVID-19 by suppressing the immune response that, in adults, may lead to uncontrolled inflammation.

"Selective, age-associated mortality render[s] COVID-19 a unique, infectious disease. Insights into age-related variability in pathophysiological processes may offer critical observations, revealing focused paths of therapeutic investigation. Multidisciplinary collaboration between physicians and scientists, engaged in both pediatric and adult pursuits, holds significant promise and should be encouraged," the authors wrote.

"Understanding the age divide in COVID-19: Why are children

overwhelmingly spared?" is published ahead of print in the *American Journal of Physiology-Lung Cellular and Molecular Physiology*.

More information: Krithika Lingappan et al. Understanding the age divide in COVID-19: Why are children overwhelmingly spared?, *American Journal of Physiology-Lung Cellular and Molecular Physiology* (2020). DOI: 10.1152/ajplung.00183.2020

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