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# Possible Biological Explanations for Kids' Escape from COVID-19

Infected children may harbor SARS-CoV-2 while showing less-severe symptoms than adults. The young immune systems, ACE2 receptor levels, and even exposure to other coronaviruses might play a role in their resilience.

**Anthony King**
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Since SARS-CoV-2, the virus responsible for the COVID-19 pandemic, was first recognized as a close cousin of the virus that caused the SARS outbreak of 2003, scientists have looked to the experience of that earlier epidemic to glean insight into the current global health crisis.

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Kids were largely unaffected in the original SARS outbreak. In Hong Kong, no one under the age of 24 years died, while more than 50 percent of patients over 65 succumbed to the infection. Globally, less than 10 percent of those diagnosed with SARS were children, and only 5 percent of them required intensive care.

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> —Robin Shattock, Imperial College London

"There were repeated incursions from animals to humans, with both SARS and MERS, and the assumption by ma was maybe children are just not exposed to the infected civet cats or camels," says virologist Kanta Subbarao of th Doherty Institute in Melbourne, Australia.

A very similar pattern has been observed with the new outbreak of COVID-19. Within Wuhan, no children tested positive between November 2019 and the second week of January, and the elderly proved particularly vulnerable The Chinese Centers for Disease Control and Prevention reported in mid-February that out of 44,672 confirmed cases of COVID-19, 86.6 percent were between 30 and 79 years of age. The oldest among them were at greatest ris of death. And in a study of 1,099 patients in China, just 0.9 percent of confirmed cases were under the age of nine while only 1.2 percent were between 10 and 19 years old.

Now, evidence is emerging that while few children suffer severely from COVID-19, they do get infected. A recent study even found evidence of viral excretion in children from rectal swabs. "At the moment it doesn't seem to be causing much in the way of serious disease in young people, particularly children," says virologist Robin Shattock Imperial College London. However, he adds, "it is quite likely that children are an important source of the virus."

"There is good evidence that children get infected and have a fairly high titre of virus but just don't have serious disease," agrees Ralph Baric, a coronavirus researcher at the University of North Carolina at Chapel Hill. He saw a similar phenomenon in his mouse studies with the original SARS coronavirus (SARS-CoV). Although SARS-CoV

replicate fairly well, "younger animals are really resistant to infection in terms of the disease," he says. When Bari tested older animals, he says, the severity of SARS illnesses rose. In one experiment, one-fifth of mice infected wi SARS aged 3–4 weeks died, whereas all of the mice 7–8 weeks old died.

Subbarao has also found that young adult mice, at six weeks old, can clear SARS-CoV with no significant clinical symptoms. "When we used the same virus in 12-month-old mice, which is by no means really old, there were mc clinical signs," she says. These results indicate that both the original SARS-CoV and the one circulating now may infect children, but not make them ill. "The animal data supports the idea that they are infected but do not devel disease, because our young mice have the same levels of virus as old mice but do not get sick," says Stanley Perlm an immunologist at the University of Iowa. "It is not a question of infection."

The work on mice is now being supported by emerging epidemiological data. A preprint posted to *medRxiv* on March 4 analyzed 391 COVID-19 cases and 1,286 of their close contacts. The authors concluded that children are similar risk of infection as the general population, though less likely to have severe symptoms.

## An aging immune system

One explanation for the correlation between age and disease severity is that as humans' immune systems age, mc cells become inactive. "As you age, your immune system undergoes senescence and loses its capacity to respond effectively or be regulated as effectively," says Baric.

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>
> —Kingston Mills, Trinity College Dublin

Another explanation, which Perlman favors, is tied to the aging lung environment. In order for individuals not to easily develop asthma or overreact to environmental irritants such as pollen or pollution, aged lungs counter the usual immune reaction with some tamping down of inflammation. As a result, says Perlman, the lungs do not respond quickly enough to a viral infection. For instance, when his group makes the lungs of older mice more lik those of young mice by altering prostaglandins, compounds that respond to tissue injury, "then the mice do well they can clear the [SARS] infection and don't get sick," says Perlman.

In experiments reported in 2010, Perlman and his colleagues showed that T cells are especially important in clea viruses from mice infected with SARS-CoV. "It is almost certain we need both an antibody- and T cell–response t do well" against COVID-19 infection, says Perlman. His suspicion is that the young immune system and its efficie T cells do a superior job of responding to SARS-CoV-2. A 2010 study led by Subbarao also stressed the importanc of CD4+ helper T cells, which stimulate B cells to make antibodies against pathogens, in controlling SARS-CoV infection in mice.

"It could be that the type of T cell that dominates early in life is better at repelling this virus," says immunologist Kingston Mills of Trinity College Dublin. He also proposes that young children's higher production of a type of T cell called Th2 might guard against runaway inflammatory responses to SARS-CoV-2. Perlman doesn't support th proposed role of a bias toward Th2 cells in the case of this viral infection, but he does agree that an immune overreaction is problematic.

"The innate response is delayed in the elderly, so ends up playing catch-up and is exuberant," Perlman writes in a email to *The Scientist*.

## ACE2 receptor

SARS-CoV and SARS-CoV-2 both use the same keyhole to enter cells, the ACE2 receptor. There's an abundance o this receptor in cells in the lower lung, which may explain the high incidence of pneumonia and bronchitis in thc with severe COVID-19 infection. A recent study showed that ACE2 is also highly expressed in the mouth and tong granting the virus easy access to a new host. ACE2 receptor abundance goes down in the elderly in all these tissue but, counterintuitively, this might place them at a greater risk of severe illness.

This is because the ACE2 enzyme is an important regulator of the immune response, especially inflammation. It protects mice against acute lung injury triggered by sepsis. And a 2014 study found that the ACE2 enzyme offers protection against lethal avian influenza. Some patients with better outcomes had higher levels of the protein in their sera, and turning off the gene for ACE2 led to severe lung damage in mice infected with H5N1, while treatin mice with human ACE2 dampened lung injury.

A fall in ACE2 activity in the elderly is partly to blame for humans' poorer ability to put the brakes on our inflammatory response as we age, according to emailed comments from Hongpeng Jia of Johns Hopkins Medicin Reduced abundance of ACE2 receptors in older adults could leave them less able to cope with SARS-CoV-2, says Baric, though the hypothesis still needs more research.

## Exposure to other coronaviruses

There are four other coronaviruses that infect humans, with symptoms typical of a common cold. These viruses common in children. "We don't know which of them, if any, might provide some cross immunity," says Subbarao could be that immunity to viral proteins, obtained from circulating "common cold" viruses, moderates the cours COVID-19.

This is a "hand-waving hypothesis," Subbarao adds, but one that is worth testing. Recently, it has been suggested t plasma from people who've recovered from COVID-19 could be transfused into patients infected with SARS-CoV to treat them.

"I don't think anyone in the field knows why the disease is less robust in extremely young animals or humans," Ba tells *The Scientist*. It is also still too early to know how much learned from the first SARS coronavirus applies to SARS-CoV-2. "SARS-CoV-1 will tell us a lot, but I think there is new information we are going to learn about SARS CoV-2," Perlman acknowledges.

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