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After extremely low case rates in New York City early this summer, the number of children testing positive for SARS-CoV-2 has begun to rise.

KIDS AND COVID: WHY YOUNG IMMUNE SYSTEMS ARE STILL ON TOP

Innate immunity might explain why children have fared better with the virus. But the Delta variant poses fresh unknowns. **By Smriti Mallapaty**

Early last year, children's hospitals across New York City had to pivot to deal with a catastrophic COVID-19 outbreak. "We all had to quickly learn — or semi-learn — how to take care of adults," says Betsy Herold, a paediatric infectious-disease physician who heads a virology laboratory at the Albert Einstein College of Medicine. The reason: while hospitals across the city were bursting with patients, paediatric wards were relatively quiet. Children were somehow protected from the worst of the disease.

Data collected by the US Centers for Disease Control and Prevention from hospitals across the country suggest that people under the age of 18 have accounted for less than 2% of hospitalizations due to COVID-19 — a total of 3,649 children between March 2020 and late August 2021. Some children do get very sick, and more than 420 have died in the United States, but the majority of those with severe illness have been adults — a trend that has been borne out in many parts of the world.

This makes SARS-CoV-2 somewhat anomalous. For most other viruses, from influenza to respiratory syncytial virus, young children and older adults are typically the most vulnerable; the risk of bad outcomes by age can be represented by a U-shaped curve. But with COVID-19, the younger end of that curve is largely chopped off. It's "absolutely remarkable", says Kawsar Talaat, an infectious-disease physician at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. "One of the few silver linings of this pandemic is that children are relatively spared."

The phenomenon was not entirely surprising to immunologists, however. With other viruses, adults have the advantage of experience. Through prior infection or vaccination, their immune systems have been trained to deal with similar-looking pathogens. The novelty of SARS-CoV-2 levelled the playing field,

and showed that children are naturally better at controlling viral infections. "We always think of children as germ factories," says Dusan Bogunovic, an immunologist and geneticist at the Icahn School of Medicine at Mount Sinai, in New York City. But it's not because their immune systems are ineffective; they're just inexperienced, he says.

Research is beginning to reveal that the reason children have fared well against COVID-19 could lie in the innate immune response — the body's crude but swift reaction to pathogens. Kids seem to have an innate response that's "revved up and ready to go", says Herold. But she adds that more studies are needed to fully support that hypothesis.

The emergence of the Delta variant has made finding answers more urgent. Reports suggest that in the United States and elsewhere, children are starting to make up a larger proportion of reported infections and hospitalizations. These trends might be due to Delta's high transmission rate and the fact that many adults are now protected by vaccines.

For now, there is no clear evidence that children are more vulnerable to or more affected by Delta compared with earlier variants. But SARS-CoV-2, like all viruses, is constantly mutating and becoming better at evading host defences, and that could make understanding childhood's protective benefits more important. "We haven't paid much attention to age-related differences in immune responses because it hasn't had huge clinical implications previously," says Lael Yonker, a paediatric pulmonologist at Massachusetts General Hospital in Boston. "COVID-19 highlights that we need to better understand these differences."

Brainstorming ideas

Why are children better than adults at controlling SARS-CoV-2? At first, researchers thought that children were simply not getting infected as often. But the data show that they are — at least nearly (children under age ten might be slightly less susceptible)[1].

The American Academy of Pediatrics found that, up until late last month, some 15% of all COVID-19 cases in the United States had been in individuals aged under 21 — that's more than 4.8 million young people (see 'Young and infected'). And a survey in India that tested people for antibodies against SARS-CoV-2, which are produced after infection or vaccination, found that more than half of children aged 6–17 — and two-thirds of the population overall — had detectable antibodies.

Clearly, children are getting infected. So maybe the virus can't replicate in them as well as it does in adults. Some researchers proposed that children might have fewer ACE2 receptors, which the virus uses to enter and infect cells. There is conflicting evidence on age-related differences in ACE2 expression in the nose and lungs, but scientists who measured the 'viral load' — the concentration of viral particles — in people's upper airways have seen no clear difference between children and adults[2].

In one analysis[3] of 110 children, posted as a preprint on 3 June, researchers found that infants through to teenagers could have high viral loads, especially soon after being infected. "Not only is the virus there and detectable, but it's live virus," which means these individuals are also infectious, says Yonker, who led the study.

Another proposal is that children, who seem to be sniffling all year round, might be more exposed to other coronaviruses that cause the common cold, and therefore have a squad of antibodies at the ready with some ability to latch on to the pandemic coronavirus. But the weight of evidence suggests that adults also have this immunity. Strikingly, these 'cross-reactive' antibodies don't offer any special protection — if anything, they could lead to a misguided response.

Having largely discounted these hypotheses, Herold and her colleagues set out to look at whether there was something specific in children's immune response that gave them a benefit.

Some clues were circulating in the blood of those who have been infected. In a study[4] comparing 65 individuals aged under 24 with 60 older people, Herold and her colleagues found that, overall, the younger patients (who had milder symptoms) produced similar levels of antibodies to the older cohort. But they had reduced levels of specialized antibodies and cells related to the adaptive immune response, the arm of the immune system that learns about a pathogen and helps to quickly quash it if it ever returns. Specifically, kids had lower levels of 'neutralizing' antibodies that block SARS-CoV-2 from infecting cells; antibodies that label infected cells to be gobbled up and destroyed by other cells; and white blood cells known as regulatory and helper T cells.

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By contrast, the children in the study had higher levels of the signalling proteins interferon-γ and interleukin-17, which alert the immune system to the arrival of a pathogen. These were probably produced by cells that line the airways, and are involved in mediating innate immunity. Herold suspected that the children mounted a less robust adaptive immune response because their innate response was more efficient at eliminating the threat. An overactive adaptive response in adults, she says, could be causing some of the complications in COVID-19.

Another study[5], by researchers in Hong Kong, of adults and children infected with SARS-CoV-2 also found that the adaptive response — specifically that of T-cells — was less potent in children, suggesting that something was happening early on that triggered the difference, says study co-author Sophie Valkenburg at the University of Hong Kong.

But, she says, other factors such as reduced inflammation and a more targeted adaptive response could also be important. The researchers found that infected children had lower levels of cells known as monocytes, including inflammatory monocytes, which act as a bridge between the innate and adaptive immune systems. But these children did have higher levels of T follicular helper cells, which are important for making an early antibody response.

First responders

Herold and her colleagues have since tried to measure more directly the innate response in children. They took nose and throat swabs from people arriving at the emergency department, including 12 children with milder disease and 27 adults, some of whom died. The children had higher levels of signalling proteins such as interferons and interleukins, and higher expression of the genes that code for such proteins[2].

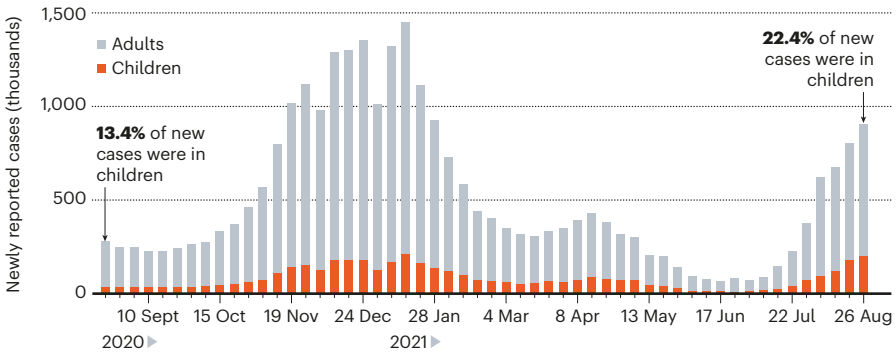
One broad category of immune cells that could be playing an important part in children, says Yonker, are innate lymphoid cells, which are among the first to detect tissue damage and secrete signalling proteins that help to regulate the innate and adaptive immune responses. In one study[6] posted as a preprint on 4 July, Yonker and her colleagues found that the number of innate lymphoid cells in the blood of people who did not have COVID-19 declined with age and was lower in men — mirroring the greater risk of severe disease observed in older men. Adults with severe disease and children with symptoms also had reduced levels of these cells.

Compared with adults, children recently infected with SARS-CoV-2 have also been found to have higher levels of activated neutrophils, cells that are on the front line in the response to unfamiliar invaders[7]. Neutrophils ingest viral particles before they have a chance to replicate, says Melanie Neeland, an immunologist at the Murdoch Children's Research Institute (MCRI) in Melbourne, who led the work. Furthermore, they become less effective with age.

Epithelial cells that line the insides of the nose could also be coordinating the quick response. In children, these cells are flush with receptors that can recognize molecules commonly found in pathogens; specifically, researchers have found that children have significantly higher expression of genes encoding MDA5, a receptor known to recognize SARS-CoV-2, than do adults[8]. After spotting the viral

YOUNG AND INFECTED

Over the course of the COVID-19 pandemic, nearly 15% of all confirmed cases in the United States have been in children. In the last week of August 2021, just over 22% of weekly reported cases were in children, a rise that may be attributable to higher vaccination rates in adults.



intruder, these cells immediately trigger the production of interferons. "For us adults, it takes two days to ramp up the viral defence system to a level that we see from day zero with children," says study co-author Roland Eils, a scientist in computational genomics at the Berlin Institute of Health. "It's the time lag which makes the difference between children and adults."

Studies of rare, inherited, immune disorders also point to a predominant role for innate immunity in thwarting respiratory pathogens such as influenza.

Isabelle Meyts, a paediatric immunologist and physician at the Catholic University of Leuven in Belgium, regularly sees children with immune disorders. When the pandemic hit, she prepared a plan to protect them. "The patients I was most scared for were actually the patients who have innate immune defects," says Meyts.

Her hunch has so far proved correct. Children with disorders affecting their adaptive immune response — those who don't produce antibodies or have faulty B-cell and T-cell production, for example — did not encounter problems when infected with SARS-CoV-2. Among those that became severely ill were children with shortcomings in their innate immune response, she says. "It's not really the adaptive immune system that is helping you to beat this virus."

A study in adults[9] also found that a small number of people with severe COVID-19 have mutations that disrupt type 1 interferon activity, which plays a part in the innate immune response to viruses. Separate analyses found that one in ten people with life-threatening COVID-19 produced antibodies that blocked the activity of these interferons[10], and that the prevalence of such antibodies increases with age in people who have not previously been infected with the coronavirus[11].

But, an overactive innate response might be detrimental as well. People with Down's syndrome, for example, are more at risk of severe COVID-19, which Meyts says could be because the extra chromosome they have contains several genes involved in the type 1 interferon response. There is an intriguing balance to be struck between a deficient initial response and an excessive one, says Meyts. "It needs to be exactly right on the spot, and the timing needs to be perfect."

Tickling bad memories

Innate immunity is hardly the whole story, say researchers, especially given how interconnected it is with the adaptive response.

"The idea that the immunologic tone is different in children seems likely," says Laura Vella, an immunologist and paediatric infectious-diseases researcher at the Children's Hospital of Philadelphia, Pennsylvania. "But what's contributing to that difference?" It could be many things working together, she says.

Some researchers propose that years of exposure to other human coronaviruses could mean that adult immune systems approach SARS-CoV-2 the way they would those other viruses, resulting in a less effective response — a concept known as original antigenic sin. By contrast, kids could be producing a fresh, more finely tuned response to a brand-new virus.

Amy Chung, an immunologist at the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia, has seen some evidence of this in an expansive study[12] of antibodies in the blood of a few hundred children and adults, including 50 infected with SARS-CoV-2. She and her colleagues found that adults had more cross-reactive antibodies targeted at parts of SARS-CoV-2 that were similar to bits of other coronaviruses, whereas children tended to produce a broader range of antibodies against all sections of the virus.

Researchers are also looking at other factors that are known to worsen with age, such as the ability to control inflammation and heal damaged tissue. Children are less prone to clots forming in blood vessels, and this could offer some protection, says Vera Ignjatovic, a biochemist who studies paediatric haematology at the MCRI.

Of course, not all children have asymptomatic or mild infection. Some, many of whom have underlying conditions such as chronic heart disease or cancer, get serious pneumonia. And estimates vary widely for the prevalence of 'long COVID', in which symptoms persist for months or more. A recent preprint suggested that up to 14% of young people who test positive for COVID-19 have multiple symptoms three months after the diagnosis[13]. And a small group of otherwise healthy children — some 3 out of 10,000 infected individuals aged under 21 — experience a condition known as multi-system inflammatory syndrome in children (MIS-C). They generally respond well to the initial infection, but about a month later are admitted to hospital with a host of symptoms, from heart failure to abdominal pain and conjunctivitis, with minimal damage to the lungs. "It's a sick group of kids," says Vella.

Michael Levin, a paediatrician and infectious-diseases physician at Imperial College London, thinks MIS-C is probably the result of an outsized antibody or T-cell reaction to the infection. But despite hundreds of papers on the topic, "exactly what distinguishes children who get MIS-C from the rest of the child population is completely unknown", says Levin.

As the pandemic wears on, researchers worry that the virus could evolve in ways that thwart some part of kids' innate protection. Some researchers have found that the Alpha variant, which was dominant in some parts of the world for a time, developed tricks that allowed it to suppress the body's innate immune response. They worry that Delta could do the same. For now, increased hospitalizations of children in regions where Delta is circulating seem to be the result of its enhanced infectivity across all ages, coupled with the fact that many adults are vaccinated or have already been infected with SARS-CoV-2. But researchers are watching carefully.

"Almost all viruses have developed ways of evading the innate immune system, and COVID-19 is no exception to that rule," says Herold. "Right now — knock on wood — the kids are still winning with their innate immunity." But for how much longer? "We don't know."

Smriti Mallapaty writes for *Nature* from Sydney, Australia.

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