

Scientists Examine Kids' Unique Immune Systems as More Fall Victim to COVID

What protects most children from becoming seriously ill? And why does that protection sometimes fail?

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Eighteen months into the COVID-19 pandemic, with the delta variant fueling a massive resurgence of disease, many hospitals are hitting a heartbreaking new low. They're now [losing babies](#) to the coronavirus.

[The first reported COVID-related death of a newborn](#) occurred in Orange County, Florida, and [an infant has died](#) in Mississippi. [Merced County in California](#) lost a child under a year old in late August.

"It's so hard to see kids suffer," said Dr. Paul Offit, an expert on infectious diseases at Children's Hospital of Philadelphia, which — like other pediatric hospitals around the country — has been inundated with COVID patients.

Until the delta variant laid siege this summer, nearly all children seemed to be spared from the worst ravages of COVID, for reasons scientists didn't totally understand.

Although there's no evidence the delta variant causes more severe disease, the virus is so infectious that children are being hospitalized in large numbers — mostly in states with low vaccination rates. Nearly 30% of COVID infections reported for the week that ended September 9 were in children, according to the American Academy of Pediatrics.

Doctors diagnosed [more than 243,000 cases in children](#) in the same week, bringing the total number of covid infections in kids under 18 since the onset of the pandemic to [5.3 million](#), with [at least 534 deaths](#).

Experts say it's a question of basic math. "If 10 times as many kids are infected with delta than previous variants, then, of course, we're going to see 10 times as many kids hospitalized," said Dr. Dimitri Christakis, director of the Center for Child Health, Behavior and Development at the Seattle Children's Research Institute.

But the latest surge gives new urgency to a question that has mystified scientists throughout the pandemic: What protects most children from becoming seriously ill? And why does that protection sometimes fail?

“This is an urgent and complex question,” said Dr. Bill Kapogiannis, senior medical officer and infectious-disease expert at the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

“We are doing everything we can to address it, using all the tools we have available,” Kapogiannis said. “Answers can’t come soon enough.”

Investigating Immune Systems

For much of the pandemic, doctors could only guess why children’s immune systems were so much more successful at rebuffing the coronavirus.

Despite the alarming number of hospitalized children in the recent surge, young people are much less likely to become critically ill. Fewer than 1% of children diagnosed with covid are hospitalized and about 0.01% die — rates that haven’t changed in recent months, according to the [American Academy of Pediatrics](#). Most children shrug off the virus with little more than a sniffle.

A growing body of evidence suggests that kids’ innate immune systems usually nip the infection early on, preventing the virus from gaining a foothold and [multiplying](#) unchecked, said Dr. Lael Yonker, an assistant professor of pediatrics at Massachusetts General Hospital.

In a series of studies published in the past year, the husband-and-wife team of Drs. Betsy and Kevan Herold found that children have particularly [strong mucosal immunity](#), so called because the key players in this system are not in the blood but in the [mucous membranes](#) that line the nose, throat and other parts of the body that frequently encounter germs.

These membranes act like the layered stone walls that protected medieval cities from invaders. They’re made of epithelial cells — these also line many internal organs — which sit side by side with key soldiers in the immune system called dendritic cells and macrophages, said Betsy Herold, chief of the division of pediatric infectious diseases at the Albert Einstein College of Medicine.

Significantly, these cells are covered in proteins — called pattern recognition receptors — that act like sentries, continuously scanning the landscape for anything unusual. When the sentries notice something foreign — like a new virus — they alert cells to begin releasing proteins called interferons, which help coordinate the body’s immune response.

In an August study in [Nature Biotechnology](#), Roland Eils and his colleagues at Germany’s Berlin Institute of Health found that kids’ upper airways are “pre-activated” to fight the novel coronavirus. Their airways are teeming with these sentries, including ones that excel at recognizing the coronavirus.

That allows kids to immediately activate their innate immune system, releasing interferons that

help shut down the virus before it can establish a foothold, Eils said.

In comparison, adults have far fewer sentinels on the lookout and take about two days to respond to the virus, Eils said. By that time, the virus may have multiplied exponentially, and the battle becomes much more difficult.

When innate immunity fails to control a virus, the body can fall back on the adaptive immune system, a second line of defense that adapts to each unique threat. The adaptive system creates antibodies, for example, tailored to each virus or bacterium the body encounters.

While antibodies are some of the easiest pieces of the immune response to measure, and therefore often cited as proxies for protection, kids don't seem to need as many to fight COVID, Betsy Herold said. In fact, the Herolds' [research](#) shows that children with COVID have fewer neutralizing antibodies than adults. (Both kids and adults usually make enough antibodies to thwart future coronavirus infections after natural infection or vaccination.)

While the adaptive immune system can be effective, it can sometimes cause more harm than good.

Like soldiers who kill their comrades with friendly fire, a hyperactive immune system can cause collateral damage, triggering an inflammatory cascade that tramples not just viruses, but also healthy cells throughout the body.

In some COVID patients, uncontrolled inflammation can lead to life-threatening blood clots and [acute respiratory distress syndrome](#), which occurs when fluid builds up in the air sacs of the lung and makes it difficult to breathe, Betsy Herold said. Both are common causes of death in adult COVID patients.

Because kids typically clear the coronavirus so quickly, they usually avoid this sort of dangerous inflammation, she said.

[Research](#) shows that healthy children have large supplies of a type of peacekeeper cell, called innate lymphoid cells, that help calm an overactive immune system and repair damage to the lungs, said Dr. Jeremy Luban, a professor at the University of Massachusetts Medical School.

Kids are born with lots of these cells, but their numbers decline with age. And both children and adults who are sick with COVID tend to have fewer of these repair cells, Luban said.

Men also have fewer repair cells than women, which could help explain why males have a higher risk of dying from COVID than females.

Both children and adults can develop "long COVID," the lingering health issues experienced by about [10% of younger adults and up to 22% of those 70 and older](#). [Studies suggest that 4% to 11% of kids](#) have persistent symptoms.

Unanswered Questions

Scientists have fewer clues about what goes wrong in certain children with COVID, said Kevan Herold, who teaches immunobiology at the Yale School of Medicine.

Research suggests that children have more robust innate immune systems than adults because they have experienced so many recent respiratory infections, within their first few years, which may prime their immune systems for subsequent attacks.

But not all children shrug off COVID so easily, Eils said. Newborns haven't been alive long enough to prime their immune systems for battle. Even toddlers may fail to mount a strong response, he said.

At Children's Hospital New Orleans, half of COVID patients are under 4, said Dr. Mark Kline, a specialist in infectious diseases and physician-in-chief.

"We've had babies as young as 7 weeks, 9 weeks old in the ICU on ventilators," Kline said. "We had a 3-month-old who required ECMO," or extracorporeal membrane oxygenation, in which the patient is connected to a machine similar to the heart-lung bypass machine used in open-heart surgery.

Even previously healthy children sometimes die from respiratory infections, from COVID to influenza or respiratory syncytial virus (RSV).

But studies have found that [30% to 70% of children](#) hospitalized with COVID had underlying conditions that increase their risk, such as Down syndrome, obesity, lung disease, diabetes or immune deficiencies. Premature babies are also at higher risk, as are children who've undergone cancer treatment.

One thing hospitalized kids have in common is that almost none are vaccinated, said Dr. Mary Taylor, chair of pediatrics at the University of Mississippi Medical Center.

"There's really no way to know which child with COVID will get a cold and be just fine and which child will be critically ill," Taylor said. "It's just a very helpless sensation for families to feel like there is nothing they can do for their child."

Although scientists have identified [genetic mutations](#) associated with [severe COVID](#), these variants are extremely rare.

Scientists have had more success illuminating why certain adults succumb to COVID.

Some cases of severe COVID in adults, for example, have been tied to misguided antibodies that target interferons, rather than the coronavirus. An August study in [Science Immunology](#) reported that such "autoantibodies" contribute to 20% of covid deaths.

Autoantibodies are very rare in children and young adults, however, and unlikely to explain why

some youngsters succumb to the disease, said study co-author Dr. Isabelle Meyts, a pediatric immunologist at the Catholic University of Leuven in Belgium.

Although [hospitalizations are declining](#) nationwide, some of the most serious consequences of infection are only now emerging.

Two months into the delta surge, hospitals throughout the South are seeing a second wave of children with a rare but life-threatening condition called multisystem inflammatory syndrome, or MIS-C.

Unlike kids who develop COVID pneumonia — the major cause of hospitalizations among children — those with MIS-C typically have mild or asymptomatic infections but become very ill about a month later, developing symptoms such as nausea, vomiting, a rash, fever and diarrhea. Some develop blood clots and dangerously low blood pressure. More than 4,661 children have been diagnosed with MIS-C and 41 have died, according to the [Centers for Disease Control and Prevention](#).

Although scientists still don't know the exact cause of MIS-C, research by Yonker of Massachusetts General and others suggests that viral particles may leak from the gut into the bloodstream, causing a system reaction throughout the body.

It's too soon to tell whether children who survive MIS-C [will suffer lasting health problems](#), said Dr. Leigh Howard, a specialist in pediatric infectious diseases at Vanderbilt University Medical Center.

Although an August study in [The Lancet](#) shows that delta doubles the risk of hospitalization in adults, scientists don't know whether that's true for kids, said Dr. Anthony Fauci, the country's top infectious-disease official.

"We certainly don't know at this point whether children have more severe disease, but we're keeping our eye on it," he said.

To protect children, Fauci urged parents to vaccinate themselves and children age 12 and up. As for children too young for COVID shots, "the best way to keep them safe is to surround them by people who are vaccinated."

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