# Why the coronavirus hits kids and adults so differently [1]

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EXCERPTS

Only after New York City passed its current coronavirus peak did pediatricians notice a striking, new pattern: Dozens of kids who had been exposed to COVID-19 were coming in sick, but they weren't coughing. They didn't have severe respiratory distress. Instead, they had sky-high inflammation and some combination of fever, rashes on their hands and feet, diarrhea, vomiting, and very low blood pressure. When ICU doctors around the world gathered for a weekly online COVID-19 call on May 2, doctors elsewhere began sharing similar observations. "The tenor of the meeting completely changed," says Steven Kernie, the chief of critical-care medicine at New York–Presbyterian Morgan Stanley Children's Hospital, who was on the call.

Until then, the news about children and COVID-19, the disease caused by the novel coronavirus, had been largely good: Kids can get seriously sick, but they rarely do. They can spread the disease, but they do it less than adults. Study after study—in China, Iceland, Australia, Italy, and the Netherlands—has found that children get less sick and are less contagious.

But a very small number of children seem to have a delayed reaction to the novel coronavirus —one that takes many weeks to manifest. What pediatricians first saw in Europe and New York is now named "pediatric multi-system inflammatory syndrome" (PMIS) or, per the Centers for Disease Control and Prevention, "multisystem inflammatory syndrome in children." Since the New York City Health Department issued an alert on May 4, 82 such cases have been confirmed in the city. Most patients have recovered or are recovering, but one child has died. Across the country, doctors are finding similar cases. PMIS does seem to be a phenomenon unique to kids.

But the virus is the same, whether it infects adult or child. The question is, why does COVID-19 affect them so differently? Both striking patterns in kids—the fact that most do not get very sick but a small number still end up with a delayed inflammation syndrome—may be rooted in a child's still-developing immune system. And although COVID-19 is a new disease, these patterns are seen with other viruses too.

Immune systems change with age, becoming weaker or stronger in different ways. An adult's body might be better armed against familiar threats, but more inflexible against novel ones. The two human viruses most closely related to the coronavirus that causes COVID-19 are the ones behind SARS and MERS—both also coronaviruses, a large family that infects many animal species. SARS likely jumped from bats to civet cats to humans in 2002, and MERS from camels to humans in 2012. Both have a much higher fatality rate than COVID-19 and neither exploded into a pandemic on the current scale, giving us smaller numbers from which to draw conclusions. Still, they too seemed to have largely spared children.

Like COVID-19, SARS and MERS were caused by viruses entirely new to humans, and adult immune systems are unused to dealing with entirely new viruses. By and large, the ones that sicken adults year after year are altered versions of viruses they've encountered before, such as seasonal flu. Children, on the other hand, are constantly dealing with viruses that are not necessarily novel but are novel to them. "Everything an infant sees, or a young child sees, is new," says Donna Farber, an immunologist at Columbia University. Thus, their immune system is primed to fight new pathogens in a number of ways.

Babies are born, for example, with a complete repertoire of immune cells called T cells. Every T cell has a unique receptor, and taken together, the pool of millions of T cells can recognize virtually any hypothetical pathogen. As the child begins encountering pathogens, though, their immune system winnows this diverse repertoire. It keeps the T cells involved in fighting off pathogens as a pre-stocked arsenal of "memory T cells," should those pathogens appear again, but it begins losing the others. This is why adults are able to mount a rapid immune response to previously encountered pathogens, but also why they might have trouble fighting a new one. Diseases such as rubella and chicken pox are also, for various reasons, more severe in adults than in children. The pattern with seasonal flu is different, Farber says, but that may be because immunity against previous strains of the flu offer some crossover protection in adults.

The same may actually be true for coronaviruses, too, only in children. Another hypothesis for why most kids are spared is that they are frequently infected with the four coronaviruses that cause some common colds. These cold coronaviruses are not as closely related to COVID-19 as SARS or MERS, but they still share some similarities. Immunity against these cold coronaviruses wanes over time, so children who have been recently exposed might have some protection that adults don't.

Yet another hypothesis has to do with the receptor ACE2, which the new coronavirus uses to enter a cell. The number of ACE2 receptors in the lungs seems to decrease with age, at least according to data in rats. Why would having more ACE2 decrease the severity of COVID-19? No one is quite sure, but ACE2 also seems to have other functions in the body linked to decreased inflammation and scarring, which may protect against severe disease. And in fact, viral infection decreases levels of ACE2. "It's not going to be as black-and-white as more receptors equal more virus infection, simply because this receptor does other things in the body," says Kirsty Short, a virologist at the University of Queensland. The story is rather complicated—and illustrative of how science is only starting to understand the virus behind COVID-19.

When the inflammatory syndrome now called PMIS first appeared in Europe and New York, its connection to COVID-19 wasn't totally clear. Not all the kids with PMIS symptoms were testing positive for the coronavirus. But as antibody testing has become more readily available, it is showing that most of them do have antibodies to the novel coronavirus—meaning they probably had the virus at one point in mild or asymptomatic form, and fought it off. Yet their immune system had kept ramping up instead of down, and this is the likely cause of the inflammation. A body's immune response usually peaks four to five weeks after infection, says Kernie, so it makes sense that New York is just now seeing a spate of PMIS cases, more than a month after its peak of COVID-19 cases.

Although PMIS is new, syndromes like it are not. "Having a post-viral-infection immune reaction is not uncommon in children," Kernie says. Common viruses such as herpes, hepatitis, and adenoviruses that cause colds can also lead to inflammation of the heart. PMIS also shares some symptoms with a mysterious inflammation of the blood vessels called Kawasaki disease. Scientists haven't identified a particular pathogen that triggers Kawasaki, but its symptoms also include fever, rashes, and, in some cases, damage to the arteries that carry blood from the heart.

The inflammation in these cases would be the result of low levels of lingering virus. Or it could be the consequence of an immune system that has mistakenly mobilized against the body itself. "When you mount a response to a virus, you can produce antibodies or T cells that actually recognize parts of the body," Farber says. And this might lead the immune system to start attacking other healthy tissue in the heart or nerves or gut. It's more common in young people, according to Farber, but not exclusive to them.

In general, the PMIS that appears in some kids may be analogous to the immune overreaction in some adults critically ill with COVID-19-damaged lungs. It's just happening in those kids without the lung damage first.

A very small percentage of children—usually with underlying health conditions—can get very sick right after contracting COVID-19, but another very small percentage end up getting PMIS weeks later, despite having mild or even no symptoms initially. These scenarios look very different. A recent analysis of the first group—48 children admitted to the ICU with COVID-19—found that most had respiratory symptoms and more than a third needed a ventilator. PMIS does not primarily affect the lungs. "This is not the same," says Jane Newburger, a pediatric cardiologist at Boston Children's Hospital.

And the new syndrome appears to be very rare. It's only become noticeable in the U.S. and Europe because so many kids have been exposed to COVID-19 that even rare effects become apparent. (Few PMIS-like cases have been reported out of Asia—possibly because fewer children there have gotten COVID-19 and possibly because of a higher background rate of Kawasaki-like symptoms in that region.) Gabriela Marón Alfaro, an infectious-disease doctor at St. Jude Children's Research Hospital who runs the Pediatric COVID-19 U.S. Registry, which tracks cases in kids, says her team is going back to review cases with symptoms suggestive of PMIS.

At this point, Kernie says, hundreds of thousands of kids may have gotten COVID-19 in New York alone, most of them with cases too mild to have warranted testing. But when a virus infects hundreds of thousands of people, even the extremely rare complications that affect only a fraction of a percent of patients will become more obvious. "We've never seen so many kids with the same virus at the same time," Kernie says.

PMIS is serious enough to require hospitalization, but it is not usually life-threatening. Newberger says all six patients at Boston Children's have recovered. Kernie's hospital in New York has had more than 30 PMIS cases, and the patients have responded to standard treatment for inflammation, including steroids and immunoglobulins. "I do try to make the point," Kernie says, "that the kids seem to do really well."

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