PNAS NEWS FEATURE

Understanding Kids and COVID

As researchers learn more about why COVID-19 tends to be much less severe in children, they're finding strategies that could help protect all age groups.

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Recent findings point to features of children's immune systems that may help protect them from the worst COVID-19 outcomes. Image credit: Shutterstock/David Tadevosian.

Since the start of the pandemic, even as the circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus shifted from Alpha to Beta to Delta variants, it was clear that most infected children got far less sick than infected adults. We counted our blessings. "The one thing that has allowed us to tolerate this pandemic better than we otherwise would have," former US Food and Drug Administration (FDA) Commissioner Scott Gottlieb said in a December interview with *USA Today*, "is that kids weren't getting very sick. If kids were excessively vulnerable to this the way older people were, I think it would have changed how society grappled with this."

Omicron's arrival threatened to change the story, as record numbers of pediatric cases began to surface. In early January, the Centers for Disease Control and Prevention (CDC) reported that more children were hospitalized with coronavirus disease 2019 (COVID-19) than at any previous time during the pandemic. Driving the frightening figures, scientists say, is a highly contagious—rather than more virulent—variant and a high rate of unvaccinated children. "When you have a heat-seeking missile like Omicron looking for hosts that don't have an immunity wall, it's going to find these kids who are not vaccinated," says Eric Topol, director of the Scripps Research Translational Institute in La Jolla, CA.

Thankfully, even with more Omicron cases, severe illness among infected kids remains extremely rare: The death rate for Americans under age 18 has stayed

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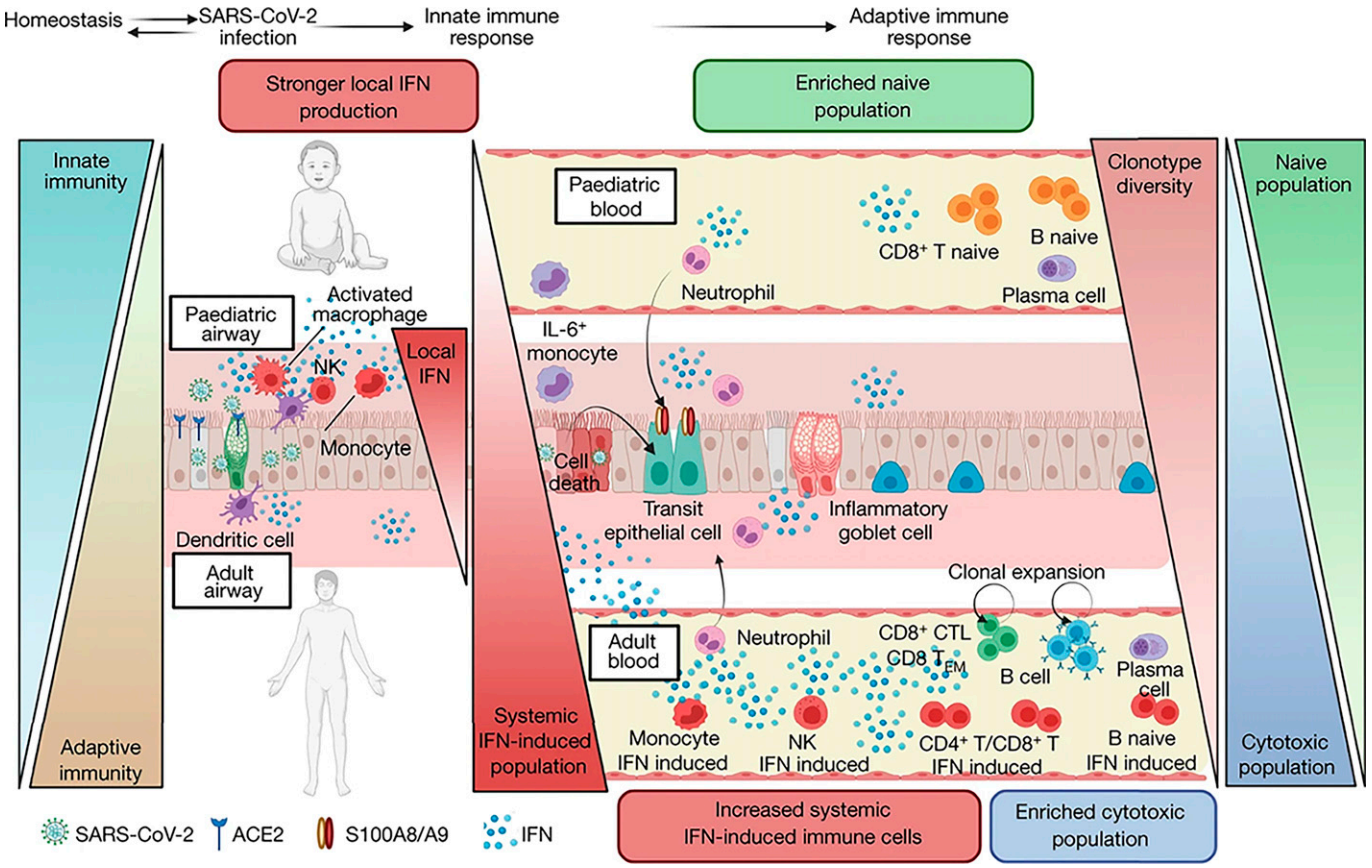

The differing maturation of kids' vs adults' immune systems has led to differences in the airway and systemic immune responses to SARS-CoV-2 infection. Immune cell proportions change throughout healthy childhood and adulthood, with a notable innate to adaptive immunity switch. In the airways, the local innate interferon response to SARS-CoV-2 is stronger in kids' immune cells. The systemic innate interferon response to SARS-CoV-2 is stronger in adults; their adaptive immune response is characterized by expanded cytotoxic populations, whereas there tend to be naïve populations in children. Epithelial cells with an inflammatory gene expression are found in COVID-19 patients. Clonotype diversity decreases with age. Image credit: Reprinted from ref. 1, which is licensed under CC BY 4.0.

at about 0.01%. "I don't think there's some magic threshold when you're 17 and 364 days or you're 18 and one day," says Emma Duncan, a professor of clinical endocrinology at King's College London in England. "But this is a disease where severity very much correlates with age."

The magnitude of the Omicron surge added both urgency and opportunity to solve that mystery of why children fare better than adults with COVID-19. Many clues now point to features of children's immune systems that may help protect them from the worst outcomes. Answers about how could point to needed strategies for preventing and treating COVID-19—in all its potential variant forms and for all age groups.

Innate Interference

It was clear early on that having relatively few comorbidities—obesity, diabetes, cancer, and other chronic conditions—helped spare most children from poor COVID-19 outcomes. And we have also long known that the immune system weakens and becomes increasingly dysregulated with age. But additional clues have since emerged. Most curiously, children and adults show fundamentally different immune responses to SARS-CoV-2 in their airways and blood (1).

The immune system consists of two key layers of protection: the innate and the adaptive responses. Present from birth, the innate immune response includes macrophages and other specialized cells that recognize and react rapidly to danger signals on bacteria and viruses. This first line of defense can also include responses, such as release of interferons, launched by nonimmune cells.

If viral or bacterial intruders break through the wall of innate immunity, the adaptive immune system initiates specific attacks on pathogens with T and B cells. Each time a child is exposed to a new pathogen, some proportion of these cells, those with the right receptors, recognizes the invader then divides and expands into an army of memory T cell clones. This happens repeatedly during a lifetime, building up an immunological memory.

Central to a child's superior response to the SARS-CoV-2 virus, according to recent studies, are a strong innate immune response and plentiful naïve T cells (1, 2)—those T cells that haven't yet matured into memory cells. Kerstin Meyer, a principal staff scientist at the Wellcome Sanger Institute in Cambridge, England, and coauthor of one of these studies, says that she was surprised to find a high level of interferons—immune proteins that contribute greatly to the control of viruses—ready and waiting in the mucosal lining of the airways of children, even in kids not infected by the virus. "The nasal epithelium was primed to prevent viral infections," explains Meyer.

A plethora of at-the-ready interferons is particularly useful in battling SARS-CoV-2, as the virus has proven very

good at suppressing the induced interferon response waged by the body (3). The virus disrupts several steps in the protein production process that typically boosts the interferon response more than 1,000-fold on virus detection, according to one study (4). Already primed interferons, though, are harder to evade. [A preprint paper suggests that Omicron may be somewhat less able to thwart interferon, including the induced response, than other variants (5).]

As soon as kids' immune systems see the pathogen, "they are revved up and ready to respond," says Betsy Herold, chief of the division of pediatric infectious diseases at the Albert Einstein College of Medicine in New York. "So, they can clear the virus a little quicker, which means it doesn't have the opportunity to replicate to as high a level in the lungs." Herold, working with her husband Kevan, a professor of immunology and endocrinology at Yale University in New Haven, CT, also found a vigorous mucosal immune response with high levels of interferon and fewer adaptive immune cells activated in children who were infected with SARS-CoV-2 relative to adults, supporting the idea that less virus was able to breach the innate fortress (6).

Despite these immune system advantages, children don't necessarily have fewer infections with SARS-CoV-2. In fact, notes Betsy Herold, at least older children may get COVID-19 at a rate comparable with or even higher than adults (7). It's hard to know because high numbers of asymptomatic kids could mean underestimates in case numbers and overestimates in hospitalization rates. But what's clear is that, despite more cases among younger children since the Omicron variant emerged and subsided, kids still don't get as sick as adults. The most recent US data estimate that children represent about 18.4% of all cases and just 1.7% to 4.4% of all COVID-associated hospitalizations.

One important caveat, notes Kevan Herold: A powerful innate response can also backfire, even in kids. There are still rare cases of multisystem inflammatory syndrome in children (MIS-C), in which a delayed immune response goes into overdrive and renders various body organs and systems dangerously inflamed. Scientists are still working on determining exactly what causes MIS-C, but evidence thus far points to involvement of the innate system. "Interestingly, there have been fewer cases of this outcome with the current Omicron variant," he says. "This might be because children have some memory from the first time they saw the virus, whether that was an Alpha or Beta or another variant."

Naïveté Can Be a Good Thing

As we age, the adaptive immune system's T and B cells take on a bigger role. Unfortunately, this slow shift during childhood and into early adulthood, toward a more memory-based adaptive system, comes with slowed production of new naïve T cells. The body is left with fewer unique immune receptors to potentially match with new pathogens.

To make matters worse, as we age, old naïve cells are less effective than new naïve cells, says Donna Farber, an immunologist at Columbia University in New York City. So older people have far fewer cells that can effectively recognize and respond to a novel threat like SARS-CoV-2. (Although when faced with a virus that their immune system remembers, such as influenza or respiratory syncytial virus [RSV], they may well have the advantage over children.)

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>
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"A young person's immune system, with more newly developed naive cells, is just more adapted for rapid responses to new antigens," says Farber. "That's what the system is designed to do: to respond to new antigens and to respond very well. Otherwise, we wouldn't survive childhood."

Farber coauthored a study published in December that found naïve cells in infant animals proliferated faster and were better able to travel to the site of infection in response to a lower dose of antigen compared with adult cells (8). And in a November 2021 paper (9) on the distinct immune responses to SARS-CoV-2 in adults and children, Farber reported that children generated fewer antibodies that target viral replication—suggesting a superior ability to eliminate the virus early on post-infection.

Meyer's work has also shown rapid production of additional naïve T cells after children were infected with SARS-CoV-2. In adults, however, only effector T cells and cytotoxic T cell clones expanded in response to the virus.

Stubborn Mysteries

And yet, even with all the clues researchers have collected, some of the factors aiding children remain a mystery. One theory suggests that children are protected by having fewer ACE2 receptors, which SARS-CoV-2 uses to get into cells (10). Lawrence Steinman, a pediatric immunologist at Stanford University, CA, and colleagues concluded in 2020 that reduced ACE2 in the respiratory tract was one of several likely explanations for milder illness in children (11). However, other results are mixed, and experts remain divided on whether children have lower ACE2 numbers or expression (12). There is even evidence that Omicron can enter host cells without ACE2 via endocytosis, being engulfed by the cell membrane into sacs called endosomes inside cells. An ACE2-independent mechanism could help explain the higher number of pediatric cases with this variant (13).

Another proposal for why children have an edge: fewer fat cells compared with adults. COVID-19 tends to be more severe for people carrying extra pounds. A preprint published in October found that the virus infects fat cells (14). So, overweight patients are "carrying around a bigger viral load with more fat cells for the virus to gain a hold in," says Steinman. Previous data have shown that the average number of fat cells rises until the age of 20.

Children's responses may also be primed by the frequent onslaught of respiratory infections—at least for

those attending daycares or schools. “Some of the ligands that are recognized by the innate immune cells are not specific for one particular virus,” says Kevan Herold. These ligands have a more generalized response compared with the antibodies and T cell responses.

Past exposure to coronaviruses might help repel SARS-CoV-2, according to some studies. T cells primed by endemic human coronaviruses—four viruses known to trigger symptoms of the common cold—could recognize enough of SARS-CoV-2 to attempt to bind to it. The S2 domain of the spike protein is similar—and therefore potentially recognizable—across these coronaviruses, explains Paul Moss, a professor of hematology at the University of Birmingham in England. For some people, having cross-reactivity from exposure to these other coronaviruses likely bolsters the immune system (15). Children, in particular, showed a robust and sustained cross-reactive response to SARS-CoV-2, Moss’ group reported in December (16). Another study published in January underscored a potentially protective effect of cross-reactive memory T cells against SARS-CoV-2 in household contacts (17). Still, Moss emphasizes that we don’t yet know just how helpful that cross-reactivity is. Children generate strong and sustained immune responses, “likely to any antigen they see,” he says. Even when children do contract the virus, cases tend to be mild, with an average illness duration of six days, according to a study that Duncan coauthored (18).

Even so, there are rare cases of long COVID in children, a malady researchers attempted to formally define in early February [that definition asserted in part: at least one persistent physical symptom for 12 weeks or more after initial testing (19)]. And other potential delayed health effects are emerging. A report in January by the CDC linked COVID-19 infections in children with a greater risk of developing diabetes (20). “I think the mechanism of long COVID is so poorly defined,” says Topol. “We don't want children to be infected if we can avoid it.”

The next iterations of SARS-CoV-2 might bring yet more surprises. “The frightening thing is how quickly these variants have developed,” says Moss. “So, I think we have to be prepared.” Yet, scientists remain confident that children’s reliance on preactivated innate responses should continue to give them an advantage.

Of course, SARS-CoV-2 is not going to be the last novel coronavirus we face. In just the last two decades, three coronaviruses have crossed species barriers and spilled into human populations. But there is reason to believe that children may continue to be spared from the worst of each virus: Epidemiological and clinical data from both SARS-CoV and MERS-CoV suggest these viruses, too, affect children less often and less severely than adults (21).

None of this is to say that children haven’t suffered and won’t continue to suffer as a result of COVID-19. Children have not only been missing out on their academic and social education but also their immune education. Rates of many other respiratory viruses dropped off during the initial wave of the pandemic. Experts fear that the drop in circulating viruses may increase susceptibility to serious infections. Last year, RSV reemerged in a rare summer outbreak in southern US states. The loss of early life exposures to various viruses could also have long-term consequences for children, such as more severe illness later in life.

“This is why we give children vaccinations during their early years,” Farber says, “because this is when you form the memories that you need for your life.”

Larger Lessons

Nevertheless, kids’ apparent COVID-19 resilience could suggest strategies for controlling the disease, regardless of the age group.

Among them: alternative vaccine approaches for SARS-CoV-2 buoyed by our growing understanding of children’s robust nonspecific immune responses. Based on findings that memory T cells from an earlier infection may offer cross-reactive protection against SARS-CoV-2, scientists are investigating the potential for vaccines that elicit T-cell immunity, rather than antibody responses, to the virus (15). Such T-cell–priming peptide jabs have shown promise in early clinical testing and may prove especially helpful for patients who don’t mount sufficient responses after inoculation with existing SARS-CoV-2 vaccines. Meanwhile, several research groups have been investigating existing vaccines for their potential nonspecific innate immune training, including vaccines for influenza, tuberculosis, polio, measles/mumps/rubella (MMR), hepatitis, and shingles (22).

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Early in the pandemic, a theory circulated that the countries with more recent campaigns of *Bacillus* Calmette-Guérin (BCG) vaccine—used to prevent tuberculosis—fared better. BCG vaccination had been associated with lower risks of other illnesses, such as malaria, and receiving a BCG dose before influenza vaccination was even shown to boost influenza-specific immunity. So far, data suggest that BCG vaccination is at least somewhat effective against COVID-19, with studies reporting protection against symptomatic disease of between 10% and 35% (23). One study of US military veterans, however, did not find any significant COVID-19 protection from BCG vaccination at birth (24).

An ongoing Australian-led study of BCG vaccination, the BRACE trial, seeks to further clarify BCG vaccine’s efficacy against COVID-19. The trial began in March 2020 and quickly expanded internationally, enrolling thousands of healthcare workers in Australia, Brazil, The Netherlands, Spain, and the UK. As experts note, even a small boost in protection could significantly reduce COVID-19 cases, hospitalization, and mortality.

And the science behind children’s impressive innate responses speaks to more than vaccine tactics. Based on findings from children, treatment with interferon during the early phase of infection may be “very promising” for people of all ages, says Meyer. However, interferon administered during the later stages of infection could be dangerous. The virus-fighting proteins are a potent first

line of defense; yet they also act as important signaling molecules that recruit other immune cells as part of the adaptive system, she explains. Interferon-induced cells have been found to fuel the proliferation of a cytokine storm in cases of severe COVID-19. Such cases are far more common in adults; children are better able to control infections locally.

Several trials are underway investigating the protective effects of an interferon injection or nasal spray, which could supercharge protective innate immunity. Delivery through the nose may be most effective in preventing disease, because this is often the point of entry for SARS-CoV-2 into the body.

Meyer highlights another possibility: that the beneficial innate response seen in children likely exists in some adults, too. "Looking for this profile in the nose of adults would help to risk-stratify people and target other treatments more effectively," says Meyer. "We have antibody cocktails that we can now give people who we know are at great risk. So, this would be another way of finding the people that those treatments would help most." Looking for this innate signature in the airways might be particularly helpful for people unable to get vaccinated, she notes.

The infamous spike protein, and kids' immune response to it, could be key to fine-tuning further approaches against COVID-19. "Are children seeing different parts of it?" Moss asks. Current monoclonal antibody injections, for example, generally target the S1 portion of the spike protein. Given the evidence that children mount stronger cross-reactive immune responses against the S2 domain, Moss suggests that targeting S2 may add a possible route for "novel and effective therapies." The immunological leads are there, and researchers are trying to follow them. "I think we've got a lot to learn," he says, "from children's responses."

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