Nahid Bhadelia, an infectious disease physician at Boston University, agrees the data so far are promising, but says only an RCT can give a final answer. Such trials are now underway in Germany, the United Kingdom, and the United States; results are expected in the months ahead.

Researchers have already collected more data on complications, and they seem to be rare. A U.S. paper looking only at the therapy's safety in the first 5000 patients found 36 severe adverse events, including TRALI and TACO cases, but some may have been the result of COVID-19 itself. Only two events were "definitely related" to the transfusion, according to the treating physician; 23 others were deemed "possibly" or "probably" related. "I wouldn't say the [safety] concerns have been put to rest, but they have been given a nap," says one of the authors, Michael Joyner of the Mayo Clinic.

Convalescent serum could also help prevent infection in those at high risk. In a trial coordinated by Johns Hopkins, 150 health care workers exposed to COVID-19 while not wearing proper protection will receive either convalescent serum or serum collected last year. Researchers will compare how many people in each group develop disease.

If convalescent plasma is shown to work, much more of it may be needed, and supply could become a challenge, Bhadelia says. One plasma donation—the volume depends on the donor's weight but it's usually between 690 and 880 milliliters in the United States—is enough for just one or two patients, and the donor's blood type needs to match the recipient's. But recovered patients might be able to donate plasma multiple times. In New York City, there is now more than enough to go around, in part because thousands of members of the hard-hit Orthodox Jewish community have donated.

Consistency is also an issue. The mix and concentration of antibodies differs from one donor to the next, which "is one of the unfortunate reasons why the clinical evidence generated around convalescent plasma has remained rather shallow," says Thomas Kreil, head of pathogen safety at Japanese pharma company Takeda. Together with several partners, Takeda is working to produce a product called hyperimmune globulin, for which the blood of hundreds of recovered patients is pooled and the antibodies concentrated about 10-fold. Hyperimmune globulin has a longer shelf life than plasma, and its higher concentration would allow doctors to give more antibodies to patients without the risk of TACO. An efficacy trial, funded by the U.S. National Institutes of Health, could start this summer. ■

COVID-19

Doctors race to understand inflammatory condition in kids

Studies are launching to pinpoint children most at risk

By **Jennifer Couzin-Frankel**

Three children at one London hospital in mid-April, followed the next day by three at another—for Elizabeth Whittaker, a pediatric infectious disease doctor at Imperial College London, those first cases raised an alarm. The youngsters had fevers, rashes, stomach pain, and, in some cases, heart problems, along with blood markers that characterize COVID-19 in adults, including one associated with clotting. But in most, nasal swabs failed to reveal any virus.

"I don't understand—they look like they have coronavirus," Whittaker recalls thinking. Doctors nonetheless suspected a link. Within days, a survey turned up 19 additional cases across England, and an alert on 27 April asked doctors to be on the lookout for such symptoms in children. Soon after, dozens more cases surfaced in New York along with smaller clusters elsewhere, bolstering a connection to the pandemic. Reports of children on life support and some deaths put parents on edge—and were especially disheartening after earlier signs that COVID-19 largely spares children from serious illness.

It is another surprise from a virus that has proffered many, and projects worldwide are gearing up to study it. They are combing the blood and sequencing the genomes of patients—and the virus, if it can be isolated from them—to search for clues to what makes some children susceptible and how to head off the worst symptoms. There's hope that what's learned from young patients might help the many adults in whom COVID-19 also triggers a grievous overreaction of the immune system.

In some respects, "It's absolutely not shocking" to see this, says Rae Yeung, a rheumatologist and immunologist at the Hospital for Sick Children in Toronto, whose center treated about 20 children with similar symptoms over the past 3 weeks. Many pathogens occasionally trigger a similar hyperactive immune response in children, known as Kawasaki disease. Its symptoms vary but include rash, fever, and inflammation in medium-size blood vessels. Children can suffer heart complications. In rare cases, blood pressure plummets and shock sets in.

Doctors disagree on whether the variant linked to COVID-19 is Kawasaki disease or something new, with some experts calling it multisystem inflammatory syndrome in children. But as with Kawasaki disease, most patients recover with treatment, including steroids and immunoglobulins, which calm the immune system.

A girl in New Delhi gets a nasal swab to test for the new coronavirus.

PHOTO: AMARJEET KUMAR SINGH/SOPA IMAGES/LIGHTROCKET/GETTY IMAGES

In linking the inflammatory syndrome to COVID-19, "We're going on more than just a hunch," says Jesse Papenburg, a pediatric infectious disease specialist at Montreal Children's Hospital, in a city that's seen about 25 children with the condition. Kawasaki disease is rare, ordinarily affecting just one to three in every 10,000 children in Western countries, though it's more common in children with Asian ancestry. The spikes recorded so far, in COVID-19 hot spots like northern Italy and New York City, track the novel coronavirus' march around the world. And although a minority of these children test positive for SARS-CoV-2, a study published in *The Lancet* by a team in Bergamo, Italy, reported that eight of 10 children with the Kawasaki-like illness had antibodies to the virus, indicating they had been infected. Positive antibody tests have been reported in sick children elsewhere, too.

"It was obvious that there was a link," says Lorenzo D'Antiga, a pediatrician at the Papa Giovanni XXIII Hospital who led the study. The new coronavirus can elicit a powerful immune response, which he thinks may explain why shock and a massive immune reaction called a cytokine storm are more common in the COVID-19–linked cases than in textbook Kawasaki disease. And a time lag between infection and the Kawasaki-like illness could explain why many of the affected children show no evidence of the virus. The immune system's overreaction may unfold over weeks, though virus could also be hiding somewhere in the body.

"There's clearly some underlying genetic component" that puts a small number of children at risk, says Tom Maniatis, founding director of Columbia University's Precision Medicine Initiative. New York state is investigating at least 157 cases, and Maniatis is also CEO of the New York Genome Center, which is pursuing whole-genome sequencing of affected children and their parents, as well as sequencing the virus found in children, with family consent. Finding genes that heighten risk of the illness or of developing a severe case could point to better treatments or help identify children who may take a sudden turn for the worse.

Genetics may also help explain a puzzle: why the illness hasn't been reported in Asian countries, even though Kawasaki disease is far more common in children with Asian ancestry. The virus' own genetics may be important; an analysis last month indicated that the predominant viral variant in New York was brought by travelers from Europe. It's also possible that the Kawasaki-like illness is so rare that it only shows up in COVID-19 hotbeds. "The areas that have been hardest hit by coronavirus are the areas reporting this syndrome now," says Alan Schroeder, a critical care physician at Lucile Packard Children's Hospital at Stanford University, which has seen one potentially affected child, a 6-month-old baby, who recovered quickly.

Yeung is also pursuing ways to flag children with COVID-19 who are at risk of this complication. She co-leads an international consortium that's banking blood from affected children, both before and after treatment, and screening for various markers, including the cytokine molecules that indicate a revved-up immune system. The group is also searching for gene variants known to predict poor outcomes in Kawasaki disease. "There's also core COVID stuff that needs to be measured," Yeung says, such as markers of heart function and levels of D-dimer, a protein fragment in the blood that indicates a tendency toward clotting and that surges in many sick adults.

A European Union Horizon 2020 project called DIAMONDS, originally designed to improve diagnosis of pathogens in children with fevers, is recruiting children across Europe with the Kawasaki-like complication, along with those who have run of the mill COVID-19 symptoms. Scientists will study blood for pathogens—not just SARS-CoV-2—and the behavior of immune cells such as T cells and B cells.

"We have to do a deep dive into the immunology of those patients," says Elie Haddad, a pediatric immunologist and scientist at Sainte-Justine University Hospital Center who, with Yeung and Susanne Benseler at Alberta Children's Hospital, is leading a Canadian research effort on the new syndrome. These deep dives may also clarify the immune system chaos seen in many sick adults. Children are "cleaner," Haddad points out—they're less likely to have other health burdens, such as diabetes or high blood pressure, that can make it harder to tease out the virus' impact on the immune system.

Last week, young adults with possible cases of the condition were identified, suggesting it may not be limited to children. A global effort studying COVID-19 in adults, called the International Severe Acute Respiratory and Emerging Infection Consortium, will look at adults' clinical data and blood samples, Whittaker says, "to see, is this a uniquely pediatric problem?"

Eager as they are to understand this new face of the pandemic, doctors want to avoid overstating the hazards. "We need to identify early and we need to intervene early" in treating these children, Yeung says. But she also urges calm. "The kids we're seeing so far," she stresses, "they respond to the treatments we're giving." ■

ILLUSTRATION: SARA GIRONI CARNEVALE

By **Jeffrey Brainard**

Timothy Sheahan, a virologist studying COVID-19, wishes he could keep pace with the growing torrent of new scientific papers related to the pandemic. But there have just been too many—more than 5000 papers a week. "I'm not keeping up," says Sheahan, who works at the University of North Carolina, Chapel Hill. "It's impossible."

A loose-knit army of data scientists and software developers is pressing hard to change that. They are creating digital collections of papers and building search tools powered by artificial intelligence (AI) that could help researchers quickly find the information they seek. The urgency is growing: The COVID-19 literature has grown to more than 31,000 papers since January and by one estimate is on pace to hit more than 52,000 by mid-June—among the biggest explosions of scientific literature ever.

The volume of information "is like what you would get in a medical conference that used to happen yearly. Now, that's happening daily," says Sherry Chou, a neurologist at the University of Pittsburgh Medical Center who is studying COVID-19's neurologic effects.

"People don't have time to read through entire articles and figure out what is the value added … and what are the limitations," says Kate Grabowski, an epidemiologist at Johns Hopkins University's School of Medicine who leads an effort to create a curated set of pandemic papers.

It's not clear, however, whether the emerging efforts will tame the tsunami.

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