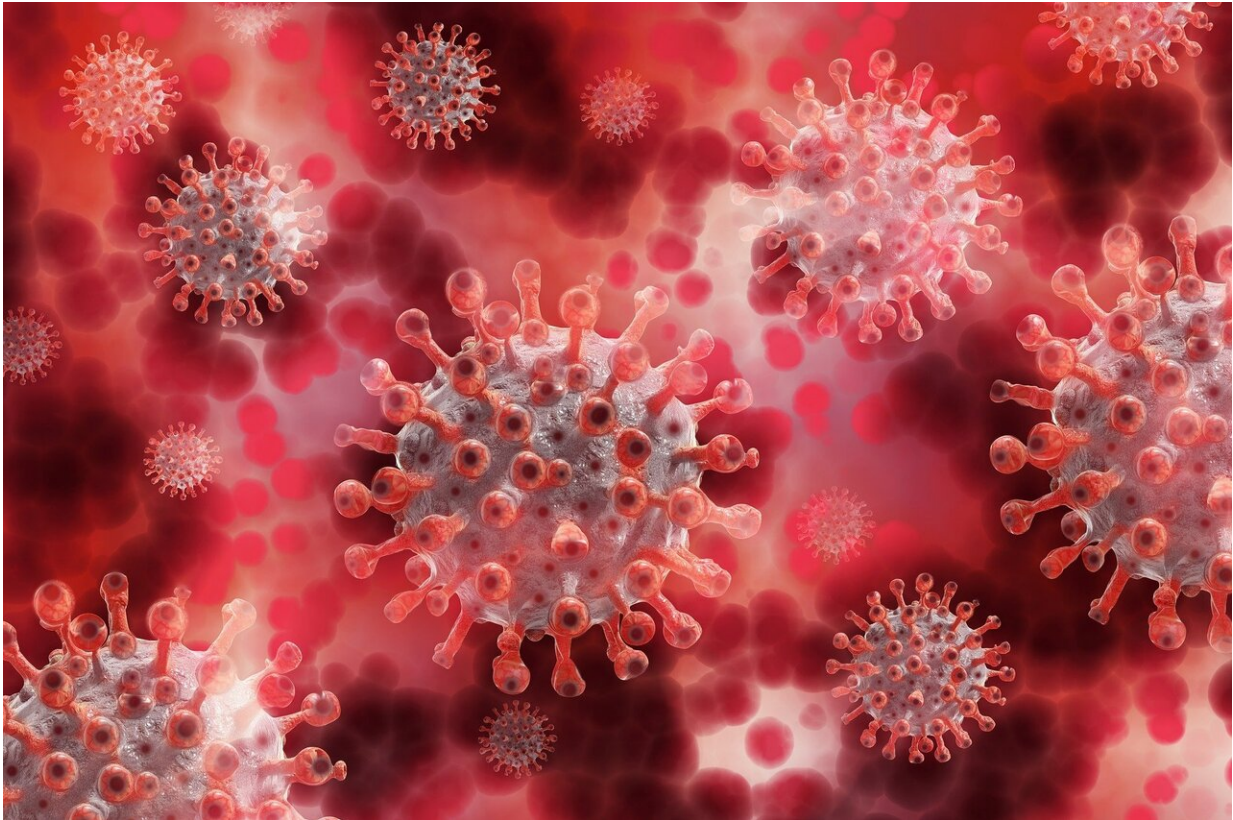


Long COVID in kids is a unique challenge

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Early in the pandemic, when children were thought to be at little risk from COVID-19, Lawrence C. Kleinman helped set the record straight—documenting some of the first cases of a severe complication called multisystem inflammatory syndrome.

In 2021, the Rutgers University pediatrician is trying to set the record straight again, studying how children, like adults, can experience "brain fog," fatigue, and other lingering symptoms known as long COVID.

It's not that long COVID is unknown in children, but Kleinman—a professor at Rutgers Robert Wood Johnson Medical School and at the university's school of public health—suspects it is underrecognized. What's more, he says these chronic symptoms present unique challenges for children, potentially interfering with development in ways that are not fully understood.

He is helping to run a new study, funded by the National Institutes of Health, to track the physical and mental health of several thousand children and young adults who have tested positive for COVID. The group includes both those with long COVID as well as those who've had the inflammatory syndrome (MIS-C), which typically emerges several weeks after the initial infection. Together, the two overlapping categories are collectively known as PASC: post-acute sequelae of COVID.

We spoke to Kleinman about the latest findings on these patients with long-term symptoms, and what more he and collaborators hope to learn from the approximately \$30 million study. He also is conducting a separate study of how to predict which children are at risk of severe and long-term complications.

How often do children develop long-term symptoms?

For PASC overall, the estimates really vary. There was a study in Italy early on that suggested it was north of 40% in kids (who had been infected). There were others that suggested it was more around 5 to 10%. If we think about children on a developing trajectory, they're growing, they're developing new skill sets. We have to think about the

symptoms that exist when you're sitting there looking at the child, and what is the impact on the child's life trajectory that might be changing—if they will learn differently, if there are disruptions that are not yet evident, or if there may be things that are present but not evident at rest.

In other words, there are clinical things that may be immediately observable. There may be biochemical or molecular markers that may be immediately available. And there may be things that emerge in response to some sort of stress. There may be things that are developmental that become apparent over time. There's a wide range, and that makes it very hard to have the exact answer.

What about the subset of kids with the inflammatory syndrome?

For each million identified COVID infections in children, a recent study identified 316 such cases, yet the rate was much higher in Blacks, Hispanics, and Asian Americans.

And keep in mind the CDC's definition of MIS-C at this point requires hospitalization. Milder inflammatory syndromes may well exist at higher numbers that don't cross that threshold, or don't get identified, or don't get associated with COVID at all.

The syndrome is characterized by fever, and the involvement of at least two organ systems. The gastrointestinal system is very commonly involved. And conditions like myocarditis and heart failure and other cardiac manifestations. There's typically a lag time of about a month from when the child first had the COVID. They may or may not even know they had the COVID. A lot of the kids end up in the ICU. Thankfully, most recover. A few die, and some have lingering

symptoms.

In young adults, it's not so much different. It's a similar pathway. The same thing is happening in the body. It's just at a different age.

What do you hope to learn about kids with long covid?

We want to understand the development trajectory in these children. If in fact that's altered, that would be unique in kids. What we see often is the child does not have a clear head. Brain fog is a term that people have been using. Another aspect is this lack of stamina or reduced exercise capacity, or inability to even take on normal aspects of daily living. I think those symptoms are similar in adults. But we don't really know in the very young [children](#). If they are acting a little differently, is that long COVID, or is it changes associated with normal childhood development?

And I think there's a second type of long COVID.

When someone in the child's life orbit has gotten COVID, there can be stress, economic deprivation, loss, grief, survivor guilt—all these kinds of things may happen. I think the whole pandemic has been traumatic to many.

If some of these long-term symptoms are due to inflammation, would anti-inflammatory medicines be helpful?

I think we know that the MIS-C piece has a lot of inflammatory components. But the long COVID, I don't think we know. There's a tremendous amount of uncertainty. It wouldn't surprise me if some of it was inflammatory.

At the moment, a lot of the focus has been looking at rheumatological drugs and immune modulators rather than general anti-inflammatories, although steroids have played a role (in treating hospitalized patients). Part of what this study may do is identify patterns of symptoms that then are sufficiently homogeneous that patients can become—should they volunteer and be willing—participants in research studies to understand treatment.

You're looking to identify distinct phenotypes: distinct groups of symptoms that seem to hang together, so that we can say 'Ah, this is a group for whom we can study both the mechanisms of the illness, and therefore how we might disrupt those mechanisms with therapeutics.' It's like the step before doing a trial. But there's no question that identifying who to treat, and various treatments and how effective they are, is the ultimate goal of this.

Tell us about your other study to predict which children are most at risk

It's ongoing. We're actually looking at a bunch of things. We're looking at what's going on in the community. We're looking at social determinants of health, various stressors that might impact the body. And we're looking at the genetics and genomics of those factors, and we're looking at the immune function. That's the focus we have, bringing that together with clinical data, what comorbidities or other illnesses they have, then also the community factors. We want to bring all of those together to try to help predict who is at greatest risk.

Are there ways to prevent long covid?

The best way to prevent long COVID is to avoid being infected with COVID.

Vaccination, among those who are eligible, is essential to the population and public health response to this. Vaccination is the first and foremost. Also masking and social distancing.

How might the omicron variant change the equation?

Each of these new variants poses a risk. As variant gives way to more variants, does that change the prevalence of long COVID? Does a less severe infection mean you're more likely to get long COVID? Less likely to get long COVID? We don't know these things. Some of them we'll never know. We'll at least be able to study them on average.

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