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Children with COVID-19 are at risk of developing long-term symptoms.

LONG COVID AND KIDS: SCIENTISTS RACE TO FIND ANSWERS

Children get long COVID too, but researchers still need to find out how frequently and how severely.

By Dyani Lewis

As COVID-19 has ripped through communities, children have often been spared the worst of the disease's impacts. But the spectre of long COVID developing in children is forcing researchers to reconsider the cost of the pandemic for younger people.

The question is particularly relevant as the proportion of infections in young people rises in countries where many adults are now vaccinated — and as debates about the benefits of vaccinating children intensify.

Most people who survive COVID-19 recover completely. But for some, the poorly understood condition known as long COVID can last for months — maybe years. Nobody yet knows.

The condition was first described in adults. But several studies have now reported a similar phenomenon, including symptoms such as headache, fatigue and heart palpitations, in children, even though they rarely experience severe initial symptoms of COVID-19.

Estimates of how common long COVID is in children vary wildly. Researchers say that pinning this down is crucial, because decisions about school closures and vaccine roll-outs can hinge on the risk the virus poses to children. Getting solid numbers is "very, very important," says Pia Hardelid, a child-health epidemiologist at University College London.

Paediatrician Danilo Buonsenso, at the Gemelli University Hospital in Rome, led the first attempt to quantify long COVID in children. He and his colleagues interviewed 129 children aged 6–16 years, who had been diagnosed with COVID-19 between March and November 2020.

In January, they reported in a preprint that more than one-third had one or two lingering symptoms four months or more after infection, and a further one-quarter had three or more symptoms. Insomnia, fatigue, muscle pain and persistent cold-like complaints were common — a pattern similar to that seen in adults with long COVID. Even children who'd had mild initial symptoms, or were asymptomatic, were not spared these long-lasting effects, Buonsenso says.

The findings, published in a peer-reviewed journal in April[1], sparked a deluge of e-mails and calls from anxious parents, he says. The hospital now runs a weekly outpatient clinic to meet demand.

Data released by the UK Office of National Statistics (ONS) in February and updated in April also sparked concern. They showed that 9.8% of children aged 2–11 years and 13% aged 12–16 years reported at least one lingering symptom five weeks after a positive diagnosis. Another report in April found that one-quarter of children who were surveyed after discharge from hospital in Russia post-COVID-19, had symptoms more than five months later[2].

The numbers reported aren't as high as they are for adults. The ONS data, for instance, show that about 25% of 35–69-year-olds had symptoms at 5 weeks. But the numbers still set off alarm bells, because severe COVID-19 in children is much rarer than in adults, and most kids were therefore assumed to have been spared the impacts of long COVID, says Jakob Armann, a paediatrician at Dresden University of Technology in Germany.

If 10% or 15% of children, irrespective of the initial severity of the disease, do have long-term symptoms after all, "that's a true problem", he says, "so this needs to be studied".

But Armann suspects numbers might not be that high. Long-COVID symptoms include fatigue, headache and insomnia. He says that other pandemic-related phenomena, such as school closures and the trauma of seeing family members sick or dying from COVID-19 could result in those symptoms too, and artificially inflate long-COVID estimates. "You need a control group to tease out what is truly infection-related," he says.

He and his colleagues have been taking blood samples from secondary-school children in Dresden since May 2020 to track rates of infection. In March and April this year, surveys were taken from more than 1,500 children — nearly 200 of whom had antibodies indicating previous SARS-CoV-2 infection — to see how many reported long COVID.

In May, Armann's group reported in a preprint that it found no difference in rates of symptoms reported by the two groups[3]. "This was kind of striking," says Armann, and suggests that the prevalence of long COVID in children is probably lower than some studies have indicated. That doesn't mean that long COVID doesn't exist in children, he says, but it does mean the number is probably below 10%, a level that would have been picked up in the study. The true figure is perhaps as low as 1%, he says.

Hardelid tapped into data gathered by the Virus Watch study, which tracks infections and symptoms in more than 23,000 households across England and Wales. As they reported in a preprint in June, she and her colleagues found that 4.6% of children with evidence of SARS-CoV-2 infection had persistent symptoms lasting more than 4 weeks[4].

Another UK study, posted as a preprint in May, found a similar rate. Of more than 1,700 schoolchildren who tested positive

for SARS-CoV-2, 4.4% had symptoms, such as headache, fatigue and loss of smell, that persisted; 1.6% had symptoms that remained for at least 8 weeks[5].

It will also be important to determine how long the condition lasts in children, says Armann. Headaches or trouble sleeping for just 6 months is a vastly different problem from having these symptoms all their life, even if it only happens for 1%, he says.

Buonsenso says that one of the challenges in working out how many kids develop long COVID is that there are no set diagnostic criteria in adults, let alone in children. Surveys to detect symptoms usually cast a wide net, and are not yet specific enough to tease out long COVID from other conditions, he says. Nevertheless, he is convinced that some children — perhaps 5–10% of those with COVID-19 — do develop the condition.

If psychological distress were a big factor in the symptoms he's seeing, as Armann has suggested, Buonsenso argues there would have been more children with symptoms from the first wave of infections in 2020, when restrictions were harshest in Rome. Instead, the second wave resulted in more cases of children with symptoms of long COVID, he says.

A proper definition of long COVID is urgently needed, says Hardelid, so that studies can determine how much of a problem it presents in children.

One suggestion, following a review of the literature in adults by the UK National Institute for Health Research, is that long COVID could be a collection of four different syndromes, including post-intensive care syndrome, post-viral fatigue syndrome and long-term COVID syndrome[6]. This could be the case in children, too, says Hardelid.

Buonsenso has also been looking at immunological changes that occur in people with long COVID, to see whether there are biological markers that could lead to treatments. In a small study posted as a preprint in May, he and his colleagues found that only the children with long COVID showed signs of chronic inflammation following infection[7].

Such investigations into the biological basis of long COVID could have far-reaching effects. In general, we know very little about chronic post-viral conditions, says Buonsenso, because most clinical attention, and funding, has focused on the acute phase of infections.

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WHAT THE RISE OF 'ARPA-EVERYTHING' WILL MEAN FOR SCIENCE

The renowned US Defense Advanced Research Projects Agency is inspiring science-agency mimics.

By Jeff Tollefson

US President Joe Biden's administration wants to create a US$6.5-billion agency to accelerate innovations in health and medicine — and revealed new details about the unit last month[1]. Dubbed ARPA-Health (ARPA-H), it is the latest in a line of global science agencies now being modelled on the highly regarded US Defense Advanced Research Projects Agency (DARPA), whose work a generation ago laid the foundation for the modern Internet.

With more DARPA clones on the horizon, researchers warn that success in replicating DARPA's hands-on, high-risk, high-reward approach is by no means assured.

"The ARPA model has been successful, and we've learned a lot," says Laura Diaz Anadon, who heads the Cambridge Centre for Environment, Energy and Natural Resource Governance at the University of Cambridge, UK. "But ARPA is not a magic bullet that will apply to everything."

Enamoured with the innovation that DARPA fostered in the United States, governments around the world, including in Europe and Japan, have attempted to duplicate the agency within their own borders. Most recently, the United Kingdom announced plans to create its version, the Advanced Research and Invention Agency (ARIA), with an initial allocation of £800 million (US$1.1 billion). And the Biden administration has proposed launching a second US agency, the $500-million ARPA-Climate (ARPA-C), to spur technologies for fighting climate change.

Scientists who have studied the DARPA model say it works if applied properly, and to the right, 'ARPA-able' problems. But replicating DARPA's recipe isn't easy. It requires the managers who build and run an agency's grant programmes to have the freedom to assemble research teams and pursue risky ideas in promising fields that have typically been neglected by conventional industrial research and development programmes. Critics aren't yet sure how ARPA-H, ARPA-C and ARIA will fare.

The US Department of Defense established DARPA in 1958, one year after the Soviet Union launched the world's first satellite, Sputnik 1. The goal was to ensure that the United States remained a world leader in technology. DARPA was instrumental in early computing research, as well as in developing technologies such as GPS and unmanned aerial vehicles.

DARPA functions differently from other major US science funding agencies, and has a leaner budget ($3.5 billion). Its roughly 100 programme managers, borrowed for

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DARPA investments have led to the creation of technologies such as unmanned aerial vehicles.