Unraveling long COVID's causes and impacts

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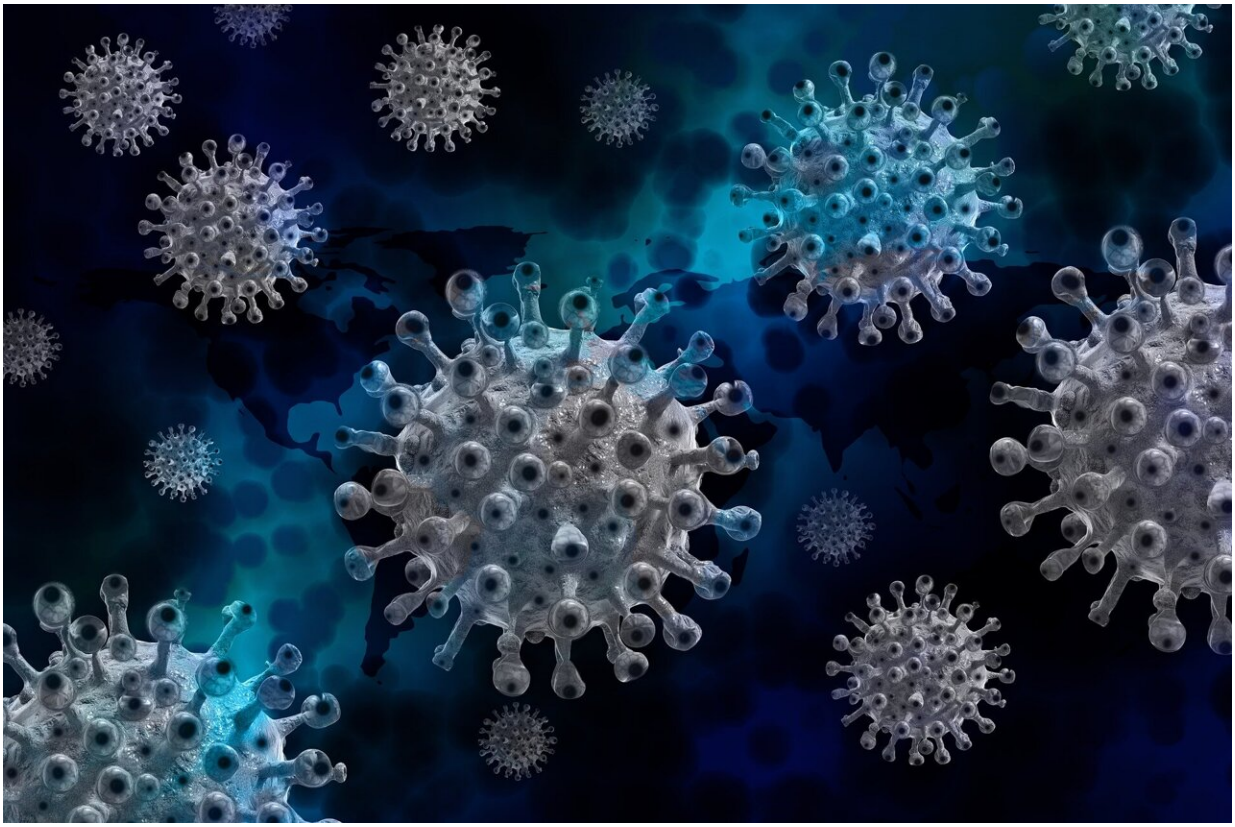

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Most of the time, viruses leave our bodies as quickly as they arrived. After we suffer a week or two of fever, muscle aches, and other indignities, a surge of antibodies sends the miniature invader on its way. Case closed.

At least, that's what is supposed to happen.

But for some, the misery doesn't abate even after all signs of virus have vanished. These individuals, though disproportionately female, hail from all socioeconomic groups, races, ethnicities, and locations. They report a perplexing range of issues, from cardiac problems and crippling pain to brain fog and shortness of breath. Many say their doctors dismiss and belittle their symptoms, and they often suffer for years before getting a diagnosis—if they get one at all.

The COVID-19 pandemic renewed scientific interest into these problems. The specter of post-acute SARS-CoV-2 infection emerged in Spring 2020, even as health systems were in the throes of the initial case surge. Soon, people with mild or even asymptomatic cases also began reporting brain fog, shortness of breath, kidney problems, and cardiac issues—problems that became known as long COVID.

Reports about the prevalence of long COVID vary widely, but a June 2022 CDC study estimates that as many as 20 million American adults—1 out of 13 people over age 18—have lingering COVID-19 symptoms that impact their lives months after infection.

"It's a mass disabling event," says Alba Azola, MD, co-director of the Johns Hopkins Post-Acute COVID-19 Team. Some of these individuals can't work and they can't be caregivers for children or aging parents, she says. "The impacts are staggering."

The onslaught of cases has given epidemiologists like Priya Duggal, Ph.D. '03, MPH '98, an opportunity to investigate why some individuals never seem to recover from COVID-19, and what factors impact how well they function.

What makes the issue a burgeoning public health crisis, Duggal says, is

the sheer number of patients affected.

"We have a scale that's unprecedented," Duggal says.

Duggal's interest in long COVID stems from a career spent studying pathogens by understanding the genomics of the people infected. Pre-pandemic, her work focused on acute flaccid myelitis, a rare syndrome affecting children. Children with AFM lose muscle strength and reflexes, affecting their ability to walk, talk, and swallow. Scientists have linked the condition to a common enterovirus. Duggal is comparing the genetic makeup of affected children with their unaffected counterparts to try and understand why and how some kids, but not others, get so sick.

In early 2020, when the first reports of a novel coronavirus emerged from Wuhan, Duggal had already spent more than a decade thinking about the long-term effects of infections. Many pathogens, epidemiologists know, can have consequences that persist long after every trace of the pathogen is gone. In the wake of West Africa's devastating Ebola outbreak in 2014–16, many of those infected continued to report lingering symptoms such as headache, muscle pain, and eye inflammation.

After a 2004 outbreak of the parasite Giardia lamblia in Norway, one in 20 of those afflicted reported long-standing intestinal and neurologic symptoms. Across the U.S. and Europe, an estimated 10% of those infected with Borrelia burgdorferi will develop post-acute Lyme disease. Regardless of the causative pathogen, many people with post-acute sequelae receive a diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Although an individual's chances of being affected by long-term sequelae after any single infection is quite small, the combined effects of all infections in an entire population is likely substantial—although no

one has yet determined how many people suffer these impacts. One issue is that it's unclear whether each pathogen has its own post-infection sequelae or whether these symptoms can be grouped together. Nor do researchers know exactly what causes them, which adds to the confusion, says virologist Andrew Pekosz, Ph.D., a professor in molecular microbiology and immunology.

To fight an infection, the immune system must carefully titrate its response, mustering an inflammatory response vigorous enough to halt the invader but not so strong that it damages the host. One of the leading theories about long-term infection sequelae is that the inflammation persists even after the virus or bacterium is vanquished. A related hypothesis is that the initial surge of antibody production leads to the formation of autoantibodies made against the body's own proteins. These autoantibodies attack the body, damaging cells. Another theory: The pathogen isn't actually gone. Some researchers hypothesize that a small, undetectable reservoir of infectious organisms persists that provokes the symptoms in these individuals.

"We always point to inflammation as the driving force for these symptoms, but it's been really difficult to find a reason why most people control the inflammatory response and a certain subset of people just don't," says Pekosz.

That's where Duggal comes in. Her work to understand AFM by studying the genomics of those affected has positioned her perfectly to untangle the complicated web of post-acute infection sequelae.

"We know lots of viruses create persistent problems—what would make this virus any different? Why wouldn't we be wanting to think about long-term impacts?" she says.

As reports of a novel coronavirus began to bubble up, the public health

and medical communities focused on slowing the virus's spread and treating the desperately ill. But Duggal was thinking along a different track. She wanted to know what happened after the initial infection. Duggal hoped she would be proven wrong—that SARS-Cov-2 would touch humans only briefly and move on—but the emergence of #longcovid hashtags on social media quickly confirmed her suspicions.

Fellow Epidemiology professors Shruti Mehta, Ph.D. '02, MPH '98, and Bryan Lau, Ph.D. '04, ScM '99, MHS '99, shared Duggal's concerns. Their work in HIV and hepatitis C had given them an interest in the ongoing issues caused by viral infections, even if the potential mechanisms were completely different. Both of them work on the ALIVE Study, which has followed people who use injection drugs in Baltimore since 1988. The study began as an effort to understand risk factors for HIV infection and subsequent progression to AIDS. Over the years, it has expanded to include co-occurring infections such as HCV and the aging process in HIV-positive individuals. Those studies, Mehta says, required a large cohort of individuals, something that she and Lau knew would be just as important with COVID-19.

In April 2020, the three epidemiologists wrote a short article calling for the formation of a longitudinal cohort study to collect baseline data on participants before being infected with the coronavirus and following them for months and years afterward. They submitted their article to peer-reviewed journals, but with so many other pressing issues surrounding SARS-CoV-2 garnering journals' attention, the article languished.

As time passed, it became increasingly obvious that the trio's concerns were prescient. "Am I surprised that there are long-term sequelae? Not necessarily. But the frequency? Absolutely," Mehta says.

The numbers were a tragedy and an indictment of global public health's

failure to contain the virus. But they also presented an opportunity to study post-acute infection sequelae in more detail. With so many people experiencing lingering symptoms from the same virus, it might be possible to learn more about who was most at risk—and why.

"Even if just one-half [of one] percent of people were affected, that's still a huge number of people," Lau says.

So Duggal, Lau, and Mehta teamed up again in February 2021 to launch the Johns Hopkins COVID Long study, a worldwide effort to gather data on the types and severity of health problems that people experience in the weeks and months following COVID-19, and how much it limits previous activities. Ideally, Lau says, they would have scaled up their initial proposal to identify a cohort of uninfected individuals in the pandemic's early days and followed them over time. To understand the changes brought by SARS-CoV-2 infection, researchers need to be able to compare post-infection biology to a pre-COVID baseline. Now, however, so many people have already been infected and/or vaccinated that finding someone with no exposure is almost impossible. And if they do find such people, scientists couldn't assume that they are representative of the population at large. In the absence of these longitudinal studies, Duggal, Mehta, and Lau are trying to capture details about how post-COVID-19 symptoms affect someone's overall health as well as their ability to perform basic activities like walking around the block, walking up steps, cooking and cleaning.

To date, their survey has accumulated over 17,500 responses; they hope to gather 25,000 for a preliminary analysis. The team has focused on disability related to long COVID, which in many cases dramatically limits people's ability to do everyday tasks.

"The knowledge that a single virus can do that is really, really humbling. All we can do is hope that we keep learning more to try to get there and

understand it better," Duggal says.

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