SCIENCEINSIDER HEALTH

In rare cases, coronavirus vaccines may cause Long Covid–like symptoms

Brain fog, headaches, blood pressure swings are being probed by NIH and other researchers

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A Long Covid patient at a hospital in Poland plays a virtual reality game to test reaction skills. BARTOSZ SIEDLIK/AFP VIA GETTY IMAGES

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In late 2020, Brianne Dressen began to spend hours in online communities for people with Long Covid, a chronic, disabling syndrome that can follow a bout with the virus. “For months, I just lurked there,” says Dressen, a former preschool teacher in Saratoga Springs, Utah, “reviewing post after post of symptoms that were just like my own.”

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As time passed, the Dressens found other people who had experienced serious, long-lasting health problems after a COVID-19 vaccine, regardless of the manufacturer. By January 2021, researchers at the National Institutes of Health (NIH) began to hear about such reports and sought to learn more, bringing Brianne Dressen and other affected people to the agency's headquarters for testing and sometimes treatment.

The research was small in scale and drew no conclusions about whether or how vaccines may have caused rare, lasting health problems. The patients had "temporal associations" between vaccination and their faltering health, says Avindra Nath, clinical director at the National Institute of Neurological Disorders and Stroke (NINDS), who has been leading the NIH efforts. But "an etiological association? I don't know." In other words, he does not know whether vaccination directly caused the subsequent health problems.

NIH's communications with patients faded by late 2021, though Nath says the work continues behind the scenes. The pullback caused bewilderment and dismay among patients who spoke with *Science*, who said the NIH researchers were the only ones helping them. Now, a small number of other researchers worldwide is beginning to study whether the biology of Long Covid, itself still poorly understood, overlaps with the mysterious mechanisms driving certain postvaccine side effects.

More discrete side effects connected to COVID-19 vaccines have been recognized, including a rare but severe clotting disorder that occurs after the AstraZeneca and Johnson & Johnson vaccines and heart inflammation, documented after the messenger RNA (mRNA) vaccines manufactured by Pfizer and Moderna. Probing possible side effects presents a dilemma to researchers: They risk fomenting rejection of vaccines that are generally safe, effective, and crucial to saving lives. "You have to be very careful" before tying COVID-19 vaccines to complications, Nath cautions. "You can make the wrong conclusion. ... The implications are huge." And complex and lingering symptoms like Dressen's are even more difficult to study because patients can lack a clear diagnosis.

At the same time, understanding these problems could help those currently suffering and, if a link is nailed down, help guide the design of the next generation of vaccines and perhaps identify those at high risk for serious side effects. "We shouldn't be averse to adverse events," says William Murphy, an immunologist at the University of California, Davis. In November 2021 in *The New England Journal of Medicine*, he proposed that an autoimmune mechanism triggered by the SARS-CoV-2 spike protein might explain both Long Covid symptoms and some rare vaccine side effects, and he called for more basic research to probe possible connections. "Reassuring the public that everything is being done, researchwise, to understand the vaccines is more important than just saying everything is safe," Murphy says. Like others, he continues to urge vaccination.

Echoes of Long Covid?

How frequently side effects like Dressen's occur is unclear. Online communities can include many thousands of participants, but no one is publicly tracking these cases, which are variable and difficult to diagnose or even categorize. The symptoms also include fatigue, severe headaches, nerve pain, blood pressure swings, and short-term memory problems. Nath is convinced they are "extremely rare."

Long Covid, in contrast, affects anywhere from about 5% to 30% of those infected by SARS-CoV-2. Researchers are making tentative progress with several ideas about the underlying biology. Some studies suggest the virus may in certain cases linger in tissues and cause ongoing damage. Other evidence indicates aftereffects of the original infection might play a role even after the body clears the virus.

For example, evidence from animal studies supports the idea that antibodies targeting the SARS-CoV-2 spike protein—the same protein that many vaccines use to trigger a protective immune response—might cause collateral damage, notes Harald Prüss, a neurologist at the German Center for Neurodegenerative Diseases (DZNE) and the Charité University Hospital in Berlin. In 2020, while hunting for antibody therapies for COVID-19, he and his colleagues discovered that of 18 antibodies they identified with potent effects against SARS-CoV-2, four also targeted healthy tissues in mice—a sign they could trigger autoimmune problems.

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> WILLIAM MURPHY | UNIVERSITY OF CALIFORNIA, DAVIS