



A Long Covid patient at a hospital in Poland plays a virtual reality game to test reaction skills.

## COVID-19

# Vaccines may cause rare, Long Covid-like symptoms

Researchers probe reports of brain fog, headaches, and blood pressure swings

By **Jennifer Couzin-Frankel** and **Gretchen Vogel**

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.”

Dressen had never had COVID-19. But that November, she’d received a dose of AstraZeneca’s vaccine as a volunteer in a clinical trial. By that evening, her vision blurred and sound became distorted—“I felt like I had two seashells on my ears,” she says. Her symptoms rapidly worsened and multiplied, ultimately including heart rate fluctuations, severe muscle weakness, and what she describes as debilitating internal electric shocks.

A doctor diagnosed her with anxiety. Her husband began to comb the scientific literature, desperate to help his wife, a former rock climber who now spent most of her time in

a darkened room, unable to brush her teeth or tolerate her young children’s touch. 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 Dressen and other affected people to the agency’s headquarters for testing and sometimes treatment.

The research 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 can’t say 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. Now, some other researchers worldwide are beginning to study whether the biology of Long Covid, still poorly understood, overlaps with the mysterious mechanisms that may drive certain postvaccine side effects.

Other, better defined complications connected to the 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.” Complex and lingering symptoms such as 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, who has 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. “Reassuring the public that everything is being done, researchwise, to understand the vaccines is more important than just saying everything is safe,” he says. Like others, he continues to urge vaccination.

**HOW FREQUENTLY** side effects like Dressen’s occur is unclear. Some online communities 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 more than 30% of those infected by SARS-CoV-2. Researchers are making tentative progress in untangling the underlying biology. Some studies suggest the virus may linger in tissues and cause ongoing problems. Other evidence indicates after-

effects of the initial infection might play a role.

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.

Early clinical data point in a similar direction. Research groups have detected unusually high levels of autoantibodies, which can attack the body's own cells and tissues, in people during and after a SARS-CoV-2 infection. In part to understand whether these autoantibodies harm people, DZNE is checking the cerebrospinal fluid of Long Covid patients for antibodies that react to mouse brain tissue—if they do react, they might attack human neural tissues as well. In a paper Prüss and his colleagues are about to submit, they describe finding autoantibodies that attack mouse neurons and other brain cells in at least one-third of those patients.

Some researchers are looking at another possible culprit for Long Covid: tiny clots in the blood. Resia Pretorius, a physiologist at Stellenbosch University in South Africa, and her colleagues published preliminary evidence in August that microscopic clots can linger after a SARS-CoV-2 infection clears. They might interfere with oxygen delivery, which could explain some Long Covid symptoms such as brain fog.

Pretorius suspects COVID-19 vaccines might also sometimes trigger subtle clotting issues. She says she has preliminary evidence that vaccination can lead to microclots, although in most cases they go unnoticed and quickly disappear—an effect she and a colleague saw in their own blood, which they sampled as part of a larger study.

**IN JANUARY 2021**, the Dressens sought out Nath, who had been studying Long Covid. Nath responded quickly and asked Brienne Dressen to join an ongoing study he leads on the natural history of inflammatory diseases of the nervous system.

Dozens more patients describing post-vaccine complications found their way to Nath and Farinaz Safavi, an NINDS neurologist. “I promise you we will report your issue and other cases we are reviewing now,” Safavi wrote to Danice Hertz in March 2021. Hertz, a retired gastroenterologist who lives in Southern California, had developed debili-

tating symptoms after one dose of the Pfizer vaccine. Senior officials at the U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention, and Pfizer, among others, were copied on the email, which Hertz shared with *Science*.

Over the first half of 2021, Nath and Safavi invited Dressen and others to NIH for testing and, in some cases, short-term treatment, for example with high-dose steroids or intravenous immunoglobulin, which can quell or modulate immune responses. The patients underwent neurological, cardiac, and other tests, including lumbar punctures and skin biopsies.

The NIH researchers were “trying to help people,” says a health care worker whose symptoms began after the Pfizer vaccine, one of four people in the study who spoke to *Science*. Nath says 34 people were enrolled in the protocol, 14 of whom spent time at NIH; the other 20 shipped their blood samples and in some cases cerebrospinal fluid.



Blood drawn from Brienne Dressen, who suffered complications after a coronavirus vaccine, is part of a National Institutes of Health study.

As time passed, however, the patients say the NIH scientists pulled back. A September visit Dressen had scheduled for neurologic testing was converted to a telemedicine appointment. In December, Nath asked her to stop sending other patients his way. “It is best for such patients to receive care from their local physicians,” he wrote to her.

For patients, the silence from NIH was distressing, especially as they struggled to find support and care elsewhere. The scientists “took the data and left us hanging,” says a person who traveled to NIH in the spring of 2021. “I have no treatment, I have no idea what’s happening to my body.”

Nath told *Science* that NIH facilities are not equipped to treat large numbers of patients long-term. Says the health care worker of the effort: “It’s too much for two people at the NIH to do.”

Two top medical journals declined to pub-

lish an NIH case series of about 30 people, which Nath says he first submitted in March 2021. He understands the rejections. The data weren’t “cut and dried; it was observational studies.” This month, the scientists submitted a case series of 23 people to a third publication, and Nath says his group has proposed expanding a Long Covid study to include patients with postvaccine side effects.

Regarding persistent effects after vaccination, a Pfizer spokesperson wrote to *Science*: “We can confirm that it’s something we’re monitoring.” Other vaccinemakers said they take side effects seriously and report them to regulators. FDA and the European Medicines Agency told *Science* they continue to monitor the vaccines’ safety.

Researchers note that the scientific community is uneasy about studying such effects. “Everyone is tiptoeing around it,” Pretorius says. “I’ve talked to a lot of clinicians and researchers at various universities, and they don’t want to touch it.”

Still, her group and others are pushing ahead. Prüss has detected autoantibodies in some patients with postvaccine symptoms, although not in others. Susan Cheng, a cardiologist at Cedars-Sinai Medical Center, and her colleagues are planning to use sophisticated imaging and diagnostic tests to study both Long Covid patients and those with postvaccine symptoms. And Pretorius and her colleagues are hoping to recruit at least 50 people to study clotting patterns before and after vaccination.

At Yale University, immunologist Akiko Iwasaki, who has been studying Long Covid, is planning to collaborate with Nath and look at any potential link between Long Covid and postvaccine effects, she says. She

has spoken with affected patients, and her lab intends to collect samples from them, potentially of blood or saliva. Murphy says more work is needed in animal models to trace the body’s response to vaccination. “We need to look at this in controlled situations,” he says.

Prüss is hunting for autoantibodies following COVID-19 vaccination in mice. And he continues to care for patients, both post-vaccine and postinfection. His clinic hopes to soon start a clinical trial of a treatment that removes most antibodies from a patient’s blood. However, even if it works well, the procedure is expensive and might not be widely available.

**PEOPLE WITH LASTING** health problems after vaccination welcome any attention to their plight. “You have this ugly stain on you, and you’re marginalized and abandoned,” Dressen says. At first, “I was really afraid of

causing vaccine hesitancy,” she says. However, when it appeared that regulators were not promptly investigating the apparent side effects, her frustration outweighed her reluctance. She took part in a June 2021 press conference about vaccine side effects held by Senator Ron Johnson (R-WI), who has been outspoken against COVID-19 vaccinations. “Talking to politicians was not our plan A ... not even close,” Dressen says. “It was more like plan J.”

Jana Ruhländer, too, feels caught. After a single dose of the Moderna vaccine, the microbiology graduate student in Kassel, Germany, developed the sensation of internal electric shocks Dressen experienced, muscle weakness, intense thirst, and wild swings in her heart rate and blood pressure. Doctors dismissed her, saying their tests found nothing wrong. She played detective, realizing her symptoms overlapped with those controlled by a hormonal system called the renin-angiotensin-aldosterone system that regulates blood pressure and fluid balance. She has connected with doctors trying to learn whether auto antibodies targeting that system might be causing her symptoms.

Despite her experience, “I still think the vaccines are great,” Ruhländer says. And the mRNA technology “has so much potential.” But these side effects, which for her have improved somewhat but haven’t disappeared, should be acknowledged and understood, she says. “We have to speak openly about it.”

Some patients who spoke with *Science* say medications that tamp down the immune system have offered a measure of relief. Nath hopes results from an NIH clinical trial testing immunoglobulin and steroids in Long Covid patients “will be applicable to the vaccine-related complications.” None of the seven patients with whom *Science* spoke has fully recovered.

Researchers exploring postvaccine effects emphasize that the risk of complications from SARS-CoV-2 infection far outweighs that of any vaccine side effect. “You see 10, 100, 1000 times less risk from the vaccine,” Prüss says. But understanding the cause of postvaccine symptoms—and whether early treatment can help prevent long-term problems—could be crucial for designing even safer and more effective vaccines, Murphy says, as well as potentially providing clues to the biology of Long Covid.

Cheng has heard from dozens of people who describe chronic postvaccine problems, and she finds the overlap between their symptoms and those of Long Covid compelling. Now, she wants to move deliberately and scientifically in a search for answers. “We’ve got to retain rigor,” she says. “There’s just this complete dearth of data.” ■



Hong Kong culled more than 2000 hamsters this month after linking a COVID-19 outbreak to a pet store. Scientists say new variants could enter the human population after evolving in animals.

#### COVID-19

## After Omicron, some scientists foresee ‘a period of quiet’

The variant’s modest toll in many countries has led to a sense of optimism. But new surprises are likely

By Kai Kupferschmidt

**B**arely 2 months after it began, the Omicron wave is already ebbing in some countries. And although it has sickened huge numbers of people, caused massive disruption, and left many health care workers exhausted, it is also leaving something unusual in its wake: a sense of optimism about the pandemic’s trajectory. In countries where many people have been vaccinated or were infected, scientists say, the worst may finally be over.

“We anticipate that there will be a period of quiet before COVID-19 may come back towards the end of the year, but not necessarily the pandemic coming back,” Hans Kluge, director of the European Region of the World Health Organization (WHO), recently said in an interview. In the United Kingdom, where the Omicron wave crested early, many restrictions were scheduled to be dropped this week, including mandatory masks in public indoor spaces and COVID-19 vaccination passes.

The optimism is shared—although couched in caveats—even by some scientists

and public health experts who have stressed the risks of the pandemic from the start and implored politicians to take stricter action. “We have reached a bit of a turning point,” says Devi Sridhar, a global health expert at the University of Edinburgh and an outspoken critic of the U.K. government’s past COVID-19 policies. Not only has the Omicron wave crested in several countries, but its toll has been smaller than feared. And the wave of infections has likely boosted immunity at the population level, which means future waves may wreak even less havoc.

Still, researchers urge caution. Omicron has shown that even a relatively mild wave can put a tremendous burden on health systems and societies as a whole, and it’s unclear how long Omicron immunity will last, how the virus will evolve from here on, and how often breakthrough infections will lead to long-term health problems. “I remain firmly in the camp of: We’ve made great progress but we still have a ways to go before this is truly over,” says Boghuma Titanji, a virologist at Emory University School of Medicine. Besides, “Wealthy countries moving on I fear will push the issues of

## Vaccines may cause rare, Long Covid–like symptoms

Jennifer Couzin-FrankelGretchen Vogel

*Science*, 375 (6579), • DOI: 10.1126/science.ada0536

### View the article online

<https://www.science.org/doi/10.1126/science.ada0536>

### Permissions

<https://www.science.org/help/reprints-and-permissions>

Use of think article is subject to the [Terms of service](#)