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The Mystery of Why Some People Keep Testing Positive for Covid-19

Inside the debate over how long the coronavirus lasts in the body



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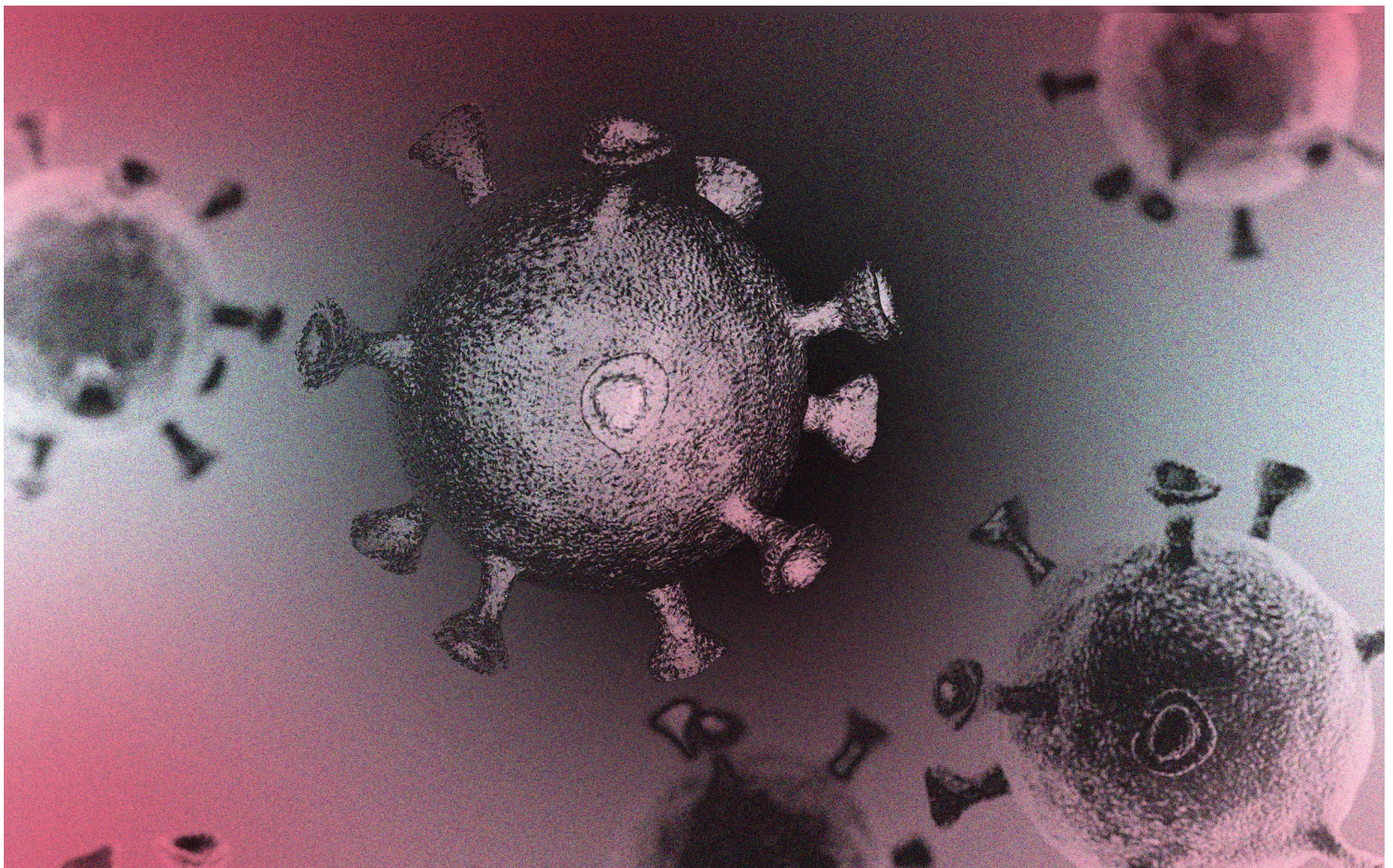


Photo illustration, source: Dowell/Getty Images

On July 22, Natalie Forouzad was dreaming of finally leaving the basement of her parents' house in North Carolina. She used to begin most days with a six-mile run, but for the last 43 days, she hadn't ventured much past the basement walls. Her ordeal began in early June when she started feeling fatigued and got feverish chills. Forouzad, a 20-year-old college student who is poised to begin her senior year at East Carolina University, had been staying since March with her parents, who are in their fifties, and wanted to ensure that she didn't have the novel coronavirus. So, she went to her doctor on June 9 and received a test for Covid-19. The result came back two days later and confirmed that she had the SARS-CoV-2 virus that causes the disease. Breathing became more difficult for her over the next couple weeks. Her resting heart rate hovered around 110 beats per minute at times while she struggled. "It felt like there was a pillow over my face for a week," she said. "It scares you — you wonder, 'Am I going to go to sleep and not wake up?'"

By July, Forouzad started to feel better gradually, but she still experienced intermittent pain deep in her lungs. Her family continued to keep their distance by leaving her meals by the door on the side of the basement that leads outside. Finally, on July 5, Forouzad felt emboldened to go to a drive-through testing site and get swabbed again. To her dismay, the test came back positive. Weeks later after that second positive test, she continued to have residual lung pain and remained frightened about infecting her family; that's why she was still in the basement. "I've been in quarantine for 43 days and I want to come out," she said. "I'm sick of being here. But no one in this whole universe is telling me if I'm contagious or not if I'm testing positive."

As the pandemic continues, a growing number of people have faced the same dilemma as Forouzad. One doctor in San Francisco had multiple positive coronavirus tests at least 90 days out from her initial diagnosis. Facebook groups for people who identify themselves as long-haulers struggling with the lasting effects of Covid-19 have cropped up and are growing. Not everyone in these groups has multiple positive tests for the virus, but some do. Hints of the lasting presence of the coronavirus even arose in the autopsy of George Floyd, which was conducted on May 26, the day after he was killed by Minneapolis police. The autopsy report noted that a nasal swab conducted that day was positive for SARS-CoV-2. Before he was killed, Floyd had tested positive on April 3.





Natalie Forouzad spent more than 40 days isolated in her parents' basement. Photo courtesy of Natalie Forouzad

Part of the mystery is that in a time of scarce tests for the coronavirus, not everyone diagnosed with Covid-19 receives follow-up testing. Guidelines updated on July 22 from the U.S. Centers for Disease Control and Prevention (CDC) recommend ending isolation on the basis of how a patient feels anytime after 10 days following symptom onset, rather than retesting. There's confusion about what a follow-up test confirming the presence of SARS-CoV-2 even means. Many tests look for the virus's genetic material, which consists of RNA, using a method called a polymerase chain reaction, or PCR for short. But CDC studies have not been able to grow any infectious virus from samples of people with Covid-19 more than nine days out from their diagnosis. This suggests to many scientists and doctors that the viral genetic material found in people after that time window is just the coronavirus fragments, which have no ability to replicate and be contagious.

But some virologists and doctors caution that there might be extremely rare yet consequential exceptions to this. Richard Randall, a virologist at the University of St. Andrews in the United Kingdom, doesn't want to scare people with Covid-19, the majority of whom recover and are not infectious afterward, but he thinks that public

health officials need to take a more nuanced view of how long the coronavirus lasts in the body. Although “it may be that 99.9% of people completely clear the virus within a few months,” he says, it’s “not an impossibility” that there might be a very tiny proportion of people who shed infectious virus for six months or a year. “Those people may act as seeds or reservoirs for the virus and potentially could be the source of a local outbreak,” Randall says. “I’m not saying that happens with Covid-19 because the data’s not there. But that happening would not be surprising.”

Anthony Fauci, MD, director of the U.S. National Institute of Allergy and Infectious Diseases, has acknowledged that the question of whether people with positive Covid-19 tests are still infectious is something that scientists are still trying to figure out. PCR tests for the virus work by trying to amplify signals of its genetic code over multiple machine replication cycles, and he said in a recent podcast interview that if it takes 35 or more cycles for the test to be positive the chances of a person being infectious are “minuscule.” But Fauci adds that knowing exactly how to interpret test results that hover around this threshold is complicated. “It’s very frustrating for the patients as well as the physicians,” he said. Infectious disease doctors note there’s no FDA-approved test that reports the number of PCR replication cycles it takes to get a positive signal. Moreover, the testing machines simply report whether the signal was detected before the 40th replication cycle, so doctors can’t get more nuanced information even if they ask.

Forouzad was still hanging on for a negative PCR test on July 22. The day before, she had driven to the building where her doctor’s office is for a follow-up test, and a nurse had come out to Forouzad’s car and swabbed her. As she awaited the results, she said the preceding weeks had been agonizing. “I want a negative test so I can have some kind of closure that I’m not going to spread this to anyone,” Forouzad said. “Because if it’s negative, it’s out of my body.”

Clues from Antarctica

In late March 1969, 14 men and five husky dogs hunkered down to spend the remainder of the year at a British survey base in the Antarctic until aircrafts were scheduled to return in mid-December to resume survey expeditions on the continent. They lived in complete isolation. The group ate from packets and cans and took vitamin supplements, and the dogs, which were used for small expeditions, were fed meat from a pile of dead seals near the base. The men were between the ages of 21 and 35, and in good health

until July rolled around. But that month began with 12 days of blowing and drifting snow, so they stayed in the safety of the central hut, in close quarters. On July 14 the first man showed signs of a respiratory cold. Over the next two weeks, eight more of the men there showed signs of respiratory illness. When scientists learned about this later they were curious — how could an illness like this come out of nowhere?

Many months later, researchers analyzed the handkerchiefs the men had blown their noses with, and looked for signs of certain pathogens, including influenza and one of the common coronaviruses that only causes mild to moderate colds. They even exposed volunteers to nasal secretions collected by the men during the outbreak to see if the volunteers would get sick. Ultimately, the research proved inconclusive. But it fueled a growing curiosity among scientists that viruses might last longer in the body than previously thought. “The occurrence of a common cold during isolation, when the chances of introduction of new infection from the outside are virtually nil, implies that in some way virus persisted, either in the environment or in the men,” the scientists concluded.

It’s been established that certain viruses stick around in the body for life after the initial infection. The varicella-zoster virus, which causes chicken pox, is one of these and can cause shingles later in life. Other examples include the Epstein-Barr virus, which causes mono, and retroviruses like HIV that integrate into a person’s DNA. But scientists are increasingly looking to see if other viruses commonly remain latent in the body, too.

“There are probably all sorts of stages in the middle between the acute infection and the persistent infection, and it’s not just an academic armchair pursuit. It may actually make a difference in terms of understanding disease.”

Measles is one example where the thinking might be changing. Doctors have known since at least the 1970s that there is a rare but devastating neurological complication called subacute sclerosing panencephalitis, which affects tissues such as the brain and

causes death usually in one to three years after symptoms such as seizures appear. The complication usually arises seven to 10 years after someone is infected with measles as a child, and vaccination to avoid ever getting sick from measles in the first place is the only known way to avoid it. It was thought to be rare for measles to hang around in the body. But autopsies conducted in 1995 on 51 healthy people in Japan who died from events such as accidents or heart attacks found that around half of them had measles virus in their body. The average age of the individuals was 54 years, and since measles is generally a childhood disease, it suggested that the virus could linger at detectable levels for decades.

Diane Griffin, MD, PhD, a virologist at the Johns Hopkins Bloomberg School of Public Health, has spent years trying to understand how long measles persists in the body. “Measles is a good example of a disease where you get sick and you get better and you develop lifetime immunity to reinfection,” she says. “But if you look for the viral RNA, it’s present for a very long period of time.” She adds that people with lingering measles virus are not transmitting the disease to new people. “In the lab, you cannot recover infectious measles virus after the rash is cleared,” Griffin explains. “But they’re PCR positive for months.”

Griffin says that one theory is that the virus may persist in the body to keep it vigilant against the pathogen. “Our current hypothesis is that it’s driving development of lifelong immunity,” she says. Exactly how this might happen — if it does — is a huge mystery. There might be cells in the lymph nodes that retain viruses or their fragments. Scientists have already shown that immune cells known as follicular dendritic cells hang on for at least a little while to particles from some viruses. The mechanism is unclear, but Griffin isn’t alone in thinking that persistent virus in the body might stimulate some sort of immune system protection.

More viruses seem persistent

The biologist Brian Foy, PhD, inadvertently shed light on the unexpected hiding places of viruses in the body through his own family’s experience. In 2008, he traveled from his home in Fort Collins, where he works at Colorado State University, to rural Senegal to help capture and study mosquitoes that spread disease. In order not to scare off the mosquitoes, he and his collaborators decided to forgo insect repellent as they went from hut to hut and vacuumed up the bloodsuckers in the early hours of the day before

sunrise. Because of the nature of the work, the team suffered countless mosquito bites. After a week Foy returned to Colorado, where he and his wife, who had been in Fort Collins the whole time, both fell ill with rashes and headaches. Foy also developed pain in his genitals and blood in his semen. The couple was tested for all sorts of infectious diseases, including malaria, but everything came back negative.

A year later a fellow scientist in Senegal suggested that their symptoms might be Zika. Tests by several different labs of the blood samples from Foy and his wife that had been frozen confirmed that was the culprit. But Zika is a disease transmitted by mosquitoes that didn't exist where Foy lived in Colorado, so his wife's infection was mysterious. Ultimately, he and other researchers, including his wife Joy, a nurse, published a scientific report concluding that it had come from his semen. Foy had had sex with his wife soon upon return from the mosquito-collecting trip to Senegal.

Scientists were surprised that a virus like Zika infiltrated the testes. And since the testes are protected to some degree from the body's immune system, they wondered how long the virus could hang out there. A subsequent study from CDC researchers published last year in the *New England Journal of Medicine* found that in a rare instance, one man's semen tested positive for Zika 281 days out from illness (calming people's fears, the authors of the paper emphasized that the vast majority of sexual transmission of the virus appears to happen only within the 20 days after infection).

Further research of semen samples suggests that a surprising range of viruses can persist in the testes, where sperm are produced. One big surprise came with Ebola, which was thought to be only an acute infection that was cleared from the body by the time people recovered. In March 2015, a 44-year-old woman in Monrovia, Liberia, fell sick with Ebola almost a month after the last reported case in that country. She had had sex a week prior with a man who had been treated six months earlier for Ebola and recovered. Ultimately, she succumbed to the illness, and since then scientists have documented the virus in men's semen up to 565 days after recovery. In the current pandemic, semen from six out of 38 hospitalized patients in a small preliminary study tested positive for SARS-CoV-2, but another study that looked at semen samples from recovering patients 8 to 75 days after diagnosis found no evidence of the virus.

Unusual findings about lingering pathogens are important, says Glenn Rall, PhD, a virologist at the Fox Chase Cancer Center who studies the long-term neurological

consequences of viral infections. He says that doctors have typically tried to create a stark division between “acute” and “persistent” infections. “The more that science begins to look at this, the more that kind of dichotomy is probably not true,” Rall says. “There are probably all sorts of stages in the middle between the acute infection and the persistent infection, and it’s not just an academic armchair pursuit. It may actually make a difference in terms of understanding disease.”

Randall says that there’s even debate around what the term “persistence” means when talking about pathogens. “It’s tricky because some people view persistence as lifelong persistence, whereas I’ve never taken that view,” he says, adding that in some cases persistence might just mean that certain viruses stay in the body a month or couple months longer than the acute infection.

A study from researchers in Brazil published earlier this year, for example, looked for influenza virus in tissue samples from tonsil removal surgery from children aged three to 13 years undergoing treatment for conditions such as recurrent tonsillitis. None of the children had any symptoms of seasonal respiratory illness during the four weeks before undergoing the procedure. Yet tissue samples of seven of the 103 children were positive for the flu, three of which had the whole virus intact. The scientists were even able to show that some of the recovered tissue was still infectious for flu. This is “a really, really important finding,” says Jonathan Yewdell, MD, PhD, who heads the cellular biology division of the U.S. National Institute of Allergy and Infectious Diseases. “It’s an example of something that we just didn’t know before,” he says.

Questions about the coronavirus

As the confusion over the meaning of PCR tests continues, scientists are racing to get a better idea of whether viral persistence truly occurs in this pandemic. Griffin notes that another coronavirus that infects mice is known to persist in the central nervous system and the liver of the animals, but she and other scientists are still very much struggling to know whether SARS-CoV-2 ever remains in the body for long. She is currently analyzing blood samples from Covid-19 patients in hopes of finding out.

Many infectious disease doctors maintain that the coronavirus patients who recover should not worry about being infectious. “I’ve had patients myself who have had persistent positivity for weeks and weeks and there’s nothing wrong with them, so I

don't think we can use viral RNA presence as any kind indicator of ongoing replication," says Amesh Adalja of the Johns Hopkins Center for Health Security in Baltimore. "I think it's viral debris."

“We’re caught in this weird zone now where we have no reliable test for determining that someone is not infectious.”

Rafi Ahmed, PhD, immunologist and director of the Emory Vaccine Center, notes that there might perhaps be cases in which the virus lingers in a meaningful way, but that is exceedingly rare. “Millions of people have been infected — it’s hard to keep count — and the people who have PCR positivity for three or four months would be a small fraction of those people,” Ahmed says.

Several studies have sought to understand exactly how long people have viral signals in their body. A small study from researchers in China published in May, for example, found PCR positive test results for severe cases up to around 49 days for nasal swabs and fecal samples. Notably, the median time for throat swabs to stop testing positive was around 16 days. According to the CDC, “Available data indicate that persons with mild to moderate Covid-19 remain infectious no longer than 10 days after symptom onset.” A new study from the Netherlands, which has not yet undergone review by other scientists, analyzed samples from severely ill Covid-19 patients, some of whom were immunocompromised, and found that one patient who was moderately immunocompromised had the infectious virus for 20 days.

“We’re caught in this weird zone now where we have no reliable test for determining that someone is not infectious,” says Daniel Griffin, MD, PhD, a specialist in infectious diseases at New York’s Columbia University Medical Center (no relation to Diane Griffin). But he’s worried that public health officials are jumping to the premature conclusion that people are not infectious after a certain number of days. “There’s a lot of political pressure to have certain things be true whether they actually are,” he says.

Is the viral signature found by PCR tests — which only look for a very short stretch of SARS-CoV-2’s genetic sequence — ever indicating the presence of a contagious virus in a

person many days after infection? Akiko Iwasaki, PhD, a viral immunologist at Yale University, says that testing people for an infectious virus — rather than just doing a PCR test — would be ideal, but it's highly impractical. It requires additional steps, such as seeing if the viral samples from a patient grow in live cells in the lab, all within a high-level biosafety facility. “Unfortunately, this is quite cumbersome,” and viruses don't always grow well in laboratory conditions, she says, so it's “not possible to implement as a public health measure.”

Even if people who test positive weeks out after falling ill are just shedding viral debris rather than a contagious virus, a further question is whether their positive PCR tests have detected viral debris that has lingered for a long time or debris from a still-active reservoir deep within the body. Kenneth Witwer, PhD, a molecular biologist at Johns Hopkins University in Baltimore, Maryland, speculates it's the latter. “I still think that this phenomenon is likely explained by a persistent cellular reservoir or low-level replication, not by residual virus particles,” he says. One argument against the idea of viral debris hanging around for weeks and weeks is that RNA usually degrades very rapidly, Witwer explains. “RNA is chemically unstable,” he says. “That's why with forensics, like crime scenes, they're always looking for DNA.”

But Ahmed notes that RNA viral particles are often bound to proteins, and those proteins might physically protect them from degrading enzymes in the body. Noninfectious fragments of the virus shielded in this way would hang around longer, and could be the signal that PCR tests are picking up weeks out from the initial infection.

Patients such as Natalie Fourouzad say that the testing confusion can cause a roller coaster of emotions. On July 27, her gloom turned to joy. Fourouzad was sipping a berry smoothie in the yard under the shade, scrolling through Instagram on her phone, when a call from her doctor's office came up on the screen. Her heart skipped a beat and she braced herself to hear the results — good or bad — of her most recent PCR test. When the nurse on the phone told her the test was negative, Fourouzad felt a weight lift. She relayed the news to the family group chat, and was inundated with happy emojis. She finally felt comfortable to decamp from the basement and was looking forward to eating dinner with her family for the first time in weeks.

But Fourouzad says that she won't soon forget the difficulties of the last month and a half. She still wishes public health officials would do a better job explaining whether

people with positive Covid-19 tests weeks out from falling sick are infectious — or at the very least that they would acknowledge the confusion. “I just wish they would talk about it,” Fourouzad says. “It’s just not talked about and it’s frustrating.”

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