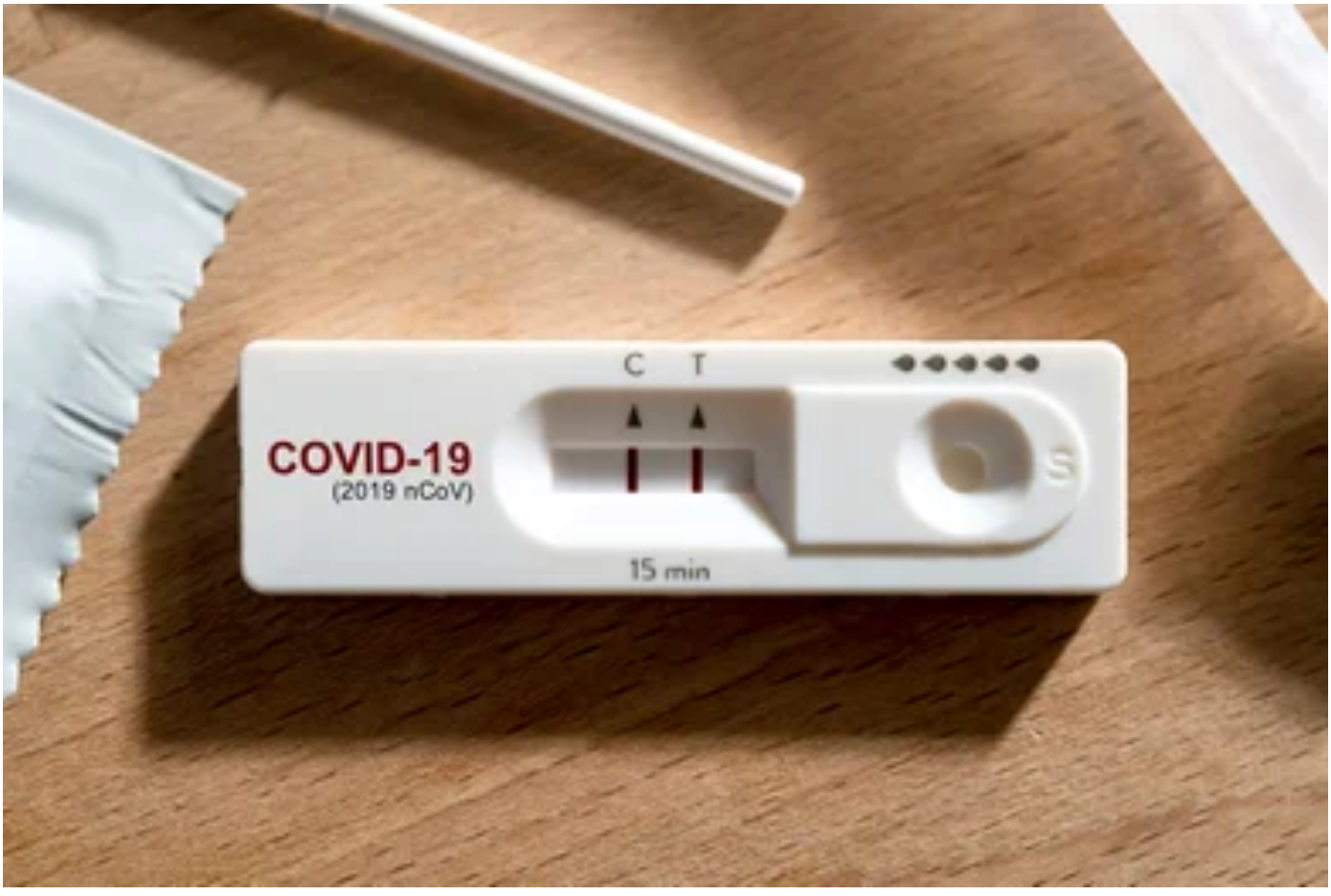
COVID Rebound Can Happen Even without Paxlovid

Concerns about Paxlovid rebound are preventing some doctors from prescribing the lifesaving drug and some high-risk patients from taking it

Lauren Gravitz February 8, 2023



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Paxlovid gets a bad rap over concerns about COVID "rebound." That's the primary takeaway from a series of

papers showing that whether or not people take the antiviral medication, many have symptoms that wax and wane before going away completely.

Over the past few months a number of peer-reviewed and preprint studies have looked at patients with COVID in the placebo groups of clinical trials for Paxlovid and other treatments. As part of the trials, the patients in these groups were required to fill out daily symptom trackers. Researchers consistently found that as many as 30 percent of those who did not take an antiviral experienced a rebound in coughing, fatigue, headache or other symptoms after initially feeling better.

The studies aim to address concerns over a phenomenon called Paxlovid rebound, which occurs when someone who has taken an antiviral such as Paxlovid (a combination of nirmatrelvir and ritonavir tablets) experiences a resurgence in symptoms or a positive test after testing negative soon after they stop taking the drug. One of the first papers to describe COVID resurgence after an antiviral was a case study co-authored by Davey Smith, an infectious disease physician and researcher at the University of California, San Diego, and his colleagues. It wasn't long before Smith's research came back to haunt him, however. As anecdotal reports of the phenomenon began to pile up last summer—reports that included high-profile cases such as President

Joe Biden and the National Institutes of Health's Anthony Fauci—public opinion of Paxlovid began to decline. The drug once hailed as a savior for high-risk patients was suddenly being dismissed as not worth the effort.

Despite Paxlovid's proved efficacy at preventing severe disease and death in people considered high-risk, Smith found increasing resistance to it. "When Paxlovid rebound started to gain traction—I'm going to be blunt—I kind of got annoyed," he says. Perhaps more worrisome, however, is the fact that some physicians have become hesitant to prescribe it. "The drug kept people out of the hospital and kept them from dying," Smith says. "My patients started saying they didn't want to take it," he adds, and "I felt guilty because I'd started it all."

Because he knew that respiratory viral symptoms have a tendency to come and go no matter the virus or treatment, Smith set out to better characterize the course of COVID itself. As chair of the U.S.-government-sponsored ACTIV-2 trial—a series of placebo-controlled studies that aims to assess new COVID treatments—he had troves of data at his fingertips, so he dove into the trials and gave the placebo groups extra scrutiny.

In one of the studies, published in *JAMA Network Open* last October, Smith and his colleagues looked at a group of placebo-group subjects in the ACTIV-2 trial and found that

30 percent experienced at least two symptom-free days before one or more of their symptoms returned. Of those who had this symptom rebound, almost all had symptoms that were mild to moderate and none required hospitalization. In another study, posted as a preprint and now undergoing peer-review, Smith and others assessed placebo-group patients for both symptom rebound and viral load (the amount of virus infected people were shedding), as measured by a PCR test, the most sensitive test for infection with SARS-CoV-2, the virus that causes COVID. The researchers found that 10 percent of their untreated subjects had recurrent symptoms after having their symptoms completely resolve, 27 percent had their symptoms improve somewhat before feeling worse again and 12 percent showed resurgence of detectable virus itself. But a viral comeback rarely coincided with worsening symptoms: only 1 to 2 percent of the study subjects experienced both.

Smith wasn't surprised by the results. "As an infectious disease doc, [I] know that respiratory disease viruses often have this waxing and waning," he says, adding that it also happens with colds, influenza and respiratory syncytial virus (RSV). "It's just their nature." This is likely because most symptoms are related to the body's inflammatory response to the virus, not the virus itself, he says. The inflammation—which is different for everyone—generally lasts longer than the virus, and it ebbs and flows as viral remnants are cleared

from the body.

Other infectious disease specialists agree. “In my view, the story of rebound was overblown,” says Ziyad Al-Aly, a clinical epidemiologist and chief of the research and education service at the Department of Veterans Affairs St. Louis Health Care System. He notes that he frequently hears of physicians who resist prescribing Paxlovid to high-risk patients for fear of rebound or the much-lamented side effect of a bitter, metallic taste. And yet, he says, “rebound never killed anyone. But COVID can put you in the hospital or, even worse, could lead to death.”

Robert Wachter, chair of the department of medicine at the University of California, San Francisco, has heard similar reactions to Paxlovid. “I’ve heard many times from patients and from a fair number of physicians that ‘I don’t like to use it because of rebound,’” he says. “I kind of understand it viscerally, but it doesn’t make sense when looking at a dispassionate ledger sheet of the medication’s benefits and downsides.... It’s not that close a call.”

Another benefit Wachter and others point to is the drug’s potential to reduce the risk of long COVID, which can manifest as a wide variety of symptoms that linger for months or even years after the initial infection. According to a recent preprint study by Al-Aly and his colleagues, taking Paxlovid in the first five days after a positive test reduced the

risk of long COVID symptoms by an average of 26 percent in a population of high-risk patients. “We started thinking about why people get long COVID,” Al-Aly says. Some hypothesize that SARS-CoV-2 “remains in them in some form and leads to clinical manifestations of fatigue, brain fog, etcetera,” he says. So he wondered, Was it possible that taking the antiviral early on might stop the virus from replicating and prevent it from running amok? The researchers looked at subjects from their high-risk population—those who smoked, were diabetic, were over 60 years old, or had other factors known to predispose someone to severe COVID. They found that Paxlovid reduced the risk of developing 10 out of the 12 long COVID symptoms that the study looked at.

So far the U.S. Food and Drug Administration has only approved Paxlovid conditionally, under an Emergency Use Authorization for treating high-risk patients. The possibility that it could reduce the risk of long COVID in lower-risk patients is tantalizing, but no one has been able to study the issue in depth because the drug hasn’t been approved for that population. “This is what I call an evidence-free zone,” Al-Aly says, and it’s one that he and others have been asking Pfizer to investigate. Pfizer, which developed and manufactures Paxlovid, abandoned studying it in lower-risk patients when its data showed no difference in hospitalization and deaths over the short-term. A study by

researchers unaffiliated with Pfizer found similar results. A spokesperson for Pfizer contacted by *Scientific American* had no comment other than that the company continues to evaluate its data.

Until more data emerge, physicians must rely on their intuition and whatever solid information they can find. Existing data consistently point to the upside of Paxlovid. "In my world, people have looked at the data and believe the benefits of medication are quite probable," Wachter says. "I'm certainly going to give it to high-risk people. Most of my colleagues who have gotten COVID have taken it." And Wachter, who is 65 years old, adds that if he tests positive for COVID, he will absolutely take the drug himself.

Physicians agree that COVID rebound after antivirals may be a nuisance, but it is far better than hospitalization or death. "Paxlovid is the best weapon we have right now for people who have COVID," says Smith, who knows the treatment landscape better than most. "It keeps people out of the hospital, keeps them from dying and probably decreases the risk of long COVID. In short, I think it's worth the bitter taste."