



A cancer patient in Louisville, Kentucky, receives a dose of a coronavirus vaccine.

COVID-19

Relief and worry for immune-suppressed people

Early studies suggest COVID-19 vaccine protection varies by ailment and treatment

By **Jennifer Couzin-Frankel**

For Eva Schrezenmeier, a nephrologist at Charité University Hospital in Berlin, the news was sobering: Among 40 patients with transplanted kidneys at her hospital who'd been vaccinated against COVID-19, only one was churning out the antibodies that would likely protect him from the disease. Because transplant patients take powerful drugs to suppress the immune system so it doesn't attack a donated organ, her team expected diminished responses to a vaccine. But Schrezenmeier, who posted a preprint describing her study last week, hadn't anticipated just how badly the vaccine might falter in her patients.

Her finding is at the grim extreme of research on how well COVID-19 vaccines work in the many millions of people whose immune systems are suppressed by drugs or disease. In many, the vaccines do seem to maintain their potency. But in others—particularly organ transplant recipients and those taking certain immune-dampening medications—effectiveness is less assured or even absent. To learn more, researchers are launching larger studies, seeking more clarity and ways to help patients whose weakened immune systems make protection against

COVID-19 all the more urgent. “There is a lot of confusion and fear among patients,” says Alfred Kim, a rheumatologist at Washington University in St. Louis who cares for people with the autoimmune disease lupus and strongly urges vaccination for them.

One source of complexity: The dozens of different medications taken by people with cancer, autoimmune or other immunologic disease, or an organ transplant. Each can gum up different gears in the immune system's intricate machinery. The ailment makes a difference, too. Solid tumors such as colon cancer don't usually interfere with the immune system (although chemotherapy does). But autoimmune diseases or blood cancers such as leukemia and lymphoma can themselves deplete or disrupt certain types of immune cells.

Past research already suggested vaccines can falter in some immune-suppressed patients. Kim says flu and pneumococcal vaccines don't always work as well in people on some common immune suppressants, like methotrexate, which treats cancer and autoimmune diseases. And a 2012 study found that just 44% of cancer patients in treatment produced antibodies to influenza after one dose of flu vaccine; most were first vaccinated 1 week after chemo-

therapy. The researchers recommended two doses after finding that a second dose boosted the number to 73%.

When they started to parse blood samples after COVID-19 vaccination, scientists were unsure how people with immune suppression would respond to the vaccines. Gauging protection is also a challenge: The vaccines are designed to propel production of antibodies, but scientists don't know what levels are needed to guard against COVID-19. Antibodies are easier to measure than T cell responses, but those, too, play an important role in protection from disease.

Still, in a research setting, the hunt for antibodies can yield important clues. In December 2020, transplant surgeons Dorry Segev and Jacqueline Garonzik Wang at Johns Hopkins University put out a call on social media for organ recipients willing to participate in a COVID-19 vaccine study. “We had 1000 enrolled in the first week,” Segev says. In March, the research team published details in *JAMA* of participants' immune responses to the first dose of the Pfizer-BioNTech and Moderna vaccines. The results foreshadowed Schrezenmeier's: Among 436 people who'd had liver, heart, kidney, and other organ transplants, just 17% had detectable antibodies.

Outcomes varied based on which medications the volunteers were taking, however. Only 9% of those on a class of drugs that includes the immunosuppressant mycophenolate had some antibodies, compared with about 40% in those not taking drugs in that category. Mycophenolate inhibits production of both B cells, which generate antibodies, and T cells, which help marshal B cells to do their job.

Segev says he and his colleagues are close to sharing results from his cohort's second vaccine dose, which show some improvement. Still, he's surprised that these organ transplant patients seem to respond even less well to COVID-19 vaccines than to flu vaccines. To learn more, he is studying their T cell, B cell, and other immune responses. "We're starting to try to say, 'What is going on here? Why is it so bad?'"

Although Segev worries about the roughly 500,000 transplant patients in the United States, he suspects the picture is much brighter for the 11 million people with autoimmune diseases, who tend to take different combinations of immune treatments or get by on lower doses. Last week, a paper in *Gastroenterology* reported that 48 people with either Crohn disease or ulcerative colitis, nearly all on immune-targeting medication, responded well to vaccination. Of the 26 whom the researchers followed through both vaccine doses, all produced antibodies, 22 at high levels.

But another study, of 133 people with various autoimmune diseases, suggested two types of medication can act as a sledgehammer against vaccine response. The work, posted as a preprint this month by Kim, rheumatologist Mary Nakamura at the University of California, San Francisco, and their colleagues, showed that on average, subjects churned out roughly one-third as many antibodies as healthy vaccinated people—a difference that doesn't strongly concern Kim. But people on therapies that destroy B cells, like rituximab, and the powerful steroid prednisone had far lower levels. Bigger studies of these patients are getting underway, including one announced last week by the National Institute of Allergy and Infectious Diseases.

In cancer patients, vaccine response likely depends at least partly on timing, because cycles of chemotherapy alternately squash immune cells and allow them to rebound, says Giuseppe Curigliano, an oncologist at the European Institute of Oncology in Milan. He reported last year that cancer patients on chemotherapy produced abundant antibodies after a bout of COVID-19, leaving him optimistic that vaccines will work well for them.

His center waits a couple of weeks after a chemotherapy cycle to offer a COVID-19 shot. Similarly, a U.K. study showed that, although many patients in treatment for solid tumors had a paltry response to the first vaccine dose compared with healthy volunteers, they appeared well-protected after the second. The researchers write that the results highlight the risks of delaying vaccine doses in cancer patients, contrary to the country's practice across its population.

There's nagging concern, though, when it comes to people with blood cancers. Ghady Haidar, a transplant infectious disease specialist at the University of Pittsburgh Medical Center, has preliminary results from patients with leukemia, lymphoma, and multiple myeloma suggesting a sizable fraction aren't producing antibodies after vaccination, particularly those with a form of chronic leukemia. Perhaps, he says, this occurs because patients "have defects in circulating white blood cells."

Physicians like Haidar say patients often ask whether to stop taking immune-suppressing medications before getting vaccinated, prompting tough choices. "No one should be stealth discontinuing meds so that they can respond to vaccines," he says. For some patients, skipping treatment can be dangerous, but doctors can sometimes delay an infusion of a therapy known to make a vaccine's job tougher.

For patients who don't appear protected by standard vaccinations, extra doses may help. Some organ recipients already get extra doses of hepatitis B vaccine, and this month, France recommended that they receive a third dose of the Pfizer-BioNTech COVID-19 vaccine. Christophe Legendre, a nephrologist at Necker Hospital in Paris, is planning antibody tests to see how well the approach works in transplant patients. Other researchers say labmade monoclonal antibodies might bolster protection for patients who still don't respond. (Although clinical trials have shown the monoclonal antibodies can prevent infection, so far they are only authorized for treating early-stage COVID-19.)

In Berlin, Schrezenmeier is planning to offer the AstraZeneca or Johnson & Johnson vaccines to some patients already vaccinated with another COVID-19 vaccine. Will mixing vaccines enhance their effectiveness? "I don't know," she admits. But she imagines that giving the immune system two different jolts might sometimes make a difference. The lone kidney transplant volunteer in her study who produced antibodies after vaccination had already survived COVID-19—which may have helped kick-start an immune response against it. ■

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WATER RESOURCES

After revival, Iran's great salt lake faces peril

Upcoming presidential election could stall efforts to restore Lake Urmia

By Richard Stone

Twenty years ago, geochemist Arash Sharifi began to drill sediment cores in Iran's Lake Urmia—then the largest lake in the Middle East—to probe its recent climate history. "I was shocked at how little was known about the lake," recalls Sharifi, now at Beta Analytic Inc. in Miami. He became entranced by the "very unique chemistry" of its hypersaline waters. He also grew alarmed: Dams on feeder rivers and a proliferation of illegal wells had made the lake, a favorite haunt of flamingos and migratory birds, "vulnerable to hydrological collapse," he wrote in an internal government report.

That dark vision came to pass: By 2013, Lake Urmia's surface area, once 6100 square kilometers, or about the size of Delaware, had shrunk by 90%, a plight reminiscent of that of the larger Aral Sea in Central Asia. To save the dying lake, Iranian President Hassan Rouhani launched a restoration initiative that has so far cost \$1 billion. Now, Lake Urmia has a stronger pulse: Water levels have risen, and last summer flamingos were spotted in large numbers for the first time in years.

But the rebound could be fleeting. The higher water appears to be almost entirely the result of a few years of unusually strong rains, a recent study concludes, but that pattern is already giving way to drier conditions. And Iran's June presidential election is expected to usher in a leader less committed to the lake's restoration than Rouhani, who can't run for reelection under the nation's constitution. "We're at a tipping point," says Somayeh Sima, a water resources specialist at Tarbiat Modares University in Tehran, Iran. Even pausing restoration work for a year or two, she says, "would be dangerous for the lake."

The shallow lake was at its most expansive in recent decades in the late 1990s, when it stretched nearly 140 kilometers

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