

What does it mean to be 'immunocompromised?'

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Throughout the COVID-19 pandemic, there have been countless news reports identifying one group of individuals as being particularly vulnerable to the virus: the immunocompromised.

We know, for example, that [immunocompromised](#) individuals are more likely to have serious COVID-19 illness and a higher mortality rate than the average population. And in mid-August, the Food and Drug Administration (FDA) authorized a third dose of the Pfizer-BioNTech and Moderna vaccines for certain immunocompromised people.

With so much attention on this one group, a question remains in the minds of many: What does it actually mean to be immunocompromised?

Simply put, it's when your immune system isn't working as well as it should to protect you from infection—or that your immune system can't distinguish between normal and foreign cells.

But there are nuances. "There are many ways people can be immunocompromised," says Stuart Seropian, MD, a Smilow Cancer Hospital hematologist who specializes in [blood cancers](#). "The immune system is complex, and made up of many different types of immune cells that serve different functions. There isn't one 'immunocompromised state.' There are many."

Seen through a COVID-19 lens, about 3% of the population in the United States is considered moderately-to-severely immunocompromised, making them more at risk for serious illness if they contract COVID-19, even after vaccination. This is because their immune systems don't mount a strong response to the vaccines. A March study showed only about 56% of immunocompromised people built sufficient levels of protection against COVID-19 after a second mRNA (Pfizer or Moderna) dose.

That's why the Centers for Disease Control and Prevention (CDC) recommends people who are immunocompromised receive an additional—or third—dose of the mRNA vaccines. Preliminary results from a study in Israel indicated that this third dose may have doubled the

rate of transplant recipients who developed antibodies against SARS-CoV-2, the virus that causes COVID-19. According to the CDC, there is not enough data to determine whether immunocompromised people who received the Johnson & Johnson COVID-19 vaccine also have an improved antibody response following an additional dose of the same vaccine, so additional doses are not recommended for them right now.

We talked with several Yale Medicine experts from the fields of transplant surgery, neurology, immunology, and oncology to better understand what makes someone immunocompromised.

What does 'immunocompromised' mean?

First, it helps to understand what the immune system does for us.

"The immune system has two basic functions: to identify foreign tissue and to provide defense against infection," Dr. Seropian explains. "We think of a person as immunocompromised primarily when they are more vulnerable to infection than healthy individuals, because of issues with at least one of those two functions."

What causes a person to become immunocompromised?

There are multiple ways an individual might be immunocompromised, says David Hafler, MD, chair of Yale Neurology and professor of immunobiology at Yale School of Medicine.

He divides the causes into two major groups: those with a genetic mutation or a disease, such as HIV, that causes a loss of immune function; and those who take certain medications, including immunotherapy, to treat specific diseases.

Immunotherapy is a treatment that can suppress, or dampen, immune responses when the immune system is "overactive," such as with an autoimmune disease in which immune cells attack healthy tissue— or with [organ transplants](#). Autoimmune diseases that create this overactive response include rheumatoid arthritis, type 1 diabetes, multiple sclerosis (MS), and inflammatory bowel disease (Crohn's and ulcerative colitis).

Immunotherapy is also used to enhance immune responses, sometimes using drugs called "checkpoint inhibitors," for example, to treat certain types of cancer. With checkpoint inhibitors, patients aren't considered to be immunocompromised, Dr. Hafler adds. "After treatment, those patients may have a perfectly normal—or even a more robust—immune response," he says.

Because each autoimmune disease is different, there are different treatments, and each can impact the immune system in its own way. "Some therapies, such as type I interferons for MS, may actually enhance the viral immune response," says Dr. Hafler. "Other treatments, though, such as B cell depletion, lead to poor responses to viruses or vaccines, resulting in increases in disease and death."

Sometimes, it's accompanying medications—and not the immunotherapy itself—that affect the immune system. "There is a cancer treatment called CAR T-Cell therapy, for example, that does not suppress the immune system; however, patients receive immunosuppressive chemotherapy before they can begin CAR T-Cell therapy," Dr. Seropian says. "Other forms of treatment may require that someone take a steroid medication such as prednisone to deal with side effects, and prednisone is an immunosuppressant."

Why are transplant recipients so vulnerable?

For organ transplant recipients, immunosuppressive drugs are necessary,

and David Mulligan, MD, Yale Medicine's chief of transplant surgery and immunology, has a simple analogy for explaining why.

"The immune system scans the 'barcode' of everything in our body. And when it doesn't recognize a new organ, for example, the T cells and B cells in our immune system will create an inflammatory reaction in an attempt to get rid of it," he says. "And that's what we call 'rejection.'"

In the early days of transplant surgery, organ rejection was a major concern. But now, with modern immunosuppressant medications, it is rare, Dr. Mulligan adds.

But even though the medications are successful in stopping organ rejection, they come with side effects, including putting patients in an immunocompromised state. "They lower the body's defenses against bacteria, fungi, and opportunistic infections, like COVID-19," Dr. Mulligan says. "And some medications strain the organ system or can cause sugar levels to go up and down. Our goal is to find the optimal amount of medication that can keep the immune system in check while minimizing those side effects."

Are cancer patients immunocompromised?

It depends on the cancer, says Dr. Seropian.

As a general rule, patients with blood cancers, such as leukemia and multiple myeloma, are more likely to receive treatment that impacts their immune system than someone with a solid tumor, Dr. Seropian explains.

"There are many targeted therapies now for tumors that aren't immunosuppressive, but with blood cancers, treatments are directed at your blood cells, which travel through your entire body. As a result, your

immune system is more likely to be injured," he says.

Traditional chemotherapy and radiation treatments, he adds, are considered less immunosuppressive than some types of immunotherapy. Plus, the immunosuppressant effects of both treatments are generally temporary, Dr. Seropian notes.

But because cancer treatment is so highly individualized now, Dr. Seropian suggests patients speak with their provider if they have questions about their own risks or immunocompromised state.

Why don't vaccines work as well on immunocompromised people?

The premise of vaccination is to provoke the immune system to make a strong response against a harmless version of a pathogen. Then, when the actual virus comes along, the body can mount a defense. But if a person's [immune system](#) is compromised, that response might either be weakened—or not exist at all.

"In general, the more immunocompromised someone is, the less effective vaccines will be for them," Dr. Seropian says.

Previous studies of vaccines against other viruses, including influenza, show that people who are immunocompromised don't mount the same response to vaccination as those who are not immunocompromised. Studies have found the same to be true for COVID-19 vaccination as well.

As part of the National Institutes of Health's Human Immunology Project Consortium, Yale researchers are investigating the precise nature of the immune response to SARS-CoV-2, and how immunosuppression

can prevent an adequate immune response to it, Dr. Hafler says.

What should immunocompromised individuals do?

The hygiene strategies that immunocompromised individuals use to stay safe are actually the same measures many of us adopted when the pandemic began. But the level of vigilance depends on how immunocompromised someone is.

In general, Dr. Seropian says it is vital that anyone who is immunocompromised stay up-to-date on their vaccines—not just a third dose for the COVID-19 mRNA vaccine, but others, including the flu and pneumococcal vaccines (which protect against pneumonia-causing bacteria). And because immunocompromised people have a harder time clearing a virus from their system, the rules of quarantine for those who are considered severely immunocompromised are strict, he adds.

But what about precautions for those who are not severely immunocompromised?

"Individuals who are less immunocompromised than a transplant recipient, for example, can generally go about their lives like the rest of us," Dr. Hafler says. "We want them to get vaccinated, wear a mask, stay outside when meeting with groups, and define the group of individuals they will spend time with—like a pod."

Dr. Seropian agrees that a patient who is on a mild immunosuppressant treatment doesn't have to be as vigilant as a transplant recipient. "They need to be concerned about viral infections, including the flu, which they should also be vaccinated against," he says. "Plus, some people who are on certain medications need to focus more on organisms in the environment, such as mold in basements or bacteria in dirt."

Dr. Mulligan says he tells his patients to be thoughtful about their actions. "You want to think about things like the escalator rails and the keypads on an ATM," he says. "I tell them to carry a bottle of hand sanitizer in their pockets."

The bottom line? Patients who are immunocompromised need to speak to their physicians about their unique risks and what protective measures they can take, Dr. Seropian says.

Provided by Yale University

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