Can a Third COVID-19 Vaccine Dose Help Protect Liver Transplant Patients?

An extra booster dose raised antibody levels in one third of people with organ transplants, but many remain unprotected.

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People with compromised immunity, including transplant recipients who take immune-suppressing drugs to prevent organ rejection, may benefit from a third COVID-19 vaccine dose, but this approach does not work for everyone, according to a study published in Annals of Internal Medicine.

“Although the third vaccine dose appears to raise the immune response of transplant recipients to higher levels than after one or two doses, these people may still be at greater risk for SARS-CoV-2 infection than the general population who have been vaccinated,” lead study author William Werbel, MD, of Johns Hopkins University School of Medicine, said in a press release. “Therefore, we recommend that transplant recipients and other immunocompromised people continue to wear masks, maintain physical distancing and practice other COVID-19 safety measures.”

People with serious immune suppression are at risk for more severe complications and death due to COVID-19. Immunosuppressed people—including transplant recipients, people taking certain medications for cancer or autoimmune conditions and people with uncontrolled HIV—can also have slower and weaker immune responses to natural infection and vaccination. People with hepatitis B, hepatitis C, fatty liver disease, liver cancer or alcoholic liver disease may require a transplant due to liver failure.

Earlier this year, Werbel’s team looked at antibody responses against SARS-CoV-2, the coronavirus that causes COVID-19, among 436 transplant recipients who received the Pfizer-BioNTech or Moderna mRNA vaccines. Most had received kidney or liver transplants, the median time since transplantation was about six years and they were using a variety of immunosuppressive regimens to prevent rejection of the donor organ.

The researchers previously reported that only 17% of the transplant recipients produced detectable antibodies a median of 20 days after their first vaccine dose. People who received antimetabolite immunosuppressive therapy were less likely to develop antibody responses, as were older patients.

The team later reported results from a larger group of 658 transplant recipients, showing that even a month after the second dose, just 54% had detectable antibodies. In comparison, the Pfizer-BioNTech vaccine was 95% effective and the Moderna vaccine was 94% effective after two doses in clinical trials, which excluded people with severe immune suppression.

Similarly, a related study of 80 liver transplant recipients followed at Tel-Aviv Sourasky Medical Center in Israel found that only 48% tested positive for SARS-CoV-2 antibodies after two doses of the Pfizer-BioNTech vaccine. What's more, liver transplant patients who did test positive had lower antibody levels than vaccinated healthy individuals. Interestingly, another study by the same group found that kidney transplant recipients had an even lower response rate than the liver recipients, at just 38%.

The Johns Hopkins researchers then asked whether administration of a third vaccine dose could improve antibody responses. Extra boosters are known to give immunocompromised individuals additional protection against other infections, including hepatitis B.

This analysis included 30 transplant recipients who had not previously had COVID-19 symptoms or tested positive for SARS-CoV-2. The median age was 57 years, a majority were men and all but one were white. Of these, 22 had kidney transplants, three had liver transplants, two had heart transplants, one had a lung transplant, one had a pancreas transplant and one received both a kidney and a pancreas. The median time since transplantation was 4.5 years. All were taking immunosuppressive therapy to prevent organ rejection, mostly including tacrolimus or cyclosporine plus mycophenolate, and 24 also received corticosteroids.

All study participants had previously received two doses of either the Pfizer-BioNTech (57%) or Moderna (43%) vaccines, yet 24 of them did not have detectable SARS-CoV-2 antibodies, and the other six had only low levels.

A median of 67 days after their second shot, participants received either a third dose of the Pfizer-BioNTech vaccine (six people) or Moderna vaccine (nine people) or a booster dose of the Johnson & Johnson vaccine (15 people). The J&J vaccine, which is usually given as a single shot, works in a different way than the two mRNA vaccines, and some experts think combining them could improve response.

Repeat antibody testing a median of 14 days after the third shot revealed that the six people with low antibody levels after two doses now had high levels. However, just six of the 24 people with undetectable antibodies (25%) achieved high levels after their third shot. Two people (8%) reached low levels, but 16 people (67%) remained antibody negative.

"Our findings revealed that a third of the participants who had negative antibody levels and all who had low positive levels before the booster increased their immune response after a third vaccine dose," said study coauthor Dorry Segev, MD, PhD, director of the Johns Hopkins Epidemiology Research Group in Organ Transplantation.

The vaccines were generally safe and well tolerated, and the transplant patients experienced the same types of side effects as the general population, mainly mild to moderate injection site reactions or fatigue. One heart transplant recipient had a case of mild organ rejection.

But antibodies don't tell the whole story. COVID-19 vaccines also trigger memory B-cell and T-cell responses, which can provide protection even if antibody levels are low. B-cell and T-cell responses are harder to measure, however, and that was not done in this study. None of the participants developed COVID-19 after vaccination, though the duration of follow-up was limited, and transplant recipients generally take precautions to guard against infections.

"Our findings suggest clinical trials are warranted to determine if transplant recipients should receive COVID-19 vaccine booster doses as standard clinical practice, similar to what is currently done with hepatitis B and influenza vaccinations for this population," Werbel said.

In addition to extra booster doses, other potential strategies for improving protection for transplant patients include using larger vaccine doses, combining vaccine types, adjusting immunosuppressive regimens and passive immunization, which refers to administration of manufactured monoclonal antibodies or convalescent plasma from people who have recovered from COVID-19. In addition, transplant recipients may be vaccinated before their transplant if it can safely be delayed. The National Institutes of Health has started a study to learn more about COVID-19 vaccine response in people with inborn or acquired immune deficiencies.

"We are seeing in our own patients, and hearing from around the country, many cases of transplant patients receiving a full vaccine series, thinking they are immune, believing that the [Centers for Disease Control and Prevention] guidelines for vaccinated people apply to them, relaxing the masking and distancing behaviors that have protected them for over a year, and sadly finding themselves hospitalized with a new COVID-19 infection. Some have even died." Segev wrote in an op-ed for MedPage Today. "We need more effort and action to spread the word that vaccination does not necessarily mean immunity in this vulnerable population."

"So, what should our transplant patients do in light of these findings? First and foremost, they should continue to practice all the protective behaviors they have thus far practiced. While the rest of the world is celebrating the new freedoms that come with vaccination, unfortunately the time is not yet right for transplant patients to do so," he continued. "Transplant patients should also make sure that everyone around them gets vaccinated, so at least their environments are safer. And, of course, this is yet another reason that everyone should want to get vaccinated—to protect the vulnerable who cannot achieve immunity for themselves, and ultimately help reach herd immunity."

UPDATE: A larger French study described in The New England Journal of Medicine confirm these findings, showing that a third vaccine dose increased the portion of transplant patients with an adequate immune response.

Nassim Kamar, MD, PhD, of Toulouse University Hospital, and colleagues looked at outcomes among 101 solid organ recipients who received a third dose of the Pfizer-BioNTech vaccine. A

majority (78) had received a new kidney, 12 had liver transplants, eight had lung or heart transplants and three had pancreas transplants; it had been eight years, on average, since transplantation.

While only 4% had SARS-CoV-2 antibodies after their first dose and 40% did so after their second shot, the proportion rose to 68% after receiving the third booster. Even among those who tested negative for antibodies after two doses, 44% had antibodies four weeks after the third shot. Those who still didn't produce antibodies after the third dose were older, had worse immune suppression and had poorer kidney function. The third vaccine was safe and well tolerated with no serious adverse events. No one came down with COVID-19, but again follow-up has been short.

"This study showed that administration of a third dose of the BNT162b2 [Pfizer-BioNTech] vaccine to solid-organ transplant recipients significantly improved the immunogenicity of the vaccine, with no cases of COVID-19 reported in any of the patients," the researchers wrote. "However, a large proportion of the patients remain at risk for COVID-19. Barrier measures should be maintained, and vaccination of the relatives of these patients should be encouraged."

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