

## Study Suggests Lasting Immunity After COVID-19, With a Big Boost From Vaccination

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**A**fter an infection with SARS-CoV-2, most people—even those with mild infections—appear to have some protection against the virus for at least a year, a recent follow-up study of recovered patients published in *Nature* suggests. What's more, this and other research demonstrates that vaccinating these individuals substantially enhances their immune response and confers strong resistance against variants of concern, including the B.1.617.2 (delta) variant.

### The Backstory

Michel Nussenzweig, MD, PhD, and colleagues previously characterized immunity in a group of recovered adult patients about 1 month and 6 months after their COVID-19 symptoms began. Some of the study participants returned in February or March for a 12-month follow-up blood draw. "We wanted to understand how immunity evolves after infection," Nussenzweig, who heads The Rockefeller University's Laboratory of Molecular Immunology, wrote in an email.

### Who They Studied

The initial study included 149 participants who were considered recovered from COVID-19. Individuals were not eligible if they had any of the following within the previous 2 weeks:

- Chronic shortness of breath or fatigue
- Deficit in athletic ability
- Three or more long-term symptoms, such as persistent unexplained fever, chest pain, or loss of taste or smell

The participants' infections either had been verified with polymerase chain reaction (PCR) testing or suspected based on symptoms and close contact with a person with a confirmed infection.

Of the original cohort, 87 individuals returned for the 6-month follow-up and 63 came back for the 12-month visit. The latter participants—the subject of the most recent study—were aged 26 to 73 years and had had relatively mild infec-

tions. Only 10% had been hospitalized for their illness during the prior year. Since then, 41% had received at least 1 dose of an mRNA vaccine an average of 40 days before the 12-month follow-up visit. All tested negative for SARS-CoV-2 at the follow-up.



### What We've Learned

Nussenzweig's team found that antibodies against SARS-CoV-2 continue to evolve up to a year after infection. Vaccines improve the immune response.

- Compared with 6 months prior, **participants who were not vaccinated** maintained most of their plasma antibodies against the virus's receptor binding domain (RBD) and their plasma had similar neutralizing activity against a nonreplicating virus engineered with the SARS-CoV-2 spike protein. Their memory B cells that produce anti-RBD antibodies were only slightly lower in number than at the previous visit and had evolved to produce a broader and more potent range of antibodies. However, their plasma had less neutralizing activity against the variants B.1.1.7 (alpha), B.1.351 (beta), B.1.526 (iota), and P.1 (gamma), with the greatest loss of activity against the beta variant first detected in South Africa.

- Compared with unvaccinated participants, **those who had received at least 1 dose** had higher plasma anti-RBD antibodies and a nearly 50-fold increase in neutralizing activity. According to Nussenzweig, vaccination boosts the memory antibodies that develop after infection, producing an "outstanding response." In this group, neutralizing antibody levels against the variants surpassed the levels observed against the wild-type virus in infected or fully vaccinated individuals in other studies. Additional research supports this. Two teams, in **North America** and the **UK**, recently published studies in *Science* demonstrating that a single dose of an mRNA vaccine substantially enhances the immune response to SARS-CoV-2 variants among patients with a prior infection—a phenomenon some are calling "hybrid immunity."

### What About the Delta Variant?

In early July, the World Health Organization [forecast](#) that the delta variant, originally detected in India, was poised to soon outcompete other variants globally. A recent [study](#) by researchers in France, also published in *Nature*, included an analysis of recovered patients' immunity against the highly transmissible variant.

Unvaccinated health care workers appeared to have less protection against the delta and beta variants compared with alpha about a year after they recovered from mild COVID-19. While 88% of this group had neutralizing antibodies against alpha, only 47% neutralized delta.

However, recovered health care workers who had received 1 dose of the AstraZeneca, Pfizer, or Moderna vaccines had a marked increase in neutralizing antibody levels against all 3 of these variants compared with their unvaccinated peers. "Vaccination of convalescent individuals boosted the humoral immune response [against delta] well above the threshold of neutralization," the authors wrote. "These results strongly suggest that vaccination of



previously infected individuals will be most likely protective against a large array of circulating viral strains, including variant [delta]."

#### What About Vaccination Alone?

Nussenzweig said an open question is how long immunity lasts after vaccination alone. One recent [study](#) found that at least 12 weeks after their second dose of Pfizer's mRNA vaccine, people who were

not previously infected had a surprisingly high number of SARS-CoV-2 spike protein-targeting B cells in the germinal centers of their lymph nodes, where these cells are trained to produce and perfect antibodies. Some of the antibodies generated from the B cells cross-reacted with seasonal [betacoronaviruses](#) or bound to unique regions of the virus's spike protein, the scientists reported in *Nature*.

According to Rachel Presti, MD, PhD, a coauthor of the study, her team's findings suggest that the mRNA vaccine likely generates a fairly durable and broad response, although she cautioned that further evidence is needed to confirm these implications. "Unless COVID mutates enough to really escape the immune response, I don't think we will need boosters soon," Presti, an associate professor in the Division of Infectious Diseases at the Washington University School of Medicine in St Louis, wrote in an email.

Nussenzweig said he believes immunized people who weren't previously infected will need boosters at some point, but it's unknown how soon that will be. In the study from France, such individuals had high neutralizing antibody levels against the alpha, beta, and delta variants 8 to 16 weeks after they received a 2-dose vaccine regimen.

#### The Clinical Takeaway

Nussenzweig predicted that variants will not cause serious illness in most people who have recovered from COVID-19. Nevertheless, he said, they should be vaccinated "because they become bulletproof when they do so." ■

**Note:** Source references are available through embedded hyperlinks in the article text online.