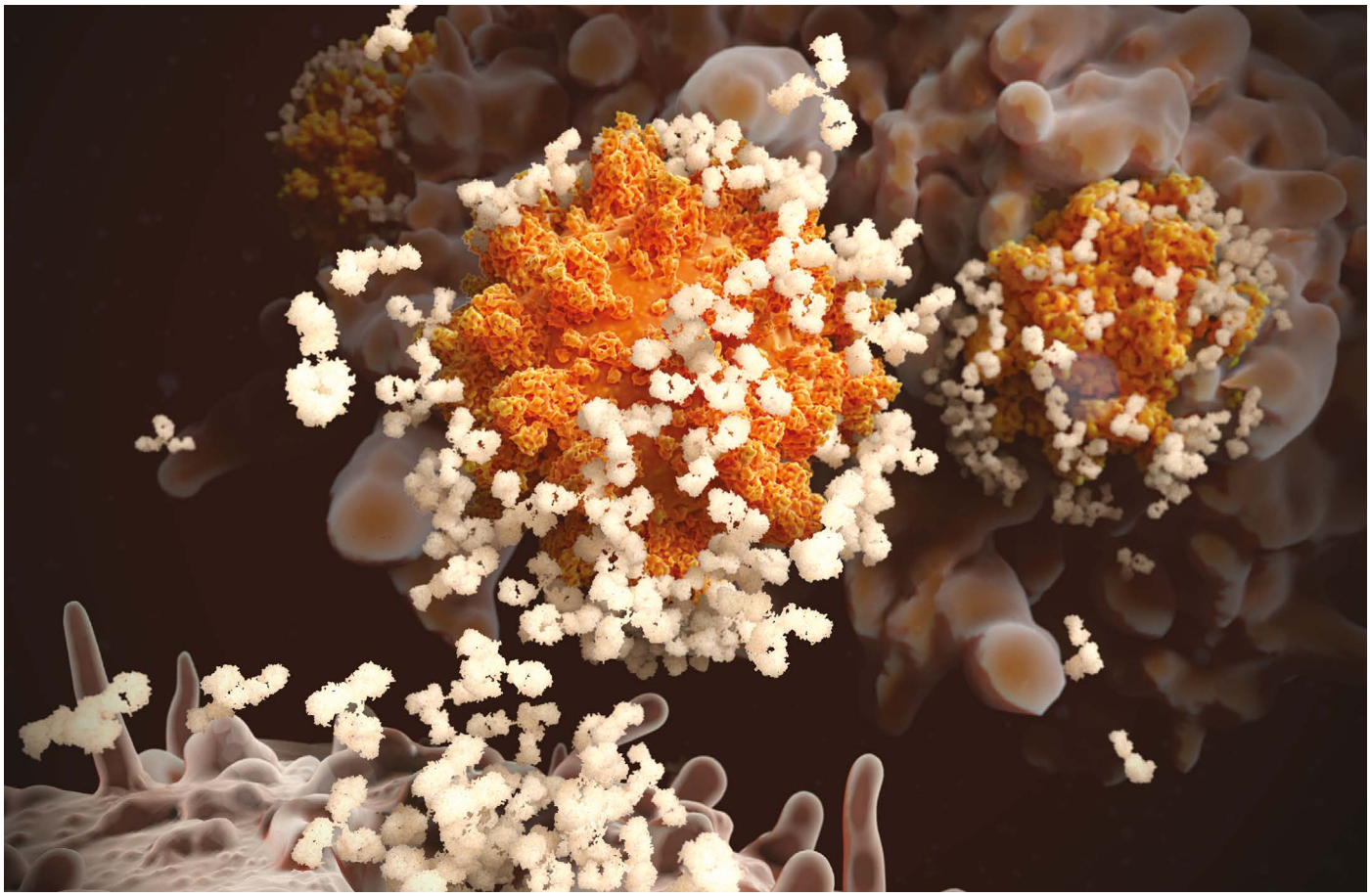
News in focus



UAN GAERTNER/SPL

Researchers are investigating enhanced immunity to SARS-CoV-2 in people who are vaccinated after recovering from COVID-19.

COVID SUPER-IMMUNITY: ONE OF THE PANDEMIC'S GREAT PUZZLES

Why do people who have previously recovered from COVID-19 have a stronger immune response after being vaccinated than those who have never been infected?

By Ewen Callaway

Around a year ago — before Delta and other variants entered the COVID-19 lexicon — virologists Theodora Hatziioannou and Paul Bieniasz, both at the Rockefeller University in New York City, set out to make a version of a key SARS-CoV-2 protein that could dodge all the infection-blocking antibodies our body makes.

The goal was to identify the parts of spike — the protein SARS-CoV-2 uses to infect cells — that are targeted by these neutralizing antibodies. The aim was to map a key part of our body's attack on the virus. The researchers mixed and matched potentially concerning mutations identified in lab experiments and circulating viruses, and tested their Franken-spikes in harmless 'pseudotype' viruses incapable of causing COVID-19. In a study published last month in *Nature*[1], they reported that a spike mutant containing 20 changes was fully resistant to neutralizing antibodies made by most of the people tested who had been either infected or vaccinated — but there were exceptions.

Those who had recovered from COVID-19 months before receiving their jabs harboured antibodies capable of defanging the mutant spike, which displays much more resistance to immune attack than does any known naturally occurring variant. These peoples' antibodies even blocked other types of coronavirus. "It's very likely they will be effective against any future variant that SARS-CoV-2 throws against them," says Hatziioannou.

As the world watches out for new coronavirus variants, the basis of such 'super-immunity' has become one of the pandemic's great

mysteries. Researchers hope that, by mapping the differences between the immune protection that comes from infection compared with that from vaccination, they can chart a safer path to this higher level of protection.

"It has implications on boosters and how our immune responses are primed for the next variant that emerges," says Mehul Suthar, a virologist at Emory University in Atlanta, Georgia. "We're flying by the seat of our pants trying to figure this stuff out."

Hybrid immunity

Not long after countries began rolling out vaccines, researchers started noticing unique properties of the vaccine responses of people who had previously caught and recovered from COVID-19. "We saw that the antibodies come up to these astronomical levels that outpace what you get from two doses of vaccine alone," says Rishi Goel, an immunologist at the University of Pennsylvania in Philadelphia who is part of a team studying super-immunity – or 'hybrid immunity', as most scientists call it.

Initial studies of people with hybrid immunity found that their serum – the antibody-containing portion of blood – was much better able to neutralize immune-evading strains, such as the Beta variant identified in South Africa, and other coronaviruses, compared with that from 'naive' vaccinated individuals who had never encountered SARS-CoV-2 (ref. 2). It wasn't clear whether this was just due to the high levels of neutralizing antibodies, or to other properties.

The most recent studies suggest that hybrid immunity is, at least partly, due to immune players called memory B cells. The bulk of antibodies made after infection or vaccination come from short-lived cells called plasmablasts, and antibody levels fall when these cells inevitably die off. Once plasmablasts are gone, the main source of antibodies becomes the much rarer memory B cells that are triggered by either infection or vaccination.

Some of these long-lived cells make higher-quality antibodies than plasmablasts, says Michel Nussenzweig, an immunologist at the Rockefeller. That's because they evolve in organs called lymph nodes, gaining mutations over time that help them to bind more tightly to the spike protein. When people who have recovered from COVID-19 are re-exposed to SARS-CoV-2's spike, these cells multiply and churn out more of these highly potent antibodies.

"You get a sniff of antigen, in this case of mRNA vaccine, and those cells just explode," says Goel. In this way, a first vaccine dose in someone who has previously been infected is doing the same job as a second dose in someone who has never had COVID-19.

Differences between the memory B cells triggered by infection and those triggered by vaccination – as well as the antibodies they make – might also underlie the heightened responses of hybrid immunity. Infection and vaccination expose the spike protein to the immune system in vastly different ways, Nussenzweig says.

In a series of studies[3–5], Nussenzweig's team, which includes Hatziioannou and Bieniasz, compared the antibody responses of infected and vaccinated people. Both lead to the establishment of memory B cells that make antibodies that have evolved to become more potent, but the researchers suggest this occurs to a greater extent after infection.

The team isolated hundreds of memory B cells – each making a unique antibody – from people at various times after infection and vaccination. Natural infection triggered antibodies that continued to grow in potency and breadth against variants for a year after infection, whereas most of those elicited by vaccination seemed to stop changing in the weeks after a second dose. Memory B cells that evolved after infection were also more likely than those from vaccination to make antibodies that block immune-evading variants such as Beta and Delta.

A separate study, not yet peer reviewed, found that, compared with mRNA vaccination, infection leads to a pool of antibodies that recognize variants more evenly by targeting diverse regions of spike[6]. The researchers also found that people with hybrid immunity produced consistently higher levels of antibodies, compared with never-infected vaccinated people, for up to seven months. Antibody levels were more stable in people with hybrid immunity, reports the team, led by immunologist Duane Wesemann at Harvard Medical School in Boston, Massachusetts.

"It has implications on boosters and how our immune responses are primed for the next variant."

'Not surprising'

Many studies of hybrid immunity haven't followed naive vaccine recipients for as long as those who recovered from COVID-19, and it's possible the naive recipients' B cells will make antibodies that gain potency with time, further vaccine doses, or both, researchers say. It can take months for a stable pool of memory B cells to establish itself and mature.

"It's not surprising that people infected and vaccinated are getting a nice response," says Ali Ellebedy, a B-cell immunologist at Washington University in St Louis, Missouri. "We are comparing someone who started the race three to four months ago to someone who started the race now."

There is some evidence that people who received both jabs without previously being infected seem to be catching up. Ellebedy's team collected lymph-node samples from mRNA-vaccinated individuals and found signs that some of their memory B cells triggered by the vaccination were gaining mutations, up to 12 weeks after the second dose, that enabled them to recognize diverse coronaviruses, including some that cause common colds[7].

A third vaccine dose might allow people who haven't been infected to achieve the benefits of hybrid immunity, says Matthieu Mahévas, an immunologist at the Necker Institute for Sick Children in Paris. His team found that some of the memory B cells from naive vaccine recipients could recognize Beta and Delta, two months after vaccination[8]. "When you boost this pool, you can clearly imagine you will generate potent neutralizing antibodies," Mahévas says. Extending the interval between doses could also mimic aspects of hybrid immunity.

Cause and effect

Understanding the mechanism behind hybrid immunity will be key to emulating it, say scientists. The latest studies focus on antibody responses made by B cells, and it's likely that T-cell responses to vaccination and infection behave differently. Natural infection also triggers responses against viral proteins other than spike. Nussenzweig wonders whether other factors unique to natural infection are crucial. During infection, millions of viral particles populate the airways, encountering immune cells that visit nearby lymph nodes, where memory B cells mature. Viral proteins stick around in the gut of some people months after recovery, and it's possible that this persistence helps B cells hone their responses to SARS-CoV-2.

Researchers say that it is also important to determine the real-world effects of hybrid immunity. A study from Qatar, not yet peer reviewed, suggests that people who get Pfizer–BioNTech's mRNA vaccine after infection are less likely to test positive for COVID-19 than are individuals with no history of infection[9].

Those studying hybrid immunity stress that – whatever the potential benefits – the risks of a SARS-CoV-2 infection mean that it should be avoided. "We are not inviting anybody to get infected and then vaccinated to have a good response," says Finzi. "Because some of them will not make it through."

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