

Repeat COVID-19 vaccinations elicit antibodies that neutralize variants, other viruses

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Health-care workers received the first doses of the COVID-19 vaccine in December 2020. A study by researchers at Washington University School of Medicine in St. Louis has found that repeat vaccination with updated versions of the COVID-19 vaccine promotes the development of antibodies that neutralize a wide range of variants of the virus that causes COVID-19, as well as related coronaviruses. Credit: Matt Miller/Washington University

The COVID-19 pandemic is over, but the virus that caused it is still here, sending thousands of people to the hospital each week and spinning off new variants with depressing regularity. The virus's exceptional ability to change and evade immune defenses has led the World Health Organization (WHO) to recommend annual updates to COVID-19 vaccines.

But some scientists worry that the remarkable success of the first COVID-19 vaccines may work against updated versions, undermining the utility of an annual vaccination program. A similar problem plagues the annual flu vaccine campaign; immunity elicited by one year's flu shots can interfere with immune responses in subsequent years, reducing the vaccines' effectiveness.

A new study by researchers at Washington University School of Medicine in St. Louis helps to address this question. Unlike immunity to [influenza virus](#), prior immunity to SARS-CoV-2, the virus that causes COVID-19, doesn't inhibit later vaccine responses. Rather, it promotes the development of broadly inhibitory antibodies, the researchers report.

The study, available online in *Nature*, shows that people who were repeatedly vaccinated for COVID-19—initially receiving shots aimed at the original variant, followed by boosters and updated vaccines targeting variants—generated antibodies capable of neutralizing a wide range of SARS-CoV-2 variants and even some distantly related coronaviruses. The findings suggest that periodic re-vaccination for COVID-19, far from hindering the body's ability to recognize and respond to new variants, may instead cause people to gradually build up a stock of broadly neutralizing antibodies that protect them from emerging SARS-CoV-2 variants and some other coronavirus species as well, even ones that have not yet emerged to infect humans.

"The first vaccine an individual receives induces a strong primary immune response that shapes responses to subsequent infection and vaccination, an effect known as imprinting," said senior author Michael S. Diamond, MD, Ph.D., the Herbert S. Gasser Professor of Medicine. "In principle, imprinting can be positive, negative or neutral. In this case, we see strong imprinting that is positive, because it's coupled to the development of cross-reactive neutralizing antibodies with remarkable breadth of activity."

Imprinting is the natural result of how immunological memory works. A first vaccination triggers the development of memory [immune cells](#). When people receive a second vaccination quite similar to the first, it reactivates [memory cells](#) elicited by the first vaccine. These memory cells dominate and shape the immune response to the subsequent vaccine.

In the case of the flu vaccine, imprinting has negative effects. Antibody-producing memory cells crowd out new antibody-producing cells, and people develop relatively few neutralizing antibodies against the strains in the newer vaccine. But in other cases, imprinting can be positive, by promoting the development of cross-reactive antibodies that neutralize strains in both the initial and subsequent vaccines.

To understand how imprinting influences the immune response to repeat COVID-19 vaccination, Diamond and colleagues including first author Chieh-Yu Liang, a graduate student, studied the antibodies from mice or people who had received a sequence of COVID-19 vaccines and boosters targeting first the original and then omicron variants. Some of the human participants also had been naturally infected with the virus that causes COVID-19.

The first question was the strength of the imprinting effect. The researchers measured how many of the participants' neutralizing

antibodies were specific for the original variant, the omicron variant or both. They found that very few people had developed any antibodies unique to omicron, a pattern indicative of strong imprinting by the initial vaccination. But they also found few antibodies unique to the original variant. The vast majority of neutralizing antibodies cross-reacted with both.

The next question was how far the cross-reactive effect extended. Cross-reactive antibodies, by definition, recognize a feature shared by two or more variants. Some features are shared only by similar variants, others by all SARS-CoV-2 variants or even all coronaviruses. To assess the breadth of the neutralizing antibodies, the researchers tested them against a panel of coronaviruses, including SARS-CoV-2 viruses from two omicron lineages; a coronavirus from pangolins; the SARS-1 virus that caused the 2002-03 SARS epidemic; and the Middle Eastern Respiratory Syndrome (MERS) virus. The antibodies neutralized all the viruses except MERS virus, which comes from a different branch of the coronavirus family tree than the others.

Further experiments revealed that this remarkable breadth was due to the combination of original and variant vaccines. People who received only the vaccines targeting the original SARS-CoV-2 [variant](#) developed some cross-reactive antibodies that neutralized the pangolin coronavirus and SARS-1 virus, but the levels were low. After boosting with an omicron vaccine, though, the cross-reactive neutralizing antibodies against the two coronavirus species increased.

Taken together, the findings suggest that regular re-vaccination with updated COVID-19 vaccines against variants might give people the tools to fight off not only the SARS-CoV-2 variants represented in the vaccines, but also other SARS-CoV-2 variants and related coronaviruses, possibly including ones that have not yet emerged.

"At the start of the COVID-19 pandemic, the world population was immunologically naïve, which is part of the reason the virus was able to spread so fast and do so much damage," said Diamond, also a professor of molecular microbiology and of pathology & immunology. "We do not know for certain whether getting an updated COVID-19 vaccine every year would protect people against emerging coronaviruses, but it's plausible. These data suggest that if these cross-reactive antibodies do not rapidly wane—we would need to follow their levels over time to know for certain—they may confer some or even substantial protection against a pandemic caused by a related coronavirus."

More information: Chieh-Yu Liang et al, Imprinting of serum neutralizing antibodies by Wuhan-1 mRNA vaccines, *Nature* (2024).
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