Vaccination, previous infection, protect against SARS-CoV-2 gamma variant in animal model

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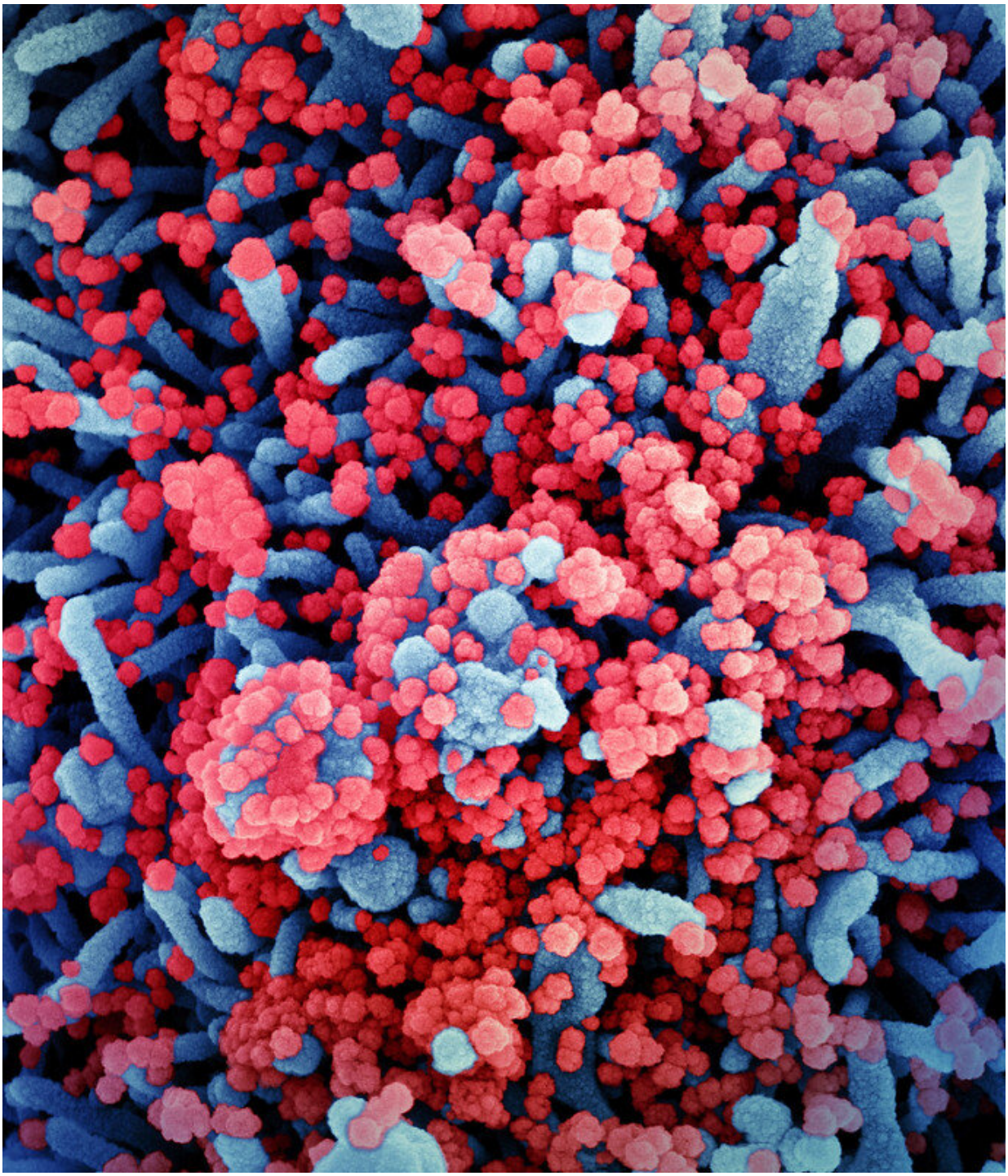

Colorized scanning electron micrograph of a cell (blue) heavily infected with SARS-CoV-2 virus particles (red), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

In early January 2021, travelers returning to Tokyo, Japan, from Amazonas, Brazil, were screened for COVID-19 at the airport. A few days later, the National Institute of Infectious Disease of Japan announced that the travelers had returned with a new variant of the SARS-CoV-2 virus.

That variant, known as gamma, or P.1, led to a deadly surge in COVID-19 cases in Brazil this spring, and has now spread across the world. More than 200 cases have been detected in Wisconsin. Whether current vaccines are as effective against the gamma variant remains unknown.

In a new study using variant virus recovered from one of the original travelers, researchers in the U.S. and Japan have found that vaccination with an mRNA vaccine induces antibody responses that would protect humans from infection with the gamma/P.1 variant. Hamsters previously infected with the virus strains first circulating in early 2020 were also protected from infection with the gamma variant nine months later.

The findings, the researchers say, suggest that previous SARS-CoV-2 infection and vaccines that are based on earlier strains of the virus still provide protection against infection with gamma. The study published in the *Proceedings of the National Academy of Sciences* on June 17, 2021.

"The animals were quite protected," says study lead Yoshihiro Kawaoka, a professor of virology at the University of Wisconsin-Madison School of Veterinary Medicine and the University of Tokyo. "There may be people who get infected with this variant even though they are vaccinated or were previously infected, but they shouldn't get severe disease."

However, he says, "that is not consistent with what has been happening in Brazil," where there have been reports of people reinfected with the gamma variant after recovering from infection with an earlier strain. It's possible, Kawaoka says, that COVID-19 immunity lasts longer in hamsters than in humans, or that cases documented as reinfections are actually first infections.

Kawaoka's research team established the Syrian hamster model for COVID-19 last year, after demonstrating that hamsters are highly susceptible to the SARS-CoV-2 virus and develop disease similar to humans, like ground glass opacity in their lungs. They also develop lasting antibodies that protect against reinfection.

"Animal models are great because (they allow us to) test vaccines, test drugs, test monoclonal antibodies and even do pathogenesis (studies)," says Kawaoka.

In fact, his team studied the gamma variant in hamsters because, while previous studies suggested P.1 might bind better to cells and resist antibodies created by previous infections or vaccination, little is known about the variant's ability to replicate in the body, how much illness or pathogenesis it causes, or how well immune responses react to the virus.

The researchers infected hamsters with either the P.1/gamma variant isolated from the traveler, or with one of two earlier strains of the virus from human samples—one isolated from a patient in February 2020, and the other from a patient with a non-variant globally predominant strain. Each of the strains replicated similarly in the nose and lungs of hamsters and caused similar illness affecting the lungs.

Next, Kawaoka's team looked at whether antibodies in convalescent sera from 35 recovered COVID-19 patients or from people who'd received the Pfizer-BioNTech mRNA vaccine could neutralize each of the three

viral strains.

Following a natural infection or vaccination, the body produces antibodies that learn to recognize the spike protein of the SARS-CoV-2 virus, which is responsible for binding to cells. Should people encounter the virus again, antibodies recognize the spike protein and subsequently fight off or limit the extent of infection.

Earlier studies have shown that a spike protein mutation—E484K, found in gamma variants—can change the spike protein's identity just enough that the variant can slip past these defenses. However, antibodies in the blood of vaccinated individuals reacted to all three strains, including gamma.

Antibodies in the blood of recovered COVID-19 patients were also effective at neutralizing each of the strains. However, of the 35 patients, one had been infected with gamma and the antibodies from this individual were less reactive to the non-variant strains.

The researchers say these findings suggest there are some important differences in the spike protein of gamma that might influence immunity, warranting further monitoring. Additionally, Kawaoka's group found that gamma, but not other strains of SARS-CoV-2, can infect and replicate in mice, suggesting that the spike protein interacts differently with cells than earlier strains.

The researchers also found that hamsters that had recovered from infection with either of the earlier strains of SARS-CoV-2 were protected against viral replication in their lungs if reinfected with either the same strain or the gamma variant, three weeks and nine months later.

However, gamma was recovered in the nasal passages of reinfected animals in both groups. The amount of virus in the nasal passages of

reinfected animals was 1,000-fold lower than animals infected for the first time.

Finally, the researchers studied whether convalescent plasma from three patients infected with SARS-CoV-2 in early 2020 could protect against viral replication in the nose and lungs of hamsters. They found that convalescent plasma, but not plasma from patients who did not have COVID-19, limited virus replication in the lungs of hamsters infected with the prevailing non-variant strain and with gamma/P.1. Virus was found in their nasal passages.

Vaccination, Kawaoka says, is the best way to seek protection from SARS-CoV-2 and emerging variants, including the delta variant, also known as B.1.617.2. The Centers for Disease Control and Prevention recently designated the delta version as a variant of concern due to evidence that it transmits more readily.

Peter Halfmann, research associate professor at UW-Madison and co-leader of the study, added that the gamma and delta variants are circulating in Madison and other parts of the U.S., highlighting the importance of vaccination.

"The difference between the original strain and (delta) and the original strain and (gamma) is similar," Kawaoka adds, noting: "The (delta) variant may become prevalent but it shouldn't be extremely concerning as long as you are vaccinated."

With SARS-CoV-2 changing as it spreads, some versions of the virus will disappear as new variants emerge, as happened with a European variant in early 2020 that quickly eclipsed the original virus first found in China.

"At least in the vast majority of the population, we don't have good

immunity to SARS-CoV-2, so the selective pressure on the virus at the moment is transmissibility," Kawaoka says, explaining why new variants that successfully spread tend to be more transmissible than those that came before. "But it will change. We should expect to see the selective pressure become immunity."

This is why vaccines will likely need to be modified in the coming years, he explains, in order to protect against a virus that will evolve to evade the protections we devise so long as spread of the virus remains high, or if our immune systems don't maintain defenses for long enough to prevent reinfections.

"We don't know which one is going to be the case ... it's too early to say how long immunity to this virus lasts," he says. "Hamsters look different from humans, anyway. It's difficult to predict."

Peter Halfmann, a research associate professor at UW-Madison, and Masaki Imai in the Division of Virology at the University of Tokyo, co-led the study.

More information: Masaki Imai et al, Characterization of a new SARS-CoV-2 variant that emerged in Brazil, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2106535118

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