PAUL A BRONSTEIN/GETTY

A patient in Singapore during the 2003 outbreak of severe acute respiratory syndrome.

COVID VACCINES ELICIT POTENT RESPONSE IN SARS SURVIVORS

Strong antibody production in people infected in 2002–04 outbreak raises pan-coronavirus jab hope.

By Smriti Mallapaty

People who were infected almost two decades ago with the virus that causes severe acute respiratory syndrome (SARS) generate a powerful antibody response after being vaccinated against COVID-19. Their immune systems can fight off SARS-CoV-2 variants, as well as related coronaviruses found in bats and pangolins.

The Singapore-based authors of a small study published today in *The New England Journal of Medicine*[1] say the results offer hope that vaccines can be developed to protect against all new SARS-CoV-2 variants, as well as other coronaviruses that have the potential to cause future pandemics.

The study is a "proof of concept that a pan-coronavirus vaccine in humans is possible", says David Martinez, a viral immunologist at the University of North Carolina at Chapel Hill. "It's a really unique and cool study, with the caveat that it didn't include many patients."

SARS-CoV-2 belongs to the sarbecovirus group of coronaviruses, which includes the virus that caused SARS (called SARS-CoV), as well as related bat and pangolin coronaviruses.

Sarbecoviruses use what are known as spike proteins to bind to ACE2 receptors in the membranes of host cells and enter them. They can jump from animals to humans, as they did before in both the current pandemic and the 2002–04 outbreak of SARS, which spread to 29 countries. "The fact that this has happened twice in the last two decades is strong rationale that this is a group of viruses that we really need to pay attention to," says Martinez.

Neutralizing antibodies

Last year, Linfa Wang, a virologist at Duke–NUS Medical School in Singapore who led the latest study, went looking for people who had survived SARS to see whether they offered any clues about how to develop vaccines and drugs for COVID-19. He detected 'neutralizing' antibodies in their blood that blocked the original SARS virus from entering cells, but did not affect SARS-CoV-2 — which he found surprising, because the viruses are closely related.

But when Singapore rolled out the Pfizer–BioNTech COVID-19 vaccine this year, Wang decided to interrogate how the SARS infection affected responses to the vaccine. What he discovered was striking. Eight vaccinated study participants, who had recovered from SARS almost two decades ago, produced very high levels of neutralizing antibodies against both viruses, even after just one dose of the vaccine.

They also produced a broad spectrum of neutralizing antibodies against three SARS-CoV-2 variants of concern — Alpha, Beta and Delta — and five bat and pangolin sarbecoviruses. No such potent and wide-ranging antibody response was observed in blood taken from fully vaccinated individuals, even those who'd also had COVID-19.

The researchers suggest that such broad protection could arise because the vaccine jogs the immune system's 'memory' of regions of the SARS virus that are also present in SARS-CoV-2, and possibly in many other sarbecoviruses.

Coronaviruses found in bats have the potential to cause future pandemics, so the fact that a broad spectrum of neutralizing antibodies is generated that protects against some "is encouraging", says Daniel Lingwood, an immunologist at the Ragon Institute of MGH, MIT and Harvard in Boston, Massachusetts. But it is not clear how long this protection lasts.

A vaccine that is widely effective against sarbecoviruses could be administered to the general population in high-risk areas close to animals that harbour them, limiting the potential spread of these viruses in people, adds Christopher Barnes, a structural biologist at Stanford University in California.

The biggest question

Barton Haynes, an immunologist at Duke University School of Medicine in Durham, North Carolina, says the study raises the question of whether a similar response could be generated if people vaccinated against COVID-19 were given a booster shot that targeted the original SARS virus. This might protect them against new variants of SARS-CoV-2 and other sarbecoviruses. Wang says preliminary studies in mice suggest that is possible.

But the latest study doesn't identify exactly which sections of the viruses induce the broad immune response, something that would be needed to develop vaccines. That's the "biggest question", says Martinez. If it is a region of the virus that is present not just in sarbecoviruses, but in the entire group of coronaviruses, there is potential for creating a vaccine against all of them, he says.

Several research groups have identified specific antibodies that prevent SARS-CoV-2 and other sarbecoviruses from spreading in cells. Others are already working on pan-coronavirus vaccines, and have synthesized components that induce strong protection in monkeys and mice.

Haynes and his colleagues, for example, have developed[2] a protein nanoparticle studded with 24 pieces of a section of the SARS-CoV-2 spike protein called the receptor-binding domain, a key target of antibodies. They found that in monkeys, the

nanoparticle induced much higher levels of antibodies against SARS-CoV-2 than did the Pfizer vaccine. It also induced cross-reactive antibodies against the original SARS virus and bat and pangolin sarbecoviruses.

Martinez and his colleagues have induced these widely reactive antibodies in mice, using a vaccine made from a combination of spike proteins from different coronaviruses[3]. But Martinez says the latest study suggests that this spike chimaera might not be necessary; a similar response could be induced simply by the original SARS virus's spike protein.

Wang says he is already working on potential vaccines that target multiple sarbecoviruses, and he now hopes to find further survivors of the 2002–04 SARS outbreak to conduct a much larger study, including testing their responses to other COVID-19 vaccines.

1. Tan, C.-W. *et al. N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2108453 (2021).
2. Saunders, K. O. *et al. Nature* **594**, 553–559 (2021).
3. Martinez, D. R. *et al. Science* https://doi.org/10.1126/science.abi4506 (2021).

THE MUTATION THAT HELPS DELTA SPREAD LIKE WILDFIRE

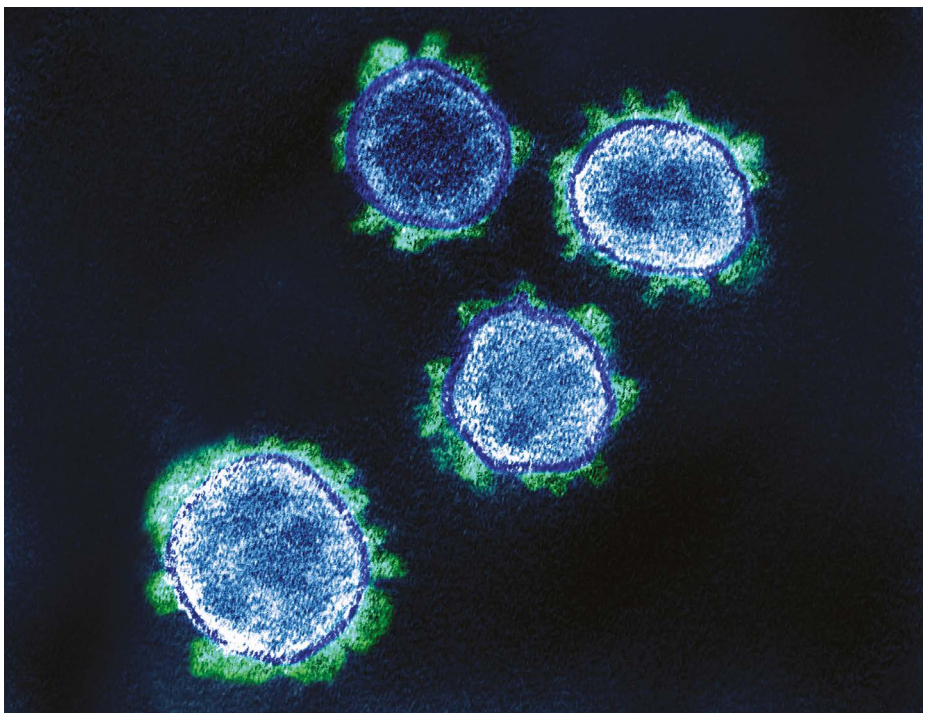
A key amino-acid change might underlie the coronavirus variant's ferocious infectivity.

By Ewen Callaway

As the world grapples with the hyper-infectious Delta coronavirus variant, scientists are racing to understand the biological basis for its behaviour. A slew of studies has highlighted an amino-acid change present in Delta that might contribute to its swift spread. Delta is at least 40% more transmissible than is the Alpha variant identified in the United Kingdom in late 2020, epidemiological studies suggest.

"The key hallmark of Delta is that transmissibility seems to be ramping up to the next notch," says Pei-Yong Shi, a virologist at the University of Texas Medical Branch in Galveston. "We thought Alpha was pretty bad, very good at spreading. This one seems to be even more."

Shi's team and other groups have zeroed in on a mutation that alters a single amino acid in the SARS-CoV-2 spike protein — the viral molecule responsible for recognizing and invading cells. The change, which is called P681R and transforms a proline residue into an arginine, falls within an intensely studied region of the spike protein called the furin cleavage site.



SARS-CoV-2 coronavirus particles isolated from a person with COVID-19.

NIH/SPL

The presence of this short string of amino acids set off alarm bells when SARS-CoV-2 was first identified in China, because it is associated with heightened infectivity in other viruses such as influenza, but had not previously been found in sarbecoviruses, the family of coronaviruses to which SARS-CoV-2 belongs. "This little insert sticks out and hits you in the face," says Gary Whittaker, a virologist at Cornell University in Ithaca, New York.

Pre-activated virus

To penetrate cells, the SARS-CoV-2 spike protein must be cut twice by host proteins. In the SARS-CoV-1 virus that causes severe acute respiratory syndrome (SARS), both incisions occur after the virus has locked on to a cell. But with SARS-CoV-2, the presence of the furin cleavage site means that host enzymes (including one called furin) can make the first cut as newly formed viral particles emerge from an infected cell. These pre-activated viral particles can then go on to infect cells more efficiently than do particles requiring two cuts, says Whittaker.

Delta wasn't the first SARS-CoV-2 variant to gain a mutation that alters the furin cleavage site. The Alpha variant has a different amino-acid change at the same location as Delta. But the available evidence suggests that the mutation's effect has been especially profound in Delta.

In a study reported as a preprint on 13 August[1], Shi's team found that the spike protein is cut much more efficiently in Delta-variant particles than in Alpha particles, echoing results reported in May by virologist Wendy Barclay at Imperial College London and her team, who compared Delta with an earlier strain[2]. Follow-up experiments by both groups showed that the P681R change was largely responsible for spike being clipped so much more efficiently. "This really nailed it, in terms of the mechanism," says Shi.

Researchers are also beginning to join the dots between P681R and Delta's ferocious infectivity. Shi's team found that, in cultured human-airway epithelial cells infected with equal numbers of Delta and Alpha viral particles, Delta rapidly outcompeted the Alpha variant, mimicking epidemiological patterns that have played out globally. But Delta's advantage disappeared when the researchers eliminated the P681R change.

The mutation might also speed up the spread of SARS-CoV-2 from cell to cell. A team led by Kei Sato, a virologist at the University