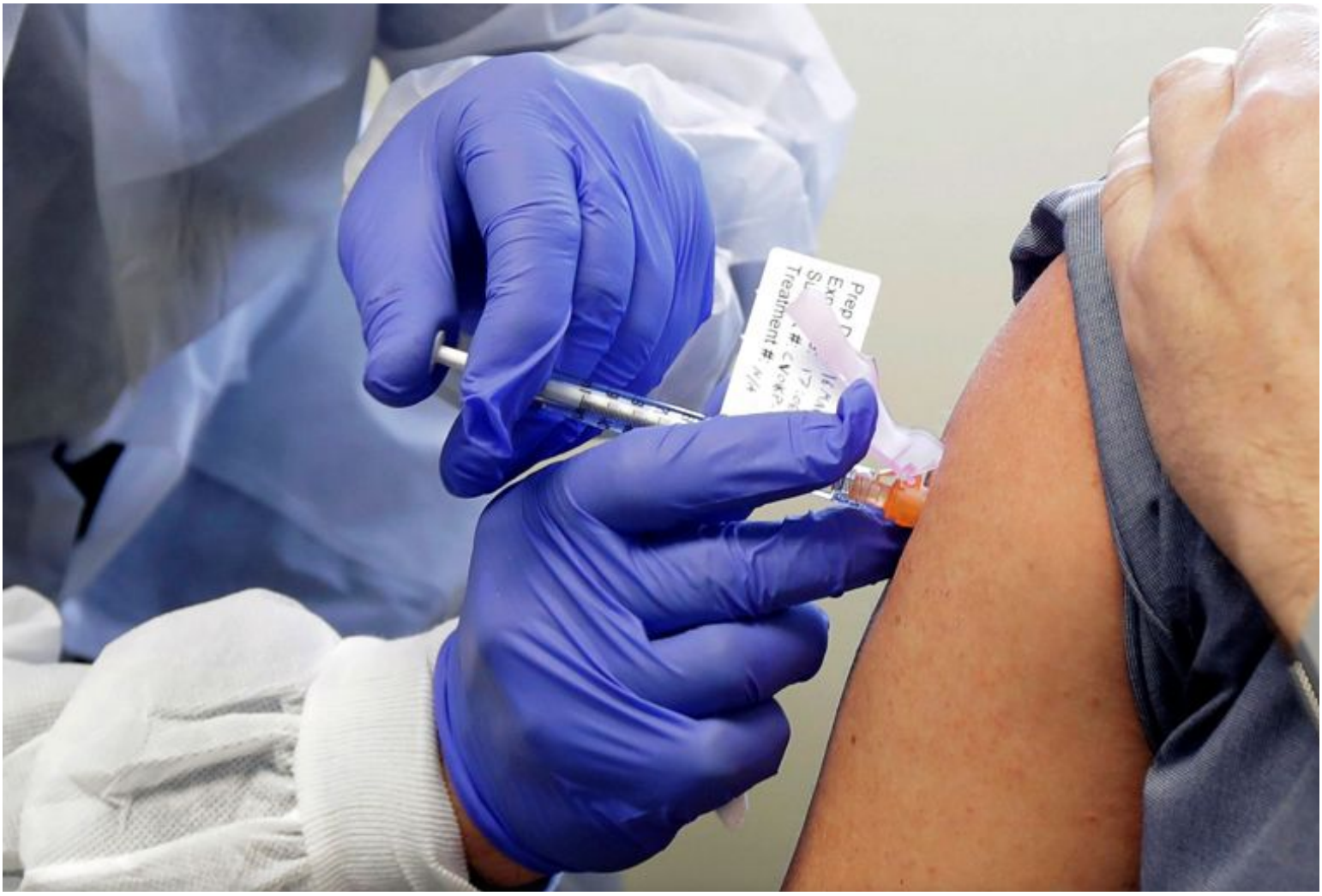
Ewen Callaway



The push to make a coronavirus vaccine is moving at breakneck speed. This week, the first of a few dozen healthy volunteers in Seattle, Washington, received a vaccine in a phase I safety trial sponsored by the US government. Similar safety trials of other coronavirus vaccines will also begin soon.

Even as these 'first in human' trials get going, key questions about how our immune system fights off the virus — and how to safely trigger a similar immune response with a vaccine — remain unanswered. Answers might come soon from studies of infected people and animal models, but some researchers say that the lack of information should not keep experts from beginning safety trials in people. Others worry that if vaccine candidates released on an accelerated schedule turn out to be ineffective or, worse, unsafe, it could send researchers back to the drawing board and end up delaying the development and wide-scale roll-out of an effective vaccine.

Here are some of the key questions that scientists hope to answer to develop a coronavirus vaccine.

Do people develop immunity?

Vaccines help a person to generate an immune response against an infection without first being exposed to the pathogen. Studies of other coronaviruses, such as the four that cause some common colds, lead most researchers to assume that people who have recovered from SARS-CoV-2 infection will be protected from reinfection for a period of time. But that assumption needs to be backed by evidence, says Michael Diamond, a viral immunologist at Washington University in St. Louis, Missouri. "We don't know that much about immunity to this virus."

A preprint[1] posted online on 14 March by a team based in China looked at two rhesus macaques (*Macaca mulatta*) that had recovered from SARS-CoV-2 infection, which caused them only mild illness. The monkeys did not seem to become re-infected when researchers exposed them to the virus for a second time four weeks after their initial exposure. Researchers will be looking for evidence that humans react in the same way, for instance by studying people potentially exposed multiple times, Diamond says.

If humans do develop immunity, how long does it last?

That's another big unknown. Immunity is short-lived for the coronaviruses that cause common colds; even people who have high levels of antibodies against these viruses can still become infected, says Stanley Perlman, a coronavirologist at the University of Iowa in Iowa City.

The evidence is more equivocal for the two other coronaviruses that have triggered epidemics: those that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Perlman says his team has found that after people recover from MERS, their antibodies against the virus drop precipitously. He also says that his team has gathered data — not yet published — showing that SARS antibodies are still present in the body 15 years after infection. But it's not clear whether this immune response is enough to prevent reinfection. "We don't have good evidence of long-lasting immunity, but we also don't have really good data from both SARS and MERS," Perlman adds.

What kind of immune response should vaccine developers look for?

The phase I trial that began this week focuses on the safety of a vaccine developed by Moderna, a company based in Cambridge, Massachusetts. But researchers will also look closely at the nature of the immune response the vaccine summons.

The Moderna vaccine consists of an RNA molecule. Like many of the other SARS-CoV-2 vaccines in development, it is designed to train the immune system to make antibodies that recognize and block the spike protein that the virus uses to enter human cells.

"I think it's reasonable as a first pass, but we will learn that, perhaps, antibody responses to the spike exclusively may not be the whole story," says Diamond. A successful SARS-CoV-2 vaccine might need to prompt the body to generate antibodies that block other viral proteins, for instance, or make T cells that can recognize and kill infected cells.

How do we know if a vaccine is likely to work?

Normally, vaccines go into human trials after tests for safety and effectiveness in animals. But

the Moderna vaccine and another being developed by Inovio Pharmaceuticals in Plymouth Meeting, Pennsylvania, are being tested in animals at the same time as human phase I trials are happening. Inovio plans to begin its first human trial in April.

"In a non-emergency situation you might do this in a more serial way, but in this case a lot of things are being done in parallel," says Barney Graham, deputy-director of the US National Institutes of Health (NIH) Vaccine Research Center in Bethesda, Maryland, which is sponsoring the Moderna vaccine trial.

In a 2 March preprint[2], researchers reported injecting Inovio's vaccine — a DNA molecule carrying instructions to make the spike protein — into mice and guinea pigs. They found that the animals produced both antibodies and T cells against the virus. Study leader Kate Broderick, Inovio's senior vice-president for preclinical research and development, says that her team has now given the vaccine to monkeys and is soon to start studies in which vaccinated animals are infected with the virus to see whether they are protected. Such 'challenge' studies are also in the works for the Moderna vaccine, says Graham.

He adds that large, costly trials of whether a vaccine can prevent infections in people won't proceed without such data from animals. Diamond expects that as researchers learn more about the infection from both human and animal studies, they will get a better sense of which vaccines are likely to work best. "It may not be the most efficient way to do it. But it may be the most expedient way to generate a vaccine," says Diamond.

Will it be safe?

Because they are given to large numbers of healthy people, vaccines usually have a higher bar for safety than do drugs administered to people who are already ill. With SARS-CoV-2 vaccines, researchers' main safety concern is to avoid a phenomenon called disease enhancement, in which vaccinated people who do get infected develop a more severe form of the disease than people who have never been vaccinated. In studies of an experimental SARS vaccine reported[3] in 2004, vaccinated ferrets developed damaging inflammation in their livers after being infected with the virus.

Peter Hotez, a vaccine scientist at Baylor College of Medicine in Houston, Texas, thinks potential vaccines should be tested in animals first to rule out disease enhancement, before trials move on to humans. He says he understands the reasoning for pushing SARS-CoV-2 vaccines to human tests quickly, but adds that, because of the possibility that a vaccine could enhance disease, "I'm not sure this is the vaccine you want to do it for".

In testing the Moderna vaccine, Graham says, the NIH will move to larger human studies only once human and animal studies confirm that the vaccine is safe. He says the risk of enhancement is low, but "the risk of not getting vaccines advanced quickly — so that we can have something available for the next winter season to at least test in the field — that risk is fairly high".

Nature **579**, 481 (2020)

doi: 10.1038/d41586-020-00798-8

Additional reporting by Monya Baker.

References

1. Bao, L. *et al.* Preprint at BioRxiv https://doi.org/10.1101/2020.03.13.990226 (2020).
2. Smith, T. R. F. *et al.* Preprint at Research Square https://doi.org/10.21203/rs.3.rs-

Nature ISSN 1476-4687 (online)