How long immunity lasts after a coronavirus infection and what that means for vaccines

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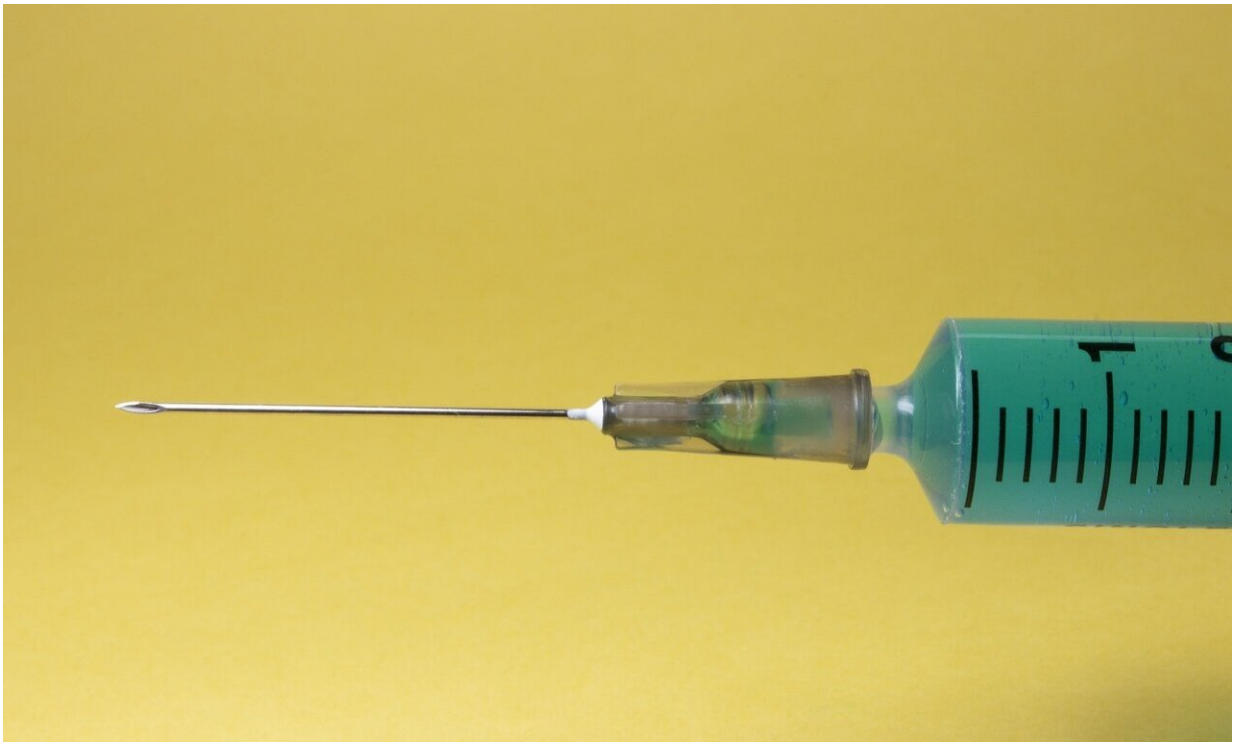

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In 1846, the measles descended on a rocky cluster of islands in the North Atlantic for the first time in decades, and its path was relentless.

The virus infected more than 6,000 of the Faroe Islands' 7,782 inhabitants, killing dozens of the old and the very young. Yet one hardy

group of elder islanders was entirely spared: 98 people who were infected the last time the virus had hit the islands, 65 years before.

The human immune system remembers measles like a bitter family feud, remaining quick to strike back for a lifetime after the initial insult. On the other end of the spectrum is norovirus, that diarrhea-inducing bane of day-care centers and cruise ships. After recovering, people can be reinfected within a few months.

No one can say for sure yet what will happen with the coronavirus. Those scattered reports of people becoming reinfected thus far have generally proven to be false alarms. But if evidence from other types of coronaviruses is any guide, the amount of time that people remain immune will be on the shorter end of the scale.

And those immunity "passports" you've heard about? More on that concept below—but for a variety of reasons, putting it in practice won't be as simple as it sounds.

The immune system's response to the coronavirus will provide clues for another closely watched front: how it will react to a vaccine. More than 100 efforts are underway to produce such drugs—designed to stimulate the type of protective response that would result from an infection without making the person sick—and the makers of several forecast they can distribute doses to high-risk populations by year's end.

That accelerated timetable, unheard-of in the field of drug development, has some scientists cautioning against too much optimism. Small batches of vaccines can be made in short order with today's technologies, but scaling up production to treat millions, and testing such drugs for safety and efficacy, normally takes years.

"When you're doing it at warp speed, there is concern about missing

things," said John P. Moore, a professor of microbiology and immunology at Weill Cornell Medical College in New York.

Some, perhaps many, of the vaccine candidates will turn out to provide a measure of protection. It's a tried-and-true concept, responsible for saving untold millions of lives in the last century. And with billions of people to be inoculated against the coronavirus, at least several such vaccines will be needed.

Yet predicting the strength and duration of the immune system's response, whether to a live infection or a vaccine, is anything but straightforward.

In the fall of 2016, Columbia University researchers began periodically swabbing the nasal passages of 191 volunteers, analyzing the genetic material within for a variety of respiratory viruses.

During the next year and a half, 86 people became infected with coronaviruses—milder cousins of the one now causing so much havoc. Twelve tested positive for the same one at least twice, including three people who each were infected three times with a coronavirus nicknamed OC43.

In one case, the second positive test occurred within a month of the first, so it might have been the same infection, said Jeffrey Shaman, a professor of environmental health sciences at Columbia's Mailman School of Public Health. But generally, it seemed the immune system couldn't recognize, and fight off, coronaviruses it had encountered just a few months before.

Why does our memory of measles, on the other hand, last a lifetime?

A key factor is the immune system's ability to make

antibodies—customized, Y-shaped proteins that block viruses from penetrating human cells.

The numbers matter. For measles, the levels are high, and they do not decline much with time. Evidence suggests they would remain high enough to protect us for 200 years, if we could live that long, said E. John Wherry, director of the University of Pennsylvania's Institute for Immunology.

With the coronavirus, the durability of the response is not yet clear. But when a person is infected with SARS or MERS, the two other coronaviruses that cause severe symptoms, antibody levels wane significantly within a year or two. Eventually, the protective proteins can no longer be detected.

That's one reason those commercial antibody tests for the new coronavirus might not be ideal for determining who can go back to life as usual.

Aside from the fact that some are not very accurate, the tests deliver a yes-no answer—were you infected? - but do not indicate the level of antibodies or, in many cases, the type. (Some antibodies are "neutralizing," meaning they are directly involved in clearing an infection, while others play more of a bystander role.)

And we don't know yet what level is sufficient for protection, or how people might respond differently. Those who've had the coronavirus are likely immune for some period of time—otherwise, there would be clear evidence of repeat infection—but the science is still young.

"Immune passports are premature," said Yonatan Grad, an assistant professor of immunology at Harvard's T.H. Chan School of Public Health.

Antibodies might not even be the most important thing to measure, said Wistar Institute researcher David B. Weiner, whose research formed the backbone for one coronavirus vaccine now being tested.

In addition to fighting infections with antibodies, the immune system responds with a second set of weapons called killer T-cells, which can destroy infected cells before the virus inside them spreads further. Weiner is betting that the vaccine he helped design, made by Inovio Pharmaceuticals in Plymouth Meeting, of which he is a board member, will stimulate the production of antibodies and T-cells.

Even more important than durability of the immune response is safety, and that, too, is not a given. One vaccine for SARS, when tested in monkeys, in some cases not only failed to prevent infections, but seemed to make them worse. Yet last month, animal studies of two vaccines against MERS showed promise. Before any such drugs for the new coronavirus can move forward, data from humans will be essential.

Viruses mutate, especially ones like the coronavirus that store their genetic information in single-stranded RNA, said Wherry, a professor at Penn's Perelman School of Medicine. Every time they copy themselves, there is a chance of a mistake—and unlike with double-stranded DNA, there is no second set of instructions as a backup. "They don't have proofreading capability," he said.

Some mistakes make a virus less of a threat, while the effect of others is neutral. Still others may allow a virus to evade our defenses. This is a key reason we need a different flu shot every winter—that, and the fact that so many strains are in circulation worldwide, waxing and waning from year to year.

For the coronavirus, many vaccines in development contain all or part of its "spike" protein—those little knobs on the surface of each virus that it

uses to grab onto, and infect, cells in the lungs.

The idea is that the immune system "sees" the protein and learns to block it in the event of a real infection. That makes sense, so long as the spike does not mutate much. But what if it does?

That is why some researchers, such as the Mayo Clinic's Gregory A. Poland, are designing vaccines that contain several kinds of proteins from the coronavirus, not just the spike. The virus might shift enough to evade antibodies that are tailored to one type of protein, but odds are against it shifting enough to avoid four or five.

"We're going to isolate pieces of all the proteins that the human immune cells see," he said. "We'll include all of them in our vaccine."

Traditional vaccines consist of weakened or inactivated forms of the virus in question, allowing the immune system to get a safe peek at the entire microbe.

Several of the coronavirus vaccines, on the other hand, consist of DNA—instructions for the body to make just a fragment of the virus. The goal was speed, given the rapid spread of disease.

At Inovio, scientists "printed" a preliminary version of a DNA vaccine in a few hours, and human tests began in April, with 40 volunteers split between Penn and Kansas City.

The DNA is inserted into skin cells with a device that a series of mild electric shocks, briefly opening "micropores" on the membranes of skin cells. While not painful, the sensation is a bit startling, said Anthony Campisi, one of 20 volunteers getting the vaccine at Penn.

"It caused my muscles to involuntarily tense," he said.

Will that stimulate the same kind of response as a whole virus? In theory, yes, though no such vaccine has yet made it to market.

A different approach is underway at Thomas Jefferson University, where Matthias J. Schnell is fusing the coronavirus spike protein onto an existing vaccine with a long track record: the one that protects against rabies.

Something about that whole virus may stimulate a more lasting immune response, both to rabies and to the coronavirus protein that is attached, said Schnell, director of the Jefferson Vaccine Center. Among other advantages, this rabies "vector" can be dehydrated and stored without refrigeration, making it ideal for use in developing countries.

Poland, the Mayo Clinic researcher, called the use of rabies a "very plausible approach."

But without testing, we can't predict the response to any of these approaches with certainty.

"There are some immunologic secrets," he said, "that have yet to be discovered."