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The coronavirus vaccines have been a success, possibly saving tens of millions of lives. However, they haven’t ended the pandemic and their effectiveness has been eroded by the evolution of variants of the SARS-CoV-2 coronavirus. A new generation of covid-19 vaccines is needed – but what exactly should this involve?

The US plans to roll out boosters that target the BA.4 and BA.5 omicron subvariants. Yet variant-specific boosters aren’t going to be a game changer, not least because newer variants will have evolved before they are administered.

Many researchers are aiming bigger: hoping to create vaccines that provide broad protection against many variants or to develop nasal vaccines that more effectively prevent infections – and preferably both combined.

Some immunologists think such second-generation vaccines could work so well that they stop transmission altogether, if enough people are vaccinated. “We have to be careful not to overpromise, but potentially there are huge benefits,” says Ed Lavelle at Trinity College Dublin in Ireland.

The main ingredient of most existing covid-19 vaccines is the spike protein of the original SARS-CoV-2 from January 2020.

Yet they haven’t stopped wave after wave of infections around the world. “Living with covid” is a problem for many reasons. While vaccines greatly reduce the threat of serious illness, they don’t eliminate it. And with each reinfection, people are at risk of getting long covid.

**Waning immunity**

Why haven’t the vaccines halted transmission? Part of the reason is that, by the time vaccines were rolled out, new variants – alpha, first detected in the UK, and beta in South Africa – had spike protein mutations that allowed them to partly evade immunity. In other words, the vaccine target – the spike protein – changes.

Jonathan Yewdell at the National Institutes of Health in Maryland says there is a more fundamental reason: no vaccine provides long-lasting protection against any virus that can be transmitted without the blood or lymph glands being involved. We should never have expected conventional vaccines to stop the pandemic, he wrote in 2021.

Take the measles virus, the most contagious virus we know, but also one that vaccines provide lifelong protection against. It doesn’t initially infect the cells lining our noses and throats. Instead, it gets into immune cells in the lungs, which carry the virus to the lymph nodes, where it spreads in the body and is coughed or sneezed out when it reaches the airways.

Vaccinated people still sometimes catch measles, but given its convoluted route to the airways, the immune system has plenty of opportunities to intercept the virus before it is transmitted to anyone else.

By contrast, many respiratory viruses directly infect cells in the mucous membrane lining the airways. When the cells shed more viruses, these can infect other people. In the weeks after vaccination against many respiratory viruses, immunity may be high enough to prevent infection, but as this wanes, the risk of getting mucosal infections and passing them on rapidly increases.

One key factor is that mucosal immunity is different from the immunity that occurs in the rest of the body. Specific immune cells sit in the mucous membranes ready to detect and respond to pathogens, such as by secreting distinct antibodies. In fact, these membranes secrete vastly more antibodies than the rest of the body produces.

In general, injected vaccines produce strong overall immunity, but not mucosal immunity specifically, which is also true of mRNA covid-19 vaccines.
Two main things must be done to create better covid-19 vaccines. The first is to create broadly protective, or universal, vaccines that the coronavirus cannot easily evade. The idea is to find parts of the coronavirus that can’t change because they have a vital function, and get our immune system to focus on them. “If they are doing something important, the survival cost to the virus of mutating them will be incompatible with existence, and those are the ones you have to hit,” says Altmann.

Next-generation vaccines

Although it might be theoretically possible to come up with a pan-coronavirus vaccine that protects against all kinds of these viruses and prevents future coronavirus pandemics, in practice, this is difficult. Despite decades of work, we still don’t have a universal flu vaccine.

But lots of effort and money are being poured into developing universal coronavirus vaccines, with some teams reporting promising results in animals and a handful being tested in people.

One of the many challenges is to get the immune system to focus on a specific part of a protein that is shared by SARS-CoV-2 variants specifically or even other coronaviruses in the overall virus class. This can be achieved by encouraging our immune system to focus on the shared part.

A vaccine candidate developed in the US consists of viral particles that have eight versions of the same part of the spike protein protruding from them, one from SARS-CoV-2 and seven from animal coronaviruses. In animal tests, this protected against severe disease from several SARS-CoV-2 variants.

It didn’t prevent infection, however, which may be hard to achieve with an injected universal vaccine.

Hence, the growing interest in the second main approach to improving vaccines: inducing strong mucosal immunity in our airways to stop infections taking hold and being passed on to others. The most powerful immune response is at the site of exposure, says Lavelle. For respiratory diseases, this usually means spraying a vaccine up the nose.

Only one intranasal vaccine has ever been approved: FluMist in 2003. There are several challenges with intranasal vaccination that have deterred vaccine-makers. One is getting vaccine proteins through the mucous membrane.

This requires larger doses, which can make such vaccines much more expensive, depending on the technology used. However, recent studies have shown that linking proteins to certain fatty molecules can help them penetrate the mucosal surface. One team recently reported that proteins modified like this induced mucosal antibody levels that were 1000-fold higher than those triggered by unmodified proteins.

SARS-CoV-2 sometimes infects the gut and boosting gut mucosal immunity appears to increase respiratory mucosal immunity too. Therefore, some groups are working on vaccines that can be swallowed in pill form. Certain cases of long covid may be due to persistent gut infections, according to Lawrence Young at the University of Warwick, UK.

“If you can generate an immune response in the mucosa in the gut, then you might protect people from some of the effects of long covid,” he says.

As with universal vaccines, dozens of teams are working on mucosal covid-19 vaccines, with some excellent results in animal studies and several being tested in people. Combining the two approaches would prevent new variants from rapidly evading intranasal vaccines.

The big question is whether any such vaccines could block transmission altogether. Yewdell is doubtful, pointing out that our immune system isn’t perfect. Others, including Lavelle and Altmann, think it is achievable.

But even if next-generation vaccines are good enough to achieve the long-sought-after goal of herd immunity, there is still the issue of getting enough people vaccinated. It will be easier to persuade people to get a spray up the nose than an injection, says Lavelle.

“If you can generate an immune response in the gut, you might protect people from long covid”