Inside the race to tweak covid-19 vaccines and stay ahead of mutations

By Michael Le Page, *New Scientist*, print issue of Feb 6, 2021

IT IS looking likely that Covid-19 vaccines will have to be updated in the coming months to remain effective against new variants of the coronavirus. Several vaccine manufacturers have confirmed that they are already working on new versions of their vaccines to make sure they remain effective. But what does updating the vaccines involve and how long will it take?

At least two vaccines are less effective against the B.1.351 variant of coronavirus that was first identified in South Africa.

Interim results from UK trials of a vaccine developed by the US firm Novavax show that it was almost 90 per effective at preventing symptomatic infections in people in the UK (see "Next-generation vaccines that are nearing approval"), but just 60 per cent effective in South Africa. "That will largely be a reflection of the South African variant," says Paul Heath at St George's, University of London, a lead researcher on the Novavax trial. But 60 per cent is still really good, he says. "This is still an effective vaccine with the South African variant."

Results from trials of the one-dose vaccine from Johnson & Johnson show a smaller difference. This was 72 per cent effective at preventing moderate or severe covid-19 in the US, 66 per cent effective in Latin America and 57 per cent in South Africa. However, it was still 100 per cent effective at preventing hospitalisations and deaths, starting 28 days after vaccination, in all these areas.

As the P.1 variant first seen in Brazil has similar mutations, the vaccines are likely to be less effective against this version too.

The Novavax results do show slightly less efficacy against the variant first identified in the UK, called B.1.1.7, with just 85 per cent efficacy compared with 95 per cent efficacy against older variants. However, Heath doesn't think this is significant. "The vaccine efficacy is pretty much the same," he says. "This is also really good news."

The bad news is that it is clear that the South African and Brazilian variants are evolving to evade the immune response sparked by older variants. It is likely that all the vaccines based on spike proteins, the part of the virus that gains entry into cells, will be less effective against these two variants. This would include the vaccines developed by Pfizer and BioNTech, the University of Oxford and AstraZeneca, and Moderna, plus many of the newer vaccines in development.

The real worry is that variants that are even better at evading the immune response will evolve, meaning that the vaccines will have to be updated. "It's almost sure going forward that we will need additional boosters with different strains," says Paul Stoffels of Johnson & Johnson.

Not everyone agrees. “I think for the vast majority of the population, the vaccines around now are going to do just fine,” says Jeremy Kamil at Louisiana State University. But Kamil still thinks we should be preparing just in case.

Either way, here is what needs to be done.

Slow the evolution of potentially dangerous variants

It is possible to reduce the opportunity for the coronavirus to evolve to be better at evading vaccines by reducing the number of people getting infected. “Every time someone is infected with the coronavirus, it’s like buying the virus a lottery ticket,” says Kamil. It is extremely unlikely for the virus to mutate in a way that helps it, but if hundreds of millions of people around the world are being infected, it will happen eventually.

“Because the pandemic has gone on so hugely unchecked by governments all over the world, with the exception of places like New Zealand, we’ve bought [the virus] a lot of lottery tickets,” says Kamil. And as more people are vaccinated or gain some natural immunity to the virus, any mutations that help evade this immunity provide a strong advantage for the virus.

Fortunately, we now have vaccines to help get case numbers down. “The best way to decrease the risk of more new variants is to as quickly as possible immunise the majority of the population in the world,” says Moncef Slaoui, former chief scientific advisor to the US vaccine effort, Operation Warp Speed.

This is another reason why it is so important that high-income countries help poorer ones vaccinate their populations rather than hogging supplies and leaving large pockets of the world unvaccinated.

Increase surveillance so we can spot dangerous new variants as soon as possible

“It’s really important that we get the surveillance system globally up to speed,” says Saul Faust at the University of Southampton, UK, who is leading a two-dose trial of the Johnson & Johnson vaccine in the UK. The sooner we spot potentially dangerous new variants, the more time we have to prepare and the more that can be done to stop them spreading around the world.

This means doing much more sequencing of viral samples, as this is the only reliable way to identify variants. “We only know what we sequence,” says Sharon Peacock, who leads the UK sequencing consortium, COG-UK. The UK has been sequencing nearly one in 20 viral samples, a higher proportion than other countries. Some do little if any sequencing. “Many countries would not know if they had particular variants,” says Peacock.

Even some high-income countries, such as the US, have been doing less sequencing, relatively, than others. “The US has really done an embarrassing job. We are behind countries like Gambia and Bangladesh,” says Kamil.

Even with better surveillance, it will still be hard to detect whether new variants are dangerous. In the UK, it only became clear that B.1.1.7 is more transmissible several months after it was first detected, by which time it had already spread to many other countries. The problem is that new variants are emerging all the time and some spread faster than others by chance.

The UK has now set up an initiative called G2P-UK to coordinate efforts to study new variants, but detecting dangerous ones remains a major challenge. Despite all the focus on the UK variant, for instance, it still isn't clear why it is more transmissible and probably deadlier.

Work out what part of the vaccine to tweak

We know a mutation called E484K plays a big part in helping the South African and Brazilian variants evade antibodies to older forms of the spike protein, so this will certainly be included in any update. But there are many other mutations that could potentially be included.

"The important question is going to be selecting which variant will provide enough spectrum of protection against the new variants yet to come," says Slaoui.

The ideal strategy would be to anticipate what mutations might come next, and block these from gaining a foothold. In other words, to vaccinate people against dangerous variants that don't yet exist in the wild. One way to do this is to let the virus evolve in the lab in the presence of antibodies from people who have been vaccinated.

An updated vaccine could be given in the form of a second booster shot – a third dose – containing a single different variant to existing vaccines. Alternatively, two or more variants could be combined in a single shot. It is already routine for flu shots to protect against three or four different flu viruses.

Explore broader vaccines that may make it harder for resistance to evolve

In Western countries, all the main vaccines that have been approved or are likely to be approved soon are based on the outer spike protein of the coronavirus. From the start, some immunologists pointed out that the spike protein was likely to mutate in ways that will reduce vaccine efficacy. They suggested that vaccines should be based on, or include, other coronavirus proteins that are less able to change.

Heath thinks that trial results justify the spike-protein approach. "They work," he says. "The focus on the spike was the right thing to do."

Others, including Matti Sällberg at the Karolinska Institute in Sweden, are exploring the possibility of creating boosters that contain other proteins. "We hope for a phase I trial in the spring," says Sällberg.

Some countries, including China and India, have developed vaccines based on the entire virus – so-called inactivated or live attenuated vaccines. These include more viral proteins and it is

possible they will provide better protection against new variants, says Heath. However, some live vaccines aren't always suitable for all individuals, such as those who are pregnant.

It is also possible that mixing existing spike-protein vaccines will provide broader protection, says Heath. Animal studies suggest that giving two doses of different vaccines will be more effective than two doses of the same one. A trial will shortly get under way in the UK in which participants will receive a shot of each of the Pfizer/BioNTech and Oxford/AstraZeneca vaccines, instead of two doses of the same vaccine. This approach could be extended to other vaccines as well.

Manufacture updated vaccines

It is likely that all vaccine makers are preparing in case they need to update their vaccines, though not all have confirmed this publicly. Johnson & Johnson, for instance, is working on an updated vaccine, says Stoffels, even before its first vaccine is approved. "We don't know if it will be needed," he says.

The mRNA vaccines made by Pfizer/BioNTech and Moderna can be updated the quickest. Once it has been decided which version of the spike protein to use, it is likely to take over a month before the first vials are ready, says Zoltán Kis at Imperial College London.

It only takes a couple of hours to manufacture each batch of mRNA, as unlike other vaccines no living cells are involved in the process. However, the mRNA is made from DNA templates that can take up to two weeks to create.

Once you have mRNA, it has to be purified, slowly mixed with lipids to encase them in fatty bubbles and finally put in vials.

Purification and mixing each take around a day, and filling the vials can be a bit longer depending on the size of a batch. These steps are sometimes done at different facilities as well, adding transport delays.

But it is the safety checks done along the way that take the most time, says Kis, adding up to as much as three weeks. "The overall time really depends on quality control," he says.

For other vaccine types, updates would take longer. The Oxford/AstraZeneca vaccine, for instance, consists of non-replicating adenoviruses grown in modified human embryonic kidney cells. It takes two months to grow each batch of cells. Purifying the vaccine, filling vials and quality control takes another month or so.

For an updated vaccine, a new seed virus would have to be produced, which could take weeks. However, once the seed virus is ready, it can be added to existing batches of cells.

Work out how to rapidly approve updated vaccines

Getting approval for updated vaccines could potentially be a big delay. None of the major regulatory agencies has yet decided what the process will be. However, both the European Medicines Agency (EMA) and the US Food and Drug Administration told *New Scientist* that seasonal flu vaccines could provide a precedent.

“Discussion is already ongoing with respect to what could be the regulatory requirements to support a change in the composition of the vaccine if needed,” says a spokesperson for the EMA. “The seasonal flu would be a precedent to look at, but there will be a need to determine if any additional clinical data would be needed as well.”

Once a particular type of flu vaccine has been shown to be safe and effective in human trials, that vaccine can be updated yearly with little or no additional human testing. “For seasonal flu you don’t need to conduct a clinical trial because we know the types of immune responses that are likely to be effective,” says Angela Rasmussen at Georgetown University in Washington DC.

Unfortunately, it still isn’t clear which aspects of the immune response – called the correlates of protection – guarantee protection against the coronavirus, which could complicate approval of updated vaccines.

“The lack of really well-defined correlates of protection are throwing a wrench into the works,” says Rasmussen.