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COVID UNANSWERED QUESTIONS

What next for covid-19 vaccines?

As omicron booster jabs are approved and rolled out for the first time, **The BMJ** asks how vaccines will evolve as we learn to live with the virus

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Will we continue to need annual covid boosters?

Eleanor Riley, professor of immunology at the University of Edinburgh, says, “It will be really interesting to see, when these new [variant] specific vaccines start to get rolled out at the end of the year, whether they make a huge difference or not.” All the main vaccines currently in use target the spike, which is susceptible to frequent mutation.

Other vaccines that present more of the virus do exist. For example, Valneva’s vaccine—approved for UK use last April¹—uses an inactivated form of the whole SARS-CoV-2 virus that can’t infect cells or replicate in the body but can still trigger an immune response. Two of the available Chinese vaccines, Sinopharm and CoronaVac, are also based on inactivated virus, as is Covaxin of India. Their published efficacy rates (from tests conducted before covid-19 variants arrived) are lower than those of the commonly used vaccines from Pfizer-BioNTech, Moderna, and AstraZeneca.

Sinopharm, CoronaVac, and Covaxin do not yet have enough publicly available data to judge their effectiveness against omicron variants (although CoronaVac has some observational study evidence showing effectiveness against the gamma variant²). Initial results for Valneva show that it “produces fewer neutralizing antibodies against the Delta and Omicron variants, indicating it provides less protection against these variants,” the World Health Organization reported.³

Riley says, “We need to start thinking more broadly about some of the other types of vaccines that have more of the virus in them, that have some of the other viral proteins in them—the killed vaccines like those used in the live attenuated poliovirus.

“Vaccines in the long run are probably going to give us more durable immunity against different variants because they’re so much like a virus, in that our immune response is going to be much more broadly based and therefore much less susceptible to occasional mutations.”

Eric Topol, professor of molecular medicine at the Scripps Research Institute in California, says, “If we had a variant proof vaccine, if we had nasal vaccines to really put a major damper on infections and transmission, and if we had back-up drugs to the only pills that are available today, we’ll be in much better stead and we’ll finally get containment.

“I’m very optimistic, actually, as compared to influenza. We’ve never had vaccines with 95% efficacy for flu. Not even close. We’re lucky with quadrivalent vaccines of influenza to be at 40%.”

He adds, “This virus is so amenable to taking it down, scientifically as opposed to influenza. But we’re just not acting like we can do this. And we can.” (Video 1)

Video 1 The BMJ Explains

Does an infection or vaccination afford better protection?

Generally, both offer lasting protection. The US Centers for Disease Control and Prevention (CDC) has reviewed the evidence and concluded in a briefing published in October 2021 that they both led to protection from subsequent infection for at least six months.⁴

A 2021 paper from US researchers indicated that the neutralising activity of vaccine induced antibodies was more targeted to the receptor binding domain of the SARS-CoV-2 spike protein than antibodies elicited by natural infection.⁵ The authors say that this may be better for the immune system in coping with future evolved forms of the virus.

The CDC briefing states that the immune response from vaccination is more reliably consistent than that from infection, which can vary. So, in terms of gaining and maintaining immunity, it’s better to rely on vaccines.

One area of study is whether certain individuals may have stronger or weaker immune responses to vaccines depending on their genes. A 13 October *Nature Medicine* paper from the University of Oxford reported that, of 1076 participants in the Com-CoV study, some demonstrated “association of HLA type [variations of the human leucocyte antigen] with covid-19 vaccine antibody response and risk of breakthrough infection, with implications for future vaccine design and implementation.”⁶

What’s so good about nasal spray vaccines?

In a nutshell, vaccines administered by nasal sprays generate an immune response in the upper respiratory system—the source of viral entry—whereas injected vaccines are administered into the muscle, generating virus destroying T cells and antibody producing B cells that are then circulated throughout the body in the blood.⁷

More specifically, a vaccine in the nose activates localised mucosal immune cells, known as tissue resident memory T and B cells, which do slightly different things from the usual T and B cells: tissue resident memory B cells, for instance, make secretory immunoglobulin A (IgA) antibodies that are weaved into the respiratory tract (although it's still unknown how much this protects against SARS-CoV-2). Such functions could potentially prevent the virus from taking hold in the body and stop not just infection but transmission too.

How close are we to rolling out nasal vaccines?

At least 12 nasal spray vaccine candidates for covid-19 are being tested around the world. As well as being easier to administer because of their needle-free delivery, nasal vaccines have the potential to block the virus at the site of entry, stopping infection and reducing transmission.⁸

However, when compared with earlier in the pandemic, these newer potential vaccines haven't received much attention. "We haven't done anything to help these trials and to get production ready," says Topol. "We could see these vaccines later this year, but it could even be sooner if we got serious about this."

What about pan-coronavirus vaccines?

A pan-coronavirus vaccine could provide protection against SARS-CoV-2 and common colds. Nothing is close to market yet.

A team at the Walter Reed Army Institute of Research in the US has the only pan-coronavirus vaccine candidate to reach clinical testing so far, the journal *Science* reported.⁹ It uses the same spike protein as current vaccines but presents it to the immune system in a different way, binding it to ferritin, a protein that normally carries iron in the blood. In early in vitro studies the vaccine "neutralised" a broad range of SARS-CoV-2 variants. No data have yet been released from the phase 1 trial.

Another team, based at the Francis Crick Institute in the UK, is in the early stages of testing a candidate targeting a specific area of the spike protein known as the S2 subunit, which allows the virus to fuse with the host cell. In a paper published in *Science Translational Medicine* in July the team reported that mice had created antibodies able to neutralise other animal and human coronaviruses, including the seasonal "common cold," the alpha, beta, and delta variants, the original omicron variants, and two bat coronaviruses.¹⁰

And DIOSynVax, a biotech spinout from the University of Cambridge, is developing an mRNA vaccine that could protect against a number of coronaviruses including SARS-CoV-1, SARS-CoV-2, and MERS. In March it received a \$42m (£38m; €43m) award from the Coalition for Epidemic Preparedness Innovations.¹¹

WHO's chief scientific officer, Soumya Swaminathan, told *The BMJ* in April that it was "scientifically quite feasible" that a pan-coronavirus vaccine would be developed in the next two years.¹²

Others are less optimistic, however, believing that urgency has subsided as the approach to the pandemic has shifted to living with the virus. Moncef Slaoui, a vaccine developer who advised the US's Operation Warp Speed, told *Science*, "Current vaccines are effectively able to deal with the pandemic, because the number one priority is mortality and morbidity. Pan-coronavirus vaccines, whatever definition you use for them, are about preparedness, rather than dealing with the actual pandemic."

Science has also emphasised that the current stage of the pandemic also means that testing, whether for pan-coronavirus vaccines or

new variant boosters, will be problematic. Much of the world has some immunity to covid-19 from vaccination, infection, or both, so proof of protection is difficult to establish, and assessing any new vaccine's ability to provide broader protection may require trials in people who have "no competition in the immune system," which in many countries would now mean infants.

Do you have a "Covid Unanswered Question"? Email mlooi@bmj.com, and we'll try to cover it in a future instalment of this series.

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