Here's why you might need a fourth COVID vaccine dose

March 16 2022, by Nathan Bartlett

When I began drafting this article, COVID cases in Australia were coming down and the situation was stabilizing.

New research released in February showed a fourth COVID vaccine dose didn't add much extra protection on top of a third dose. It looked as if doling out fourth doses to all Australians was unnecessary.

Unfortunately, the situation has changed again, and so has the risk calculation.

New South Wales Health Minister Brad Hazzard said last week omicron sub-variant called BA.2 was on the rise in Australia, and NSW should expect the variant to overtake omicron and for cases to more than double in the next six weeks. Experts expect BA.2 to become Australia's dominant strain in the next few months.

Early estimates suggest BA.2 is between 25% and 40% more transmissible than omicron (BA.1), and is already taking off in countries including Denmark, Sweden and the United Kingdom.

The Australian Technical Advisory Group on Immunisation (ATAGI) doesn't yet recommend fourth doses for everyone, but they're already available for severely immunocompromised Australians.

Coupled with new research detailing the quick waning of our third dose immunity, it's likely the coming surge means we'll need a fourth COVID

vaccine as we hit winter.

Here's why.

> Preliminary data from the University of NSW suggests there could be a doubling of coronavirus cases in the next four to six weeks as the Omicron BA.2 variant takes hold. https://t.co/fq4TEHJKmW
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> — SBS News (@SBSNews) March 14, 2022

Booster immunity waning quickly

It's clear a third dose improves immunity substantially.

But new research published this month in the *New England Journal of Medicine* shows immunity from third doses is waning quickly. Vaccine effectiveness against omicron dropped to around 45% ten weeks after a Pfizer third dose.

The main reason for this is because omicron has many mutations which mean it looks very different to the original strain, from which our vaccines are based.

Only a subset of the immune cells these vaccines generate can effectively tackle omicron, which means our immunity wanes quicker. Specifically, we generate fewer "neutralizing antibodies" that can tackle omicron. These are a type of antibody important for protection against infection.

This is almost certainly the case for BA.2, as well, which shares similar mutations to omicron but some different ones too. Research is only just beginning into BA.2 so we don't yet know how effective our vaccines are

against it. But it's likely their effectiveness is similarly reduced as with omicron BA.1.

It's important to note three doses of a COVID vaccine are currently providing excellent protection from severe illness for most people.

But by Australian winter—normally the height of cold and flu season—most people will have had their third dose more than four months ago, leaving us at greater risk of infection. So it makes sense to boost our antibodies again.

One pre-print study, yet to be reviewed by other scientists, showed a fourth dose tops up your antibody response to the peak level provided by the third dose.

Though it doesn't give additional protection, restoring antibodies to third-dose levels will be important as winter approaches and risk of virus transmission increases. But this of course must be weighed against the ethics of dispensing fourth doses when many people in developing countries haven't had their first two doses.

It's hard to tell how vulnerable we are

In 2021 health authorities broadly knew the population's level of immunity against COVID. Authorities knew how many people had two vaccine doses at any one time and how well the vaccines worked against delta, and there were very low rates of infection.

But now, millions of us have been infected, at different times, some with a third dose and some without. It's also likely many of us have been infected without knowing it.

So it's very hard for us to know the level of immunity the population has.

This makes estimating how vulnerable Australia is to BA.2 and future variants very difficult.

In this environment of uncertainty, allowing Australians to get a fourth dose would increase collective immunity and help us weather the rise of BA.2 during a winter where other cold and flu viruses are expected to make a comeback.

Too late for an omicron-specific vaccine

Evidence suggests omicron is good at evading the immunity we get from our current COVID vaccines.

This is because the variant has many mutations which means it looks very different to the original strain, from which our vaccines are based.

A vaccine tailored to omicron would, in theory, provide better protection.

But the question is, how much better than a boost with current vaccines? Early evidence suggests not much.

And by the time an omicron-specific vaccine is rolled out, BA.2 will likely already be dominant.

So how do we a tackle a virus adept at mutating and evading immunity?

A "universal" or "variant-proof" COVID vaccine could solve this conundrum.

These are vaccines targeting a part of the virus that's required for infection but that doesn't readily change (scientists call this "conserved"), meaning they're more likely to work across different variants. These are

in development.

It's possible we'll have a prototype for such a vaccine in the next couple of years.

Nasal sprays could be a game changer

The fact mRNA vaccines could achieve more than 90% protection against the original strain of SARS-CoV-2 is exceptional, because it's very challenging for a vaccine injected into your arm to ward off a respiratory virus.

Respiratory viruses replicate in the cells lining the airways. That begins in the nose and throat, and if infection progresses, down into the airways in the lungs.

The airways are at the interface of the body and the outside environment. Getting specialized immune cells from your bloodstream to the airways, particularly the nose and throat, is a big ask for an immune response initiated in your arm.

This is where intranasal vaccines and treatments come in. My team has helped develop an immune-stimulating nasal spray that's entering phase 2 clinical trials for COVID and influenza.

This works by boosting innate immunity in the tissue lining your airways to attack the virus at the point of entry in the nose and throat.

The aim is to prevent the virus from replicating there and making its way deeper into the respiratory tract where it can cause severe lung disease. It also reduces the amount of virus shedding in the nose and throat which should reduce the risk of onward transmission.

Where to from here?

Managing COVID is becoming more complicated now, and it's impossible to predict where we'll be a few months from now. As new variants continue to arise, it's very difficult to understand how immune we are.

Monitoring and characterizing new variants is essential. As new variants emerge, we need to understand how infectious and severe they are, and then adapt our vaccination strategy. This type of surveillance is what we do for the flu every year.

It could take years, but as time goes on and our immunity continues to mature, hopefully COVID settles to become a more stable, predicable, milder disease that can be effectively managed with the help of a range of new variant-proof vaccines and treatments.

Provided by The Conversation