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NEWS ANALYSIS

Covid-19: Fourth vaccine doses—who needs them and why?

What is the rationale for fourth vaccinations, and why are countries doing different things? **Gareth Iacobucci** investigates

Gareth Iacobucci

Who is being given a fourth vaccine dose?

Most countries offering a fourth vaccine are prioritising people who are immunocompromised. This is the case in the UK and the US.^{1,2} The rationale for these policies is supported by a range of evidence, including from the UK based Octave (Observational Cohort Trial T Cells Antibodies and Vaccine Efficacy in SARS-CoV-2) study, which found that four in 10 people who were clinically vulnerable generated lower concentrations of antibodies than healthy recipients after two doses of a covid-19 vaccine.³ The follow-up Octave Duo study, data from which have not yet been published, has been looking at the effect of three doses.⁴

Michelle Willicombe, a consultant transplant nephrologist at Imperial College Healthcare NHS Trust, London, leads the renal patient cohort in the Octave studies. She told *The BMJ* that data from a study by researchers at Imperial College London, alongside data from the US and France, indicate that around half of the patients who had no antibody response after two doses had some kind of response after three doses. This meant that around a quarter of immunosuppressed patients still had no responses after three doses.

“Some immunocompromised patients aren’t making any response or inadequate responses compared with healthy controls after three doses, so they need four to even get anything detectable,” Willicombe said. “Giving four doses to immunocompromised patients is a very different kettle of fish from the general population where you’re just boosting the immune response.”

What about the wider population?

On 3 January Israel began to offer fourth doses to all adults over 60, medical workers, and nursing home residents, making it the first country to offer fourth doses to this wider group of people.⁵ Germany has also indicated that it plans to administer a fourth dose to a wider section of its general population in the coming months to tackle the omicron variant.⁶

Will other countries follow suit?

The UK’s Joint Committee on Vaccination and Immunisation (JCVI) has said it is waiting for more data on waning immunity and effectiveness of vaccination in reducing hospital admission before it decides on offering a fourth jab to a wider group of people. Similarly, the US Centers for Disease Control and Prevention has not yet recommended fourth doses for the wider public there. “We’re going to take

one step at a time, get the data from the third boost, and then make decisions based on scientific data,” said the White House chief medical adviser, Anthony Fauci, on 29 December.⁷

What is the evidence for giving four doses?

Israel’s prime minister, Naftali Bennett, announced on 3 January that preliminary findings from an Israeli study showed that antibody concentrations increased fivefold a week after a fourth dose, which “most likely” meant significantly increased protection against infection, hospital admission, and severe symptoms. These findings were based on a small unpublished study of 154 hospital employees who had received a fourth dose of Pfizer’s vaccine.

No UK data on fourth dose responses are as yet available. Willicombe and a team at Imperial College London are leading the recently launched Melody (Mass Evaluation of Lateral Flow Immunoassays in Detecting Antibodies to SARS-CoV-2) study,⁸ which is investigating the proportion of immunosuppressed patients who have detectable antibodies after three and four doses of vaccine and assessing whether a lack of an antibody response correlates with the subsequent risk of SARS-CoV-2 infection and severity of disease.

Willicombe said it wasn’t surprising that the Israeli data show that a fourth dose boosted antibodies in healthy people. But the question that needed investigating was whether a fourth dose was necessary for people who weren’t immunocompromised. “If you give someone a boost, and they’ve got a normal immune system, they’re going to get a boost in response,” she said. “The question is, is it needed? I don’t know the answer to that . . . the clinical efficacy data, not just infection rates but hospital admissions, deaths, etc, would guide that.”

What can we learn from studies of three doses?

Data from the UK Health Security Agency on hospital admissions after omicron infection and vaccine effectiveness analysis show 72% protection after two doses for up to six months, rising to 88% within two weeks of a booster shot.⁹

Peter Openshaw, an immunologist and professor of experimental medicine at Imperial College London, who was not part of the study, said it added to the “now overwhelming evidence” that three doses provide good protection against severe covid-19 disease caused by omicron. “It’s a bit early to be sure,

but it seems possible that some additional boosters will be needed,” he commented. “Remember that we need four doses of vaccine to be fully protected against whooping cough or polio. The same may be true of coronavirus, but we need to wait and see.”

Should we be preparing to give fourth doses to all?

The JCVI chair, Andrew Pollard, who led the team that developed the Oxford-AstraZeneca vaccine, is cautious and has argued for a more targeted approach that focuses on preventing severe disease and protecting health systems around the world. “The future must be focusing on the vulnerable and [making] boosters or treatments available to them to protect them,” he told the *Telegraph*.¹⁰ “We know that people have strong antibodies for a few months after their third vaccination, but more data are needed to assess whether, when, and how often those who are vulnerable will need additional doses. We can’t vaccinate the planet every four to six months. It’s not sustainable or affordable.”

What if giving four doses doesn’t produce an immune response?

Willicombe said that immunocompromised patients who don’t have a response even after four doses of vaccine may benefit from pre-exposure prophylaxis with antibody treatment. To identify the most vulnerable people before they become infected, she argues that antibody testing should be brought in as part of the routine care of immunocompromised patients. “At the moment, the only time that we test for antibodies is when people are admitted to hospital [to see] whether or not they qualify for antibody therapy,” she said. “But if we have availability of testing for antibodies, then why aren’t we testing a wider field in people where we’re chasing an antibody response?”

Noting evidence from the Provent trial showing that AstraZeneca’s antibody drug AZD7442 (a combination of tixagevimab and cilgavimab) is effective at preventing and reducing severe illness,¹¹ Willicombe said, “If we [the Melody study] can show that people without antibodies are the ones at highest risk, then we would push for those patients without any detectable immune responses after four doses to have pre-exposure prophylaxis.”

Correction: In the second paragraph we had wrongly stated that the study data cited by Michelle Willicombe came from the Octave Duo study rather than from researchers at Imperial College London. We corrected this on 11 January 2022.

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