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Immunocompromised patients in the USA and UK should receive third dose of COVID-19 vaccine

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For the **JCVI's recommendation** see https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination

For the **US FDA announcement** see https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised

For the **CDC guidance** see https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

For the **preprint of the initial OCTAVE trial findings** see https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3910058

For **WHO's position on global vaccine equity** see https://www.who.int/campaigns/vaccine-equity

A third dose of COVID-19 vaccine should be offered to severely immunocompromised people to improve immunogenicity, the UK's Joint Committee on Vaccination and Immunisation (JCVI) advised on Sept 1, 2021. The decision followed similar announcements by the US Food and Drug Administration (FDA) and US Centers for Disease Control and Prevention (CDC) in August.

On Sept 14, the UK announced that a booster dose will be available to everybody older than 50 years. A week later, in the US, the FDA rejected Pfizer's application to authorise booster doses for everyone older than 16 years, which had been supported by the White House, instead endorsing a booster dose for those older than 65 years, those at high risk of severe COVID-19, and frontline workers. The CDC has now also endorsed boosters in line with the FDA recommendations.

The JCVI recommendation was welcome news, rheumatologists said.

"It is a sensible precautionary measure", said Julie J Paik (Johns Hopkins School of Medicine, Baltimore, MD, USA). "Given the wealth of information already supporting poor vaccine response in patients on immunosuppression, I think the third-dose recommendation is necessary for our most vulnerable patients, who can have severe COVID-19 without being vaccinated."

Patients older than 12 years who have advanced HIV, leukaemia, have had organ transplantation, or receive immunosuppressive medications, should be offered a third vaccine dose, the JCVI concluded.

The JCVI recommendation was based on findings from the first 600 participants in the OCTAVE trial, which included people with rheumatoid arthritis, psoriatic arthritis and other rheumatic diseases, cancers, liver disease, end-stage kidney disease, and those who have had stem cell transplants. Compared with healthy people, 40% of OCTAVE's immunocompromised participants had low concentrations of SARS-CoV-2 antibodies—and a further 11% had no detectable antibody response at all—after two vaccine doses. However, patients' T-cell responses were equivalent to those seen in healthy volunteers, even in those whose B cells were depleted.

"It is too early to comment on the clinical significance, as our data pertain only to the immune response and not to the levels of protection conferred by those antibody or T-cell responses", cautioned OCTAVE study senior investigator Iain McInnes (University of Glasgow, Glasgow, UK). "We are following our patients…to observe future infection events."

In evaluating vaccine effectiveness, surrogate endpoints like antibody levels, neutralisation assays, and T-cell responses have been used rather than infection, hospitalisation, or death, noted Jean Liew (Boston University School of Medicine, Boston, MA, USA). The minimum level of vaccine response needed to protect against severe COVID-19 outcomes remains unknown.

Immunosuppressive drugs can blunt response to COVID-19 vaccines. B-cell depleting agents like rituximab seem to be the worst offenders, Liew said. Mycophenolate and methotrexate have also been implicated in poor vaccine responses.

Experience with transplant patients suggests that immunosuppressants might also impact the efficacy of a third vaccine dose, Liew noted. Withholding immunosuppressive drugs around the time of vaccination has been widely discussed. "This could potentially improve the response", Liew said. "But the major downside is that holding necessary medications can cause a flare of their underlying rheumatic disease. This flare could be more detrimental to them in the short and long term than lower response to the vaccine."

The optimal schedule for withholding immunosuppressants and vaccination for immunosuppressed people is not yet clear. Also, "humoral response is not the whole story in assessing vaccine response," Paik noted. "We need to understand the T-cell response in greater detail in our patients on immunosuppression."

The OCTAVE team plans to assess the effects of different medications in patients with different diseases, and to study vaccine response durability. The OCTAVE Duo trial will examine third-dose efficacy in patients with absent or low antibody responses, McInnes said. The US National Institutes of Health recently launched a similar study that will examine antibody responses to a third dose in patients with autoimmune disease who did not respond to the initial two-dose regimen.

The question of booster doses has been contentious one, pitting the Biden administration against FDA scientific advisors and WHO, and leading to the resignation of two prominent members of the FDA Office of Vaccine Research and Review. WHO has criticised offering booster shots in wealthy nations when people elsewhere still await their first. Only 2% of people in Africa are fully vaccinated against COVID-19, WHO officials noted.

In the future, serological testing might be used to identify who has had COVID-19 infections and to prioritise boosters for those who have not. But for now, says Paik, a third vaccine for immunosuppressed people without such testing "makes sense since standardised serologic testing is not available everywhere".

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