

JCVI advice of a third primary dose for the immunosuppressed Q&A

What kinds of people are immunosuppressed?

- Those with weakened immune systems and are less able to fight infections naturally as a result of an underlying condition or disease. Examples include blood cancer, poorly controlled HIV or those on immunosuppressive treatment.

Who is eligible for a third primary dose?

- The JCVI has advised that a third primary dose of COVID-19 vaccine be offered to adults and children aged 12 years and over with severe immunosuppression, either due to a condition, disease or immunosuppressive treatment, at the time of the first or second COVID-19 vaccine doses.
- [Joint Committee on Vaccination and Immunisation \(JCVI\) advice on third primary dose vaccination - GOV.UK \(www.gov.uk\)](https://www.gov.uk/government/consultations/jcvi-advice-on-third-primary-dose-vaccination)

Does the JCVI recommend children be offered a third primary dose?

- Children over the age of 12 who were severely immunosuppressed at the time of their first or second dose will be offered a third primary dose.

Will people who live with someone who is immunosuppressed be invited to receive a third primary dose?

- If they are not immunosuppressed themselves, they do not require a third primary dose as they should mount a full immune response to two doses of the vaccine.

Do people who are immunosuppressed not respond well to the first two doses of vaccination?

- Some individuals who are immunosuppressed due to underlying health conditions or medical treatment may not mount a full immune response to COVID-19 vaccination.
- A few published studies describing the effect of a third dose of mRNA vaccine in persons who are immunosuppressed report increased immune responses in varying proportions of people.
- A person may test negative for antibodies against COVID-19 but could still be protected against the virus. Antibodies represent only one part of immune defences. Protection may be provided by other immune defences such as T cells.

Do vaccinated but immunosuppressed individuals have a robust immune memory?

- Immune memory refers to the ability of the immune system to recognise an infection a second time (after having been infected or vaccinated in the past). This means that the immune response to the second encounter is faster and higher than the first time around.
- The duration of protection provided by vaccines is currently not fully defined. It may be different for persons who are immunosuppressed compared to persons who are not

immunosuppressed. There are many different types and levels of Immunosuppression. These different types of immunosuppression affect different elements of the immune responses to vaccination.

Will the booster campaign be announced in September?

The JCVI is still deliberating the potential benefits of booster vaccines for the rest of the population and is awaiting further evidence to inform this decision.

What level of protection does 2 doses provide?

Preliminary data from the OCTAVE trial showed that almost everyone who was immunosuppressed mounted an immune response after 2 doses, as indicated by either antibodies or T cells. However, in around 40% of people, the levels of antibodies were low. It is not clear how much this may affect protection against COVID-19 as antibodies represent only part of a person's immune response.

What level of protection does 3 doses provide?

Studies are ongoing to see how effective a third dose is for immunosuppressed people, but it is very unlikely to cause any significant harm. Therefore, on balance, the JCVI's view is that a third dose can be safely offered as it may increase their protection.

What percentage of vaccinated but immunosuppressed individuals have subsequently died with a COVID-19 infection?

This is unknown.

What does living with an immunosuppressed person include?

- Individuals who expect to share living accommodation on most days with someone who is immunosuppressed and therefore for whom continuing close contact is unavoidable.

Will those individuals who have undergone immunosuppression following two doses of vaccination need a third primary dose?

- Most individuals whose immunosuppression commenced at least two weeks after the second dose of vaccination do not require a third primary dose at this stage.

Which vaccines will be given as a third primary dose?

- JCVI advises a preference for mRNA vaccines for the third primary dose, with the option of the AstraZeneca Vaxzevria vaccine for individuals who have received this vaccine previously where this would facilitate delivery.

Why mRNA vaccines?

- There are currently more data on the use of mRNA as third primary vaccine doses.
- mRNA vaccines are being used based on consistent evidence of higher antibody levels, even though some studies suggest that cellular responses with AstraZeneca Vaxzevria vaccine are as good or better than after mRNA vaccines.

When will a third primary dose be given?

- The decision on the timing of the third primary dose should be undertaken by the specialist involved in the care of an individual.
- In general, the third primary dose should ideally be given at least 8 weeks after the second dose, but with special attention paid to current or planned immunosuppressive therapies.
- In general, vaccines administered during periods of minimum immunosuppression (where possible) are more likely to generate better immune responses. Where possible the third primary dose should be delayed until two weeks after the period of immunosuppression, allowing time required for any treatment to “wash-out” of the body – which varies with the particular drugs prescribed. If not possible, consideration should be given to vaccination during a treatment ‘holiday’ or at the point between doses of treatment where immunosuppression is at its lowest point.

Will a third primary dose provide all people who are immunosuppressed with full protection from severe illness and death due to COVID-19?

- Based on experience with other vaccines, it is expected that some persons who are immunosuppressed may not generate a good immune response regardless of the number of vaccine doses administered.

When will these recommendations come into effect?

- These recommendations will come into effect as soon as the NHS is able to operationalise them locally.

How many people with severe immunosuppression will be offered a third primary dose? Can you provide a breakdown by condition?

We do not have a breakdown by condition, but between 400,000 and 500,000 people with severe immunosuppression are expected to be offered a third primary dose.

What evidence was this advice based on?

- Unpublished evidence shared in confidence with JCVI as well as published evidence, some of which are provided in the statement: References
- 1. Whitaker HJ et al. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups. (2021) Preprint available at:
<https://khub.net/documents/135939561/430986542/RCGP+VE+riskgroups+paper.pdf/a6b54cd9-419d-9b63-e2bf-5dc796f5a91f>
- 2. Hall VG et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. *N Engl J Med*. 2021 Aug 11. doi: 10.1056/NEJMc2111462.
- 3. Kamar, N et al. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *N Engl J Med* 2021 Aug 12;385(7):661-662. doi: 10.1056/NEJMc2108861.
- 4. Werbel, WA et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Ann Intern Med* 2021 Jun 15;L21-0282. doi: 10.7326/L21-0282.
- 5. Parry H et al. Immunogenicity of single vaccination with BNT162b2 or ChAdOx1 nCoV-19 at 5-6 weeks post vaccine in participants aged 80 years or older: an exploratory analysis. *Lancet Healthy Longev* 2021 Aug 12. doi: 10.1016/S2666-7568(21)00169-0.
- 6. Liu X et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. *Lancet*. 2021 Aug 6:S0140-6736(21)01694-9. doi: 10.1016/S0140-6736(21)01694-9.
- 7. Lim SH et al. Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. *Lancet Haematol* 2021 Aug;8(8):e542-e544. doi: 10.1016/S2352-3026(21)00199-X.
- 8. Monin L et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021 Jun; 22(6): 765–778. doi: 10.1016/S1470-2045(21)00213-8

Are there any potential harms in giving a third dose, such as increased risk of VITT?

- It is unlikely that a third primary dose to those who are immunosuppressed will cause significant harms or disadvantages.
- The risk of extremely rare cases of concurrent blood clots and low platelet count is only raised after the *first dose* of the AstraZeneca vaccine in younger persons.
- If a person has not encountered a problem of Thrombosis with thrombocytopenia syndrome (TTS) with the first dose of this vaccine, a second or third dose should not result in TTS.
- As normal part of informed consent, the patient may wish to discuss the risk and benefits of a third primary dose with their specialist care provider.

What's the difference between a third primary dose and a booster?

- Third primary dose is a top-up dose for those in whom the first 2 doses may not have generated a full immune response.
- Booster dose is an extra dose to extend the duration of protection (maintain protection) for those who have generated a full immune response to the primary vaccinations (first 2 doses).

Do any other vaccinations require three doses in such short succession? Do any health concerns arise around repeated vaccination?

- Many of our childhood and adult vaccine require repeated doses to achieve and maintain levels of protection. Some people who respond less well may require additional doses or stronger vaccine formulations to make a good response. In general, these groups are also at higher risk from the infections, so any increase in minor side effects is offset by the better levels of protection.
- Examples of vaccinations that require three doses in short succession are diphtheria, pertussis, polio, tetanus, Hepatitis B.

Why hasn't this decision been made sooner? Are those who are immunosuppressed now at greater risk of infection and severe disease?

- Persons who are immunosuppressed were one of the first people to be offered COVID-19 vaccination.
- This decision was made when the relevant evidence became available. Additional studies involving persons who are immunosuppressed are either planned or on-going. Further updates to this advice may follow as the evidence base grows.

I was previously on the shielding list so why am I not being offered a third dose?

- The majority of people identified as clinically extremely vulnerable (CEV) are not immunocompromised/immunosuppressed.
- A significant number of immunocompromised individuals are considered as CEV, however, being immunocompromised alone does not automatically confer CEV status.
- Some individuals who are immunosuppressed due to underlying health conditions or medical treatment may not achieve the same full immune response to the initial (primary) 2 dose COVID-19 vaccination course as those who are not immunosuppressed.
- The evidence is not yet certain, but JCVI has decided as a precautionary measure, to recommend that those with severe immunosuppression at the time or around the time of their first or second primary dose of COVID-19 vaccination should receive a 3 dose primary vaccination course rather than the usual 2 dose primary schedule. The purpose of the autumn boosters is to combat waning immunity. A third primary dose is being given to bring severely immunosuppressed individuals up nearer to the same level of immunity achieved by healthy individuals with two primary doses.
- Everyone on the Shielded Patient List should already have been offered a COVID-19 vaccine. If you have received your first dose, you should still ensure you take up your second dose of the vaccine. Having 2 doses should further increase your level of protection.

- Shielding was paused on 1 April 2021. Updated guidance is available here [Guidance on protecting people defined on medical grounds as clinically extremely vulnerable from coronavirus \(COVID-19\) – previously known as ‘shielding’ | GOV.WALES](#)
- CEV individuals are advised, as a minimum, to follow the same guidance as the general population. However, as they remain at a higher risk of becoming seriously ill if they were to catch COVID-19, those who are CEV may wish to take action to minimise their own risk e.g. minimise contacts, meet with others outdoors instead of indoors, when indoors keep spaces well ventilated etc.