Joint Committee on Vaccination and Immunisation

Advice on third primary dose vaccination

24 August 2021

On 5 and 19 August 2021 JCVI considered whether some individuals may benefit from a third vaccine dose as part of their primary schedule of COVID-19 vaccination (described henceforth in this document as “third primary dose”).

Third primary dose 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. Most of the currently available data come from immunogenicity studies that have measured binding or neutralising antibody levels. Some studies have also measured cellular responses. Interpretation of both types of evidence is hampered by the lack of agreed correlates of protection. It is further recognised that the correlates of protection against infection, symptomatic disease and severe COVID-19 (hospitalisation and deaths) may differ both in the short and longer term. Comparison across studies is affected by the use of different assays with different test characteristics. Some studies indicate that the profile of antibody responses do not necessarily match those of cellular responses. Most of the data relate to the Pfizer-BNT162b2 vaccine.

Preliminary results from UK studies of real-world vaccine effectiveness (VE) in persons who are immunosuppressed suggest only a modest reduction in VE against symptomatic COVID-19, but confidence intervals are wide and overlap with VE estimates for persons who are not immunosuppressed (1). Furthermore, as immunosuppression is a heterologous condition that varies widely in severity and in duration, any potential reductions in protection in specific subgroups of the immunosuppressed would be missed by the use of a broader grouping. Clinical effectiveness studies examining more homogeneous sub-groups of persons with specific types of immunosuppression are ongoing. These studies are difficult to conduct due to the relatively small numbers of persons within each sub-group.

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 persons (2-4). The OCTAVE-DUO trial is a Phase III multicentre trial randomising patients in the UK to a third dose of Pfizer-BNT162b2 or Moderna mRNA-1273 with immunogenicity outcomes. The trial is expected to report early results in mid to late September and will probably not have sufficient granularity to inform the management of all types of immunosuppression. 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 (5). Emerging evidence suggests that both antibody and cellular immune responses to the primary course are enhanced with heterologous schedules, and therefore a third primary dose with a different vaccine format may be beneficial (6).

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 administrated. However, data are not currently available to reliably identify who might, or might not, benefit from a third primary dose of a COVID-19 vaccine. A few studies have suggested that timing of vaccine administration in relation to the underlying disease process or therapy is important in determining the level of immune response. For example, responses were higher in those who had completed treatment for clinically aggressive lymphomas more than six months earlier compared to those who had had more recent treatment (7). Similarly, responses to the first dose of vaccine were higher for patients with solid cancers who had not received chemotherapy within 15 days of vaccination compared to those who had (8). These data suggest that a third dose given at an appropriate interval from a period of immunosuppression is likely to provide a better vaccine response.

JCVI recognises that many persons who are immunosuppressed remain concerned regarding their risk of COVID-19 despite having received two doses of the primary vaccine schedule as currently advised. The potential for additional protection from a third primary dose is unknown at an individual level. Whilst antibody levels may be measured, without a clear understanding of the correlates of protection against severe disease and the interaction of immune suppression with measured immune responses, clinical inferences based on the measurement of antibody levels in persons who are immunosuppressed are difficult. For instance, low antibody levels may not denote poor protection against severe disease; and conversely, high antibody levels in a person unable to generate a commensurate cellular response may not denote good protection against severe disease.

Until more data are available, any provision of a third primary dose to persons who are immunosuppressed will draw on the assumption that a third dose is unlikely to confer significant harms or disadvantages, but may offer the possibility of benefit. These uncertainties in harms and benefits will need to be communicated as part of informed consent, and expectations regarding the value of a third primary dose taken into account.

ADVICE

At the current time, JCVI advises that a third primary dose be offered to individuals aged 12 year and over with severe immunosuppression in proximity of their first or second COVID-19 vaccine doses in the primary schedule. Severe immunosuppression at the time of vaccination is defined using the guidance and timings stated below

1. Individuals with primary or acquired immunodeficiency states at the time of vaccination due to conditions *including*:

    - acute and chronic leukaemias, and clinically aggressive lymphomas (including Hodgkin's lymphoma) who were under treatment or within 12 months of achieving cure

- individuals under follow up for a chronic lymphoproliferative disorders including haematological malignancies such as indolent lymphoma, chronic lymphoid leukaemia, myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias (Note: this list is not exhaustive)
- immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/µl for adults or children > 5 years of age or <500 cells/µl for children aged 5 years or less.
- Primary or acquired cellular and combined immune deficiencies – those with lymphopaenia (<1,000 lymphocytes/ul) or with a functional lymphocyte disorder.
- those who had received an allogeneic (cells from a donor) or an autologous (using their own cells) stem cell transplant in the previous 24 months
- those who had received a stem cell transplant more than 24 months ago but had ongoing immunosuppression or graft versus host disease (GVHD)
- persistent agammaglobulinaemia (IgG < 3g/L) due to primary immunodeficiency (e.g. common variable immunodeficiency) or secondary to disease / therapy

2. Individuals on immunosuppressive or immunomodulating therapy at the time of vaccination *including*:

- those who were receiving or had received immunosuppressive therapy for a solid organ transplant in the previous 6 months.
- those who were receiving or had received in the previous 3 months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but in this case the recipient would be considered immunosuppressed for a 6 month period), T-cell co-stimulation modulators, monoclonal tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors., IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors. (Note: this list is not exhaustive)
- those who were receiving or had received in the previous 6 months immunosuppressive chemotherapy or radiotherapy for any indication.

3. Individuals with chronic immune-mediated inflammatory disease who were receiving or had received immunosuppressive therapy prior to vaccination including:

- high dose corticosteroids (equivalent to ≥ 20mg prednisolone per day) for more than 10 days in the previous month
- long term moderate dose corticosteroids (equivalent to ≥10mg prednisolone per day for more than 4 weeks) in the previous 3 months
- non-biological oral immune modulating drugs, such as methotrexate >20mg per week (oral and subcutaneous), azathioprine >3.0mg/kg/day; 6-mercaptopurine >1.5mg/kg/day, mycophenolate >1g/day) in the previous 3 months
- certain combination therapies at individual doses lower than above, including those on ≥7.5mg prednisolone per day in combination with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) and those receiving methotrexate (any dose) with leflunomide in the previous 3 months

4. Individuals who had received high dose steroids (equivalent to >40mg prednisolone per day for more than a week) for any reason in month before vaccination

   Individuals who had received brief immunosuppression (≤40mg prednisolone per day) for an acute episode (e.g. asthma / COPD / COVID-19) and individuals on replacement corticosteroids for adrenal insufficiency are not considered severely immunosuppressed sufficient to have prevented response to the primary vaccination.

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. In exceptional circumstances, persons aged 40 years or over who received a mRNA COVID-19 vaccine previously may be offered a third primary dose of AstraZeneca Vaxzevria vaccine following a decision by a health professional on a case-by-case, individualised basis.

The decision on the timing of the third primary dose should be undertaken by the specialist involved in the care of the patient. In general, vaccines administered during periods of minimum immunosuppression (where possible) are more likely to generate better immune responses. The third primary dose should be given at least 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies. Where possible the third primary dose should be delayed until two weeks after the period of immunosuppression, in addition to the time period for clearance of the therapeutic agent. If not possible, consideration should be given to vaccination during a treatment 'holiday' or at a nadir of immunosuppression between doses of treatment.

As with current advice in the Green Book (chapter 14a) JCVI has advised that "individuals who have received a bone marrow transplant after vaccination should be considered for a re-immunisation programme for all routine vaccinations and for COVID-19". Re-vaccination with a 2-dose schedule should be considered 3-6 months post autologous and allogeneic human stem cell transplant or CAR-T therapy. A third primary dose of vaccine should be administered, at least 8 weeks after the second dose (in line with the advice above).

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. Alongside those with lower levels of immunosuppression, they are likely to become eligible for a booster dose as part of a routine booster programme from around six months after the second dose, pending further advice.

It is expected that severely immunosuppressed inviduals will become eligible for a booster dose as part of a routine booster programme from around six months after their third primary dose, pending further advice.

Implementation

To optimise vaccine use, specialists who are unable to offer the vaccine themselves should take responsibility for providing clear advice to the patient's general practitioner about the need for a third primary dose of vaccine and the optimal timing.

Organisational support within deployment teams to enable vaccination of these persons within the optimal timing window for them should be considered a priority. Patients should be initially identifiable using IT specifications for immunosuppression with further triage by the patient's specialist. A template form for recommendation on timings will be developed for the specailist managing each patient's immunosuppression which can be used to help local vaccination teams schedule appointments at the appropriate time for each individual to achive the maximum benefit from the third primary dose.

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