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Dear Colleagues

COVID-19 VACCINATION PROGRAMME: JCVI ADVICE ON THE VACCINATION OF SEVERELY IMMUNOSUPPRESSED INDIVIDUALS

This letter provides details of a Joint Committee on Vaccination and Immunisation (JCVI) statement, published 01 September 2021, on a third primary dose of the COVID-19 vaccination being offered for those who are severely immunosuppressed individuals.

A third primary dose is being offered to those who are severely immunosuppressed on the basis they may not have generated a full immune response to the first two doses.

KEY OBJECTIVES

1. To update on the advice from the JCVI on a third primary dose for severely immunosuppressed individuals.

2. To clarify operational guidance.

3. The Scottish Government is guided by the clinical and scientific advice on vaccination provided by the JCVI.

4. The JCVI has recommended that a third primary dose of COVID-19 vaccination is to be offered to individuals aged 12 years and over with severe immunosuppression in proximity of their first or second vaccine doses in their primary schedule of the COVID-19 vaccination. Joint Committee on Vaccination and Immunisation (JCVI) advice on third primary dose vaccination - GOV.UK (www.gov.uk)

5. This offer is separate to the booster programme. The JCVI will review whether those identified as severely immunosuppressed require a further booster at a later date, following completion of their 3-dose primary course.

6. Preliminary data from the OCTAVE trial showed that almost everyone who was immunosuppressed mounted an

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Deputy Chief Nursing Officer
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Addresses

For action
Chief Executives, NHS Boards
Medical Directors, NHS Boards
Primary Care Leads, NHS Boards
Directors of Nursing & Midwifery, NHS Boards
Chief Officers of Integration Authorities
Chief Executives, Local Authorities
Directors of Pharmacy
Directors of Public Health
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immune response after two doses, as indicated by either antibodies or T Cells levels. 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 but these people may not mount a full response and therefore may be less protected than the wider population.

7. People with severe immunosuppression are more likely to be severely ill if they do catch COVID-19.

8. Severe immunosuppression at the time of vaccination is defined using the guidance and timings set out in the JCVI advice. In summary this includes:

   - Individuals with primary or acquired immunodeficiency states;
   - Individuals on immunosuppressive or immunomodulating therapy;
   - Individuals with chronic immune-mediated inflammatory disease who were receiving or had received immunosuppressive therapy prior to vaccination;
   - Individuals who had received high dose steroids (equivalent to >40mg prednisolone per day for more than a week) for any reason in a month before vaccination.

   The full definition included in the JCVI advice of what constitutes severe immunosuppresion at the time of vaccination is set out in Annex A.

9. 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. Decisions on eligibility for a third primary dose and the timing of the third primary dose should be undertaken with advice from the specialist involved in the care of the patient and should be guided by the following principles:

   - 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.

10. For those aged 18 years and over, the JCVI advises a preference for mRNA COVID-19 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 who received an 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. For those aged 12-17 years the Pfizer-BNT162b2 vaccine remains the preferred choice, as set out in JCVI advice of 4 August 2021.

11. 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. The JCVI has advised that alongside those with lower levels of immunsupression, they will be eligible for a booster dose (as opposed to a third primary dose) from around 6 months after the second dose. Clinicians should consider this on a case by case basis and consult with the individuals concerned.

12. As with current advice in the Green Book (chapter 14a), the 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 two dose schedule should be considered 3-6 months post-autologous and allogenic 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 JCVI advice set out above).

Operational Considerations

13. This advice cannot be fully operationalised via routine scheduling. Careful engagement with clinicians treating some of this group will be required to identify who could benefit from the offer of a third primary dose and the optimum timing for this.

14. The JCVI advice sets out clearly that the decision on eligibilty of the patient to receive a third primary dose and the timing of the third primary dose should be undertaken by the specialist involved in the care of the patient. As a general guide, the third dose should usually be at least 8 weeks after the second dose but with flexibility to adjust the timing so that, where possible, immunosuppression is at a minimum when the third vaccine dose is given.

15. This will mean that it is not possible to routinely schedule appointments for all of this group using the National Vaccination Scheduling Service (NVSS). This will require a high level of engagement with clinicians leading treatment of those who are severely immunosuppressed and will have time and resource implications for primary and secondary care.

16. In addition, given the specific conditions and timing, in remote and rural areas small numbers of people, spread across geographic areas, may require a third dose. This will mean no single delivery route is possible and there will be a need to carefully consider supply and waste management particularly given the characteristics of mRNA vaccines.

17. For these reasons we anticipate it will take several weeks to appropriately roll out this offer to all those eligible. These challenges have also been reflected by 4 nations counterparts.

18. A short life working group has been set up and they will provide feedback to Health Boards regarding operational aspects. This will be carried out via the Delivery Group and the Planning Forum Teams Channel. This will include the ability to identify patients through national databases, if appropriate, engagement with the Clinical Leadership Group in terms of links to specialist clinicians and any other pertinent information that will assist Health Boards in the vaccination of this cohort. Information has already been issued to Boards about scheduling the initial cohort based on parts 1, 2 and 5 of the previous Shielding list (now known as the highest risk list).

Communications

19. For those individuals who are within the criteria specified as requiring a third dose, there will be a combination of messaging routes. NHS Inform has been updated with information about the conditions and clinical circumstances included; the individual's clinicians will also communicate with their patient, and information leaflets will be provided by Public Health Scotland. News releases by Scottish Government have been undertaken and key communication material will be provided to each Health Board communication lead.

20. The JCVI will review whether those identified as severely immunosuppressed require a further booster, at a later date, following completion of their 3-dose primary course. Communications explaining the rationale for those who are not severely immunosuppressed and who will not be offered a third primary dose of a COVID-19 vaccine will be covered via a number of routes such as news releases, social media, local Health Board communications, and national information on NHS Inform. The National Contact Centre will also take enquiries on this matter for people with non-digital access.

21. Once the delivery plan is finalised by the dedicated short life working group along with the timeframe for delivery – there will also be a dedicated communications plan with tailored messaging for this group.

22. Materials to support communications will be provided to Health Boards, which will be able to access a list of FAQs to support this approach. Please find the FAQ attached at Annex B.

Action

23. Health Boards should consider how best to engage with clinicians treating patients with the criteria outlined in Annex A to identify who will require a third dose and how those third doses will be best delivered. The short life-working group will provide further information as soon as possible following discussions with key stakeholders.

Thank you for your continued support in delivering the COVID-19 vaccination programme.

Yours sincerely

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Chief Medical Officer	**Deputy Chief Nursing Officer**	**Chief Pharmaceutical Officer**

JCVI ADVICE ON THE VACCINATION OF SEVERELY IMMUNOSUPPRESSED INDIVIDUALS

DEFINITION OF CONDITIONS CAUSING SEVERE IMMUNOSUPPRESSION

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 three 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 three 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 three 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.

5. 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.

6. For the most up to date advice please refer to the Chapter 4 of the Green Book

FAQ - SEVERE IMMUNOSUPPRESSION

1. Who is eligible for a third dose?

- Some individuals who are severely immunosuppressed due to underlying health conditions or medical treatment may not achieve the same full immune response to the initial (primary) two dose COVID-19 vaccination course as those who are not immunosuppressed.

- The evidence is not yet certain, but the JCVI has recommended that those aged 12 and above with severe immunosuppression in proximity of their first or second COVID-19 vaccine doses in the primary schedule should receive a three-dose primary vaccination course rather than the usual two dose primary schedule. A third primary dose is being given to bring severely immunosuppressed individuals to the same level as those not immunosuppressed as it may increase the protection for those who may not have generated a full immune response to the first two doses. This would be different to the COVID-19 booster programme, the purpose of which would be to combat waning immunity.

- Severe immunosuppression at the time of vaccination is defined using guidance and timings outlined in the COVID-19 chapter of the Green Book: Immunisation against infectious disease.

2. Who is eligible for a third dose?

- As with the vaccination of other at-risk individuals, eligible individuals will be identified and invited for a vaccination by the Health Board where they are resident in consultation with their consultant and/or GPs.

3. How effective are the COVID-19 vaccines at protecting the immunosuppressed?

- The JCVI advised that a third dose be given to those who are severely immunosuppressed and studies are ongoing to see how effective a third dose is for immunosuppressed people. The JCVI advice notes that immunosuppression varies widely in severity and duration. Some studies have shown that some people who are immunosuppressed have lower levels of antibodies after their COVID-19 vaccination.

- As part of the COVID-19 Immunity National Core Study, UK Research and Innovation (UKRI) is providing funding of £4 million towards the OCTAVE study. The OCTAVE study is examining responses to COVID-19 vaccines in clinically at-risk groups (including in patients with certain immunosuppressed conditions).

- The OCTAVE trial preliminary results, published on 24 August 2021, show that the majority (60%) of clinically at-risk people produce strong immune responses following two doses of a vaccine. However, 40% of patients mounted a low, or undetectable, immune responses after two doses. Participants in the trial received either Pfizer/BioNTech or AstraZeneca vaccines.

- A separate study from Public Health England in July which looked at antibody response and vaccine effectiveness against symptomatic infection also showed that those who were immunocompromised had lower antibody responses. It also found

that protection from COVID-19 (vaccine effectiveness against symptomatic disease) for those who are immunosuppressed of all ages after one dose was 4%, but after two doses, it was 74%, providing similar protection to those who are not in an at-risk group. Again, vaccine effectiveness may vary by specific condition and severity of that condition.

4. How effective will a third dose be?

- The potential for additional protection from a third primary dose is uncertain at an individual level for people with severe immunosuppression. Until more data are available, any provision of a third primary dose to persons who are immunosuppressed will draw on JCVI's assumption that a third dose is unlikely to confer significant harms or disadvantages but may offer potential benefit.

5. When will the third dose be scheduled for those about to receive immunosuppressive therapy again?

- The specialist involved should advise on whether the patient fulfils the eligibility criteria and on the timing of any third primary dose.

- In general, vaccines administered during periods of minimum immunosuppression (where possible) are more likely to generate better immune responses. The third primary dose should ideally be given at least 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies guided by the following principles: a) 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, b) if not possible, consideration should be given to vaccination during a treatment 'holiday' or at a nadir of immunosuppression between doses of treatment.

- The JCVI has advised that it will review at a later date whether severely immunosuppressed individuals will also require a COVID-19 booster vaccination after completion of their 3-dose primary vaccine course.

6. Are individuals who are about to receive immunosuppressive therapy be eligible for a third dose?

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

- The JCVI will review whether this group requires a further booster at a later date, following completion of their 3-dose primary course.

7. Which vaccine will be given?

- For individuals 18 and over, JCVI advises a preference for mRNA vaccines (Pfizer and Moderna) 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 who received a mRNA COVID-19 vaccine previously may be offered a third primary dose of AstraZeneca vaccine following a decision by a health professional on a case-by-case, individualised basis.

- For those aged 12-17 years, the Pfizer-BNT162b2 vaccine remains the preferred choice, as set out in JCVI advice of 4th August 2021.

8. If AstraZeneca was given for the first two doses will it also be used for the third 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.

9. Why is a preference for mRNA vaccines being advised for third doses?

- mRNA vaccines are recommended based on consistent evidence of higher antibody levels, even though some studies suggest that cellular responses with AstraZeneca vaccine are as good as or better than after mRNA vaccines. The mix and match vaccine studies undertaken in the UK and elsewhere suggest that this combination may provide the best-combined immune response.

- In light of this, JCVI advises a preference for mRNA vaccines for the third primary dose, with the option of the AstraZeneca vaccine for individuals who have received this vaccine previously where this would facilitate delivery. In exceptional circumstances, persons who received a mRNA COVID-19 vaccine previously may be offered a third primary dose of AstraZeneca vaccine following a decision by a health professional on a case-by-case, individualised basis.

10. Will individuals receiving a third dose also receive a booster shot?

- The primary doses are not being offered to combat waning immunity (unlike the COVID-19 booster programme, the purpose of which is to combat waning immunity). Third primary doses are being offered to severely immunocompromised individuals to attempt to bring these individuals up nearer to the same level of immunity as the non-immunosuppressed achieve from two doses.

  The JCVI have advised that they will review at a later date whether severely immunosuppressed individuals require a booster dose following completion of their 3-dose primary vaccine course.

11. Are individuals who were previously on the shielding list going to be offered a third dose?

- The majority of people identified on the highest risk list (previously known as the 'shielding list') are not severely immunosuppressed, and will be eligible for a booster dose as opposed to a third dose

- Some individuals who are severely immunosuppressed due to underlying health conditions or medical treatment may not achieve the same full immune response to the initial (primary) two dose COVID-19 vaccination course as those who are not immunosuppressed.

- The evidence is not yet certain, but the JCVI has recommended that those aged 12 and above with severe immunosuppression in proximity of their first or second COVID-19 vaccine doses in the primary schedule should receive a three-dose primary vaccination course rather than the usual two dose primary schedule. A third primary dose is being given to try to bring severely immunosuppressed individuals up nearer to the same level of immunity achieved by healthy individuals with two primary doses. This would be different to the booster programme for COVID-19 vaccinations, the purpose of which would be to combat waning immunity.

- Everyone on the highest risk 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 two doses should further increase your level of protection.

- Updated guidance as to how people on the highest clinical risk can manage the risks to themselves and to others was published on 12 July 2021. Coronavirus (COVID-19): advice for people at highest risk - gov.scot (www.gov.scot)

- Clinically Extremely Vulnerable (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, CEVs may wish to think particularly carefully about additional precautions they might wish to take.

- If any CEV individual is concerned about their physical or mental wellbeing, they should contact their GP practice or specialist who can provide them with support and guidance on any further measures they can take to further reduce their risk of infection.

12. Will children as well as adults who are severely immunosuppressed be offered a third dose?

- At the current time, JCVI advises that a third primary vaccine dose should be offered to individuals aged 12 and above with severe immunosuppression in proximity of their first or second COVID-19 vaccine doses in the primary schedule.

13. Are individuals who have received a bone marrow transplant eligible for a third dose?

- 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". A third dose of vaccine should be administered to complete the primary course, at least 8 weeks after the second re-immunising dose.