SARS-CoV-2 vaccination following haematopoietic stem cell transplant (HSCT) and chimeric antigen receptor T-cell (CAR-T) therapy. Prepared by the British Society of Blood and Marrow Transplantation and Cellular Therapy Vaccination Sub-Committee (BSBMTCT-VSC); updated 4th April 2024

This update reflects the likely availability of SARS-CoV-2 vaccines in the UK as 05/04/2024 and summary recommendations on use following HSCT or CAR-T therapy, based on the UKHSA and NHSE national protocol for adults (27th March 2023) and children (3rd April 2023), UK Green Book and joint consensus statement from the BSBMTCT, Children’s Cancer and Leukaemia Group (CCLG) and British Infection Association. The current update aligns with the February 2024 version of the UK Green Book COVID-19 chapter, reflecting availability of SARS-CoV-2 vaccines in the UK and changes in delivery of SARS-CoV-2 vaccines during and in between seasonal booster campaigns. Please see prior versions of this document for more extensive discussion on SARS-CoV-2 vaccines, including other licensed vaccines in the UK which may no longer be readily available.

Re-vaccination Schedules in HSCT Recipients
After HSCT, a decline in antibody titres to vaccine preventable diseases is apparent within weeks and may continue for years post-HSCT.1-10 International groups therefore recommend that HSCT recipients are considered never-vaccinated and offered a full re-vaccination schedule.11-13 Vaccine efficacy studies in HSCT recipients are lacking, and schedules are based largely on immunogenicity data. Although responses against other vaccines are generally lower than in immunocompetent individuals, pneumococcal conjugate vaccines may be immunogenic from as early as 3 months post-HSCT and some other vaccines from 6 months.14,15 International guidelines recommend re-vaccination schedules are commenced from 3-6 months post-HSCT time-point.12,13 Data describing the impact of Graft versus Host Disease (GvHD) on vaccine immunogenicity are conflicting, and most international groups advocate vaccination regardless of GvHD, and any therapy required for this condition. UK post-HSCT vaccination practice varies considerably for both paediatric and adult HSCT recipients in both autologous and allogeneic settings.16,17

SARS-CoV-2 Vaccination in HSCT Recipients
HSCT and CAR-T recipients are in a COVID-19 high-risk group and conferring immunity by vaccination at the earliest effective timepoint is desirable. Seroconversion following two doses of Pfizer vaccine has been shown to occur in 50 – 84.7% of allogeneic HSCT recipients and 60 – 84% of autologous HSCT recipients,18-22 which was significantly lower than in healthy control participants when included.20 Similar antibody titres between autologous and allogeneic HSCT recipients have been noted.23 Several studies have also observed lower antibody induction in individuals within the first 12 months following HSCT.19,20,23 Data from vaccinated CAR-T therapy recipients are limited, but there are indications that immunogenicity may be lower than in HSCT recipients.18,20,21 A study reporting on the immunogenicity of a 3rd primary Pfizer vaccine dose in HSCT recipients demonstrated that 42% of prior non-responders achieved an antibody titre above a pre-defined antibody threshold predictive of neutralising activity.24

BSBMTCT recommendations for the vaccination of HSCT and CAR-T recipients
Vaccination at too early a time-point may be poorly immunogenic, while late vaccination may leave HSCT and CAR-T recipients at unnecessary risk for a prolonged period. A national expert group on behalf of BSBMTCT has prepared the following statements. The group draws on expertise in adult and paediatric bone marrow transplant, CAR-T therapy, infectious diseases, vaccinology and immunology. The limitations of these statements are acknowledged, but they offer a pragmatic position in the face of existing clinical evidence in this patient population. These statements are focused on potentially offering some degree of protection to a very high-risk population in the context of ongoing SARS-CoV-2 transmission.

Taking into consideration the evidence available and expert opinion from this group, the following recommendations are proposed:

Vaccination before HSCT and CAR-T
- For patients who have not received any SARS-CoV-2 vaccines and have an HSCT or CAR-T procedure scheduled in the immediate future (i.e. weeks to a month), an assessment of risk should inform whether SARS-CoV-2 vaccination is offered pre or post-procedure. Where vaccination is offered pre-procedure, it
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Timing of 2\textsuperscript{nd} dose: The immunogenicity of the first SARS-CoV-2 vaccine dose can be poor in allogeneic HSCT recipients.\textsuperscript{23,27} Until further data are available to guide scheduling of re-vaccination in HSCT/CAR-T recipients, the BSBMTCT Vaccines Sub-Committee favours administration of the 2\textsuperscript{nd} dose in HSCT and CAR-T recipients following the minimum licensed interval i.e. a 3 week interval for Pfizer mRNA vaccines and a 4 week interval for Moderna mRNA vaccines. The UK Green book acknowledges that the interval may be reduced to this minimum licensed duration on specialist clinical advice, such as those provided in recommendations for re-vaccination following HSCT/CAR-T by transplant centres.\textsuperscript{25} Transplant centres are advised to stipulate in local guidance sent with each patient that their specialist clinical advice is to use the minimum licensed duration for the first two doses (3-4 weeks), according to Green Book guidance. These first two doses can be administered via the out of season pathway provided by the NHS (see text box).

A further booster dose should be offered with a SARS-CoV-2 mRNA vaccine between 3 and 6 months following the 2\textsuperscript{nd} dose according to Green Book guidance.\textsuperscript{25} If this timing coincides with a seasonal campaign in the UK which includes the offer of a booster dose to HSCT/CAR-T recipients, then delivery of this 3\textsuperscript{rd} dose post-procedure may be given via the seasonal booster campaign. However, if this is unlikely to occur and delays beyond 6 months are anticipated until receipt of this booster dose, then it may be delivered via the NHS out of season pathway for HSCT/CAR-T recipients according to specialist clinical advice, as stated in the UK Green Book.\textsuperscript{25}

Vaccination after HSCT or CAR-T

• HSCT and CAR-T recipients who have received a SARS-CoV-2 vaccine pre-procedure should be considered never-vaccinated in keeping with updated Green Book guidance.\textsuperscript{25}

• Consider vaccination with a SARS-CoV-2 vaccine from 3-6 months post autologous HSCT, allogeneic HSCT, or CAR-T therapy in individuals ≥ 6 months.

• Dosing regimen and choice of vaccine (adults):
  o HSCT and CAR-T patients ≥18 years can receive any of the SARS-CoV-2 mRNA vaccines currently licensed in the UK and should be encouraged to accept the first vaccine they are offered. A preference for a vaccine type for the re-vaccination course in adults ≥18 years may emerge from ongoing studies, but at present there are insufficient data for a strong recommendation for the primary doses. Only monovalent mRNA vaccines targeting XBB strains are expected to be deployed from Spring 2024 onwards. No other vaccines are available as part of the UK NHS programme at present.

If all mRNA vaccines are clinically contraindicated, then alternatives such as the HIPRA bivalent Beta/Alpha COVID-19 vaccine (BIMERVAX®) or Novavax XBB COVID-19 vaccine (Nuvaxovid®XBB.1.5), may be used if available. These are expected to enter the private UK market in 2024 and will likely require administration via a specialist service. The AstraZeneca ChadOX1-S vaccine and Sanofi Pasteur COVID-19 vaccine (VidPrevtn Beta®) are no longer supplied for routine use in the UK.
**Out of Season Pathway (for patients in England)**

NHS England have asked all Integrated Care Boards (ICBs) to ensure there are arrangements for HSCT and CAR-T recipients to receive their SARS-CoV-2 vaccines regardless of the time of year, including outside of seasonal campaigns. Contact details for these “Out of Season” pathways in each ICB are available here: https://www.england.nhs.uk/coronavirus/covid-19-vaccination-programme/local-covid-19-vaccination-contacts/.

The BSBMTCT is aware of ongoing issues with securing appointments through these pathways. Any ongoing difficulties should be flagged to yasmin.sheikh@anthony Nolan.org for cascading to the national NHS England team.

- **Dosing regimen and choice of vaccine (children):**
  - Children aged 12 – 17 years old should be vaccinated using a 2-dose mRNA vaccine primary course in keeping with current licensure and Green Book guidance, with a preference for a Pfizer mRNA vaccine due to a reported lower rate of myocarditis. The minimum interval between each vaccine dose should be 8-12 weeks. Further booster doses should follow recommendations in national booster campaigns, at 3 to 6 months from the 2nd dose.
  - Children aged 6 months – 11 years old should be vaccinated using a 2-dose Pfizer mRNA vaccine primary course in keeping with current licensure and Green Book guidance. The 2nd dose should be given at a minimum of 12 weeks after the 1st dose. A booster dose should be given at 3 to 6 months after the 2nd dose.
  - The addition of severely immunosuppressed children aged 6 months to 4 years to those eligible for a 2-dose primary SARS-CoV-2 vaccine course was recommended by the JCVI in early 2023.
  - If the timing for booster doses coincides with a seasonal campaign in the UK which includes the offer of a booster dose to HSCT/CAR-T recipients, then delivery of this 3rd dose post-procedure may be given via the seasonal booster campaign. However, if this is unlikely to occur and delays beyond 6 months are anticipated until receipt of this booster dose, then it may be delivered via the NHS out of season pathway for HSCT/CAR-T recipients according to specialist clinical advice, as stated in the UK Green Book.

- For allogeneic HSCT recipients who are receiving immunosuppressive therapy (IST) consider indication, intensity and expected duration of IST when deciding whether to vaccinate or defer. When patients are approaching the end of an IST weaning schedule a short deferral may be reasonable.
- Consider vaccination of patients with chronic GvHD. Consider intensity and expected duration of GvHD targeted therapy when deciding whether to vaccinate or defer.
- If there is reasonable concern that a short deferral for a clinical reason may in practice result in a longer delay due to vaccine administration issues (e.g. appointment availability, regional shortage etc.) then vaccination is suggested over deferral.
- Government shielding guidance has now come to an end. However, HSCT and CAR-T patients should be advised to continue being cautious in their contacts even after receiving a 2-dose primary course as vaccine immunogenicity and efficacy in these patients is at present not fully defined.

**Vaccination of Household Members**

- Unvaccinated household members of HSCT and CAR-T recipients should be offered vaccination in accordance with JCVI recommendations, with a 2-dose primary course and further booster dose at least 3 months following the 2nd dose. Household contacts of HSCT and CAR-T recipients are not currently...
being offered booster vaccinations but this may be reinstated in future seasonal campaigns. COVID-19 vaccines will be available to buy privately for the first time from April 2024. Household contacts of immunosuppressed individuals may choose to access vaccination in this way.

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Donor Vaccination
Guidelines for vaccination of stem cell donors are available from the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC).

Available SARS-CoV-2 vaccines and doses in the UK (2024)

<table>
<thead>
<tr>
<th>Vaccination type (adults aged 18 and over)</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Moderna (Spikevax® XBB.1.5)</td>
<td>0.5ml (50mcg)</td>
</tr>
<tr>
<td>Pfizer BioNTech (Comirnaty® XBB.1.5)</td>
<td>0.3ml (30mcg)</td>
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<table>
<thead>
<tr>
<th>Vaccination type (children)</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>12-17 year olds – Pfizer BioNTech (Comirnaty®XBB.1.5)</td>
<td>0.3ml (30mcg)</td>
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<tr>
<td>5-11 year olds – Pfizer BioNTech (Comirnaty®10 XBB.1.5)</td>
<td>0.3ml (10mcg)</td>
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<tr>
<td>6 months to 4 years – Pfizer BioNTech (Comirnaty®3 XBB.1.5)</td>
<td>0.3ml (3mcg)</td>
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These statements will be regularly reviewed and updated as appropriate when further data emerge.

Correspondence update April 2024

Representatives of the BSBMT-CT Vaccines sub-committee as of 4th April 2024

Professor Thushan de Silva (Chair, Vaccination Sub-Committee)
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Dr. Anjum Khan
Yasmin Sheikh (Anthony Nolan)
Dr. Soonie Patel
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Aileen Nield (Nurse representative)
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BSBMT-CT Vaccination Sub-Committee
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References


