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 (BSBMT-CT-VSC); updated 1st August 2023

This update reflects the likely availability of SARS-CoV-2 vaccines in the UK as of 01/08/2023 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. 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[12] 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

In the absence of optimum data to guide vaccination strategies in HSCT recipients, pragmatic recommendations are required. 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 evidence for established vaccines 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

is preferable to complete the 3-dose primary vaccination schedule prior to conditioning. Second doses may be offered at less than the 8-week interval (but adhering to minimum licensed intervals) if this would allow completion of the course prior to the procedure, in keeping with Green Book guidance.[25] Third doses should be given after the minimum 8-week interval following the 2nd dose.

- In patients who have received prior SARS-CoV-2 vaccines and a future HSCT or CAR-T procedure is planned, the next scheduled dose according to disease-specific and latest national guidance should be offered prior to the procedure, adhering to the minimum recommended intervals between doses in the Green Book.[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.[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)**:
    - 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. If all mRNA vaccines are clinically contraindicated then Novavax NVX-CoV-2373 may be used instead if available. The AstraZeneca ChadOX1-S vaccine is no longer supplied for routine use in the UK.

    - Timing of 2nd dose*:* Due to evidence that immunogenicity and/or vaccine efficacy is higher with longer intervals between doses, the JCVI recommends a minimum 8-week interval between the first two doses. Available efficacy data for the Pfizer vaccine is based on the administration of a second dose within a limited window of 19-42 days. Immunogenicity data in UK healthcare workers show that extended dosing regimens (average 10 weeks) for the Pfizer vaccine results in greater humoral immunogenicity than the short 3-week interval.[26] Despite data in healthy adults demonstrating the benefit of extended dosing intervals, the immunogenicity of the first SARS-CoV-2 vaccine dose can be poor in allogeneic HSCT recipients and the first dose vaccine effectiveness against the B.1.617.2/delta variant was reduced, even in the general population.[23,27] Until further data are available to guide scheduling of re-vaccination the BSBMTCT Vaccines Sub-Committee favours administration of the 2nd dose in HSCT and CAR-T recipients following the minimum licensed interval i.e. a 3 week interval for Pfizer mRNA vaccines and Novavax NVX-CoV-2373 vaccine, and a 4 week interval for Moderna mRNA vaccines.

    - A 3rd primary dose should be offered with a SARS-CoV-2 mRNA vaccine at a minimum interval of 8 weeks following the 2nd dose according to Green Book guidance.[25] If an mRNA vaccine is not considered clinically suitable, then a dose of Novavax NVX-CoV2373 or Sanofi Pasteur (VidPrevtyn Beta®) vaccine may be used.[25]

    - A 4th booster dose should be offered no sooner than 3 months after the 3rd primary dose. The JCVI recommends that an mRNA vaccine is used for the 4th booster dose, unless a patient is unable to receive an mRNA vaccine in which case a dose of Novavax NVX-CoV2373 or Sanofi Pasteur (VidPrevtyn Beta®) vaccine may be used.[25]

- **Dosing regimen and choice of vaccine (children)**:
    - Children aged 12 – 17 years old should be vaccinated using a 3-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.[25] The minimum interval between each vaccine dose should be 8 weeks. If mRNA vaccines are clinically contraindicated then NVX-CoV-

2373 vaccines may be used instead. Further (booster) doses should follow recommendations in national booster campaigns, with a minimum of 3 months from the 3rd primary dose.

- Children aged 6 months – 11 years old should be vaccinated using a 3-dose Pfizer mRNA vaccine primary course in keeping with current licensure and Green Book guidance.[25] The 2nd dose should be given at a minimum of 12 weeks after the 1st dose. A 3rd primary dose should be given a minimum of 8 weeks after the 2nd dose. Further (booster) doses should follow recommendations in national booster campaigns, with a minimum of 3 months from the 3rd primary dose.

  The addition of severely immunosuppressed children aged 6 months to 4 years to those eligible for a 3-dose primary SARS-CoV-2 vaccine course was recommended by the JCVI in early 2023.[25] Unlike other age groups where bivalent vaccines are now used (see below), the Pfizer mRNA formulation currently used for children aged 6 months to 4 years continues to be the monovalent ancestral vaccine.

- **Role of bivalent omicron-containing vaccines:**
  - There are currently no immunogenicity or safety data on the use of bivalent omicron-containing vaccines in a multi-dose primary vaccination course as required in post-HSCT revaccination schedules. However, monovalent ancestral vaccines (e.g. Pfizer BNT162b2 and Moderna mRNA-1273 vaccines) are increasingly unavailable, other than for children aged 6 months to 4 years old.
  - JCVI now advises using bivalent vaccines for primary course doses in addition to booster doses, including for those who have not received these vaccines previously.[25]
  - Adults aged 18 years and over may be given either the Moderna mRNA (Spikevax®) bivalent vaccine or the Pfizer-BioNTech mRNA (Cominarty®) bivalent vaccine. Children aged 5 – 17 years should be given the Pfizer-BioNTech mRNA (Cominarty®) bivalent vaccine. Children aged 6 months to 4 years should continue to receive the Pfizer-BioNTech mRNA monovalent ancestral vaccine.

- 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 3-dose primary course as vaccine immunogenicity and efficacy in these patients is at present not fully defined.
- Available vaccines are not currently licensed for use in the under 12-year age group.

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. Persons aged 5-49 years who are household contacts of HSCT and CAR-T recipients should be offered ongoing booster vaccinations in keeping with ongoing JCVI recommendations. Further updates will be provided following announcement of Autumn 2023 booster campaigns and beyond.

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 (2023)

Vaccination type (adults)	**Primary doses 1 and 2**	**3rd primary and booster doses**
Moderna (Spikevax®) bivalent Original/Omicron BA.4-5 (**50/50** micrograms)/ml	**0.5ml**	**0.5ml**
Pfizer BioNTech (Comirnaty®) bivalent Original/Omicron BA.4-5 (**15/15** micrograms)/dose	**0.3ml**	**0.3ml**
Sanofi Pasteur (VidPrevtyn Beta®) (**5** micrograms)/dose	Not to be used for the first 2 doses	**0.5ml**

Vaccination type (children)	**All doses**
12-17 year olds – Pfizer BioNTech (Comirnaty®) bivalent Original/Omicron BA.4-5 (**15/15** micrograms)/dose	**0.3ml**
5-11 year olds – Pfizer BioNTech (Comirnaty®) bivalent Original/Omicron BA.4-5 (**5/5** micrograms)/dose	**0.2ml**
6 months to 4 years – Pfizer BioNTech (Comirnaty®) (**3** micrograms)/dose (monovalent)	**0.2ml**

These statements will be regularly reviewed and updated as appropriate when further data emerge.

Correspondence update August 2023

Representatives of the BSBMT-CT Vaccines sub-committee as of 1st August 2023

Professor Thushan de Silva (Chair, Vaccination Sub-Committee)
Dr. Fiona Dignan (Chair, BMT CRG)
Professor Paul Heath
Dr. Anjum Khan
Yasmin Sheikh (Anthony Nolan)
Professor Rod Skinner
Dr. Soonie Patel
Professor Alex Richter
Professor John Snowden
Aileen Nield (Nurse representative)

BSBMT-CT Vaccination Sub-Committee
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References

1. Patel SR, Ortín M, Cohen BJ, Borrow R, Irving D, Sheldon J, Heath PT. Re-immunization with measles, tetanus, poliovirus, *Haemophilus influenzae* type b, meningococcal C and pneumococcal vaccines in children following hematopoietic stem cell transplantation. Clin Infect Disease 2007;44(5):625-634
2. Ljungman P, Lewensohn-fuchs I, Hammarstrom V, Aschan J, Brandt L, Bolme P *et al.* Long-term immunity to measles, mumps, and rubella after allogeneic bone marrow transplantation. *Blood* 1994; **84**: 657--63.
3. Pauksen K, Duraj V, Ljungman P, Sjolin J, Oberg G, Lonnerholm G *et al.* Immunity to and immunization against measles, rubella and mumps in patients after autologous bone marrow transplantation. *Bone Marrow Transpl* 1992; **9**: 427--32.
4. Ljungman P, Fridell E, Lonnqvist B, Bolme P, Bottiger M, Gahrton G *et al.* Efficacy and safety of vaccination of marrow transplant recipients with a live attenuated measles, mumps, and rubella vaccine. *J Infect Dis* 1989; **159**: 610--615.
5. Ljungman P, Wiklund-Hammarsten M, Duraj V, Hammarstrom L, Lonnqvist B, Paulin T *et al.* Response to tetanus toxoid immunization after allogeneic bone marrow transplantation. *J Infect Dis* 1990; **162**: 496--500.
6. Ljungman P, Duraj V, Magnius L. Response to immunization against polio after allogeneic marrow transplantation. *Bone Marrow Transpl* 1991; **7**: 89--93.
7. Engelhard D, Handsher R, Naparstek E, Hardan I, Strauss N, Aker M *et al.* Immune response to polio vaccination in bone marrow transplant recipients. *Bone Marrow Transpl* 1991; **8**: 295--300.
8. Parkkali T, Stenvik M, Ruutu T, Hovi T, Volin L, Ruutu P. Randomized comparison of early and late vaccination with inactivated poliovirus vaccine after allogeneic BMT. *Bone Marrow Transpl* 1997; **20**: 663--8.
9. Winston DJ, Ho WG, Schiffman G, Champlin RE, Feig SA, Gale RP. Pneumococcal vaccination of recipients of bone marrow transplants. *Arch Intern Med* 1983; **143**: 1735--7.
10. Giebink GS, Warkentin PI, Ramsay NK, Kersey JH. Titers of antibody to pneumococci in allogeneic bone marrow transplant recipients before and after vaccination with pneumococcal vaccine. *J Infect Dis* 1986; **154**: 590--596.
11. Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR. Guidelines for Preventing Infectious Complications among Haematopoietic Cell Transplant Recipients : A Global Perspective. 2009; **15**: 1143--1238.
12. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M *et al.* 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; **58**: 1--57.
13. Cordonnier C, Einarsdottir S, Cesaro S, Blasi RD, Mikulska M, Rieger C *et al.* Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis* 2019; **19**: e200--e212.
14. Parkkali T, Olander RM, Ruutu T, Vuontela K, Volin L, Eskola J *et al.* A randomized comparison between early and late vaccination with tetanus toxoid vaccine after allogeneic BMT. *Bone Marrow Transpl* 1997; **19**: 933--938.
15. Parkkali T, Kayhty H, Anttila M, Ruutu T, Wuorimaa T, Soininen a *et al.* IgG subclasses and avidity of antibodies to polysaccharide antigens in allogeneic BMT recipients after vaccination with pneumococcal polysaccharide and Haemophilus influenzae type b conjugate vaccines. *Bone Marrow Transpl* 1999; **24**: 671--678.
16. Miller PDE, Silva TI de, Skinner R, Gilleece M, Peniket A, Hamblin A *et al.* Routine vaccination practice after adult and paediatric allogeneic haematopoietic stem cell transplant: a survey of UK NHS programmes. *Bone Marrow Transpl* 2017; **52**: 775--777.
17. Gilleece M, Towlson K, Wilson M, Littlewood T, Cook G, Marks D. Vaccination against Infection after Haematopoietic Stem Cell Transplant : A Survey of Practice in the UK and Ireland. *BBMT* 2007; **21**: S614--S708.

18. Dhakal B, Abedin S, Fenske T, Chhabra S, Ledeboer N, Parameswaran H & Hamadani M. Response to SARS-CoV-2 vaccination in patients after haematopoietic cell transplantation and CAR T-cell therapy. *Blood* 2021; 138(14):1278-1281.
19. Redjoul R, Le Bouter A, Beckerich F, Fourati S & Maury S. Antibody response after second BNT162b2 dose in allogeneic HSCT recipients. *Lancet* 2021; 398(10297):298-299.
20. Bergman P, Blennow O, Hansson L, Mielke S, Nowak P, Chen P *et al.* Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunosuppressed patients and healthy controls in a prospective open-label clinical trial. *MedRxiv* 2021; doi: https://doi.org/10.1101/2021.09.07.21263206
21. Ram R, Hagin D, Kikozashvilli N, Freund T, Amit O, Bar-On Y *et al.* Safety and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in patients after allogeneic HCT or CD19-based CART therapy – a single-centre prospective cohort study. *Transplantation and Cellular Therapy* 2021; 27(9): 788-794.
22. Chiarucci M, Paolasini S, Isidori A, Guiducci B, Loscocco F, Capalbo M & Visani G. Immunological response against SARS-CoV-2 after BNT162b2 vaccine administration is impaired in allogeneic but not in autologous stem cell transplant recipients. *Front Oncol* 2021; 11:737300
23. Maneikis K, Sablauskas K, Ringeleviciute U, Vaitekenaite V, Cekauskiene R, Kryzauskaite L *et al.* Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective study. *Lancet Haematol* 2021; 8(8):e583-e582.
24. Redjoul R, Le Bouter A, Parinet V, Fourati S & Maury S. Antibody response after third BNT162b2 dose in recipients of allogeneic HSCT. *Lancet Haematol* 2021;8(10):e681-e683.
25. Green Book Chapter 14a: COVID-19 - SARS-Cov-2. UKHSA, 2021.
26. Payne RP, Longet S, Austin JA, Skelly DT, Dejnirattisai W, Adele S *et al.* Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. *Cell* 2021; 184 (23): P5699-5714.
27. Easdale S, Shea R, Ellis L, Bazin J, Davis K, Dallas F *et al.* Serologic responses following a single dose of SARS-CoV-2 vaccination in allogeneic stem cell transplantation recipients. *Transplantation and Cellular Therapy* 2021;27(10):e880.e1-880.e4