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 31st October 2022

National SARS-CoV-2 Vaccination Strategy

The Joint Committee on Vaccination and Immunisation (JCVI) advised a phased approach to vaccination in the UK. In phase 1, the JCVI identified 9 priority groups determined by age, exposure risk and comorbidities. Clinically extremely vulnerable (CEV) individuals were included in group 4 and individuals with underlying health conditions in group 6, with individuals vaccinated according to their highest risk group. Group 4 includes people with cancers of the blood or bone marrow who are at any stage of treatment, and people who have had bone marrow or stem cell transplants in the last 6 months or who are still taking immunosuppressive therapy (IST). Group 6 includes bone marrow and stem cell transplant recipients who are not captured in group 4. In March 2021 the JCVI recommended that those aged over 16 who are household contacts of immunosuppressed adults should also be offered vaccination in group 6.[1]

On 01 September 2021, the JCVI recommended 3rd primary doses for certain immunosuppressed groups, including individuals who have received an autologous or allogeneic HSCT within the last 24 months, or had ongoing immunosuppression or graft versus host disease (GvHD) at the time of their 1st or 2nd vaccine dose,[2] regardless of time from transplant. This recommendation was soon followed by guidance offering a booster dose to other groups who had a 2-dose primary course, including those aged over 16 who live with someone who is more likely to get infections.

On 29 November 2021 the JCVI recommended that all highly immunosuppressed individuals should receive a 4th booster dose from 3 months after their 3rd primary vaccine dose. Following the emergence of the Omicron variant, the JCVI also recommended a shorter gap between the 2nd primary dose and the booster, from 6 to 3 months, for all other adults.

Children aged 12 to 17 with immunosuppressive conditions (including HSCT recipients) are now eligible for 3 primary doses of SARS-CoV-2 vaccines in line with recommendations for adults aged 18 and over. Children aged 12 to 15 living with individuals at high risk of infection are also eligible for a 2-dose primary course.

The autumn 2022 booster vaccine campaign involves use of new bivalent omicron-containing mRNA vaccines, used in high-risk populations as a single booster dose.

SARS-CoV-2 Vaccines

Several SARS-CoV-2 vaccines are licensed for use in the UK. All of these vaccines induce immune responses to the spike component of SARS-CoV-2.

On 2 December 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) approved use of the Pfizer/BioNTech SARS-Cov-2 vaccine (BNT162b2) in the UK. BNT162b2 is a first-in-class mRNA vaccine. In a phase 3 study, BNT162b2 was administered to participants aged 16 or over in a 2-dose regimen[3]. The vaccine was 95% efficacious against symptomatic COVID-19 from 7 days after the 2nd dose. Included in this analysis were those patients who had received the 2nd dose within the pre-defined window of 19-42 days following the first. In the interval between the first and second dose, vaccine efficacy was 52%, although the authors acknowledge the study was not designed to assess a single-dose regimen. Most cases were within the first 10 days after vaccination, and efficacy between days 15-21 may be higher[4,5]. Efficacy was consistent across age, gender and ethnicity, and no serious safety concerns were reported. The dataset included 76 patients with leukaemia and lymphoma who responded with similar efficacy (though detailed information about these patients was not included in the safety pack). A real-world study of BNT162b2 in staff of UK NHS hospitals showed vaccine effectiveness of 70% 21 days after the first dose, and 85% 7 days after 2 doses.[6]

The AstraZeneca chimpanzee adenoviral vector ChAdOx1 nCOV-19 vaccine was approved for use by the MHRA on 30 December 2020. Across four studies participants received a 2-dose regimen at a range of 4-26 weeks. In a pooled analysis overall vaccine efficacy was 70.4% with confidence in the estimate up to 12 weeks. From 22 days post dose 1, vaccine efficacy was 73.4% with analysis censored at 12 weeks or from administration of dose 2. A longer interval between first and second dose was associated with increased immunogenicity. Vaccine efficacy in participants aged over 55 was not assessed[7] although similar immunogenicity across a range of ages is reported. Again, no serious safety concerns were reported. In a post-hoc exploratory analysis, efficacy of a single dose against symptomatic COVID-19 was 76% from days 22-90. A longer dosing interval was associated with greater efficacy post-second dose; with a dosing interval of <6 weeks efficacy was 54.9%, and at ≥12 weeks it was 80.7%.[8]

The Moderna mRNA SARS-CoV-2 vaccine (mRNA-1273) was approved for use by the MHRA on 8 January 2021. In a phase 3 study overall vaccine efficacy was 94.1% for prevention of symptomatic COVID-19, with 98% of participants receiving the 2nd dose of vaccine within the predefined period of 25-35 days.[9] In the placebo group there were 30 cases of severe COVID-19 and none in the vaccine group. Vaccine efficacy was consistent across age (18 to <65, and >65 years of age), sex, and ethnic groups. There were no major safety signals.

The Novavax COVID-19 vaccine NVX-CoV2373 (Nuvaxovid®) contains recombinant spike protein combined with Matrix-M™ adjuvant. Two doses given 3 weeks apart as a primary course demonstrated a 89.7% efficacy against symptomatic disease in a Phase 3 studies in adults[10]. Nuvaxovid® was approved in the UK in February 2022.

In August and September 2022, bivalent vaccines produced by Moderna and Pfizer-BioNTech containing both ancestral and omicron-variants (BA.1) spike mRNA constructs were approved by the MHRA. The Moderna vaccine (Spikevax bivalent Original/Omicron) contains 25μg of the ancestral SARS-CoV-2 spike and 25μg of the Omicron BA.1 variant spike mRNA. The Pfizer-BioNTech vaccine (Cominarty bivalent Original/Omicron) contains 15μg of the ancestral SARS-CoV-2 spike and 15μg of the Omicron BA.1 variant spike mRNA. Immunogenicity data show that when used as a second booster dose in participants who have already received a 2-dose primary course followed by a single monovalent booster dose, these vaccines result in greater neutralising antibody responses against SARS-CoV-2 omicron lineage variants, when compared to a monovalent ancestral mRNA vaccine booster.[11]

Vaccination may have a modest impact on transmission. PCR positivity (asymptomatic and symptomatic) was reduced by 67% after a single standard dose of the ChAdOx1 nCOV-19, and by 49.5% after 2 standard doses suggesting the potential for an impact on transmission.[7] Data from Public Health England demonstrates that following vaccination with ChAdOx1 nCOV-19 and BNT162b2, there is a 40-50% reduction in household transmission from individuals who are subsequently infected with COVID-19.[12] However, there may be less impact on transmission of newer variants (such as Delta or Omicron).[13]

Vaccine Induced Thrombosis and Thrombocytopenia (VITT)

A rare syndrome of thrombosis and thrombocytopenia with high levels of d-dimers, low levels of fibrinogen, and with platelet factor 4 (PF4) antibodies detectable by enzyme-linked immunosorbent assay (ELISA) has been described between 5-28 days after administration of the first dose of ChAdOx1 nCOV-19 vaccine.[14-16] This appears to be an idiosyncratic reaction to the first dose of the AstraZeneca vaccine and no risk factors have been identified. The JCVI has recommended that adults under 40 years of age who are not in a clinical priority group should be offered an alternative to the Astra Zeneca vaccine where possible, but that the benefits outweigh the risks in CEV groups under 40 years. Therefore CEV patients including HSCT and CAR-T recipients may be offered vaccination with any of the available products, including the AstraZeneca vaccine, for the first two vaccine doses providing there are no other contraindications. There are no specific recommendations for post-vaccination laboratory monitoring.

SARS-CoV-2 Vaccine Scheduling

The following scheduling is recommended in the UK Green Book for the first two vaccine doses[5]:-

- Pfizer mRNA BNT162b2 Vaccine. 2 doses 3-12 weeks apart in individuals ≥12 years of age
- Moderna mRNA-1273 Vaccine. 2 doses a minimum of 28 days apart in individuals ≥12 years of age

- Novavax NVX-CoV2373 Vaccine. 2 doses at minimum of 21 days apart in individuals ≥12 years of age
- AstraZeneca ChAdOX1-S Vaccine. 2 doses 4-12 weeks apart in individuals ≥18 years of age. This vaccine is no longer being supplied for routine use in the UK.

Due to evidence that immunogenicity and/or vaccine efficacy is higher with both the adenovirus vector and mRNA vaccines given with longer intervals between doses, the JCVI recommends a minimum 8-week interval between the first two doses. Administration of the Astra Zeneca vaccine on a 12-week schedule is in keeping with phase 3 and post-hoc exploratory data.[8,17-19] 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.[18]

Re-vaccination Schedules in 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[20-29]. International groups therefore recommend that HSCT recipients are considered never-vaccinated and offered a full re-vaccination schedule[30-32] 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[31] and some other vaccines from 6 months[34,35]. International guidelines recommend re-vaccination schedules are commenced from 3-6 months post-HSCT time-point[31,32]. Data describing the impact of 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[36,37].

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. There are emerging data on the immunogenicity of SARS-CoV-2 vaccines in HSCT recipients, mostly to the Pfizer mRNA BNT162b2 vaccine. 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,[38-42] which was significantly lower than in healthy control participants when included.[40] Similar antibody titres between autologous and allogeneic HSCT recipients have been noted.[43] Several studies have also observed lower antibody induction in individuals within the first 12 months following HSCT.[39,40,43] Data from vaccinated CAR-T therapy recipients are limited, but there are indications that immunogenicity may be lower than in HSCT recipients.[38,40,41] There are currently no published data comprehensively comparing the immunogenicity of the AstraZeneca ChAdOX1-S Vaccine and mRNA vaccines in HSCT or CAR-T recipients. One published study to date has reported on the immunogenicity of a 3rd primary Pfizer vaccine dose in HSCT recipients, with 42% of prior non-responders achieving an antibody titre above a pre-defined antibody threshold predictive of neutralising activity.[44]

Pragmatic vaccination statements in the absence of a complete evidence base

In the absence of data to guide optimum vaccination strategies in HSCT recipients, pragmatic recommendations are required now. 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 starting position in the absence of clinical evidence in this patient population. These statements are focussed on potentially offering some degree of protection to a very high-risk population in the context of a global pandemic.

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 2-dose schedule prior to conditioning, and 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.[5]
- 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 national guidance should be offered prior to the procedure, adhering to the minimum recommended intervals between doses in the Green Book.[5]

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 May 2021 Green Book guidance[5], and offered re-vaccination with a 3-dose primary course and a 4th booster dose in accordance with the following statements.
- HSCT and CAR-T patients ≥18 years can receive any of the SARS-CoV-2 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 first 2 doses. The 3rd primary dose should be an mRNA vaccine whenever possible, in line with Green Book guidance.[5]
- Children 12 – 17 years old should receive a 3-dose primary course with an mRNA vaccine in keeping with current licensure and Green Book guidance, with a preference for the Pfizer BNT162b2 Vaccine due to a reported lower rate of myocarditis.[5] The Moderna mRNA 1273 vaccine is also approved in children. If mRNA vaccine receipt is not clinically suitable, then a primary course of Novavax NVX-CoV2373 may be used.[5] Further advice will follow on the timing of a 4th (booster) dose for this group.
- Consider vaccination with a SARS-CoV-2 vaccine from 3-6 months post autologous and allogeneic HSCT in individuals aged ≥12 years.
- Consider vaccination with a SARS-CoV-2 vaccine from 3-6 months following CAR-T therapy in individuals aged ≥12 years.

- **Dosing regimen**:
    - Timing of 2nd dose*:* 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.[44,45] Until further data are available to guide scheduling of re-vaccination the BSBMTCT-VSC favours administration of the 2nd dose in HSCT and CAR-T recipients after the minimum licensed interval i.e. a 3 week interval for Pfizer BNT162b2 and Novavax NVX-CoV2373, and 4 week interval for AstraZeneca ChAdOX1-S and Moderna mRNA 1273 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.[5] If an mRNA vaccine is not considered clinically suitable, then a dose of Novavax NVX-CoV2373 may be used.[5]
    - 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 may be used.[5].

- **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.

- Until further data are available, HSCT recipients aged 12 years and older should be given a primary 2-dose vaccination course with ancestral monovalent vaccines as per current practice. A bivalent omicron-containing vaccine should be used as the 3rd dose in order to optimise immune responses to currently circulating omicron-lineage viruses. If bivalent vaccines are not available when the 3rd dose is due, then a monovalent ancestral mRNA vaccine should be used according to current practice and a bivalent omicron-containing vaccine used for the 4th dose. If bivalent omicron-containing vaccines are still not available, then a monovalent ancestral vaccine should be used for the 4th dose. **At any point in the schedule, the priority should be given to receiving an available vaccine rather than a specific type.**
- 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 12 – 17 years should be given the Pfizer-BioNTech mRNA (Cominarty) bivalent vaccine.
- If monovalent vaccines are not available when the next dose is due, a bivalent omicron-containing vaccine should be used as a substitute, keeping in mind that repeated dosing of bivalent omicron-containing vaccines would be used off label, and should be prescribed following discussion with the patient.
  1.

- 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

- Adult household members (aged 16 or over) 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. Children aged 12 – 15 living with HSCT or CAR-T recipients should be offered vaccination with a 2-dose primary course of an mRNA vaccine. Persons aged 5-49 years who are household contacts of HSCT and CAR-T recipients should be offered a booster vaccination with a bivalent omicron-containing mRNA vaccine in Autumn 2022 as per JCVI recommendations. All adults aged over 50 years are included in the Autumn 2022 bivalent vaccine booster campaign.

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)

Knowledge gaps and future research needs

Unanswered questions include:

1) What immune responses (and thresholds) are associated with protection against COVID-19 and are these different in HSCT/CART recipients compared to immunocompetent individuals?
2) What is the earliest time-point post-HSCT that SARS-CoV-2 vaccines are immunogenic?
3) At what time point post-HSCT is the SARS-CoV-2 vaccine maximally immunogenic and is this comparable to the response in immunocompetent individuals?
4) Does the immune response decay at a similar rate to immunocompetent individuals?

5) Which of the emerging SARS-CoV-2 vaccines (or combination of vaccines) are more immunogenic in HSCT recipients? Is there a role for heterologous vaccination in this specific group?
6) What is the optimal schedule (including dosing interval as well as number of doses) of SARS-CoV-2 vaccines in this population?
7) What is the impact on immunogenicity of patient, donor and transplant variables?
8) What is the safety of vaccines post HSCT, including whether immune related complications such as GVHD or autoimmunity may be triggered by vaccination?
9) Are bivalent omicron-containing mRNA vaccines safe and immunogenic in HSCT recipients when used as a multi-dose primary vaccination course?

These aspects need to be considered separately for

- Autologous HSCT
- Allogeneic HSCT, where there is an impact of
    a. GvHD and GvHD prophylaxis and therapy
    b. Types of allogeneic HSCT, with varying degrees of HLA mismatch
    c. Unpredictable recovery of immune function
- CAR-T and other cellular therapies
- Paediatric HSCT recipients
- Other aspects such as use of serotherapy before, during and after HSCT (ATG, alemtuzumab, rituximab, daratumumab and other monoclonals)

In addition, there is a need to consider the administration of SARS-CoV-2 vaccination in:

- Healthy donors

Future studies at national and international level should seek to address these questions urgently. In the future case-by-case assessment of immune response to SARS-Cov-2 vaccines as part of clinical practice may help to inform decisions around administration of booster dosing as vaccine supply allows. However, this is not currently recommended as the correlates of protection for SARS-CoV-2 are not yet fully defined. There is also an urgent need for standardised assays of both humoral and cellular immunity to SARS-CoV-2. These remain research tools at present, until immune correlates of protection are established.

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

Correspondence update October 2022

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BSBMT-CT Vaccination sub-committee
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