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 18 February 2021

National SARS-CoV-2 Vaccination Strategy

The Joint Committee on Vaccination and Immunisation (JCVI) has advised a phased approach to vaccination in the UK. In phase 1 the JCVI has identified 9 priority groups determined by age, exposure risk and comorbidities. Frontline health and social care workers are in priority group 2, clinically extremely vulnerable (CEV) individuals are in group 4, and individuals with underlying health conditions are in group 6. Individuals will be 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. Adults under 50 years of age who do not fall into another risk category will not be vaccinated in phase 1. However, GPs and specialists can make an individual case for any HSCT patient to be covered by the CEV criteria, where they are not explicitly covered in priority group 4.

SARS-CoV-2 Vaccines

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(1). 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(2,3). 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).

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 (4) 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 80.7% at at ≥12 weeks. PCR positivity (asymptomatic and symptomatic) was reduced by 67% after a single standard dose, and by 49.5% after 2 standard doses suggesting the potential for an impact on transmission(5).

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 efficacy was 94.1%, with 98% of participants receiving the 2nd dose of vaccine within the predefined period of 25-35 days(6).

All three of the vaccines above induce immune responses to the spike component of SARS-CoV-2. None of these studies have included immunocompromised participants or HSCT recipients.

SARS-CoV-2 Vaccine Scheduling

In a statement on 30 December 2020 the four UK Chief Medical Officers (CMO) supported the JCVI in prioritising first vaccine doses, with the following scheduling recommendations(7):-

- Pfizer mRNA BNT162b2 Vaccine. 2 doses 3-12 weeks apart in individuals ≥ 16 years of age

- AstraZeneca ChAdOX1-S Vaccine. 2 doses 4-12 weeks apart in individual $\geq$ 18 years of age

A CMO/JCVI scheduling statement for the Moderna nRNA-1273 vaccine has not yet been released. The licensed schedule is 2 doses 28 days apart.

Evidence for Vaccination in HSCT Recipients

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 (8) and some other vaccines from 6 months(9,10). T-cell responses to influenza vaccine have been reported from 3 months post HSCT(11). 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(14,15).

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. At present, the immunogenicity and efficacy of SARS-CoV-2 vaccines in immune-impaired patients including autologous and allogeneic HSCT recipients is unknown. Furthermore, the impact of GvHD and IST on SARS-CoV-2 vaccine immunogenicity is unknown.

Unanswered questions include:-

1) What is the earliest time-point post-HSCT that SARS-CoV-2 vaccines are immunogenic?
2) At what time point post-HSCT is the SARS-CoV-2 vaccine maximally immunogenic and is this comparable to the response in immunocompetent individuals?
3) Does the immune response decay at a similar rate to immunocompetent individuals?
4) Which of the emerging SARS-CoV-2 vaccine technologies (or combination of technologies) are more immunogenic in HSCT recipients?
5) What is the optimal schedule (including dosing interval as well as number of doses) of SARS-CoV-2 vaccines in this population?
6) What is the impact on immunogenicity of patient, donor and transplant variables.
7) What is the safety of vaccines post HSCT, including whether immune related complications such as GVHD or autoimmunity may be triggered by vaccination

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 application of SARS-CoV-2vaccination 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.

Pragmatic Vaccination Statements in Absence of Evidence Base

In the absence of data to guide optimum vaccination strategies in HSCT recipients, pragmatic recommendations are required now. Clearly, 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 immunogenicity and efficacy of SARS-Cov-2 vaccines in HSCT and CAR-T recipients is unknown, and research studies to guide vaccination strategies in these vulnerable patients should be prioritised.
- HSCT and CAR-T patients can receive any of the SARS-CoV-2 vaccines currently licensed in the UK and should accept the first vaccine they are offered.
- All HSCT and CAR-T recipients should be considered clinically extremely vulnerable (CEV) regardless of time from treatment, indication (malignant or non-malignant) and age. Where necessary GPs and specialists should make an individual case for patients to be considered CEV and offer vaccination to those aged ≥16 years within priority group 4.
- Consider vaccination with a SARS-CoV-2 vaccine from 2-6 months post autologous and allogeneic HSCT in individuals aged ≥16.
- Consider vaccination with a SARS-CoV-2 vaccine from 3-6 months following CAR-T therapy in individuals aged ≥16.
- For allogeneic HSCT recipients who are receiving immunosuppressive therapy (IST) take into account 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. Take into account intensity and expected duration of cGvHD 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.
- HSCT and CAR-T patients should be advised to continue shielding in accordance with national guidelines even after receiving one or two vaccine doses as immunogenicity and efficacy in these patients is at present unknown.
- Available vaccines are not licensed for use in the under 16 age group. Off-license use may be considered on a case-by-case basis using clinician judgement for clinically extremely vulnerable children aged over 12 in accordance with JCVI Green Book Guidance(3). The BSBMTCT-VSC considers this group to include paediatric allogeneic and autologous HSCT and CAR-T recipients with additional comorbidities (eg. neurological, respiratory and cardiac).

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

Timing of Second Vaccine Dose

The BSBMTCT-VSC acknowledges the public-health need for prioritisation of first vaccine doses with a delay of second doses for up to 12 weeks. While HSCT and CAR-T recipients (and other CEV groups) will benefit indirectly from population-level herd immunity, it is essential that individual protection in high-risk immunocompromised patients is also prioritised. The delay of the second dose is in keeping with phase 3 and post-hoc exploratory data

for the AstraZeneca vaccine. Available efficacy data for the Pfizer vaccine is based on the administration of a second dose within a limited window of 19-42 days, and it is unknown whether administration of this vaccine on a 12 week schedule is as immunogenic and efficacious in immunocompromised individuals. On this basis, at present the BSBMTCT-VSC would favour administration of the Pfizer vaccine in HSCT and CAR-T recipients on a 21 day schedule, but recognises that this public-health decision has been taken at a national level based in-part on data not in the public sphere. The BSBMTCT-VSC feels there is an urgent need for existing data to be made available, and for prospective studies to evaluate the 12 week schedule in immunocompromised groups.

Vaccination of Household Members

Based on JCVI prioritisation summarised above and a statement from 30 December 2020(16), there is currently no recommendation to vaccinate household members in order to provide indirect protection to high-risk individuals. Emerging post-hoc exploratory data indicates that PCR positivity (asymptomatic and symptomatic) is reduced by one or two doses of the AstraZeneca vaccine. In light of these emerging data, and in keeping with existing guidance for influenza vaccination, the BSBMTCT-VSC favours vaccinating household members age ≥16 (according to vaccine licensing) in order to offer high-risk adult and paediatric recipients of HSCT and CAR-T therapy a valuable layer of protection from COVID-19.

Where household members fall into a priority group themselves they should be encouraged to receive the vaccine. If household members are vaccinated social distancing measures inside and outside the household should still be maintained in accordance with government guidance.

Meeting date 5 February 2021

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Apologies received for meeting:

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Professor Gordon Cook
Professor Charlie Craddock
Dr Robert Danby
Dr Thushan de Silva
Professor Paul Heath
Dr Soonie Patel
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