Routine Vaccination Practice after Adult and Paediatric Allogeneic Haematopoietic Stem Cell Transplant: A Survey of UK NHS Programmes

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No conflicts of interest to declare

Despite advances in supportive care, infection remains a significant cause of morbidity and mortality post haematopoietic stem cell transplant (HSCT). Impaired humoral immunity, marked by a decline in antibody titres to vaccine preventable diseases (VPD), is observed within months and may continue for years post-HSCT(1). HSCT recipients are at increased risk of morbidity and mortality from influenza virus infection and invasive pneumococcal disease(2,3), two relatively common VPDs. The impact of declining antibody titres post-HSCT on susceptibility to other VPDs is unclear, but cases of *Haemophilus influenzae*, pertussis, and measles are documented(4–6). It is therefore considered best practice to try and offer HSCT recipients the same level of protection against all VPDs as the general population, and immunogenicity studies have demonstrated that post-HSCT antibody titres can be boosted by vaccination(7–9). FACT-JACIE International Standards for Haematopoietic Cellular Therapy require, therefore, that schedules are in place(10). To define this schedule of post-HSCT vaccination, UK HSCT programmes can refer to guidelines from several major societies, along with consensus conference proceedings and recommendations from national paediatric groups(11–14). In the absence of supportive data, guidelines recommend standard vaccination schedules unmodified by disease indication, stem cell source or conditioning regimen, however the specifics of the schedules vary across these guidelines.

We surveyed the adult and paediatric allogeneic HSCT programmes of the UK National Health Service (NHS) with the aim of assessing homogeneity of practice and determining how clinical care aligns with current evidence, recommendations and guidelines. We defined a Routine Vaccination Programme (RVP) as a 'series of scheduled vaccinations administered after allogeneic HSCT as standard post-transplant care' and developed a 25 question web-based survey, with questions grouped into four themes: RVP service organization, RVP vaccine selection, RVP commencement and delay, and

monitoring of response to vaccines. Response options were mapped to current recommendations and guidelines, and asked specifically about current RVP practice. Respondents were advised to refer to local guidelines or standard operating procedures (SOP) when completing the survey. The survey was developed in conjunction with an infectious disease physician, senior adult and paediatric alloHSCT physicians, and alloHSCT nurse specialists all with an interest and expertise in vaccination. The survey was piloted with 5 HSCT specialists and optimized accordingly. An invitation to participate was e-mailed by the British Society of Blood and Marrow Transplantation (BSBMT) to all 27 adult and 12 paediatric UK alloHSCT programme directors. Directors were invited to complete the survey or delegate to the healthcare professional taking primary responsibility for RVP. The survey was open between May and December 2015.

100% of adult and 83% of paediatric HSCT programmes responded to the survey. The age range of patients treated by paediatric programmes is 0-20 years. The majority of surveys were completed by HSCT programme directors (54%) or consultant grade HSCT physicians (30%), with the remainder completed by HSCT nurse specialists (8%), pharmacists (5%) or non-consultant grade physicians (3%). 95% of responding programmes were JACIE accredited having completed at least 1 cycle, with 5% working towards JACIE accreditation.

All responding adult and paediatric programmes recommend a RVP for HSCT recipients. However, only a minority of adult (8%) and paediatric (10%) programmes offer vaccination on site; the remainder refer HSCT recipients to primary care for vaccine administration. Nearly two-thirds (65%) of programmes do not maintain a record of vaccine administration in patients' case notes. RVP practice has been audited by 54% of HSCT programmes that maintain vaccination records compared to only 29% that do not. The survey did not enquire about the scope of audits undertaken. Most adult (97%) and

paediatric (80%) programmes maintain a document controlled SOP detailing RVP schedules. Adult programmes mostly base RVP SOPs and/or RVP practice on international HSCT specific vaccination guidelines(11,12) (70%). In contrast, paediatric programmes tend to use national HSCT specific guidelines(14) (60%), with a minority (10%) using international guidelines. HSCT programmes were not asked to submit SOPs for analysis.

Almost all adult and paediatric programmes recommend an inactivated vaccine targeting the VPDs covered by the UK NHS vaccination schedule: diphtheria-tetanus-pertussis, *Haemophilus influenzae* B, pneumococcal, seasonal influenza virus, meningococcal and polio virus vaccines (Table 1). The exception to this is the Human Papilloma Virus (HPV) vaccine, which is recommended for female HSCT recipients by all paediatric programmes but only 15% of adult programmes. Where a number of vaccine formulations are available, programmes vary in their selection with some recommending vaccines known to be poorly immunogenic in this patient group, for example the 23-valent pneumococcal polysaccharide vaccine. In a minority of cases vaccine selection is left to the discretion of the administering primary care practitioner. In the UK, high risk individuals are immunized against Hepatitis B; a minority of adult (33%) and paediatric (20%) programmes recommend this vaccine as routine. Adult programmes appear cautious around administration of live attenuated vaccines, with only half recommending Measles-Mumps-Rubella (MMR) vaccines to measles seronegative patients. In contrast, all paediatric programmes recommend this vaccine. A minority (20%) of paediatric programmes, and no adult programmes recommend a live attenuated varicella vaccine to seronegative recipients.

Programmes commence RVP at a range of time points from 3 to 18 months post HSCT (Table 2). 20% of paediatric programmes distinguish between recipients of related and

unrelated donors, commencing RVP in the former at 12, and the later at 18 months. Most adult programmes (74%) do not use a marker of immune reconstitution to guide initiation of RVP, while 70% of paediatric programmes use lymphocyte subsets alone (40%) or with immunoglobulin levels (30%).

The approach to vaccination of HSCT recipients with chronic graft versus host disease (cGVHD) or on immunosuppressive therapy (IST) varies across programmes. Programmes were asked to indicate the lowest or 'threshold' cGVHD grade by NIH criteria, and lowest or 'threshold' combination of IST, that necessitates deferral of inactivated and live attenuated vaccines. While the majority of paediatric (80%) and adult (74%) programmes defer inactivated vaccines if recipients have active cGVHD, the threshold grade prompting deferral varies (Table 2). The remaining 20% of paediatric and 26% of adult programmes administer inactive vaccines to HSCT recipients with active cGVHD regardless of grade. All paediatric and the majority (78%) of adult programmes defer inactivated vaccines if recipients are on IST. Again, there is no consensus on the lowest IST combination that necessitates deferral (Table 2). Concerning live attenuated vaccines, 19% of adult and 60% of paediatric programmes give moderate or severe cGVHD as the threshold grade for deferral, but would administer to recipients with mild cGVHD. A single adult programme reports dual agent IST as the threshold combination for deferral of live attenuated vaccines, otherwise all programmes defer if recipients are taking any single agent IST including corticosteroids.

Half of paediatric programmes, and 44% of adult programmes routinely monitor serological response to vaccinations. 30% of adult programmes monitor serological response to vaccine if clinically indicated. Indications given are as follows: illness from a VPD (100%), Ongoing IST (75%), active GVHD (38%). All of the 30% of paediatric

programmes that monitor response if clinically indicated, give illness from VPD as the sole indication.

With a 95% response rate, this survey provides a current and comprehensive picture of RVP practice across adult and paediatric UK NHS allogeneic HSCT programmes. A weakness of the survey format is that it relies on self-reporting, rather than independent verification of practice. Reassuringly, routine post-HSCT vaccination has been adopted by all responding adult and paediatric programmes, representing 100% and 83% of all UK allogeneic programmes respectively. However, we identified variation across all survey themes. This heterogeneity may be attributed to an evidence base insufficient to provide detailed practical guidance, conflicting recommendations between guidelines, tension between international recommendations and national vaccine licensing restrictions, and in some cases a lack of familiarity with current guidelines.

Our findings highlight the need for review of local post-HSCT vaccination schedules alongside the current evidence base. Areas that are particularly pressing include vaccine selection, and vaccination of HSCT recipients with cGVHD or on IST. In the UK (and elsewhere), this may be best delivered at national level as a harmonized guideline and/or policy that synthesizes best practice recommendations and national licensing considerations, thereby providing HSCT programmes and primary care teams who administer vaccines a single reference source. In the UK national vaccination programmes are commissioned for delivery by primary care and most HSCT programmes refer recipients for vaccine administration. A recent single centre audit reported that completion rate of vaccination schedules is low(15). Given that many HSCT programmes are not maintaining records of vaccine administration, communication with primary care, monitoring and audit should form a central

component of national guidelines, and may be facilitated by the inclusion of a vaccination checklist.

In summary, this national survey has highlighted highly variable delivery of RVP across a national healthcare system, with limited quality assurance as to whether accepted practice recommendations are met. Although there remains a clear need for robust data to better inform re-vaccination practice following HSCT, harmonized health service policies are warranted to ensure coordinated delivery of this important aspect of post-transplant care by HSCT teams, patient referral centres and primary care.

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Table 1. Vaccines and specific formulations (where applicable) routinely recommended post-HSCT in 10 paediatric and 27 adult UK allogeneic HSCT programmes

Vaccine or formulation	**Paediatric n (%)**	**Adult n (%)**
Pneumococcal	10 (100)	27 (100)
23 valent polysaccharide	2 (20)	5 (18)
13 valent conjugate	7 (70)	21 (78)
no specific recommendation	1 (10)	1 (4)
Tetanus-diphtheria-pertussis	10 (100)	27 (100)
Full dose (DTaP)	4 (40)	17 (63)
Reduced dose (Tdap)	1 (10)	7 (26)
Full (DTaP) or reduced (Tdap) dose depending on age	3 (30)	0 (0)
No specific recommendation	2 (20)	3 (11)
Meningococcal	10 (100)	26 (96)
Men C conjugate	4 (40)	16 (62)
Men ACWY conjugate	2 (20)	6 (23)
Men B conjugate	0 (0)	0 (0)
Men C or ACWY depending on age	2 (20)	0 (0)
No specific recommendation	2 (20)	4 (15)
Haemophilus influenzae B	10 (100)	27 (100)
Inactivated poliovirus	10 (100)	26 (96)
Inactivated influenza	10 (100)	26 (96)
Measles-Mumps-Rubella (if measles seronegative)	10 (100)	14 (52)
Human papillomavirus – female recipients	10 (100)	4 (15)
Human papillomavirus – male recipients	4 (40)	1 (4)
Varicella (if seronegative)	2 (20)	0 (0)
Hepatitis B	2 (20)	9 (33)

Table 2. Timing of commencement and reasons for delaying routine vaccination in 10 paediatric and 27 adult UK allogeneic HSCT programmes

	Paediatric n (%)		Adult n (%)	
Timing of Commencement	**Sibling or Syngeneic donor**	**Unrelated Donor**	**Sibling or Syngeneic donor**	**Unrelated Donor**
3 months	0 (0)	0 (0)	4 (15)	4 (15)
6 months	1 (10)	1 (10)	8 (30)	8 (30)
9 months	1 (10)	1 (10)	1 (4)	1 (4)
12 months	8 (80)	6 (60)	13 (48)	13 (48)
18 months	0 (0)	2 (20)	1 (4)	1 (4)
Reasons for delaying RVP	**Live attenuated vaccines**	**Inactivated Vaccines**	**Live attenuated vaccines**	**Inactivated Vaccines**
cGVHD**				
Would not delay for cGVHD	0 (0)	2 (20)	1 (4)*	7 (26)
Mild	4 (40)	2 (20)	20 (77)*	8 (30)
Moderate-Severe	6 (60)	6 (60)	5 (19)*	12 (44)
IST **				
Would not delay for IST	0 (0)	0 (0)	0 (0)*	6 (22)
Single agent IST including corticosteroid	10 (100)	9 (90)	25 (96)*	15 (56)
Dual agent IST	0 (0)	1 (10)	1 (4)*	6 (22)
Triple agent IST	0 (0)	0 (0)	0 (0)*	0 (0)
Acute illness	9 (90)	8 (80)	20 (75)	22 (81)
CD4 Count < 200 cells/ul	9 (90)	9 (90)	9 (33)	4 (15)
CD20 Antibody in last 6 months	8 (80)	6 (60)	9 (33)	2 (7)
IVIg in last 6 months	4 (40)	2 (20)	2 (7)	1 (4)

* Data available from n = 26 programmes

** Lowest cGVHD grade or IST combination necessitating deferral indicated