

Immunization of hematopoietic stem cell transplant recipients against vaccine-preventable diseases

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Worldwide, over 40,000 hematopoietic cell transplants (HCT) are carried out each year, with the majority of patients surviving long term. Owing to their new immune systems, these patients are susceptible to a variety of preventable infectious diseases. The 2009 influenza pandemic, the increase in pertussis and antibiotic-resistant pneumococcus, as well as recent outbreaks of measles and mumps in immunocompetent individuals further highlight the need for effective revaccination of HCT recipients. Post-transplant vaccine guidelines, including those published in 2009, recommend immunization of all patient groups at fixed times post-HCT. Although early vaccination to protect against vaccine-preventable diseases is desirable, there are still limited data on whether this approach is efficacious in patient groups whose immune recovery differs from recipients of an unmodified HLA-matched sibling transplant. In the absence of such data, prospective trials are needed to better define the optimal timing for immunizing recipients of alternative donors. Ideally, such trials should be designed to identify biological markers that will predict an optimal and durable vaccine response.

KEYWORDS: hematopoietic cell transplantation • HLA-matched sibling • immune reconstitution • immunization • T-cell depletion • unrelated donor

Over the past 15 years, the number of hematopoietic cell transplant (HCT) survivors returning to family life, school, the workplace and overseas travel has steadily increased [1,201]. Infections caused by pneumococcus [2], influenza [3], herpes zoster virus [4,5] and *Bordetella pertussis* [6,7] cause significant morbidity and, to a lesser extent, mortality even in immunocompetent individuals [2,8]. Many of these infections occur more frequently in HCT recipients and remain a significant cause of morbidity, re-hospitalization and mortality after successful HCT [9–20]. Invasive pneumococcal infections occur in 590 out of 100,000 and 199 out of 100,000 allogeneic and autologous HCT recipients per year, respectively, compared with 11.5 out of 100,000 age-matched controls [12]. Shingles, disseminated zoster, encephalitis, pneumonitis and postherpetic neuralgia occur more frequently in long-term survivors of autologous and allogeneic HCT than in age-matched controls [13–16]. The annual incidence of herpes zoster in healthy individuals ranges from 1.2 to 3.4 cases per 1000

persons [4]. In allogeneic transplant recipients, shingles occurs in 20–59% of patients within the first 5 years following HCT with an incidence of postherpetic neuralgia and peripheral neuropathy as high as 68% [13–16].

Following autologous and allogeneic transplantation, patients lack immunity against pertussis (reviewed in [21,22]) and rapidly lose protection against pneumococcus and *Haemophilus influenza* (reviewed in [23,24]). Approximately 50% of patients with positive tetanus and polio titers at the time of allogeneic transplant will become seronegative at 1 year and most will be unprotected against both by 2 years [25]. In the absence of revaccination, the majority of patients will become susceptible to measles, mumps and rubella by 3–5 years post-HCT [23,24]. An exception is seen in patients who previously had measles who may retain protective titers against measles for an extended period of time following HCT [26]. Following an autologous HCT, the time to lose immunity to infections against which a recipient was previously vaccinated

varies by diagnosis, patient age, receipt of anti-CD20 monoclonal antibodies (rituximab), and degree of immunity present prior to stem cell harvest (reviewed in [24,27–29]). Whereas Horwitz *et al.* showed that only 55% of patients who received rituximab for B-cell lymphoma had positive tetanus titers by 12–15 months post-HCT [27], Nordøy *et al.* found durable tetanus immunity in all patients evaluated 4–10 years postautologous HCT who were not exposed to rituximab [28]. Of 110 adult survivors of an autologous peripheral blood stem cell transplant performed primarily for Hodgkin's lymphoma (n = 59) or non-Hodgkin's lymphoma (n = 58), Small *et al.* found that at a median of 25.2 months post-HCT, 90, 58, 40, 23 and 16% of patients lacked protective titers against pneumococcus, *H. influenzae*, measles, tetanus and polio, respectively [30].

National & international guidelines for immunization post-HCT

In an effort to protect HCT recipients against vaccine-preventable diseases in a standardized fashion, the European Group for Blood and Marrow Transplantation (EBMT) in 1995 [31] and 2005 [32] and the CDC in 2000 [33], published post-HCT immunization guidelines. These recommendations differed in the number of recommended doses of tetanus, polio and *H. influenza* vaccines (two vs three), PPV23 (one vs two), as well as the time to initiate revaccination (6–12 months vs 12 months) (TABLE 1) [31–33]. In view of these differences, in 2009, an international committee of infectious disease and transplant physicians met under the auspices of the Center for International Blood and Marrow Transplant Research (CIBMTR) to develop an updated, unified international set of vaccine guidelines for autologous and allogeneic transplant recipients. These guidelines were approved by the National Marrow Donor Program; the European Blood and Marrow Transplant Group; the American Society of Blood and Marrow Transplantation; the Canadian Blood and Marrow Transplant Group; the Infectious Disease Society of America; the Society for Healthcare Epidemiology of America; the Association of Medical Microbiology and Infectious Diseases Canada; and the CDC [23]. They differ from prior guidelines primarily by:

- Inclusion of the seven-valent protein conjugated pneumococcal vaccine (PCV-7) (three monthly doses) in all patients starting at 3–6 months post-HCT, followed by the 23-valent pneumococcal polysaccharide vaccine (PPV23) in patients without chronic graft-versus-host disease (GVHD) and consideration of a fourth PCV-7 in patients with chronic GVHD;
- Use of the live varicella vaccine in select patient groups starting at 24 months post-HCT;
- Optional use of vaccines licensed since 2005 such as the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine for adolescents and adults (reviewed in [7]), the recombinant human papilloma vaccine [34] and the protein-conjugated meningococcal vaccine [35].

The guidelines were recently revised owing to the 2010 approval of the 13-valent protein-conjugated pneumococcal vaccine (PCV-13) for healthy children and discontinued production of PCV-7 in the USA and Europe [36,37]. The newer vaccine contains the same antigens present in PCV-7 as well as antigens derived from pneumococcal serotypes 1, 3, 5, 6A, 7F and 19A, in an effort to provide broader coverage. Although PCV-13 has not been tested in immunocompromised hosts, an international trial in allogeneic transplant recipients over the age of 2 years is currently underway.

The 2009 CIBMTR guidelines [23], similar to the CDC and EBMT guidelines [31–33], advocate initiation of vaccination of all patients at the same time post-HCT, irrespective of their level of immune competence. It is not clear, however, whether this strategy will protect patients with delayed immune reconstitution on the basis of donor source (e.g., cord blood), graft processing such as T-cell depletion, reduced intensity conditioning, advanced patient age, presence of GVHD and/or receipt of immunomodulatory agents such as the B-cell monoclonal antibody rituximab [38–43]. These are critical variables that must be tested.

Immunogenicity of vaccines post-HCT

Studies have demonstrated the superior response of patients reimmunized with three doses of tetanus toxoid, inactivated poliovirus vaccine (IPV) and/or the protein-conjugated *H. influenza* (Hib) vaccine compared with those given a single vaccine [25,44–49] as well as the benefit of donor immunization prior to stem cell harvest in the case of Hib vaccine, diphtheria and tetanus toxoid [47–49]. Comparison of studies testing the same vaccine, however, often show different response rates even among recipients of a HLA-matched sibling HCT. This is likely due in part to the age of the recipient/donor pairs studied, the percentage of vaccinated patients with GVHD, and criteria and assays used to measure vaccine response. For example, following vaccination with a single IPV (n = 19), Ljungman *et al.* reported that 42,

Table 1. Summary of post-transplant vaccine guidelines.

Vaccine	CDC (2000)	EBMT (1995, 2005)	CIBMTR (2009)
Td, IPV, Hib	Two doses 12, 14 months	Three doses 6–12 months	Three doses 6–12 months
Pneumococcal	23-valent 12, 24 months	23-valent 12 months	7-valent 3–6 months
HepB	Optional	Recommended	Country policy
MMR	24 months	24 months	24 months
Live-attenuated varicella vaccine	No	No	Selected patients

CIBMTR: Center for International Blood and Marrow Transplant Research; EBMT: European Blood and Marrow Transplant Group; HepB: Hepatitis B; Hib: *Haemophilus influenzae* type b; IPV: Inactivated poliovirus vaccine; MMR: Measles, mumps and rubella; Td: Tetanus and diphtheria.
Data from [31–33].

36 and 21% mounted a $\geq$ fourfold response to serotypes 1, 2 and 3, respectively, compared with 52, 48 and 48% of patients ($n = 36$) immunized with three IPV at 12, 13 and 13 months post-HCT [44]. By contrast, Parkkali *et al.* demonstrated that $>95\%$ of patients vaccinated with IPV at 3, 6 and 12 months post-allogeneic HCT developed a $\geq$ fourfold response to all three polio serotypes with or without donor vaccination prior to bone marrow harvest [47]. In a study of 219 patients vaccinated with three IPV following acquisition of minimal milestones of immune competence ($CD4 >200/\mu\text{l}$; phytohemagglutinin [PHA] within 75% of the lower limit of normal; $\text{IgG} >500 \text{ mg/dl}$), 96% of patients developed a $>$ fourfold response to all three polio serotypes, including recipients of an unrelated and/or T-cell-depleted HCT [50]. Patel *et al.* assessed 38 pediatric patients immunized according to the Royal College of Paediatrics and Child Health guidelines for transplant recipients [51]. Unlike most guidelines, these varied the time to initiate vaccination based on donor type owing to concerns of delayed immune reconstitution following unrelated HCT. Following an autologous ($n = 10$), HLA-matched sibling ($n = 8$) or unrelated ($n = 20$) HCT, patients received three monthly doses of diphtheria, tetanus and pertussis, IPV and Hib vaccine. Unrelated HCT recipients were immunized starting at 18 months; the other groups at 12 months post-HCT. Using this schedule, 92% of children responded to polio. A fourfold rise in tetanus and *H. influenzae* titers was observed in 94 and 86% of children, respectively. Unfortunately, this study did not include correlative *in vitro* immune studies to compare immune competence among the three HCT groups.

Pure polysaccharide vaccines

Hematopoietic cell transplant recipients respond poorly to vaccines containing pure polysaccharide antigens such as the nonconjugated *H. influenzae* vaccine and PPV23, suggesting a deficiency of critical B lymphocytes or antigen-presenting cells capable of responding to T-cell-independent B-cell antigens [52–56]. Barra and colleagues demonstrated that 25% of adult allogeneic transplant recipients given the nonconjugated *H. influenzae* vaccine developed a specific IgG response [53]. Following a single dose of PPV23, Avanzini *et al.* demonstrated that $<30\%$ of children vaccinated 6–12 months post-HCT and only 50% of those vaccinated between 12 and 24 months responded [55]. By contrast, 100% of children vaccinated >2 years after an autologous or allogeneic bone marrow transplant (BMT) responded [55]. In multivariate analysis, response was only predicted by time between transplant and immunization. Spoulou *et al.* demonstrated that in 21 out of 38 children immunized with PPV23 <18 months post-HCT, the vaccine was not sufficiently immunogenic, with titers returning to baseline levels by 9 months postimmunization. By contrast, Hib vaccine responses were durable in 27 out of 38 children [56]. Limited response to pure polysaccharide vaccines post-HCT may be due to the predominance of immature B cells expressing CD1c, CD5, CD38 and CD23⁺, similar to circulating B cells found in healthy infants and young children [38], populations who also respond poorly to polysaccharide antigens. Limited response may also reflect deficits in CD27⁺ memory B cells capable of isotype switching, a subset that can take years to recover post-HCT, even in young children [57–59].

Protein-conjugated polysaccharide vaccines

Following HCT, response to protein-conjugated vaccines is significantly better than response to nonconjugated vaccines. Response to a series of three Hib vaccines ranges from 47 to 92%, with higher response rates observed in patients whose donors were immunized prior to stem cell collection [47–49,56] and patients vaccinated following acquisition of pre-set immune milestones [60]. Several studies have shown a response of 60–74% following a series of PCV-7 including that of Molrine *et al.* in 43 recipients of HLA-matched sibling BMT [61], Antin *et al.* in 61 recipients of an autologous HCT [62], and Meisel *et al.* in 43 patients <16 years of age demonstrated responses of 60–74% [63]. In 2009, the results of a randomized, prospective multicenter trial performed in 158 patients (5–65 years of age) transplanted at 13 European centers was reported by Cordonnier *et al.* [64]. This study tested noninferiority of vaccine response ($>0.15 \mu\text{g/ml}$) to all seven serotypes contained in PCV-7 1 month after receipt of three monthly doses of PCV-7 starting at 3 or 9 months post-HCT. All patients received an allogeneic HCT and myeloablative conditioning. Approximately 65% of patients in both groups had no acute GVHD and limited or no chronic GVHD was seen in 56 and 33% of patients, respectively. Although the study demonstrated similar responses in both groups when tested 1 month after the third PCV-7 dose (79 vs 82%; $p = 0.64$), the percentage of patients who still had positive titers to all seven serotypes at 24 months post-HCT was significantly lower in patients vaccinated early versus later post-HCT (59 vs 83%; $p = 0.013$). Other factors associated with poor response were presence of chronic GVHD and older donor age. Patients in this study also received PPV23 at 8 months following their last PCV-7 immunization, at 12 and 18 months in the early and late groups, respectively. Response to pneumococcal serotypes 1 and 5 specific to PPV23 was similar in both groups 1 month following immunization (80 vs 87%) when $>0.15 \mu\text{g/ml}$ was used as the threshold for response, compared with 42 versus 60% when $>0.5 \mu\text{g/ml}$ was used ($p = 0.08$) [65]. Pao *et al.* retrospectively analyzed the response of 127 allogeneic HCT recipients with a median age of 23 years [60]. Three PCV-7 were administered in the majority of patients when minimal milestones of immune reconstitution were achieved, defined as $CD4 >200/\mu\text{l}$, $\text{IgG} >500 \text{ mg/dl}$ and PHA within 60% of the lower limit of normal. Median time to vaccination was 13.2 months. In total, 62% of patients responded to PCV-7 (45 out of 51 children; 34 out of 76 adults; $p < 0.001$). Of the 127 patients concomitantly vaccinated with Hib, the overall response was 86% in 115 patients with pre- and post-titers, including 77% of PCV-7 nonresponders. Although PCV-7 response was adversely affected by older age ($p < 0.001$), 11 out of 19 individuals ≥ 50 years old responded significantly better if vaccinated following acquisition of the specific minimal milestones of immune competence (11 out of 19 vs 0 out of 8 who did not achieve these milestones; $p < 0.006$). A similar trend was observed in patients with limited chronic GVHD. In all patients, higher levels of circulating $CD4^+CD45\text{RA}^+$ cells correlated with improved PCV-7 response. Meerveld-Eggink *et al.* published one of the few studies on vaccine response in patients following reduced intensity

conditioning [66]. PCV-7 response was measured in 26 patients (median age: 56.5 years; range: 44–67 years) conditioned with fludarabine (25 mg/m²/day × 5 days) and cyclophosphamide (500 mg/m²/day × 5 days), 200 cGy of single-dose total body irradiation, or fludarabine (30 mg/m²/dose × 3) and 200 cGy of total body irradiation. Patients were immunized if they were a minimum of 12 months post-HCT and no longer required immunosuppressive therapy (IST). Owing to ongoing GVHD, only 35% met vaccination criteria at 12 months. The median time to first vaccination was 15 months (range: 12–36 months). Following the second PCV-7 administered 6 weeks after the first, 73% of patients responded to all seven serotypes, except serotype 6B when 0.35 µg/ml was the threshold for response, and 62% when the threshold was 1.0 µg/ml.

Recombinant hepatitis B vaccine

Vaccination against hepatitis B is often mandatory for entry to school and required for certain jobs (reviewed in [67]). Machado *et al.* reported a 100% seroconversion rate in five autologous and 45 HLA-matched related HCT recipients immunized ≥1 year after transplant [68,69]. Despite this excellent initial response, 60% of patients failed to sustain titers for more than 1 year after vaccination [69]. In a study of 267 allogeneic transplant recipients immunized with recombinant hepatitis B vaccine following acquisition of pre-set milestones of immune competence, 64% seroconverted [50], including 73% of 99 children, and 59% of 168 adults ($p = 0.02$). In multivariate analyses, response was adversely affected by age >18 years ($p < 0.01$) and history of prior chronic GVHD ($p < 0.0001$) but not by donor type, use of T-cell depletion, adoptive immunotherapy or post-transplant rituximab [50]. Evaluation of serial titers in 98 patients demonstrated that 80 remained seropositive 5 years after their last vaccine. The greater proportion of patients with sustained immunity in this study, compared with that of Machado *et al.* (40%), suggests qualitative and/or quantitative differences in the circulating memory T and/or B cells present at the time of vaccination. This is likely true for other vaccines. As the time to develop normal numbers of CD27⁺IgD⁺ memory B cells and CD4 helper cells varies among different allogeneic HCT populations [58–60], surrogate markers such as these may be instrumental in determining the need and timing of booster immunizations to maintain durable protection.

Measles, mumps & rubella vaccine, live-attenuated varicella vaccine & influenza vaccine

Although outbreaks of measles and mumps have occurred within the last 5 years in multiple parts of the world [70,71] and receipt of two doses of measles, mumps and rubella (MMR) vaccine is required for healthy children to return to school [72], there are limited data on the immunogenicity and durability of response to MMR following alternative donor HCT or response to mumps following any type of HCT. Following MMR vaccination, Pauksen *et al.* found that 20 of 23 allogeneic and five of 12 autologous HCT recipients susceptible to measles responded ($p < 0.05$) [73]. Ljungman *et al.* studied the measles response in 20

seronegative recipients of an HLA-matched sibling BMT immunized with MMR, all of whom had no evidence of GVHD and were off IST [74]. Response to measles, mumps and rubella was observed in 77, 64 and 75% of patients, respectively. In total, 68% of 22 children given MMR vaccine at a median of 48 months post-HCT responded to all three attenuated viruses [75]. During a large outbreak of measles in Brazil [76], Machado *et al.* [68] evaluated the responses of 51 patients (41 allogeneic, ten autologous) vaccinated early with MMR 9–18 months following a HLA-matched sibling HCT [77]. Approximately half of the patients were on IST, the majority due to extensive chronic GVHD. No patient had a serious adverse event. Seven out of nine patients with negative titers (<100 IU/ml) seroconverted and the majority of patients with pre-existing titers mounted a threefold response. Of 113 children immunized with MMR at Memorial Sloan-Kettering Cancer Center (NY, USA) following a HLA-matched sibling ($n = 60$) or unrelated ($n = 38$) HCT, the response was 70% following a single MMR vaccine, including 42 recipients of a HLA-matched related HCT and 27 recipients of an unrelated HCT ($p = \text{nonsignificant}$). There were no significant adverse reactions, even in nonresponders [78].

Although prolonged administration of low-dose acyclovir can decrease the risk of shingles, cessation of drug at any point post-transplant is associated with rebound disease in approximately 25–50% of patients [79,80]. High-dose acyclovir (800 mg orally twice daily) or Valtrex (1 g orally twice daily) given for 1 year post-transplant can reduce this rebound effect but is expensive and not without side effects [81]. Although a live-attenuated varicella zoster vaccine, Zostavax[®] [5], was approved in 2005 for prevention of herpes zoster in healthy, immunocompetent individuals ≥60 years, this vaccine has not been tested in an immunocompromised population and should not be confused with the live-attenuated varicella vaccine indicated to prevent primary varicella in varicella zoster seronegative individuals. A report of a 76-year-old woman receiving chemotherapy for recurrent breast cancer who developed disseminated varicella following administration of the live-attenuated varicella zoster vaccine emphasizes the risk of this vaccine in patients whose immune system may be ill-equipped to respond [82]. Until studied in the context of a trial, Zostavax is contraindicated in the 2009 CIBMTR vaccine guidelines [23].

Since licensing of the live-attenuated varicella vaccine (LAVV) in 1995, an increasing number of children, adolescents and young adults undergoing HCT or donating stem cells have been protected against varicella by one or two doses of the LAVV. It is known that the LAVV generally induces lower levels of antibody titers than natural infection, and that titers decrease with time postvaccination (reviewed in [83,84]). For these reasons, two LAVV are recommended for varicella zoster seronegative individuals [85]. The effect of pre-HCT vaccination on the post-transplant risk of primary varicella is currently unknown. Although the safety and benefit of a heat-inactivated varicella vaccine in reducing varicella zoster virus reactivation following autologous HCT has been demonstrated by Hata *et al.*, this vaccine, which would be ideal post-HCT, is not currently commercially available [86]. A limited

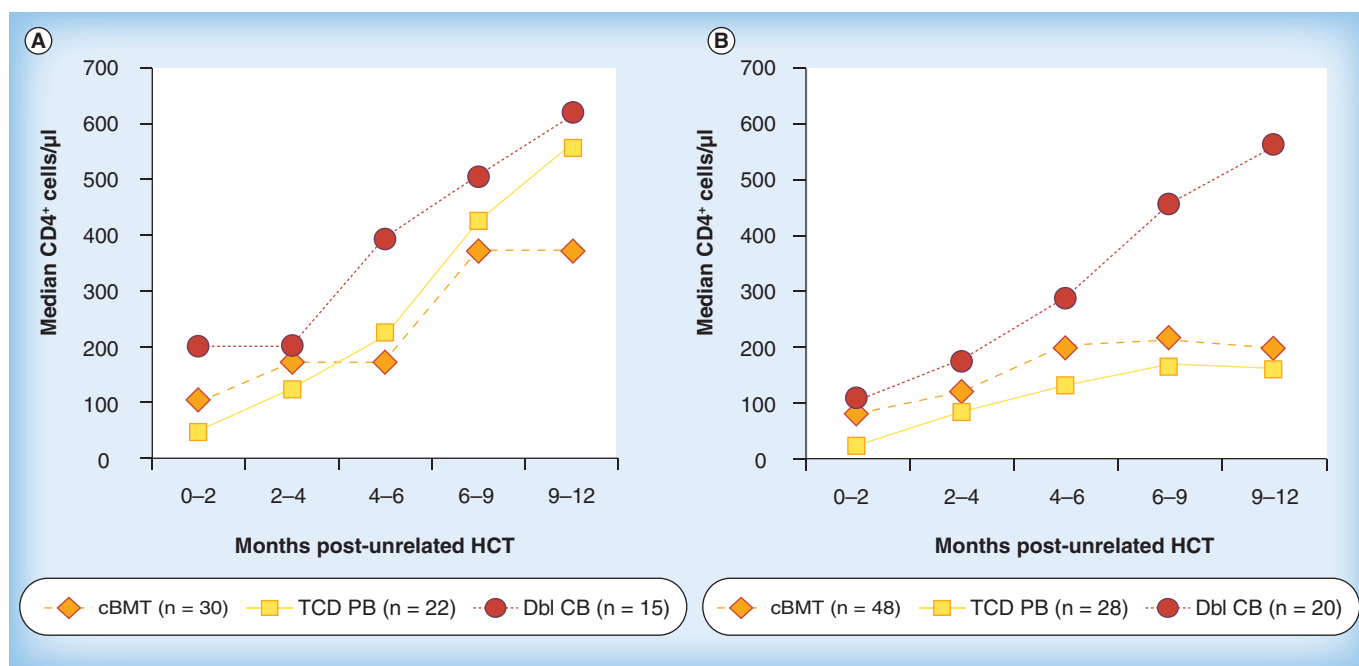


Figure 1. Kinetics of CD4⁺ cell recovery in children and adults following unrelated T-cell-depleted peripheral blood, conventional unmodified bone marrow and double cord blood transplantation. (A) Patients <18 years of age. (B) Patients >18 years of age.

cBMT: Conventional unmodified bone marrow transplant; Dbl CB: Double cord blood; HCT: Hematopoietic cell transplant; TCD PB: T-cell-depleted peripheral blood.

number of studies have evaluated the LAVV in children post-HCT. Sauerbrei and colleagues vaccinated 15 children (median age: 18 months) following an autologous ($n = 7$) or allogeneic ($n = 8$) HCT [87]. Eligibility for vaccination included a circulating lymphocyte count of $>1000/\mu\text{l}$, IgG $>500 \text{ mg/dl}$, and a positive skin test to a recall antigen such as *Candida*. Eight out of nine seronegative patients seroconverted [87]. Immunization was safe and appeared to be effective as none of the vaccinated patients developed varicella or varicella zoster virus within the 2 years following immunization compared with 26.3% of nonvaccinated patients. Ljungman *et al.* studied the live-attenuated varicella vaccine in adults immunized early (3–4 months) following an autologous BMT [88]. Only one patient developed herpes zoster, which was successfully treated with oral acyclovir. Kussmaul *et al.* studied the safety of the LAVV in 68 HCT recipients, 25 of whom were evaluable for response [89]. Patients were required to have a CD4 count $>200 \text{ cells}/\mu\text{l}$, a PHA response of 50% of the lower limit of normal control, a humoral response to IPV, and a T- and B-cell response to tetanus toxoid. The median time to the first LAVV was 32 months post-HCT (range: 16–144 months). No patient suffered a vaccine-related adverse event. Response, defined as seroconversion, was clearly documented in 72% (18 out of 25) of evaluable patients. Small *et al.* studied LAVV response in 34 Varicella Zoster seronegative patients following a HLA-matched related ($n = 16$), HLA mismatched related ($n = 5$) or unrelated ($n = 13$) HCT, including ten patients transplanted for an immunodeficiency disorder [90]. A total of 11 out of 34 patients received a T-cell-depleted graft. Only patients off IST without clinical GVHD were eligible for vaccination. In addition,

patients were required to have a circulating CD4 cell count $>200 \text{ cells}/\mu\text{l}$, a PHA response $>75\%$ of the lower limit of normal and demonstrate antibody response to $>one$ vaccines administered post-HCT. The median time to vaccination was 48 months. One out of 34 patients developed a transient rash, which resolved within 24 h. In total, 70% (22/31) of evaluable patients seroconverted. There was no significant difference in response between recipients of an unrelated or HLA-matched related HCT. All five recipients of a T-cell-depleted HLA-mismatched HCT for a primary immune disorder responded. These studies suggest that the LAVV is safe and immunogenic, particularly when given according to preset clinical and immunologic requirements forming the basis of the 2009 CIBMTR guidelines for use in select patient populations.

Influenza, particularly if acquired early post-HCT, can be associated with significant morbidity and mortality [18–20]. In a study by Nichols *et al.*, influenza occurred in 1.3% of 4797 patients <120 days post-HCT, and was not affected by donor type (autologous, HLA-matched or mismatched related or unrelated) [18]. In total, 18 of the 62 patients developed pneumonia, which was fatal in five [18]. In a large prospective study by Martino and colleagues, the 2-year incidence of influenza was 13.1 and 6.1% in allogeneic and autologous HCT recipients, respectively [19]. Of those who developed pneumonia following an allogeneic HCT, 23% died. Although immunization with the inactivated influenza vaccine has been shown by Machado *et al.* to decrease the risk of influenza when administered >6 months post-HCT (two out of 19 vaccinated vs 12 out of 24 unvaccinated) [20], the majority of serious infections occur earlier post-HCT, when vaccine response to

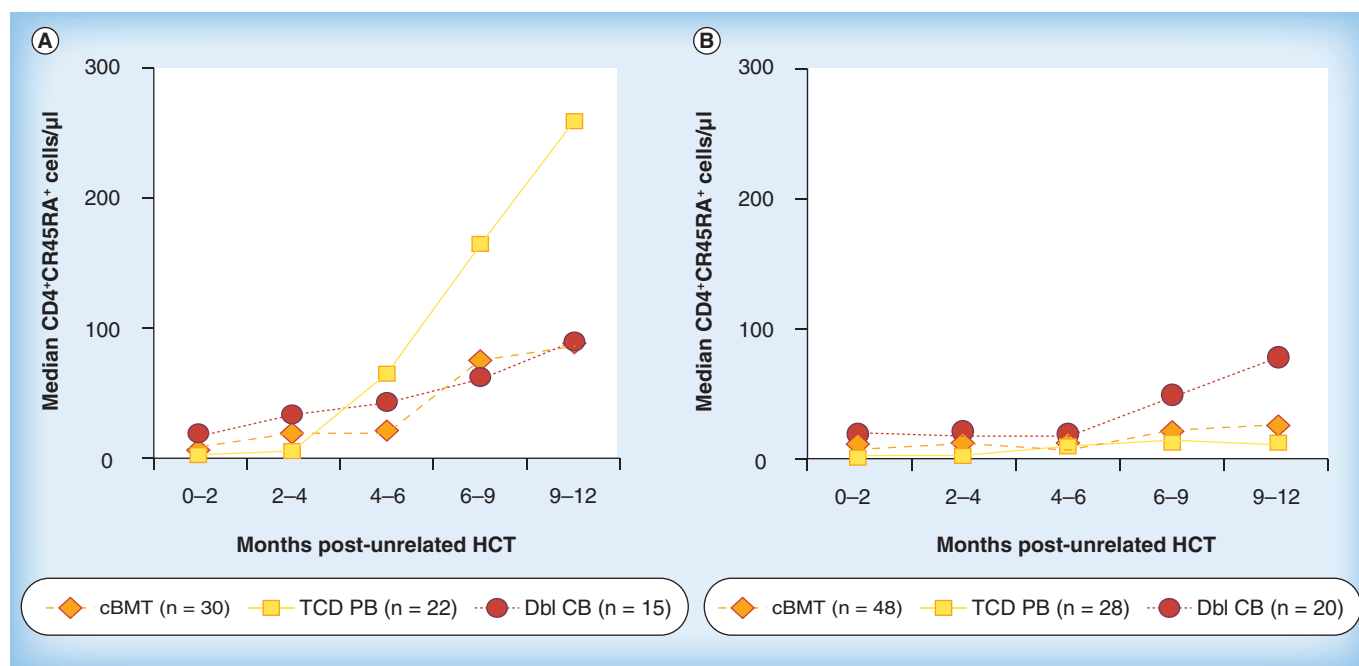


Figure 2. Kinetics of CD4⁺CD45RA⁺ recovery in children and adults following unrelated T-cell-depleted peripheral blood, conventional unmodified bone marrow or double cord blood transplantation. (A) ≤18 years of age. (B) >18 years of age. cBMT: Conventional unmodified bone marrow transplant; Dbl CB: Double cord blood; HCT: Hematopoietic cell transplant; TCD PB: T-cell-depleted peripheral blood.

influenza is very poor. Following one dose of an inactivated triple subunit influenza vaccine, Engelhard *et al.* showed that none of the ten patients immunized <6 months after an autologous or T-cell-depleted allogeneic HCT developed protective hemagglutination inhibition titers (≥1:40) compared with nine out of 14 patients immunized >2 years post-HCT [91]. Receipt of a second immunization 4 weeks later did not significantly increase the number of responders [91]. Several other studies have also demonstrated limited protection afforded by early vaccination against influenza in both allogeneic and autologous HCT recipients [18,92,93]. Current vaccine guidelines therefore recommend yearly inactivated influenza vaccination in patients ≥6 months post-HCT, strongly advocate immunization of household members and carers, and stress prompt evaluation of patients with respiratory symptoms so that early antiviral therapy can be instituted in infected patients [23]. As some very small studies have shown induction of influenza A-specific T-cell proliferative responses [94] or B-cell responses by enzyme-linked immunosorbent spot [95], even when patients were immunized as early as 3–6 months post-HCT, during influenza epidemics, the inactivated influenza vaccine is recommended as early as 3–6 months in patients without GVHD [23].

Vaccines approved since 2005

Meningococcus

In 2005, a protein-conjugated meningococcal vaccine was licensed in the USA, which unlike the pure polysaccharide vaccine has the potential to induce long-term memory [96]. Parkkali *et al.* demonstrated that although allogeneic HCT recipients including those with GVHD are capable of responding to the polysaccharide meningococcal vaccine, a rapid decrease in antibody titers was

observed 6 months after vaccination [97]. Mahler *et al.* evaluated the immunogenicity of the tetraivalent meningococcal conjugated vaccine (MCV4) in 40 patients following a HLA-matched related (n = 15), mismatched related (n = 2) or unrelated (n = 23) HCT, primarily for the treatment of acute leukemia [98]. The median ages at HCT and at vaccination were 13 and 17 years, respectively. In total, 50% of patients received an unmodified HCT. Patients were vaccinated at a median of 3.2 years (range: 0.7–12.5 years) post-HCT. Prior to vaccination, 90% of patients were susceptible to all four serotypes contained in MCV4 (A, C, Y and W-135). Although 58% of patients responded to at least one serotype, response to all four vaccine serotypes occurred in only 11 patients, eight of whom received a transplant from a related donor. Responses were significantly worse in recipients of an unrelated HCT, particularly those who received post-transplant rituximab (n = 6). Of the seven nonresponders given a second immunization, three out of four evaluated patients mounted a response. These data suggest that although HCT recipients respond to MCV4, the response is suboptimal, that pre- and post-vaccine titers, particularly in patients entering college, should be assessed to ensure adequate protection, and that secondary immunizations should be explored in this patient population.

Tetanus, reduced diphtheria & acellular pertussis

In the last decade, pertussis has steadily increased in adolescents and adults, with an estimated incidence of 800,000 to 3.3 million cases per year (reviewed in [6]). In 2005, two vaccines containing tetanus, reduced diphtheria and acellular pertussis (TDaP) were approved for these populations [6]. These vaccines contain similar amounts of tetanus and diphtheria toxoid, but different amounts

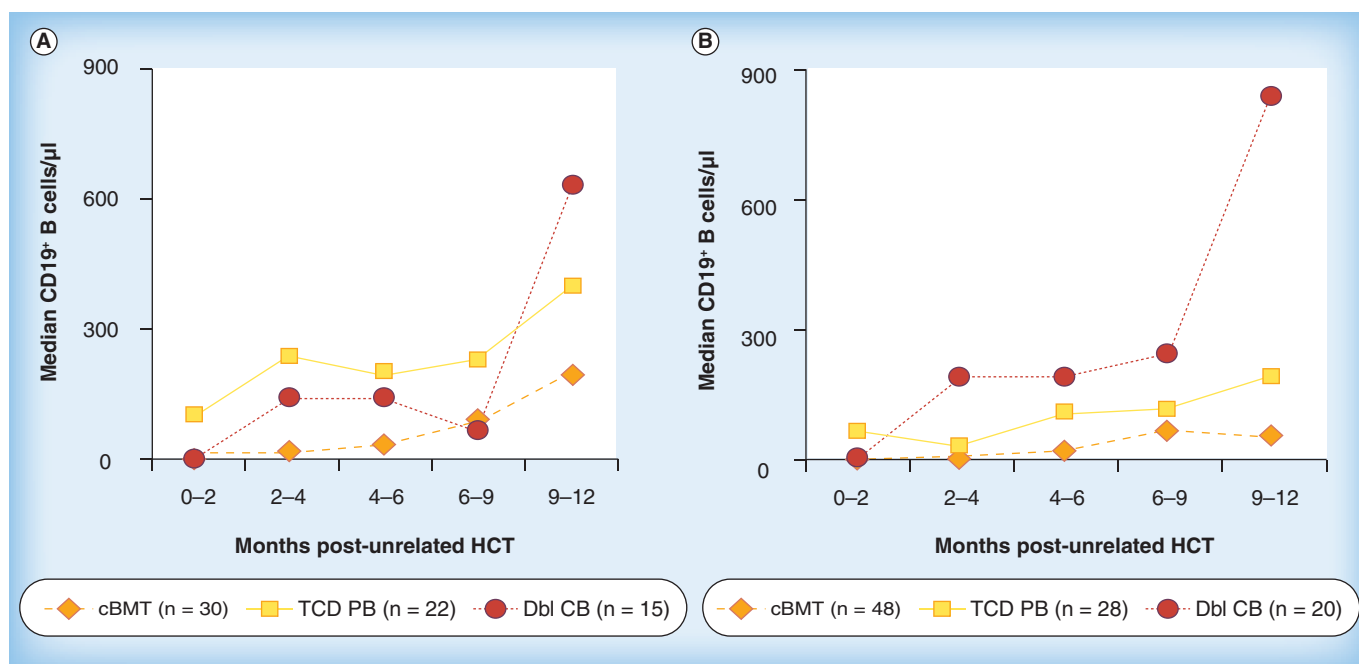


Figure 3. Kinetics of CD19⁺ B recovery in children and adults following unrelated T-cell-depleted peripheral blood, conventional unmodified bone marrow transplant or double cord blood transplantation. (A) ≤18 years of age. (B) >18 years of age.

cBMT: Conventional unmodified bone marrow transplant; Dbl CB: Double cord blood; HCT: Hematopoietic cell transplant; TCD PB: T-cell-depleted peripheral blood.

of pertussis toxoid (PT); (2.5 vs 8 μg/dose). In December 2008, the upper age limit for Tdap containing 8 μg/dose of PT was extended from 18 to 64 years [99]. In 2006, the Advisory Committee on Immunization Practices recommended that all adolescents and adults receive a single dose of Tdap [6]. Two studies have demonstrated that response to pertussis following immunization with a single Tdap containing 2.5 μg PT/dose is poor. Of 41 adult and pediatric allogeneic HCT recipients immunized, only seven out of 41 patients responded to pertussis, six of whom were children [21]. Only two out of 28 patients given Tdap following an autologous HCT responded [22]. These results are likely due in part to the small amount of PT contained in the vaccine and the limited numbers of memory-specific T and B cells transferred from the graft capable of a pertussis response. Based on these results, the 2009 CIBMTR guidelines recommended a series of Tdap containing 8 μg of PT/dose [23]. In total, 14 out of 24 patients who received two immunizations with Tdap containing 8 μg PT/dose developed an anti-PT response [100].

Expert commentary & five-year view

The 2009 CIBMTR vaccine guidelines [23], as well as the prior EBMT [31,32] and CDC guidelines [33], have never been tested prospectively in large numbers of patients, particularly recipients of alternative donor transplants. Given the significant increase in the use of unrelated and cord blood donors and of conditioning regimens of varying intensity over the last 10 years, it is reasonable to question the validity of a 'one size fits all' approach to post-transplant immunization. Currently, most articles addressing

vaccination post-HCT have concentrated on unmodified HLA-matched sibling transplant recipients, with few studies including large numbers of unrelated HCT recipients, or details about the extent or amount of IST in patients with chronic GVHD. There are no studies devoted exclusively to recipients of cord blood transplants, a population whose response to immunizations may differ significantly from other transplant groups owing to the lack of transfer of memory T and B cells in the cord blood graft(s). As shown in FIGURES 1–3, there is marked variability in the kinetics of CD4, CD4⁺CD45RA⁺ and CD19⁺ cell number recovery among recipients of an unrelated, unmodified, T-cell-depleted and double cord blood HCT [SMALL TN, PERS. COMM.].

All vaccine guidelines, including those published in 2009 [23], acknowledge the variability in immune reconstitution following alternative donor transplants (reviewed in [101]) and the lack of studies assessing vaccine responses in these patient populations. Although immunization of all patients using a standard timetable without documentation of pre- and post-vaccine titers is a less complicated and more cost-effective intervention, the protection afforded by this strategy may not be adequate for all patient groups and may ultimately be more costly. Vaccination based on fixed times post-HCT will likely be sufficient for highly immunogenic vaccines, such as tetanus and polio. For others, such as hepatitis B and pneumococcus, some studies have suggested that vaccination prior to the acquisition of critical populations of T and B cells may hinder the response. It is hoped that in the next 5 years prospective multicenter, potentially international, trials assessing the efficacy of the 2009 CIBMTR in diverse transplant groups will be

undertaken. These studies should include vaccines approved since 2005, including PCV-13, to provide evidence-based guidelines for their use. Studies assessing pneumococcal conjugate vaccines should standardize the threshold for response, which vary considerably in currently published trials from 0.15 to 1 µg IgG/ml [61–66], often differing from that chosen by the WHO as protective (>0.35 µg/ml) [102]. As it is currently unknown what level is protective in HCT recipients, international reporting of invasive pneumococcal infections following allogeneic and autologous transplantation should be undertaken. This could be accomplished by reporting to the CIBMTR and EBMT.

Future vaccine trials should ideally include parallel assessments of *in vitro* parameters of immune reconstitution to determine whether surrogate markers of immune reconstitution can predict vaccine

response. *In vitro* correlates of vaccine responses might allow earlier revaccination of patients with the requisite T- and B-cell populations and prevent premature vaccination and/or risk in patients unable to respond. For patient groups with poor response, trials assessing immunomodulatory agents [100] and/or vaccine adjuvants (reviewed in [103]) should be undertaken.

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Key issues

- Increases in vaccine-preventable diseases in healthy individuals highlight the need for effective vaccination of the growing number of transplant survivors not only for their individual protection but to avoid a public health crisis.
- Vaccine response rates vary considerably depending on age of recipient, immunogen, type of donor, stem cell source and presence of chronic graft-versus-host disease.
- Prospective studies testing the efficacy of current vaccine guidelines in recipients of reduced intensity conditioning, pre- and post-hematopoietic cell transplant rituximab, and/or unrelated adult volunteer or cord blood hematopoietic cell transplant are needed as the immunogenicity of vaccines in these populations is currently unknown.
- Trials are needed to determine the timing and number of vaccine doses required to protect the growing population of vulnerable hematopoietic cell transplant recipients against pertussis, the human papilloma vaccine, and the conjugated meningococcal vaccine.
- Trials evaluating earlier vaccination of children without graft-versus-host disease against varicella, measles, mumps and rubella are needed. Vaccination at 24 months is arbitrary, and studies have shown earlier vaccination is safe.

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