Open Forum Infectious Diseases

BRIEF REPORT

High Rates of Seroprotection and Seroconversion to Vaccine-Preventable Infections in the Early Post–Autologous Stem Cell Transplant Period

Victoria G. Hall,[1,2] Natalie R. Saunders,[2] Emily Klimevski,[2] Gayani S. Tennakoon,[2] Amit Khot,[1,3] Simon Harrison,[1,3] Leon J. Worth,[1,2] Michelle K. Yong,[1,2,4] Monica A. Slavin,[1,2,4] and Benjamin W. Teh[1,2]

[1]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia, [2]Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Australia, [3]Department of Clinical Hematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia, and [4]Department of Infectious Diseases, Royal Melbourne Hospital, Parkville, Australia

In patients early post–autologous stem cell transplant, seroprotection rates were high for *Hemophilus influenzae* type B and tetanus toxoid (70%–90%) but lower for *Streptococcus pneumoniae* (30%–50%) including after revaccination. There were high rates of seropositivity (67%–86%) to measles, mumps, and rubella and varicella zoster virus. Durability of protection requires assessment.

Keywords. autologous stem cell transplant; seroconversion; seroprotection; vaccination.

Patients are considered high risk for vaccine-preventable infections (VPIs) following hematopoietic stem cell transplantation (HCT). It is therefore recommended to consider HCT patients vaccine-naïve and require a full revaccination schedule, commencing 6 months after transplantation [1, 2]. Despite differences in conditioning chemotherapy, stem cell source, immunosuppressive regimens, and patterns of immunological recovery, there is no difference in the recommended vaccination schedule for autologous HCT (autoHCT) compared with allogeneic HCT (alloHCT) patients [1, 2]. This is due to the lack of studies evaluating immunity to key VPIs in autoHCT patients.

There is increasing evidence of high seroconversion and seroprotection rates of up to 80% following completion of a course of vaccination in autoHCT patients [3–5]. However, little is known about immunity to VPIs before commencement of vaccination, especially to infections contained within live vaccines such as measles, mumps, and rubella [5]. Knowledge about early retention of immunity to infections such as measles is vital as vaccination with a live vaccine is contraindicated until 2 years post-transplant [1, 2]. Early immune response to commencement of vaccination at 6 months following autoHCT as recommended also remains poorly studied.

To address these evidence gaps, we aimed to define rates of seroprotection to a range of VPIs in the early post-transplant period and to evaluate seroconversion to the first dose of vaccination at 6 months post-autoHCT.

METHODS

We performed serological assessment on stored blood samples from a prior influenza vaccination trial (ACTRN1261 9000617167) to assess seroprotection and seroconversion to common VPIs in the early post-transplant period [6]. In that trial, 68 patients post-autoHCT were recruited [6]. Available stored sera at 1–3 months, 3–6 months, and 6–9 months post-transplantation were utilized (study schema, Figure 1*A*). Receipt of intravenous immunoglobulin was an exclusion criterion for this study. Demographics, underlying disease, treatment history, and vaccination status were previously collected and available from an electronic REDCap database hosted at Peter MacCallum Cancer Centre, Melbourne.

Enzyme-linked immunosorbent assay (ELISA) was performed at all 3 time points for quantitative detection of immunoglobulin G (IgG) against the 23 polysaccharides isolated from *Streptococcus pneumoniae* and contained in pneumococcal vaccines (VaccZyme product code MK012), tetanus toxoid IgG (MK010), and *Haemophilus influenzae* type B (HiB) IgG (VaccZyme MK016), as per the manufacturer's instructions (The Binding Site Group Ltd, Birmingham, UK). Seroprotection was defined as a pooled serotype pneumococcus IgG antibody titer ≥51.5 mg/L (correlates with World Health Organization cutoff of 0.35 mg/L for protection against invasive pneumococcal disease [7, 8]), tetanus toxoid IgG titer ≥0.15 IU/mL, and HiB IgG titer ≥0.15 mg/L before vaccination and ≥1.0 mg/L postvaccination, as previously described [9, 10].

Seroconversion was analyzed for IgG antibodies to pneumococcus, HiB, and tetanus toxoid. Titers at 3–6 months were compared with titers at 6–9 months in those who, 6 months post-transplantation, underwent routine revaccination with the 13-valent pneumococcal conjugate vaccine (PCV-13), HiB conjugate vaccine, and inactivated diptheria-tetanus-pertussis-polio vaccine. Seroconversion for pneumococcus was defined as an antibody titer of ≥51.5 mg/L and ≥2-fold

Received 25 September 2023; editorial decision 26 September 2023; accepted 30 September 2023; published online 5 October 2023

Correspondence: Victoria G. Hall, MBBS, MPHTM, Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne 3000, Australia (victoria.hall@petermac.org; v.hall2@student.unimelb.edu.au).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad497

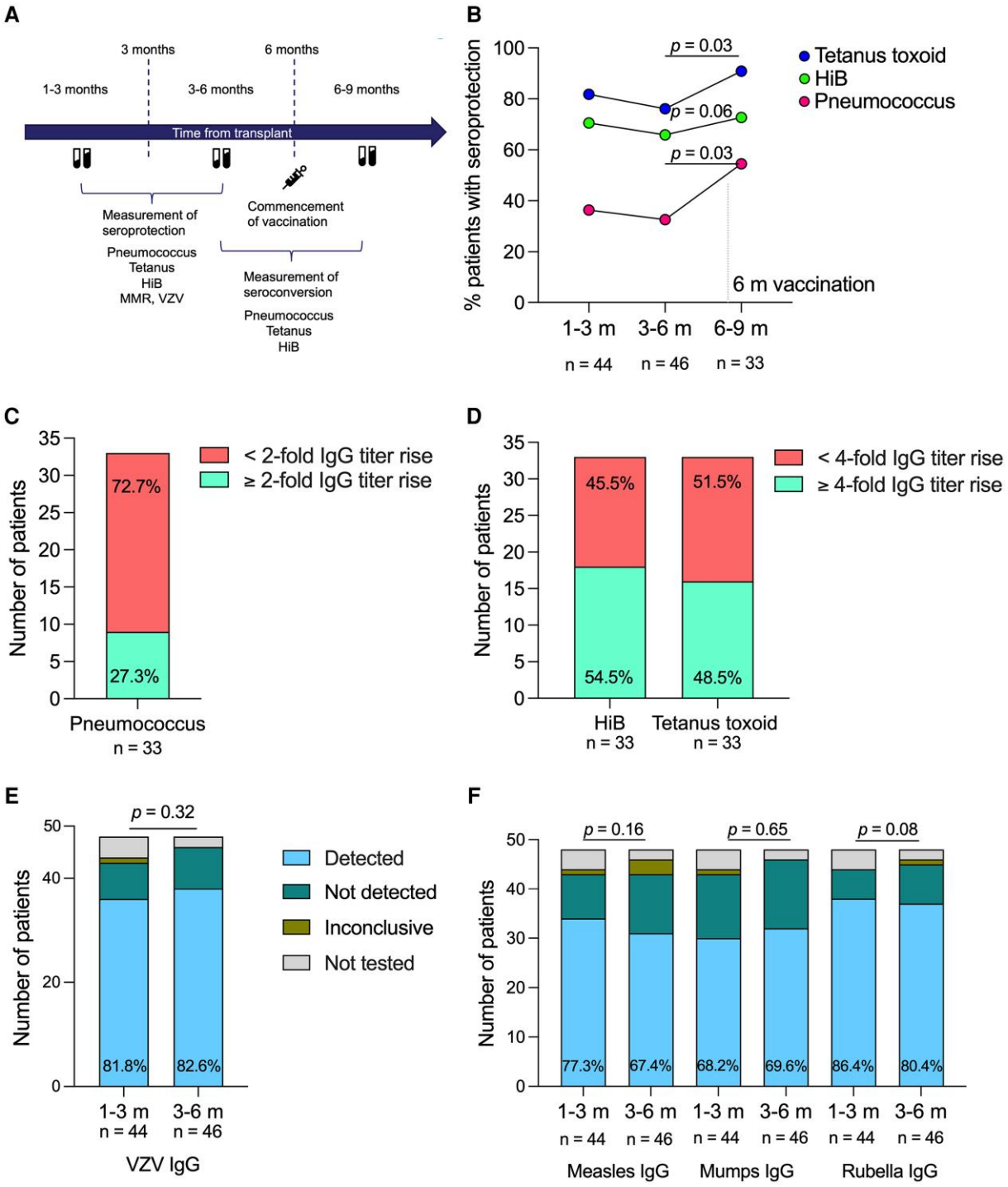

Figure 1. Seroprotection and seroconversion to common vaccine-preventable infections in the early post–autologous stem cell transplant period. A, Study schema of cohort. B, Connecting line graph displaying percentage of patients with seroprotection at 1–3 (n = 44), 3–6 (n = 46), and 6–9 months (n = 33) post-transplantation against pneumococcus, HiB, and tetanus toxoid. Light gray dotted line indicates 6-month revaccination post-autoHCT. Seroprotection was defined as pooled serotype pneumococcus IgG titer ≥51.5 mg/L, HiB IgG titer ≥0.15 mg/L before vaccination, and ≥1.0 mg/L postvaccination and tetanus toxoid IgG titer ≥0.15 IU/mL. Proportions of patients with seroprotection were compared between time points by McNemar test. Only patients who underwent routine vaccination at 6 months (n = 33) with PCV-13, HiB conjugate vaccine, and inactivated diptheria-tetanus-pertussis-polio vaccine were included in the 6–9-month time point. C, Number of patients and rates of seroconversion (for n = 33 patients) after the first dose of vaccination at 6 months post-autoHCT against pneumococcus. D, Number of patients and rates of seroconversion (for n = 33 patients) after the first dose of vaccination at 6 months post-autoHCT against HiB and tetanus toxoid. E, Rates of VZV IgG detection at 1–3 and 3–6 months post-autoHCT. Proportions of detected vs not detected VZV IgG were compared by McNemar test. F, Rates of measles IgG, mumps IgG, and rubella IgG detection at 1–3 and 3–6 months post-autoHCT. Proportions of detected vs not detected IgG at each time point were compared by McNemar test. Abbreviations: autoHCT, autologous hematopoietic stem cell transplantation; HiB, *Hemophilus influenzae* type B; IgG, immunoglobulin G; MMR, measles, mumps, rubella; PCV-13, 13-valent pneumococcal conjugate vaccine; VZV, varicella zoster virus.

rise postvaccination; for HiB ≥1.0 μg/mL and ≥4-fold rise postvaccination; and for tetanus toxoid ≥0.15 IU/mL and ≥4-fold rise postvaccination based on established literature [7–10].

ELISA was also performed at the 1–3 and 3–6-month time points post-transplant for qualitative detection of IgG antibodies to varicella zoster virus (VZV; product code ab108782), measles (ab108750), mumps (ab108752), and rubella viruses (ab108767), as per the manufacturer's instructions (Abcam Pty Ltd, Cambridge, UK). Cutoff values led to classification of IgG as detected, not detected, or inconclusive. Rates of detection are given only for those patients with available samples for testing at each time point.

Demographics were summarized by descriptive statistics. Categorical variables were assessed by chi-square test. The Mann-Whitney *U* test (unpaired) and Wilcoxon signed-rank test (paired) were used for comparisons between 2 groups. A McNemar test was used to compare the proportion of seropositivity or seroprotection between 2 time points. The proportion of patients with seroprotection at the 6–9-month time point was only given for patients who underwent vaccination at 6 months post-transplant. All statistical analyses were performed using IBM SPSS (version 28.0) or Prism (version 9, GraphPad Software, Boston, MA, USA), with $P < .05$ considered statistically significant.

Patient Consent

Ethical approval was granted from the institutional Human Research Ethics Committee (HREC/88292/PMCC), and prior written patient consent was provided for future related research.

RESULTS

A total of 48 patients with samples at appropriate time points were eligible for serological analysis. Baseline demographics have been described previously [6] and are provided in Supplementary Table 1. The median age (interquartile range [IQR]) was 60.6 (52.0–66.7) years, with male predominance (34/48 patients, 70.8%). The median time of observation in the cohort (range) was 5.9 (5.5–6.1) months. Most patients were diagnosed with myeloma (38/48, 79.2%), and the median time from diagnosis of underlying disease to autoHCT (IQR) was 1.5 (1.4–3.2) years.

The median time from autoHCT to the time of each blood sample is provided in Supplementary Table 1. Seroprotection rates at each time point are displayed in Figure 1*B* for pneumococcus, HiB, and tetanus toxoid. At 1–3 months, 16/44 (36.4%) patients had seroprotection for pneumococcus, 31/44 (70.5%) for HiB, and 36/44 (81.8%) for tetanus toxoid. These rates were relatively similar at 3–6 months, with no statistical difference between the proportion of patients with seroprotection at 3–6 months vs 1–3 months post-transplantation (Supplementary Figure 1*A–C*).

Patients who received routine revaccination at 6 months were included for analysis at the 6–9-month time point. Seroprotection rates subsequently increased, with 18/33 (54.5%) patients with seroprotection against pneumococcus ($P = .03$), 28/33 (72.7%) for HiB ($P = .06$), and 30/33 (90.9%) for tetanus toxoid ($P = .03$). Raw values are provided in Supplementary Figure 2*A–C* for the cohorts for pneumococcus, HiB, and tetanus toxoid IgG titers, with similar significant increases observed in the median IgG titers at 6–9 months compared with 3–6 months post-transplantation.

There were modest rates of seroconversion after the first dose of vaccine at 6 months post-transplantation: 9/33 (27.3%) patients achieved a ≥2-fold IgG rise in pneumococcus IgG titers (Figure 1*B*), 18/33 (54.5%) patients achieved a ≥4-fold IgG titer rise to HiB, and 16/33 (48.5%) patients achieved a ≥4-fold IgG titer rise to tetanus toxoid (Figure 1*D*). There were no significant factors identified (Supplementary Tables 2–4) that may influence seroconversion to any of the examined VPIs. There was a significant rise (Supplementary Figure 3*A–C*) postvaccination in IgG titers for pneumococcus, HiB, and tetanus toxoid, respectively (all $P < .0001$).

Overall, there were high rates of immune retention to VPIs contained in live virus vaccines, including Varicella zoster virus (VZV) IgG, measles IgG, mumps IgG, and rubella IgG at 1–3 and 3–6 months post-autoHCT (Figure 1*E* and *F*). It is standard of care at our center to undergo pretransplant VZV IgG testing. Of the patients who were tested for VZV IgG pretransplant (n = 45), 38/45 (84.4%) patients had detectable VZV IgG, and 7/45 (15.6%) patients were seronegative. This rate was similar post-transplantation, with 36/44 (81.8%) patients having a detectable VZV IgG at 1–3 months and 38/46 (82.6%) patients having a detectable VZV IgG at 3–6 months post-autoHCT (Figure 1*E*). There were no recorded episodes of VZV reactivation in the study period from 0 to 9 months post-autoHCT.

Pretransplant serology for measles, mumps, and rubella IgG was not available for comparison. The post-transplant measles IgG detection rate was 34/44 (77.3%) at 1–3 months, with a lower value at 3–6 months in 31/46 (67.4%) patients tested (Figure 1*F*). Post-transplant mumps IgG was slightly lower, with 30/44 (68.2%) patients having mumps IgG detected at 1–3 months and similar detection at 3–6 months (Figure 1*F*). Rates of positive rubella IgG post-transplant were higher, however, with 38/44 (86.4%) and 37/46 (80.4%) patients having detectable rubella IgG at 1–3 and 3–6 months post-autoHCT, respectively (Figure 1*F*).

DISCUSSION

This serosurvey of VPIs, focusing on a previously understudied and expanding population, identified a moderate to high

rate of seroprotection and immune retention in the early post-autoHCT period. Although only ∼30%–50% achieved seroconversion, there was a significant antibody titer rise after the first dose of routine revaccination at 6 months post-transplantation. In contrast to a prior report, we did not find any association between immune or transplant-specific factors and seroconversion, although numbers were small [11]. These findings are encouraging and reinforce the timing of revaccination given that, despite intense myelodepletion, there is still some degree of seroprotection until 6 months and that vaccinating at this time allows for adequate immune reconstitution.

Given the high rates of seroprotection after 1 dose of vaccine (70%–90% for tetanus and HiB), it may be that routine revaccination at 6 months could act as a booster vaccination without further doses in some patients. This has the potential to personalize the revaccination schedule and reduce needle and outpatient clinic burden, representing a cost-effective strategy. The lower rate of seroprotection (∼55%) and seroconversion post–first dose of pneumococcal vaccination, however, is supportive of use of sequential doses in current clinical practice [1]. Given that patients received PCV-13, future study is suggested to focus on these 13 core serotypes rather than pooled analysis as performed against the 23 serotypes.

The high degree of seropositivity against viruses contained in live virus vaccines is also reassuring and higher than what has been previously described in the alloHCT population [1, 12]. For example, the probability of becoming seronegative to measles 5 years after allogeneic HCT has been found to be 60% in a longitudinal cohort study [12]. In contrast, 33% of our cohort was seronegative to measles at 3–6 months post-autoHCT. This is supported by the high immune retention to VZV observed in our cohort (82.6% VZV IgG positive at 6 months post-transplant). This provides further evidence of the differences in immunological recovery in autoHCT compared with allogeneic HCT recipients, and that the extrapolation of the revaccination schedule of alloHCT recipients to all autoHCT recipients should be reconsidered.

Prophylaxis at our center for autoHCT patients includes trimethoprim-sulfamethoxazole as *Pneumocystis jiroveci* pneumonia prophylaxis for 6 months and valaciclovir for herpes simplex virus and VZV prophylaxis for 12 months post-transplantation. We do not routinely use fluoroquinolone prophylaxis, which can impact pneumococcal rates. In VZV IgG–positive patients, we are now administering inactivated adjuvant recombinant zoster vaccine (Shingrix) at ∼7 and 9 months post-autoHCT and then discontinuing valaciclovir prophylaxis after the second dose of vaccine dependent on concomitant immunosuppression. This present study was conducted in 2019, before the availability of Shingrix in Australia (mid-2021). Testing was not performed to assess vaccine response, that is, anti-glycoprotein E antibody. Therefore, based on our study and findings, we cannot comment on potential implications to current prophylaxis approaches, including antiviral prophylaxis.

The limitations of our study include a relatively small number of participants and heterogeneity in the population, which prohibit the assessment of clinical end points and extrapolation to a generalized postautograft population. There was limited observation time in the cohort to detect vaccine effectiveness. Further study is required to assess long-term seroprotection (beyond 6 months post-autoHCT) and the cost-effectiveness of an individualized vaccination schedule with testing. Follow-up immunogenicity analysis with blood sampling at least 12 months post-autoHCT as part of a larger prospective study is suggested as an area for future research.

In summary, we demonstrate relatively high rates of seroprotection and seroconversion in the early post-autoHCT period. These data act as a pilot study for a more expansive prospective trial and provide the basis for investigation of a more personalized vaccination schedule post-autoHCT.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The authors would like to thank all patients and staff members who were involved in the initial clinical trial.

Author contributions. Study design: all authors. Data analysis: V.G.H., N.R.S., E.K., G.S.T., B.W.T., M.K.Y., M.A.S. Data collection: V.G.H., B.W.T., N.R.S., E.K., G.S.T. Manuscript writing and decision to submit: all authors.

Data sharing. De-identified data that support the findings of this study are available for ethics-approved studies from the corresponding author upon reasonable request. Data transfer agreement will be required.

Financial support. This study was the recipient of a Peter MacCallum Cancer Centre Foundation grant (VGH/BWT).

Potential conflicts of interest. V.G.H. is supported by an NHMRC postgraduate PhD scholarship (#2014210). M.Y. has received honoraria from MSD and Takeda. M.A.S. has been on data safety monitoring and adjudication committees for Cidara, Roche, and Pfizer. She has received research funding from Gilead Sciences, Merck, and F2G and sat on advisory boards for Gilead Sciences, F2G, Cidara, Takeda, and Merck. M.A.S. is supported by Australian Government National Health and Medical Research Council Investigator (#1173791) and Synergy Grants (#2011100). B.W.T. has been on advisory boards for Moderna, Takeda, and CSL-Behring and received research funding from MSD and Seqirus. B.W.T. has received honoraria paid to the institution from Pfizer, Alexion, and Janssen. B.W.T. is supported by the Australian Government Medical Research Future Fund Investigator Fellowship (EL-2, #1195894). All other authors report no potential conflicts.

References

1. Cordonnier C, Einarsdottir S, Cesaro S, 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:e200–12.
2. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant **2009;** 15:1143–238.

3. Merz AMA, Merz M, Zhang Y, et al. Serological response to vaccination after autologous transplantation for multiple myeloma is associated with improved progression-free and overall survival. Transplant Cell Ther **2021;** 27:245.e1–8.
4. Palazzo M, Shah GL, Copelan O, et al. Revaccination after autologous hematopoietic stem cell transplantation is safe and effective in patients with multiple myeloma receiving lenalidomide maintenance. Biol Blood Marrow Transplant **2018;** 24:871–6.
5. Pandit A, Leblebjian H, Hammond SP, et al. Safety of live-attenuated measles-mumps-rubella and herpes zoster vaccination in multiple myeloma patients on maintenance lenalidomide or bortezomib after autologous hematopoietic cell transplantation. Bone Marrow Transplant **2018;** 53:942–5.
6. Teh BW, Leung VKY, Mordant FL, et al. A randomised trial of two 2-dose influenza vaccination strategies for patients following autologous haematopoietic stem cell transplantation. Clin Infect Dis **2020;** 73:e4269–77.
7. Rose MA, Buess J, Ventur Y, et al. Reference ranges and cutoff levels of pneumococcal antibody global serum assays (IgG and IgG2) and specific antibodies in healthy children and adults. Med Microbiol Immunol **2013;** 202:285–94.
8. Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol **2012;** 130(Suppl 3):S1–24.
9. Peltola H, Käyhty H, Virtanen M, Mäkelä PH. Prevention of *Hemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. N Engl J Med **1984;** 310:1561–6.
10. Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med **1995;** 332:761–6.
11. Haynes AS, Curtis DJ, Campbell K, et al. An immune recovery-based revaccination protocol for pediatric hematopoietic stem cell transplant recipients: revaccination outcomes following pediatric HSCT. Transplant Cell Ther **2021;** 27: 317–26.
12. Ljungman P, Lewensohn-Fuchs I, Hammarström V, et al. Long-term immunity to measles, mumps, and rubella after allogeneic bone marrow transplantation. Blood **1994;** 84:657–63.