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Immunity Gaps and Delayed Vaccination Assessment in Children After Hematopoietic Stem Cell Transplantation: A Single-Center Real-World Assessment

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Abstract

Objectives: Hematopoietic stem cell transplantation (HSCT) is curative for many children with high-risk hematologic diseases but can lead to loss of vaccine-acquired immunity, leaving survivors highly susceptible to vaccine-preventable diseases (VPDs). Although systematic revaccination is recommended internationally, real-world evidence from China is scarce. This study described post-HSCT antibody levels, vaccination practices, and parental attitudes and identified factors affecting timely vaccination assessment. Methods: This single-center real-world study included 211 pediatric HSCT survivors attending a dedicated post-transplant vaccination clinic (June 2022–December 2024). Antibody titers against six VPDs were measured at the first visit, before revaccination. Clinical data were extracted from medical records; parental questionnaires captured vaccination status, adverse events, and willingness. Chi-square tests and logistic regression identified factors associated with hepatitis B surface antibody (HBsAb) positivity. Results: HBsAb positivity was 30.54% (62/203), and other antibody positivity ranged from 12.5% to 43.3%. Immunosuppressant exposure > 2 years was independently associated with lower HBsAb positivity (OR = 0.457, 95% CI: 0.244–0.859, $p = 0.015$). The median interval from HSCT to first assessment was 34 months (IQR: 29–43). Among 161 vaccinated children, adverse reactions were limited to transient fever in 5 (3.1%). Parental willingness was high (94.9%, 188/198), yet 18.7% remained unvaccinated; the leading barrier was unmet clinical criteria (51.4%), followed by community health center refusal (29.7%) and parental safety concerns (18.9%). Conclusions: Substantial immunity gaps and delayed vaccination assessment persist despite high parental willingness, with clinical ineligibility the primary barrier. These findings support closer monitoring of

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immunosuppressive therapy and immune recovery, alongside coordinated specialist–community pathways, to improve vaccination coverage and timeliness in HSCT survivors.

Keywords: HSCT; children; vaccination; immunity gap; delayed assessment; parental attitudes

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment for both malignant and non-malignant diseases in children [1–3]. With continuous advances in transplantation techniques and supportive care, long-term patient survival rates have improved significantly, shifting the clinical focus from merely improving survival to enhancing the long-term quality of life and overall health of survivors. However, because conditioning regimens can completely ablate the recipient's immune memory, transplanted children become highly susceptible to vaccine-preventable diseases (VPDs). Although vaccination is administered prior to transplantation, serum protection rates among post-transplant patients generally remain low [4], and both vaccination adherence and immune response rates are suboptimal [5]. Pediatric recipients are particularly vulnerable, with higher rates of hospitalization and mortality from VPDs [6], highlighting the necessity of early, proactive immunization strategies in this population.

Additionally, slow immune reconstitution after transplantation further increases the risk of infection [4,7]. Rebuilding immunity through revaccination is essential, and multiple international guidelines provide standardized recommendations regarding the timing and sequence of vaccination following HSCT [4,8,9]. Inactivated vaccines are typically initiated 3 months post-transplant to restore protection against common pathogens such as influenza and *Streptococcus pneumoniae* [4]. Both the European Society for Blood and Marrow Transplantation (EBMT) and the Infectious Diseases Society of America (IDSA) guidelines emphasize that post-transplant vaccination should be individually tailored based on the presence of graft-versus-host disease (GVHD) or immunosuppressive therapy. Despite these factors potentially affecting the immune response to vaccines, patients with GVHD remain likely to benefit from vaccination due to their higher risk of infection [4]. Beyond clinical factors, systemic barriers also contribute to suboptimal vaccination coverage in pediatric HSCT recipients, including variation in immunization schedules across regions, vaccine hesitancy, and uncertainties regarding optimal vaccination timing [10]. Parental concerns about vaccine safety and a lack of awareness regarding the need for revaccination further hinder timely immunization in this population [11].

While recent studies have examined post-HSCT immunity and revaccination in Chinese children [12], data on residual antibody levels prior to revaccination, the spectrum of VPDs beyond hepatitis B, and the practical barriers faced by patients' families and healthcare providers in clinical practice remain scarce. A significant gap persists between guideline recommendations and real-world practice, particularly in China, where understanding the natural waning of pre-existing antibodies is critical for planning timely catch-up vaccination.

To address this gap, we conducted a comprehensive real-world study at a single tertiary children's hospital in China. The objectives of this study were: (1) to describe residual antibody titers against six VPDs at the first post-HSCT vaccination assessment, (2) to identify host factors associated with HBsAb persistence, (3) to characterize vaccination uptake, timing, and safety in routine practice, and (4) to document parental attitudes and barriers to vaccination. Our findings are expected to inform more effective

vaccination strategies for this vulnerable population and to highlight the public health significance.

2. Materials and Methods

2.1. Study Design and Participants

2.1.1. Study Design

This was a single-center, retrospective, real-world study conducted at Shenzhen Children's Hospital. The study population consisted of pediatric patients who underwent HSCT before 18 years of age and survived to the post-transplant vaccination assessment, all of whom were born after the implementation of China's universal birth-dose hepatitis B vaccination policy. According to the historical practice at our center, post-HSCT vaccination assessment was generally undertaken after systemic immunosuppressive therapy had been discontinued for approximately 6 months. This represented a local clinical practice rather than a universal requirement for all vaccines or immunosuppressive regimens. All antibody titers reported in this study were measured at the first assessment clinic visit, which occurred prior to any post-HSCT revaccination. Thus, these titers reflect residual immunity from pre-transplant vaccination or natural infection, not vaccine responses after post-HSCT immunization. Vaccination safety data were collected from those who subsequently received vaccines after this initial assessment.

2.1.2. Study Population

Inclusion criteria: (1) Pediatric patients who underwent HSCT before 18 years of age; (2) survived HSCT; (3) underwent HSCT before June 2024 and attended the post-transplant vaccination assessment clinic between June 2022 and December 2024; (4) available medical records with sufficient data for analysis. It should be noted that age was defined at the time of HSCT; at the time of assessment, one patient was 18 years and 9 months old.

Exclusion criteria: (1) Incomplete clinical or laboratory data that precluded analysis; (2) patients who did not survive to the first post-transplant vaccination assessment.

2.1.3. Ethical Considerations

This study was approved by the Ethics Committee of Shenzhen Children's Hospital (Approval No. 202312802). Informed consent was obtained from all subjects and their legal guardians. Full details are provided in the Institutional Review Board Statement and Informed Consent Statement at the end of the manuscript.

2.2. Information Collection

Transplant cases from June 2019 to June 2024 were retrieved using the hospital's clinical data management system; cases of transplant recipients who visited the vaccination clinic between June 2022 and December 2024 were retrieved using the outpatient medical record system. The electronic medical record system query included the following information: basic patient information, details before and after transplantation, immunosuppressant usage, and the presence of post-transplant graft-versus-host disease (GVHD). In addition, patients who tested positive for HBsAg were specifically followed up to obtain additional clinical details. A structured questionnaire was administered by telephone to parents or guardians. It covered: post-transplant vaccination status (not vaccinated, partially completed, or fully completed), adverse reactions following vaccination, willingness to vaccinate, reasons for non-vaccination or unwillingness, and history of infectious diseases after transplantation.

2.3. Antibody Titer Determination

Serum antibodies against six vaccine-preventable diseases (hepatitis B, measles, rubella, tetanus, pertussis, and hepatitis A) were measured at the first post-HSCT vaccination clinic visit using commercial kits; the platform, kit, manufacturer, cut-off, and interpretation of each assay are summarized in Table S1. Hepatitis B surface antibody (anti-HBs) and hepatitis B surface antigen (HBsAg) were measured by chemiluminescent microparticle immunoassay (CMIA) on the Abbott Alinity i platform (Abbott Ireland Diagnostics Division, Sligo, Ireland); an anti-HBs titer ≥ 10 mIU/mL was considered protective (WHO), and an HBsAg result < 0.05 IU/mL was considered negative. IgG antibodies against measles, rubella, tetanus, pertussis, and hepatitis A were measured by qualitative colloidal gold immunochromatographic lateral-flow assays (Wuhan Life Sciences Co., Ltd., Wuhan, China), read visually. The test lines of these assays are calibrated such that a positive result indicates that the antibody concentration has reached the corresponding protective threshold: measles IgG ≥ 200 mIU/mL, rubella IgG ≥10 IU/mL, tetanus toxoid IgG ≥ 0.1 IU/mL, pertussis toxoid/filamentous hemagglutinin (FHA) IgG ≥ 50 IU/mL, and hepatitis A IgG ≥ 20 mIU/mL.

Humoral immune function was assessed by measuring serum immunoglobulin levels (IgG, IgA, IgM) using immunoturbidimetry (Abbott Ireland Diagnostics Division, Sligo, Ireland). Lymphocytic immunity was evaluated by flow cytometric (BD Biosciences, Franklin Lakes, NJ, USA) analysis of peripheral blood lymphocyte subsets, including T-cell ($CD3^+$, $CD4^+$, $CD8^+$), B-cell ($CD19^+$), and natural killer (NK) cell subsets. For both assessments, results were classified as normal or abnormal according to age-specific reference ranges. The percentage of patients with normal immunity was calculated as the number of patients classified as normal divided by the number of patients tested.

2.4. Statistical Analysis

Continuous variables were expressed as mean ± SD if normally distributed, or as median [Q1, Q3] if non-normally distributed, and categorical variables were presented as frequency (%). Chi-square test or Fisher's exact test was used to analyze differences in various factors between HBsAb-positive and HBsAb-negative patients. Variables with a univariate p-value < 0.05, together with sex, were entered into a binary logistic regression model; a backward likelihood-ratio stepwise procedure was applied, with $p > 0.10$ as the criterion for variable removal. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are reported. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corp, Armonk, NY, USA) and R software (version 4.5.1).

Of note, HBsAb was selected as the primary outcome for the multivariable analysis for the following reasons: (1) data completeness, as HBsAb results were available for a larger proportion of patients compared to other antibodies (e.g., measles, rubella); (2) clinical relevance, given that China is a country with moderate hepatitis B endemicity and HBsAb-negative patients are at risk of hepatitis B virus (HBV) reactivation after HSCT; and (3) T-cell dependence, because the hepatitis B vaccine is T-cell dependent and the immunosuppressive agents used in this study (e.g., tacrolimus, mycophenolate mofetil) inhibit T-cell function, making HBsAb a particularly relevant marker for studying the impact of immunosuppression on vaccine-induced immunity.

3. Results

3.1. General Overview

Between June 2019 and June 2024, a total of 1200 pediatric HSCT patients were assessed at our center. Among these, 184 patients (15.33%) subsequently attended our post-HSCT vaccination assessment clinic. Between June 2022 and December 2024, the clinic evaluated 211 pediatric HSCT survivors, including 27 patients (12.80%) who had undergone transplantation at other institutions or prior to June 2019 (Figure 1). The number of first visits peaked around July each year (Figure 2A). The mean age at first assessment clinic was 120.5 ± 40.5 months (median: 121 months; Figure 2B). The median interval from HSCT to the first post-transplant vaccination assessment was 34 months (IQR: 29–43 months; Figure 2C). Thalassemia was the most common underlying disease, accounting for 85.78% (181/211) of cases (Figure 2D).

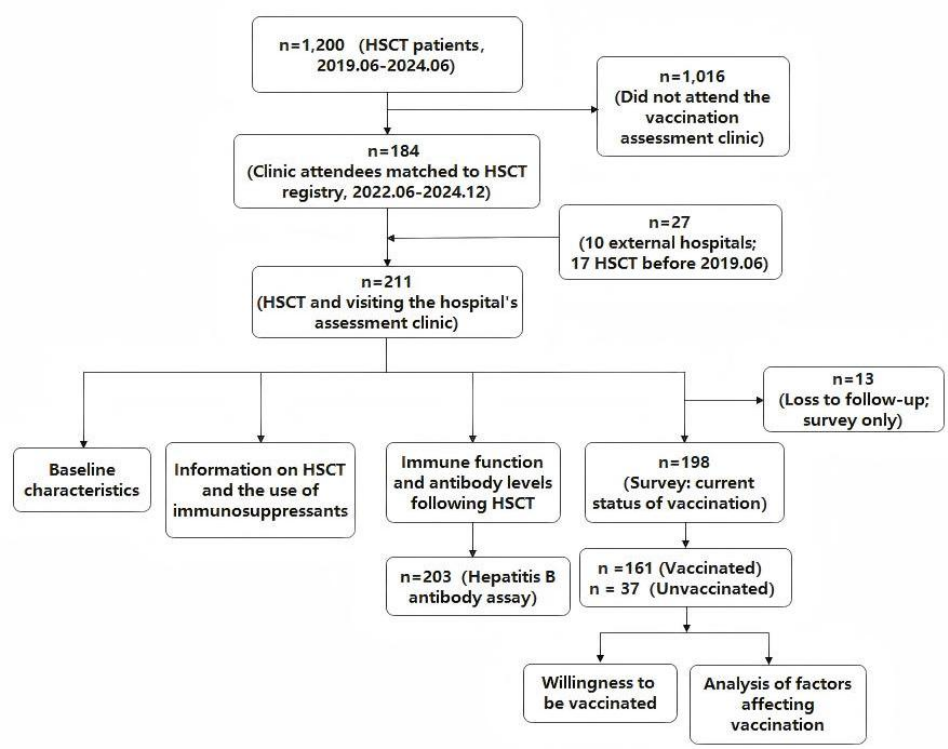


Figure 1. Flow diagram of cohort construction and analysis denominators. Of 1200 unique pediatric HSCT patients (June 2019–June 2024), 184 attended the vaccination clinic (June 2022–December 2024); 27 additional attendees were included (10 transplanted at other hospitals; 17 transplanted at our center before June 2019), yielding an analytic cohort of 211. Thirteen patients lost to follow-up were excluded from the questionnaire-based analysis only (n = 198); of these 198 respondents, 161 had been vaccinated and 37 had not. The cohort includes 2 sibling pairs (4 patients), treated as independent individuals.

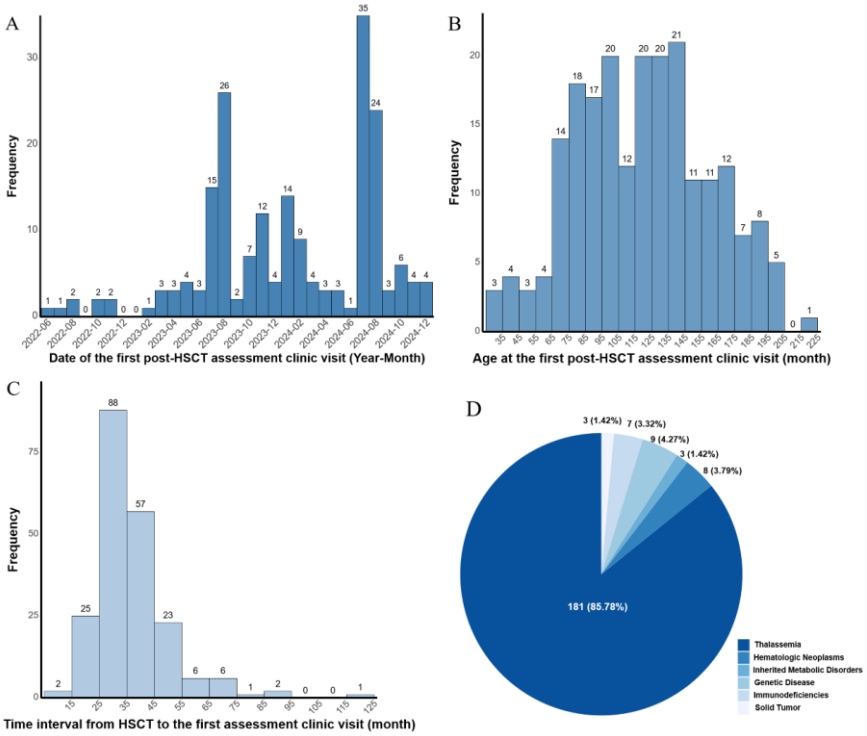


Figure 2. (**A**) Distribution of the First Assessment Clinic Visit Dates. (**B**) Age Distribution at the First Assessment Clinic Visit. (**C**) Time Interval from HSCT to the First Assessment Clinic Visit. (**D**) Distribution of Underlying Diseases in HSCT Patients.

3.2. Transplantation and the Use of Immunosuppressants

Transplantation characteristics are summarized in Table 1. More than half of the patients (132, 62.56%) received a single HSCT with multiple stem cell sources. The most common stem cell sources were peripheral blood combined with umbilical cord blood (68, 32.23%) and peripheral blood alone (65, 30.81%); donors were predominantly unrelated with non-sibling relatives (86, 40.76%). Tacrolimus (150, 72.12%) and mycophenolate mofetil (163,78.37%) were the most frequently used immunosuppressants. The mean duration of immunosuppressant exposure was 27.25 ± 9.62 months (range: 3–63 months). GVHD was documented in 59 patients (28.10%), with cutaneous involvement being the most common (45, 21.43%).

Table 1. Transplantation and Immunosuppressant Use in Pediatric Patients (*n* = 211).

Transplant Type and Immunosuppressant Use	Number of Patients	Percentage (%)
Source of Hematopoietic Stem Cells [a1]		
Bone Marrow Stem Cells	3	1.42
Peripheral blood stem cells	65	30.81
Umbilical Cord Blood Stem Cells	11	5.21
Bone Marrow + Peripheral Blood Stem Cells	15	7.11
Bone Marrow + Cord Blood Stem Cells	2	0.95
Peripheral Blood + Cord Blood Stem Cells	68	32.23
Bone Marrow + Peripheral Blood + Cord Blood Stem Cells	47	22.27
Donor Source [a2]		
Unrelated donor	25	11.85
Non-sibling related donor	8	3.79
Sibling-related donor	40	18.96
Autologous	2	0.95
Unrelated + non-sibling related donor	86	40.76
Unrelated + sibling-related donor	45	21.33

Semi-related + related donors	3	1.42
Unknown	2	0.95
Immunosuppressant Usage [b]		
Tacrolimus	150	72.12
Cyclosporine	81	38.94
Mycophenolate mofetil (MMF)	163	78.37
Sirolimus (Rapamycin)	45	21.63
Methotrexate (MTX)	17	8.17
Cyclophosphamide (CTX/PT-Cy)	89	42.79
Corticosteroids	70	33.65
Monoclonal antibodies, cytokines, and their receptor antagonists	8	3.85
GVHD in pediatric patients [c]		
Skin	45	21.43
Intestinal	8	3.81
Hepatic	7	3.33
Oral mucosa	3	1.43
Pulmonary	2	0.95
Neurological	1	0.48
None	151	71.90
Duration of immunosuppressant exposure (months, mean ± SD) [d]	27.25 ± 9.62	

Note: [a1/a2]: Combinations refer to a single HSCT procedure using multiple stem cell sources or donor types, not multiple transplants. [b]: A single patient may have used multiple immunosuppressants; excluding 2 cases of autologous transplantation and 1 case with unknown status, $n = 208$. [c]: A single patient may have presented with multiple symptoms; excluding 1 case with unknown status, $n = 210$. [d]: Excluding 3 cases where immunosuppressants were not discontinued, 2 cases of autologous transplantation that did not require their use, and 1 case with unknown status, $n = 205$.

3.3. Assessment of Immune Function Following HSCT

3.3.1. Serological Assessment After HSCT

Antibody titers against six vaccine-preventable diseases were measured at the first post-HSCT vaccination assessment (Table 2). HBsAb testing was performed in 203 patients (Of the 207 patients tested, 4 were HBsAg-positive and excluded from HBsAb analysis), with 62 (30.54%) testing positive. Positivity rates for the remaining antibodies were: measles 12.50% (13/104), rubella 43.30% (42/97), tetanus 17.78% (8/45), pertussis 14.89% (7/47), and hepatitis A 12.79% (11/86). In these 4 patients who tested positive for HBsAg (1.93%), 2 were HBV DNA-positive and received antiviral therapy (1 was later lost to follow-up), while the other 2 were HBV DNA-negative with normal liver function and required no treatment. Regarding the overall immune status, serum immunoglobulin levels were within age-appropriate reference ranges in 201 of 210 patients tested (95.71%). In contrast, lymphocyte subset counts were within normal ranges in 89 of 209 patients tested (42.58%).

Table 2. Seropositivity Rates of Vaccine-Preventable Diseases After Transplantation.

Antibody Type	Number Tested (Total)	Negative	Positive	Seropositivity Rate (%)
Hepatitis B Antibody	203	141	62	30.54
Measles Antibodies	104	91	13	12.50
Rubella Antibodies	97	55	42	43.30
Tetanus Antibodies	45	37	8	17.78
Pertussis Antibodies	47	40	7	14.89
Hepatitis A Antibodies	86	75	11	12.79

Note: The denominators for each test were: HBsAb ($n = 203$), measles ($n = 104$), rubella ($n = 97$), tetanus ($n = 45$), pertussis ($n = 47$), and hepatitis A ($n = 86$). Number tested = sum of negative and positive results; Seropositivity Rate (%) = positive ÷ number tested × 100%.

3.3.2. Factors Associated with HBsAb Positivity

Pediatric patients were divided into HBsAb-positive and HBsAb-negative groups based on their HBsAb status following HSCT (Table 3). In univariate analysis, age ≤ 12 years at first assessment was associated with higher HBsAb positivity compared to age > 12 years (34.44% vs. 19.23%, $p = 0.04$). Similarly, patients who attended the first assessment within 2 years post-HSCT had higher HBsAb positivity than those who attended after 2 years (50.00% vs. 27.93%, $p = 0.035$), and those with immunosuppressant exposure ≤ 2 years had higher positivity than those with exposure > 2 years (42.86% vs. 24.41%, $p = 0.007$). No significant associations were observed for gender, immunosuppressant regimen (monotherapy vs. combination), immunoglobulin levels, lymphocyte subset, or GVHD status.

Table 3. Analysis of Differences Between HBsAb-Positive and HBsAb-Negative Groups.

Factors	HBsAb-Positive Group (N1 = 62)	HBsAb-Negative Group (N2 = 141)	χ^2	p
Gender			0.227	0.634
Male	40 (31.75%)	86 (68.25%)		
Female	22 (28.57%)	55 (71.43%)		
Age at first post-HSCT assessment clinic visit, years			4.216	0.04
≤12	52 (34.44%)	99 (65.56%)		
>12	10 (19.23%)	42 (80.77%)		
Time interval from HSCT to first assessment clinic visit, years				0.035
≤2	12 (50.00%)	12 (50.00%)		
>2	50 (27.93%)	129 (72.07%)		
Duration of immunosuppressant exposure post-HSCT [e], years			7.184	0.007
≤2	30 (42.86%)	40 (57.14%)		
>2	31 (24.41%)	96 (75.59%)		
Post-HSCT immunosuppressant regimen			0.281	0.596
Monotherapy	17 (34.00%)	33 (66.00%)		
Combination therapy	45 (30.00%)	105 (70.00%)		
GVHD status				
None	43 (29.86%)	101 (70.14%)	0.108	0.742
Present	19 (32.20%)	40 (67.80%)		
Immunoglobulin levels [f1]				
normal	58 (30.1%)	135 (69.9%)		1.000
abnormal	3 (33.3%)	6 (66.7%)		
Lymphocyte subset [f2]				
normal	25 (29.4%)	60 (70.6%)	0.061	0.805
abnormal	36 (31.0%)	80 (69.0%)		

Note: [e]: Excluding 3 cases where immunosuppressants were not discontinued, 2 cases of autologous transplantation where immunosuppressants were not required, and 1 case with unknown status, $n = 197$. [f1/f2]: Of the 210 patients with immunoglobulin results, 202 had concurrent HBsAb results; of the 209 patients with lymphocyte subset results, 201 had concurrent HBsAb results.

Gender and all variables with a univariate p-value < 0.05 (age at first assessment, time interval from HSCT to first assessment, and duration of immunosuppressant exposure) were included in the multivariable logistic regression model. However, the time interval from HSCT to assessment was excluded from the multivariable model due to a lack of statistical significance ($p = 0.216$). In the final model (Table 4), immunosuppressant exposure >2 years remained independently associated with lower HBsAb positivity (OR = 0.457, 95% CI: 0.244–0.859, $p = 0.015$). Age >12 years at the first post-HSCT vaccination

assessment showed a trend toward lower positivity but did not reach statistical significance (OR = 0.498, $p = 0.080$).

Table 4. Logistic Regression Analysis of Factors Influencing HBsAb Seropositivity.

Variable	b	S_b	$Wald\chi^2$	p	OR	95% CI
Duration of immunosuppressant exposure post-HSCT	−0.782	0.321	5.926	0.015	0.457	0.244~0.859
Age at first post-HSCT assessment clinic visit	−0.698	0.399	3.056	0.080	0.498	0.228~1.088

Note: n = 203. Reference categories: age at first assessment ≤ 12 years and duration of immunosuppressant exposure ≤ 2 years.

3.4. Assessment of the Safety and the Current Sociological Status

We conducted a questionnaire survey among pediatric patients, with a total of 198 parents responding. Among them, 148 (74.75%) had partially completed vaccination, and 13 (6.57%) had completed the full vaccination series, resulting in a vaccination rate of 81.31%. The primary method of completing the vaccination (45.34%) was "consultation at pediatric hospital special outpatient clinics, combined with vaccination at hospitals and community health centers"; regarding reasons for non-vaccination, more than half (19, 51.35%) were limited by "Insufficient time since discontinuation of immunosuppressants or the child not meeting vaccination criteria." For further details, see Table 5.

Among 161 patients who received post-HSCT vaccines, adverse reactions were limited to transient fever in 5 cases (3.11%); no serious adverse events were reported. Parental willingness to vaccinate was high, with 188 (94.95%) expressing willingness. Of the 37 unvaccinated children, 28 (75.68%) parents expressed willingness to vaccinate. For the 10 parents who were unwilling to vaccinate, the most frequently reported reason was safety concerns (90.00%). Additionally, 102 (51.52%) expressed willingness to undergo post-vaccination antibody testing.

Table 5. Vaccination Status of Pediatric Patients After Transplantation.

Vaccination Status	Number of Patients	Percentage (%)
Vaccination Status (n = 198)		
Not vaccinated	37	18.69
Partially completed	148	74.75
Fully completed	13	6.57
Vaccination Route (Vaccinator) (n = 161)		
Consultation and vaccination at the Special Needs Clinic of Shenzhen Children's Hospital	42	26.09
Consultation at Special Needs Clinic, vaccination at local community health center	46	28.57
Consultation at Children's Hospital Special Needs Clinic, mixed vaccination at hospital and community health center	73	45.34
Adverse reactions after vaccination (Vaccinator) (n = 161)		
None	156	96.89
Fever	5	3.11
History of infectious diseases after HSCT [g] (n = 198)		
Hepatitis B	1	0.51
Pertussis	1	0.51
Influenza	36	18.18
Chickenpox or Shingles	27	13.64
COVID-19	40	20.20
Hand, Foot, and Mouth Disease	5	2.53
None	104	52.53
Reasons for Not Being Vaccinated (Unvaccinated Individuals) (n = 37)		
Considered vaccination unnecessary or worried about adverse reactions	7	18.92
Inconvenient travel, inadequate local medical services, or community health center refusal	11	29.73

Insufficient time since discontinuation of immunosuppressants or child does not meet vaccination criteria	19	51.35
Willingness to Vaccinate After Transplant (n = 198)		
Unwilling	10	5.05
Willing	188	94.95
Reasons for Unwillingness to Vaccinate [h] (n = 10)		
Safety concerns	9	90.00
Unclear policies, unwilling to take risks	4	40.00
Travel inconvenience	1	10.00
Willingness to undergo antibody testing after vaccination (n = 198)		
Unwilling	96	48.48
Willing	102	51.52

Note: [g]: One person may exhibit multiple symptoms. Hepatitis B history was parent-reported; routine serology identified 4 HBsAg-positive patients (Results 3.3.1), but only 1 was clinically known to parents. [h]: Parents could select multiple reasons for unwillingness; percentages may exceed 100%.

4. Discussion

International guidelines accordingly recommend systematic revaccination after HSCT. In this Chinese single-center cohort, this recommendation was far from met in practice: seropositivity for six VPDs was substantially lower than published values for healthy children, the median interval from HSCT to the first vaccination assessment was 34 months, and 18.69% of children remained unvaccinated. Notably, this occurred despite parental acceptance of revaccination reaching 94.95%.

4.1. Immunity Gaps: Low Seropositivity and Delayed Vaccination Assessment

4.1.1. Low Seropositivity and Associated Factors

In this cohort, immunity gaps were observed across the six vaccine-preventable diseases assessed, with seropositivity rates ranging from 12.50% for measles to 43.30% for rubella. HBsAb was positive in only 30.54% of the 203 patients tested, well below the rates of 56.68% [13] and 87.24% [14] reported in separate studies of healthy Chinese children. The gap was similarly wide for measles (12.50% vs. 88.36–97.06% in healthy children) [13,15], and even rubella—the antibody with the highest positivity in this cohort (43.30%)—fell below the healthy reference of 77.29% [16]. For tetanus, seropositivity in our cohort (17.78%) was below the 91.22% reported in a meta-analysis of healthy Chinese children aged 7–14 years [17]. Positivity for pertussis and hepatitis A antibodies was similarly low, although the numbers tested for some of these antibodies were small (Table 2). Beyond these serological gaps, HBV infection is a particular clinical concern in this population. Crucially, all 4 HBsAg-positive patients in our cohort had been vaccinated before HSCT (3 were HBsAb-positive and 1 was HBsAb-negative), had no history of HBV infection, and none had received antiviral prophylaxis. Despite this, all 4 developed HBV infection within 1–2 years post-transplant. This case series illustrates that even documented pre-HSCT vaccine-induced immunity can be lost after transplantation, underscoring the need for HBV prophylaxis in HBsAb-positive HSCT recipients and serologic monitoring in all recipients.

In the multivariable analysis, immunosuppressant exposure > 2 years remained independently associated with lower HBsAb positivity (OR = 0.457, 95% CI: 0.244–0.859, p = 0.015). A plausible explanation is that tacrolimus and mycophenolate mofetil—the agents most commonly used in this cohort—inhibit T-cell activation and T-helper function, thereby reducing the B-cell help required for antibody production and memory B-cell reconstitution [18]. Because hepatitis B vaccination is T-cell dependent [19,20] and B-cell recovery after HSCT may take 2–5 years [21], prolonged immunosuppression plausibly

delays immune reconstitution and accelerates the loss of residual vaccine-induced antibody [22]. Notably, patients with >2 years of exposure did not show a significantly higher incidence of overt GVHD (38/132, 28.79%), suggesting that the low HBsAb positivity in this subgroup reflects persistent pharmacological suppression rather than GVHD-related tissue damage. In practice, maintenance therapy beyond two years usually reflects a cautious tapering strategy to prevent GVHD [23]; the present data indicate that this necessary caution carries an immunologic cost. In a country with moderate hepatitis B endemicity [24,25], HBsAb-negative recipients on long-term immunosuppressive therapy are at risk of HBV reactivation [26]. Age showed a parallel pattern: HBsAb positivity was higher in children ≤ 12 years (34.4% vs. 19.2%, $p = 0.04$) in the univariate analysis, and in the multivariable model age > 12 years showed a trend toward lower positivity that did not reach statistical significance (OR = 0.498, 95% CI: 0.228–1.088, $p = 0.080$), plausibly reflecting age-related thymic involution and reduced thymic output of naive T cells and peripheral T-cell diversity [27]. In this setting, older long-term survivors deserve particular attention, and post-vaccination serologic monitoring with booster immunization when indicated remains a guideline-endorsed strategy [28].

In this cohort, 201 of 210 patients (95.71%) had normal immunoglobulin levels, whereas only 89 of 209 (42.58%) had normal lymphocyte subsets, indicating that humoral immunity had largely recovered whereas cellular immune reconstitution remained incomplete in a substantial proportion of patients. This pattern is consistent with the well-described differential recovery after HSCT, in which cellular reconstitution typically lags behind humoral recovery [29]. Accordingly, neither immunoglobulin levels ($p = 1.000$) nor lymphocyte subsets ($p = 0.805$) were significantly associated with HBsAb seropositivity in the cross-tabulation analysis (Table 3), suggesting that HBsAb status at assessment was not explained by these global markers of immune reconstitution.

4.1.2. Delayed Vaccination Assessment

The median interval from HSCT to the first vaccination assessment visit was 34 months (IQR: 29–43 months). International consensus recommends that children without active GVHD who are not receiving high-dose immunosuppressive therapy may begin inactivated vaccine series 3 to 6 months after HSCT, with live-attenuated vaccines considered from 24 months post-transplant [4]; Chinese expert consensus has proposed similar recommendations [28]. The prolonged interval to assessment implies a delay in revaccination. This substantial delay is not isolated. A survey of European pediatric transplant centers shows that, although most recommend post-HSCT immunization, the initiation window for live-attenuated vaccines (MMR/varicella) is typically 16–24 months and is implemented by only a minority [30]. Similarly, a recent review notes that, despite vaccination schedules following HSCT being well recognized, the optimal timing of revaccination remains a key consideration, and practices may vary across centers due to variations in immune reconstitution and treatment-related factors [31].

Nevertheless, the consequences of delay are evident in the serologic data: in the univariate analysis, HBsAb positivity was higher among children assessed within 2 years of HSCT than among those assessed later (50.0% vs. 27.9%, $p = 0.035$), suggesting that residual vaccine-induced antibodies continue to wane as the interval lengthens. Prolonged delay thus leaves children susceptible to vaccine-preventable diseases while their remaining protection is eroding.

4.2. Vaccination Safety Profile

Timely revaccination is the obvious response to the immunity gaps and delays described above, and its safety is a common concern of clinicians and parents alike. In this cohort, the overall adverse reaction rate was only 3.11%, consisting solely of transient, self-

limiting fever, with no serious adverse events reported. Notably, the overall adverse reaction rate observed here (3.11%) was comparable to that reported in a center-based cohort of similar design, in which adverse reactions occurred in 6.5% (30/464) of children revaccinated after allogeneic HSCT and were limited to local redness, swelling, or fever [32]. True adverse event rates for measles–mumps–rubella (MMR) in a placebo-controlled trial were 0.5–4.0% [33], and systematic reviews confirm that fever is among the most common but generally self-limiting reactions to these vaccines [34,35]. Collectively, these findings indicate that for children without active GVHD or severe immunosuppression, initiating or resuming vaccination is supported by a reliable safety profile.

4.3. Barriers to Revaccination Uptake

Parental acceptance of revaccination was high (94.95%), yet 18.69% of the children remained unvaccinated. Among the 37 unvaccinated children, the most frequently cited barrier was medical ineligibility—insufficient time since discontinuation of immunosuppressants or failure to meet vaccination criteria (19, 51.35%)—followed by access barriers such as inconvenient travel, inadequate local medical services, or refusal by community health centers (11, 29.73%), while the belief that revaccination was unnecessary or concerns about adverse reactions were the least commonly reported (7, 18.92%). In addition,51.52% of parents also indicated willingness to undergo antibody testing, supporting the feasibility of serology-based monitoring in this population.

For some children, deferral reflects genuine contraindications. The barrier reported most often in this cohort—insufficient time since discontinuation of immunosuppressants—suggests that eligibility is often equated with complete drug withdrawal in practice. This is a narrower interpretation than guidelines intend [4,28]. Of note, the above analysis showed that residual protection continued to decline during the waiting period: HBsAb positivity fell from 50.0% among children assessed within 2 years of HSCT to 27.9% among those assessed later, and prolonged immunosuppressant exposure was independently associated with lower positivity (OR = 0.457). Deferral until complete discontinuation therefore prolongs the period in which children remain unvaccinated and their residual antibodies continue to decline. These observations support the need for individualized vaccination strategies based on vaccine type, immune reconstitution, and the specific immunosuppressive regimen, which may allow earlier vaccination in selected patients.

The second barrier reflects the fragmentation between specialist and community care. Community health centers in China serve predominantly healthy children, and when faced with a complex patient on long-term immunosuppression, community physicians often cannot judge whether vaccination might trigger GVHD or other adverse reactions; postponement or refusal then becomes a risk-averse default. Transplant specialists are generally familiar with post-transplant vaccination guidelines [36], but the handover of vaccination responsibility to community physicians frequently leaves gaps in care [37,38], and vaccination rates increase when clinicians actively promote vaccination during follow-up visits [37,39]. Parental hesitancy, by contrast, was the least common barrier, consistent with the high overall acceptance of revaccination; targeted education remains worthwhile but is unlikely to be the primary limiting factor.

These barriers are largely modifiable. We propose an integrated pathway linking transplant centers, the Chinese Center for Disease Control and Prevention, and community health services: (1) Develop localized, guideline-based vaccination pathways specifying timing, dosing, and contraindications, so that eligibility decisions do not default to “after full discontinuation of immunosuppressants”; (2) Establish specialist–community collaborative vaccination mechanisms, including specialist assessment and recommendation, community physician training for local vaccination delivery, and

information platforms for sharing immunization records and immune status; and (3) Implement tiered parental education to translate high willingness into timely action.

4.4. Limitations and Future Directions

This study was a single-center retrospective analysis, with a sample primarily composed of children with thalassemia (85.78%), which introduces selection bias and limits the representativeness of the sample. More importantly, the study population consisted exclusively of patients who sought consultation at the vaccination clinic, representing a cohort of self-referred individuals. This group typically exhibits better compliance and a stronger willingness to be vaccinated; therefore, the study may have overestimated the vaccination rate and willingness among the broader HSCT population.

Second, data collection had several limitations. Due to the constraints of the retrospective design, we were unable to dynamically monitor seroconversion rates before and after vaccination, limiting our ability to directly assess vaccine immunogenicity. In addition, post-transplant infection data were collected as a parent-reported categorical checklist via telephone interview, without pathogen confirmation, onset dates, or verification against medical records or laboratory testing; vaccine administration dates and dose history were likewise not systematically collected. These data should therefore be interpreted with caution: they are subject to recall bias and cannot be used to assess vaccine effectiveness or infer vaccine failure. Moreover, the parental questionnaire was a non-scale, descriptive instrument, and formal psychometric validation was not performed.

Third, the seropositivity data may not solely reflect endogenous vaccine-induced immunity. Other potential sources of passive antibodies include the administration of intravenous immunoglobulin (IVIG) or hepatitis B immunoglobulin (HBIG), frequent blood transfusions in patients with thalassemia, and donor-derived immunity transferred during HSCT. Additionally, some patients may have received vaccinations at local community centers prior to their first clinic visit, which could potentially overestimate the seropositivity rates. Furthermore, the healthy comparators used in our discussion were derived from published literature rather than a matched control group, introducing potential differences in age and assay methods. We also lacked matched healthy comparator data for pertussis and hepatitis A.

Fourth, we acknowledge that prolonged immunosuppressant exposure (>2 years) is highly collinear with a longer time since HSCT. Although time since HSCT was included in the initial multivariable model, it was excluded due to a lack of statistical significance (p = 0.216). In a sensitivity analysis using continuous variables, the duration of immunosuppressant exposure remained independently significant (p = 0.024), while time since HSCT was not (p = 0.883). We could not perform further adjustments for disease, donor type, and stem cell source due to the limited sample size and the predominantly single-disease cohort (85.78% thalassemia).

Fifth, pre-transplant vaccination history was incompletely documented. Although universal birth-dose hepatitis B vaccination in China permitted relatively reliable ascertainment of hepatitis B status, records of other vaccines were fragmentary due to treatment interruptions. We were therefore unable to adjust for pre-transplant vaccination status, and the observed seropositivity gaps may partly reflect incomplete baseline immunization rather than the transplant itself.

Future multicenter, prospective cohort studies with broader disease spectra, standardized serological monitoring, validated assessment instruments, and well-documented vaccination histories are needed to confirm these findings and guide individualized revaccination strategies.

5. Conclusions

This single-center cohort study of pediatric HSCT survivors found that antibody titers against most VPDs were lower than in healthy peers. Prolonged immunosuppressive treatment emerged as the dominant predictor for HBsAb waning, while the median interval from HSCT to the first vaccination assessment was 34 months. Despite high parental willingness, 18.69% of children remained unvaccinated, mainly due to clinical ineligibility. These findings support intensified monitoring of immunosuppressant duration and immune recovery, along with collaborative mechanisms between specialist centers and community health services, to identify eligible children and ensure timely vaccination at the appropriate level of care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/vaccines14110946/s1, Table S1. Details of the serological assays used in this study.

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Informed Consent Statement: Informed consent was obtained from all subjects and their legal guardians, as approved by the Shenzhen Children's Hospital Ethics Committee (Approval No. 202312802).

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to patient privacy and ethical restrictions.

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