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MAJOR ARTICLE

Immunogenicity and Reactogenicity of High- or Standard-Dose Influenza Vaccine in a Second Consecutive Influenza Season

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Background. Pediatric hematopoietic cell transplant (HCT) recipients are at high risk for morbidity from influenza virus infection. We demonstrated in a primary phase 2 randomized controlled trial that 2 post-HCT doses of high-dose trivalent influenza vaccine (HD-TIV) given 4 weeks apart were more immunogenic than 2 doses of standard-dose quadrivalent influenza vaccine (SD-QIV). Herein, we present the immunogenicity and safety of influenza vaccination in a consecutive season post-HCT using the same dosing regimen.

Methods. A subcohort of study participants reenrolled and had hemagglutinin inhibition titers measured at baseline and 4 weeks after each vaccine dose in year 2. We estimated geometric mean fold rise in hemagglutinin inhibition titer from baseline for each group and used linear mixed effects models to estimate adjusted geometric mean ratios (comparing HD-TIV vs SD-QIV) for each antigen at each time point. We described systemic and injection site reactions.

Results. A total of 65 subcohort patients participated (33 SD-QIV, 32 HD-TIV). Postvaccine geometric mean fold rise and adjusted geometric mean ratio estimates were higher for both groups following a single influenza vaccine dose in year 2 as compared with 2 doses of the same formulation in year 1. Both groups had similar frequencies of injection site and systemic reactions.

Conclusions. A single dose of HD-TIV or SD-QIV was more immunogenic in year 2 than 2 doses of the same formulation in year 1. Reactogenicity was comparable between groups. One dose of influenza vaccine may be sufficient after a 2-dose schedule in the prior year post-HCT.

Clinical Trials Registration. NCT02860039 (ClinicalTrials.gov).

Keywords. high dose; influenza; pediatrics; stem cell recipients; vaccination.

Influenza virus infection is associated with severe disease in patients who are immunocompromised and contributes to significant morbidity and mortality in pediatric hematopoietic cell transplant (HCT) recipients. Its clinical presentation varies from self-limited upper respiratory tract infections to severe lower respiratory tract infections with respiratory failure, secondary bacterial pneumonia, and even death [1–3]. Despite availability of influenza vaccination, approximately 11% of hospitalizations due to respiratory viral infections in HCT recipients are attributed to influenza virus infection with an associated mortality rate of 10% to 15%, even when antiviral therapy is administered; thus, improved prevention strategies are essential [1, 2].

The primary approach for preventing influenza virus infection is vaccination with inactivated influenza vaccine. For HCT recipients 6 months and older, annual influenza immunization is recommended beginning at least 3 months post-HCT [3]. However, the optimal timing, dose, and frequency of influenza vaccination

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for pediatric HCT recipients were unclear; recommendations were primarily based on adult data [4, 5]. To fill this knowledge gap, we conducted a phase 2 multicenter clinical trial based on a double-blinded randomized controlled design comparing the safety and immunogenicity of 2 doses of high-dose trivalent influenza vaccine (HD-TIV) with 2 doses of standard-dose quadrivalent influenza vaccine (SD-QIV) in pediatric allogeneic HCT recipients who were 3 to 35 months post-HCT (median, 7.9 months). We demonstrated that 2 doses of HD-TIV administered 4 weeks apart was superior to 2 doses of SD-QIV in the same influenza season [6]. Yet, the immunogenicity of 1 or 2 doses of HD-TIV or SD-QIV in the subsequent influenza season is unknown. Therefore, we conducted a substudy to evaluate the safety and immunogenicity of 2 doses of HD-TIV or 2 doses of SD-QIV administered within 2 consecutive seasons.

METHODS

The parent study was a phase 2 multicenter trial based on a double-blind randomized controlled design (Pediatric HCT Flu Study; ClinicalTrials.gov, NCT02860039) that compared immunogenicity and safety between HD-TIV and SD-QIV in children and adolescents 3 to 17 years of age who had received an allogeneic HCT 3 to 35 months preceding enrollment. Inclusion and exclusion criteria were maintained in the subsequent year of participation; participants with graft-vs-host disease (GVHD) were eligible if their disease and GVHD therapy were stable for at least 4 weeks prior to enrollment. Participants with evidence of hematologic malignancy or disease relapse posttransplant were excluded. Full details regarding inclusion and exclusion criteria can be found in the supplementary appendix. The study schedule of events has been published [6, 7]. Participants who were enrolled and vaccinated in 2016–2017, 2017–2018, or 2018–2019 were given the opportunity to reenroll in the subsequent influenza season following their initial enrollment, and they retained their initial enrollment vaccination regimen from their primary season. This substudy was conducted over the 3 subsequent influenza seasons (2017–2018, 2018–2019, and 2019–2020) at the same 9 US study sites. Participants in the substudy, herein "repeaters," were required to have received both assigned vaccine doses in the first influenza season to be included in the current analysis (Figure 1).

The study was reviewed and approved by the institutional review board at each study site. All parents/guardians provided written informed consent; participants provided assent per site-specific institutional review board requirements. Study data were collected and managed by REDCap electronic data capture tools hosted at Vanderbilt University Medical Center [8, 9].

Vaccine

Vaccines were supplied by Sanofi. Investigational pharmacies at each institution distributed the assigned study vaccines, which were administered in a blinded manner as previously described [6, 7]. SD-QIV contained 15 μg of antigen for each strain (A/H1N1, A/H3N2, B/Victoria, B/Yamagata); HD-TIV contained 60 μg of antigen from each strain except B/Yamagata, which was not part of HD-TIV (Supplementary Table 1).

Study Procedures

For both influenza seasons, two 0.5-mL intradermal injections were administered approximately 4 weeks apart, at visits 1 and 2 (ie, first year) and visits 1R and 2R (ie, second year). Blood was obtained prior to administration of each dose (at visits 1/1R and 2/2R) and approximately 1 month (visit 3/3R) and 6 months (visit 4) after the second vaccine dose to evaluate complete blood count, $CD4^+/CD8^+/CD19^+$ cells, immunoglobulin M and G levels, and immunogenicity assays. For repeater participants, if visit 4 from the previous influenza season and visit 1R from the subsequent influenza season occurred on the same day, laboratory results from visit 4 were considered the same results for visit 1R for the following year. In addition, visit 4R was deemed optional for repeaters in their second influenza season (Figure 2).

Safety Evaluations

Parents and/or participants recorded injection site and systemic reactions using a memory aid for 7 days after each vaccine dose for both seasons. Reactions were graded according to a toxicity scale (mild, moderate, severe) and entered into REDCap [7–9]. Additionally, grade ≥3 unsolicited adverse events and severe adverse events were collected following each vaccination [6, 7].

Immunogenicity Assays

Sera were centrifuged and frozen until shipment to Sanofi Global Clinical Immunology laboratory for hemagglutination inhibition (HAI) testing for each vaccine-specific antigen, per standard testing protocol [10]. When blood volume was limited, HAI testing of influenza A antigens was prioritized.

Influenza Surveillance

Active laboratory-based influenza surveillance occurred during each site-specific influenza season, defined as ≥10% clinical or research laboratory sample positivity rate for influenza in 2 consecutive weeks [11, 12]. During each site's influenza season, nasal swabs were obtained at each study visit regardless of symptoms and between study visits if participants had influenza-like illness.

Statistical Analyses

For all study participants in the repeater cohort, we generated baseline descriptive statistics for each year (visit 1/1R; enrollment year 1 or 2) and within each dose group (SD-QIV or HD-TIV): median (IQR) for continuous variables and absolute/relative frequencies for categorical variables.

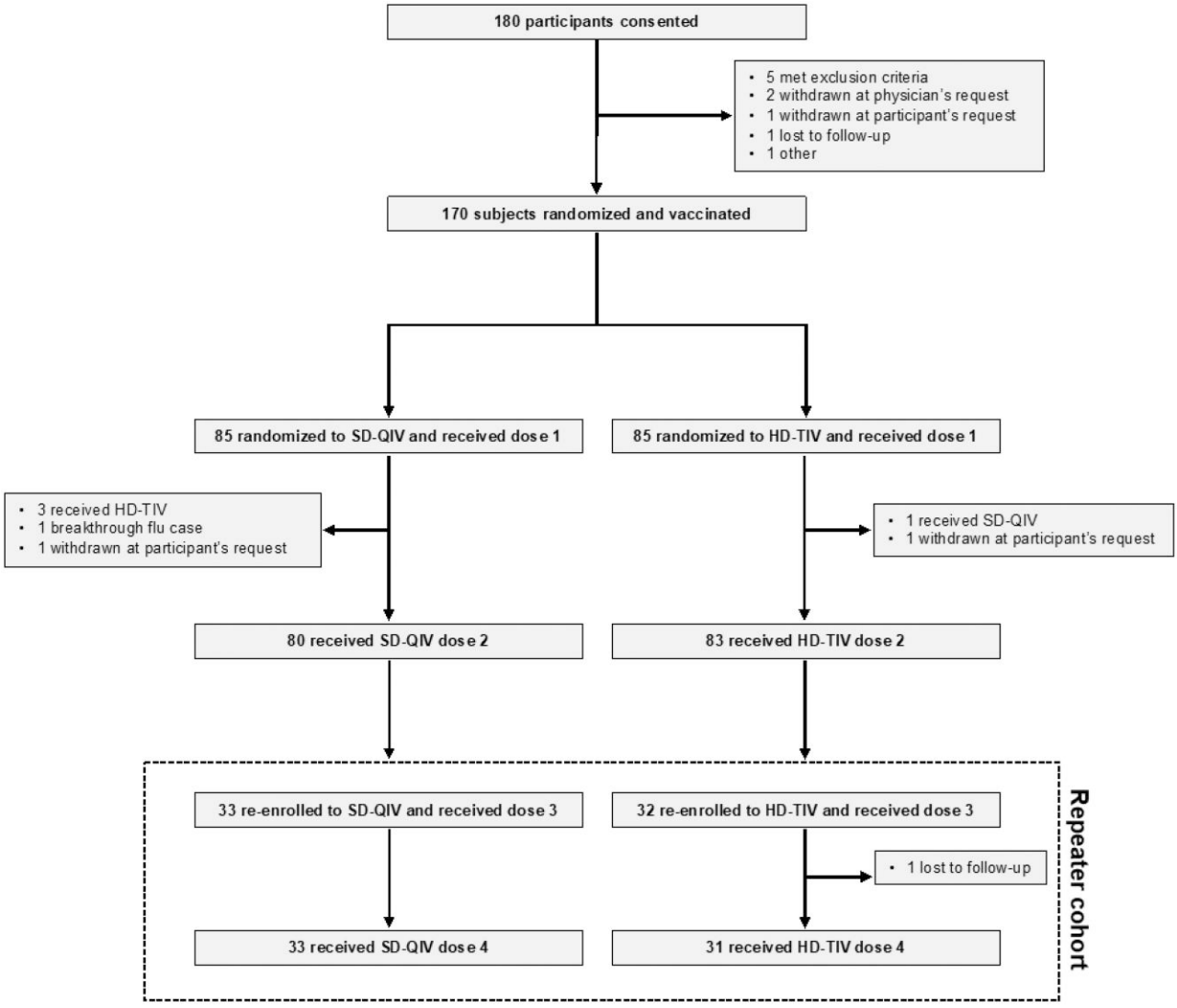

Figure 1. CONSORT diagram displaying the cohort of study repeaters. Of the 163 participants who received both doses in year 1 (n = 80 for SD-QIV and n = 83 for HD-TIV), 65 (39.9%) reenrolled for a subsequent influenza season (n = 33 for SD-QIV and n = 32 for HD-TIV). HD-TIV, high-dose trivalent influenza vaccine; SD-QIV, standard-dose quadrivalent influenza vaccine.

HAI titers to each antigen were summarized within each vaccine group at each visit as follows: geometric mean titer (GMT); proportion achieving dilutions ≥1:40, ≥1:80, and ≥1:160 (various proxies for seroprotection); proportion achieving ≥4-fold rise from visit 1/1R; and geometric mean fold rise from each year's baseline titer measurement.

In our model-based analyses of immunogenicity, missing data (including missing values resulting from incorrect vaccine doses) were addressed via multiple imputation by chained equations (M = 300 iterations). For titers below the lower limit of quantitation (<1:10), a value of 1:5 was imputed. Titers achieving the upper limit of quantitation (1:10 240) were supplied a value of 1:10 240. For each antigen, we used linear mixed models with log-transformed HAI titer as the outcome to estimate adjusted geometric mean ratios comparing between dose groups at a given time point (eg, HD-TIV vs SD-QIV at visit 3) and comparing within a dose group between time points in the repeater year and visit 3 of the initial year (eg, HD-TIV visit 2R vs HD-TIV visit 3); we included log-transformed baseline titer and $CD19^+$ count as adjustment covariates, in addition to participant-specific random intercepts. Note that results on B/Yamagata are reported as a control since this antigen was included in SD-QIV but not in HD-TIV.

We computed the absolute and relative frequencies of injection site and systemic reactions (overall and by reaction type) for each group following each of the 4 doses, stratified by reaction severity grade. Additionally, we computed frequencies of reactions by time postvaccine (days) and compared them with a Pearson χ^2 test.

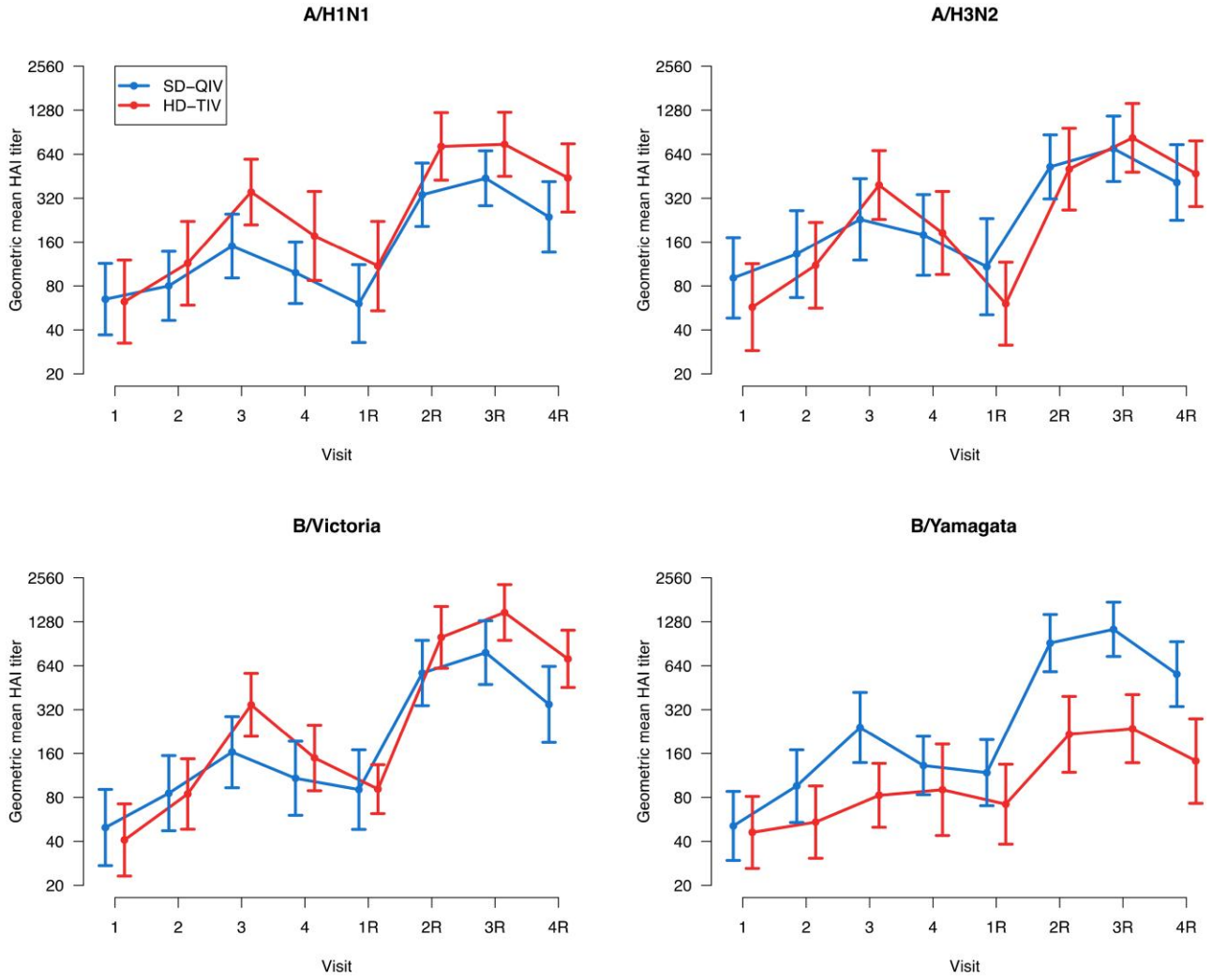

Figure 2. Point estimates and 95% CIs for geometric mean HAI titers at visits 1 through 4R, shown by antigen (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) and stratified by dose group (SD-QIV and HD-TIV). Note that B/Yamagata is not included in HD-TIV. HAI, hemagglutinin inhibition; HD-TIV, high-dose trivalent influenza vaccine; SD-QIV, standard-dose quadrivalent influenza vaccine.

RESULTS

Participants in Year 2 Cohort

In the primary study, 170 participants were randomized and received at least 1 vaccine dose. For this analysis, 65 participants (19 in 2017–2018, 28 in 2018–2019, and 18 in 2019–2020) elected to reenroll the following season, with 33 participants receiving SD-QIV and 32 receiving HD-TIV (Figure 1). Cohort demographics and clinical characteristics for participants reenrolling for a subsequent season were similar to those who participated in only the primary year of the study (Supplementary Table 2). Overall, 31 (47.7%) were male, 41 (63.1%) were White, 17 (26.2%) were Black, and 12 (18.5%) were Hispanic. The most common indication for HCT was malignancy. Severe aplastic anemia was the most common nonmalignant indication for HCT. The stem cell source for the majority of patients was bone marrow (67.7%).

The median age at year 2 of participation was similar between groups: 12.4 years (SD, 4.7 years) for the SD-QIV group and 12.0 years (SD, 4.3 years) for the HD-TIV group. Demographic, transplant-related, and clinical characteristics, with baseline laboratory values for the overall cohort and for each vaccine group, are summarized in Table 1, with additional details in Supplementary Table 3.

Antibody Responses

Figure 2 presents point estimates and 95% CIs for the GMTs for each vaccine group at each time point. Supplementary Table 4 and Supplementary Figure 3 present the data in more granular detail. Across antigens, the estimated GMTs were low at baseline for year 1; at visit 1R, estimated GMTs had largely regressed toward the baseline values of year 1 following the peak immunogenicity. Each vaccine dose in the repeater year was associated with

Table 1. Cohort Demographics and Clinical Characteristics Stratified by Treatment Arm and Year

	Year 1			Year 2		
	Control: SD-QIV (n = 33)	Experimental: HD-TIV (n = 32)	*P* Value	Control: SD-QIV (n = 33)	Experimental: HD-TIV (n = 32)	*P* Value
Sample characteristics						
Age at enrollment, y						
Mean (SD)	11.5 (4.7)	11.0 (4.3)	.69	12.4 (4.7)	12.0 (4.3)	.68
Time from transplant to enrollment, mo						
Mean (SD)	11.8 (7.6)	9.7 (6.4)	.25	23.5 (7.6)	21.3 (7.1)	.23
Median (IQR)	10.3 (5.2–15.6)	7.8 (4.5–13.1)	…	22.5 (18.0–27.7)	19.5 (16.2–24.3)	…
Time from transplant to enrollment No. (%)			.49			.51
<12 mo	20 (60.6)	22 (68.8)		0 (0)	1 (3.1)	
≥12 to <36 mo	13 (39.4)	10 (31.3)		31 (93.9)	30 (93.8)	
≥36 mo	0 (0)	0 (0)		2 (6.1)	1 (3.1)	
GVHD status at vaccine 1, No. (%)			.16			.31
Acute	1 (3.0)	2 (6.3)		0 (0.0)	0 (0)	
Chronic	1 (3.0)	5 (15.6)		0 (0)	1 (3.1)	
Baseline laboratory values at visit 1, median (IQR)						
WBC, $10^3/\mu L$	5.6 (4.4–8.2)	5.6 (4.5–6.7)	.41	7.4 (6.3–8.5)	7.6 (5.8–10.0)	.41
ANC, $10^3/\mu L$	3.2 (2.4–4.7)	2.8 (2.1–3.8)	.27	3.8 (3.0–5.0)	3.3 (2.9–5.1)	.46
ALC, $10^3/\mu L$	1.8 (1.3–2.5)	1.6 (0.99–2.5)	.61	2.6 (2.2–3.2)	2.7 (1.9–3.3)	.86
CD4 count	491 (220–769)	335 (203–594)	.39	956 (795–1049)	860 (625–1173)	.88
CD8 count	465 (288–788)	392 (208–783)	.46	660 (545–793)	734 (456–983)	.57
CD19 count	410 (254–677)	412 (205–771)	.76	665 (479–858)	683 (467–932)	.52
Hemoglobin, g/dL	13.1 (12.1–13.7)	12.6 (11.8–13.4)	.63	13.6 (12.6–14.7)	13.0 (12.3–13.9)	.15
Platelets, $10^3/\mu L$	229 (182–264)	217 (128–270)	.91	233 (182–296)	257 (190–341)	.31
Quantitative IgG, mg/dL	749 (629–1069)	645 (567–940)	.28	961 (651–1120)	834 (681–1070)	.54
Quantitative IgM, mg/dL	55 (36–102)	56 (24–103)	.67	80 (63–106)	84 (52–111)	.84

P values for continuous variables were calculated by the Student *t* test with unequal variance, and *P* values for categorical variables were calculated by the Pearson chi-square test. Years 1 and 2 indicate the first and second years that the participant was enrolled in the study.

Abbreviations: ALC, absolute leukocyte count; ANC, absolute neutrophil count; GVHD, graft-vs-host disease; HD-TIV, high-dose trivalent influenza vaccine; IgG, immunoglobulin G; IgM, immunoglobulin M; SD-QIV, standard-dose quadrivalent influenza vaccine; WBC, white blood count.

statistically significant rises in GMTs from baseline (geometric mean fold rises are reported in Table 2).

GMTs associated with a single dose in the subsequent year were higher than the GMTs associated with 2 doses of the same formulation in the first year; these findings are statistically significant for all antigens except A/H3N2 for HD-TIV (Table 3). Moreover, the GMTs associated with 2 doses in the repeater year are all significantly higher as compared with those associated with 2 doses of the same formulation in year 1. In comparing the immunogenicity of HD-TIV relative to SD-QIV following doses 1R and 2R, estimated GMTs were higher for HD-TIV for each of its 3 antigens contained in the vaccine (A/H1N1, A/H3N2, and B/Victoria), although the adjusted geometric mean ratios were not statistically significantly different (Table 2).

Of note, the World Health Organization (WHO) biological standards for influenza vaccine immunogenicity—specifically, >40% of participants achieving a ≥4-fold rise, a geometric mean fold rise >2.5, and >70% of participants achieving an HAI titer of ≥1:40—were met following a single dose of either formulation in the repeater year (Supplementary Table 5).

Reactogenicity and Safety in Year 2

The frequencies of any systemic reactions for combined years were comparable for the HD-TIV and SD-QIV groups at 59.4% and 69.7%, respectively ($P = .38$; Figure 3*A*). For the HD-TIV group, the frequency of these reactions was 43.8% in year 1 and 50.0% in year 2, whereas for the SD-QIV group, it was 45.5% in year 1 and 51.5% in year 2. The most commonly reported systemic reactions were headache and fatigue. Following the second dose in year 2, the observed frequency of any systemic reaction was similar between groups (50% for HD-TIV and 51.5% for SD-QIV, $P = .90$). Severe systemic reactions (grade 3) were consistent across groups and years: 3.1% and 0.0% in the HD-TIV group and 6.1% and 3.0% for the SD-QIV group for years 1 and 2, respectively. Systemic reactions for all vaccinations are reported by day and grade in Supplementary Figure 1.

Injection site reaction frequencies for combined years were comparable between the HD-TIV and SD-QIV groups at 78.1% and 78.8%, respectively ($P = .95$; Figure 3*B*). In year 1, the HD-TIV group reported reaction site frequencies of 71.9% as compared with 68.8% in year 2. For the SD-QIV group, 51.5% reported reactions in year 1, followed by 69.7% in year 2. The

Table 2. Point Estimates and 95% CIs for Group-Specific GMFRs and aGMRs, Comparing High vs Standard Dose, for Each Antigen at Each Follow-up Visit.

	GMFR (95% CI)		aGMR (95% CI)
	SD-QIV (n = 33)	HD-TIV (n = 32)	HD-TIV / SD-QIV
A/H1N1			
Year 1			
Visit 2	1.23 (.90–1.70)	1.83 (1.11–3.04)	1.65 (.85–3.23)
Visit 3	2.32 (1.35–3.97)	5.66 (2.88–11.1)	2.71 (1.39–5.30)
Visit 4	1.38 (.84–2.27)	2.79 (1.26–6.22)	1.93 (.92–4.09)
Year 2			
Visit 2R	5.98 (2.90–12.3)	6.40 (3.59–11.4)	1.88 (.99–3.62)
Visit 3R	7.48 (4.08–13.7)	6.96 (3.72–13.1)	1.60 (.83–3.10)
Visit 4R	3.80 (1.90–7.60)	3.23 (1.76–5.94)	1.31 (.58–2.92)
A/H3N2			
Year 1			
Visit 2	1.46 (.92–2.31)	1.94 (1.16–3.22)	1.28 (.63–2.61)
Visit 3	2.52 (1.43–4.44)	6.87 (3.09–15.3)	2.63 (1.29–5.36)
Visit 4	2.29 (1.38–3.78)	2.83 (1.44–5.54)	1.57 (.72–3.44)
Year 2			
Visit 2R	4.97 (2.58–9.56)	8.46 (4.56–15.7)	1.18 (.58–2.41)
Visit 3R	6.61 (3.54–12.4)	13.9 (7.15–27.1)	1.52 (.73–3.16)
Visit 4R	3.25 (1.39–7.60)	5.58 (2.93–10.6)	1.33 (.54–3.27)
B/Victoria			
Year 1			
Visit 2	1.72 (1.10–2.68)	2.07 (1.21–3.51)	1.18 (.59–2.37)
Visit 3	3.29 (1.80–6.03)	8.44 (4.02–17.8)	2.55 (1.27–5.10)
Visit 4	2.46 (1.19–5.11)	3.47 (1.78–6.76)	1.68 (.80–3.51)
Year 2			
Visit 2R	6.92 (3.69–13.0)	10.9 (6.21–19.3)	1.58 (.81–3.08)
Visit 3R	9.25 (5.22–16.4)	17.4 (9.99–30.1)	1.80 (.91–3.56)
Visit 4R	3.67 (1.99–6.76)	7.79 (4.64–13.1)	1.67 (.73–3.83)
B/Yamagata[a]			
Year 1			
Visit 2	1.88 (1.13–3.12)	1.18 (.89–1.56)	0.61 (.30–1.23)
Visit 3	4.73 (2.28–9.82)	1.79 (1.29–2.50)	0.37 (.18–.75)
Visit 4	2.86 (1.42–5.76)	1.84 (.83–4.09)	0.75 (.35–1.63)
Year 2			
Visit 2R	8.26 (4.00–17.1)	3.24 (2.05–5.11)	0.26 (.12–.55)
Visit 3R	9.78 (5.24–18.3)	3.27 (2.04–5.24)	0.23 (.11–.50)
Visit 4R	5.56 (2.74–11.3)	2.03 (1.20–3.43)	0.47 (.18–1.21)

Visit 2 titers are measured at a target window of 28–42 days following the first dose (prior to the second dose), visit 3 titers at a target window of 28–42 days following the second dose, and visit 4 titers at a target window of 138–222 days following the second dose.

Abbreviations: aGMR, adjusted geometric mean ratio; GMFR, geometric mean fold rise; HD-TIV, high-dose trivalent influenza vaccine; SD-QIV, standard-dose quadrivalent influenza vaccine.

[a]B/Yamagata is not included in HD-TIV.

Table 3. Point Estimates and 95% CIs for aGMRs, Comparing Each of Visits 2R and 3R vs Visit 3 (From Year 1), for Each Antigen and Each Dose Group.

	aGMR (95% CI)	
	SD-QIV (n = 33)	HD-TIV (n = 32)
A/H1N1		
Visit 2R/visit 3	2.26 (1.41–3.63)	2.06 (1.28–3.33)
Visit 3R/visit 3	2.96 (1.85–4.75)	2.29 (1.40–3.74)
A/H3N2		
Visit 2R/visit 3	2.29 (1.29–4.06)	1.32 (.73–2.38)
Visit 3R/visit 3	3.12 (1.74–5.60)	2.31 (1.26–4.25)
B/Victoria		
Visit 2R/visit 3	3.40 (2.03–5.72)	2.85 (1.68–4.84)
Visit 3R/visit 3	4.77 (2.82–8.09)	4.55 (2.67–7.77)
B/Yamagata[a]		
Visit 2R/visit 3	3.80 (2.17–6.65)	2.70 (1.50–4.84)
Visit 3R/visit 3	4.59 (2.58–8.17)	2.91 (1.59–5.33)

Visit 3 titers are measured at a target window of 28–42 days following the second dose in the first influenza season, visit 2R titers at a target window 28–42 days following the first dose in the repeater year, and visit 3R titers at a target window 28–42 days following the second dose in the repeater year.

Abbreviations: aGMR, adjusted geometric mean ratio; HD-TIV, high-dose trivalent influenza vaccine; SD-QIV, standard-dose quadrivalent influenza vaccine.

[a]B/Yamagata is not included in HD-TIV.

most common injection site reactions were pain, swelling, and tenderness, mostly grade 1 or 2 in severity (mild or moderate).

In year 2, there was no significant difference between the HD-TIV and SD-QIV groups in grade 3 injection site reactions (severe; 18.8% vs 18.2%, $P = .95$). While the percentage of children reporting any grade 3 reaction was similar in year 1 vs year 2 for the HD-TIV group (15.6% vs 18.8%, respectively; $P = .74$), there was a significant increase in the SD-QIV group between year 1 and year 2 (3.0% vs 18.2%; $P = .01$). Most of these reactions occurred within the first 2 days of vaccination (Supplementary Figure 2).

Laboratory-Confirmed Influenza Cases

During both influenza seasons, episodes of laboratory-confirmed influenza virus infections in participants were recorded (Supplementary Table 6). In the primary year, there were 6 cases: 4 in the HD-TIV group and 2 in the SD-QIV group. In the second year, there were 8 cases: 2 in the HD-TIV group and 6 in the SD-QIV group.

Of the 4 HD-TIV group cases in the primary year, 3 were attributed to B/Yamagata, a strain not present in the HD-TIV formulation. Notably, 1 SD-QIV participant tested positive for A/H1N1 22 days following the second immunization. Subsequently, this participant had an interval negative test and tested positive for B/Victoria 45 days following the second immunization.

DISCUSSION

In this extended substudy of our parent multicenter influenza vaccine study of pediatric HCT recipients in a phase 2 trial, we characterized the immunogenicity and safety of HD-TIV or SD-QIV administered in 2 consecutive influenza seasons. Our study demonstrated that a single dose of HD-TIV or SD-QIV in the second year of participation was more immunogenic than 2 doses of the same formulation in the initial influenza season. Moreover, the HD-TIV group exhibited a trend toward higher GMTs following 2 doses in the subsequent year when compared with 2 doses of SD-QIV, although

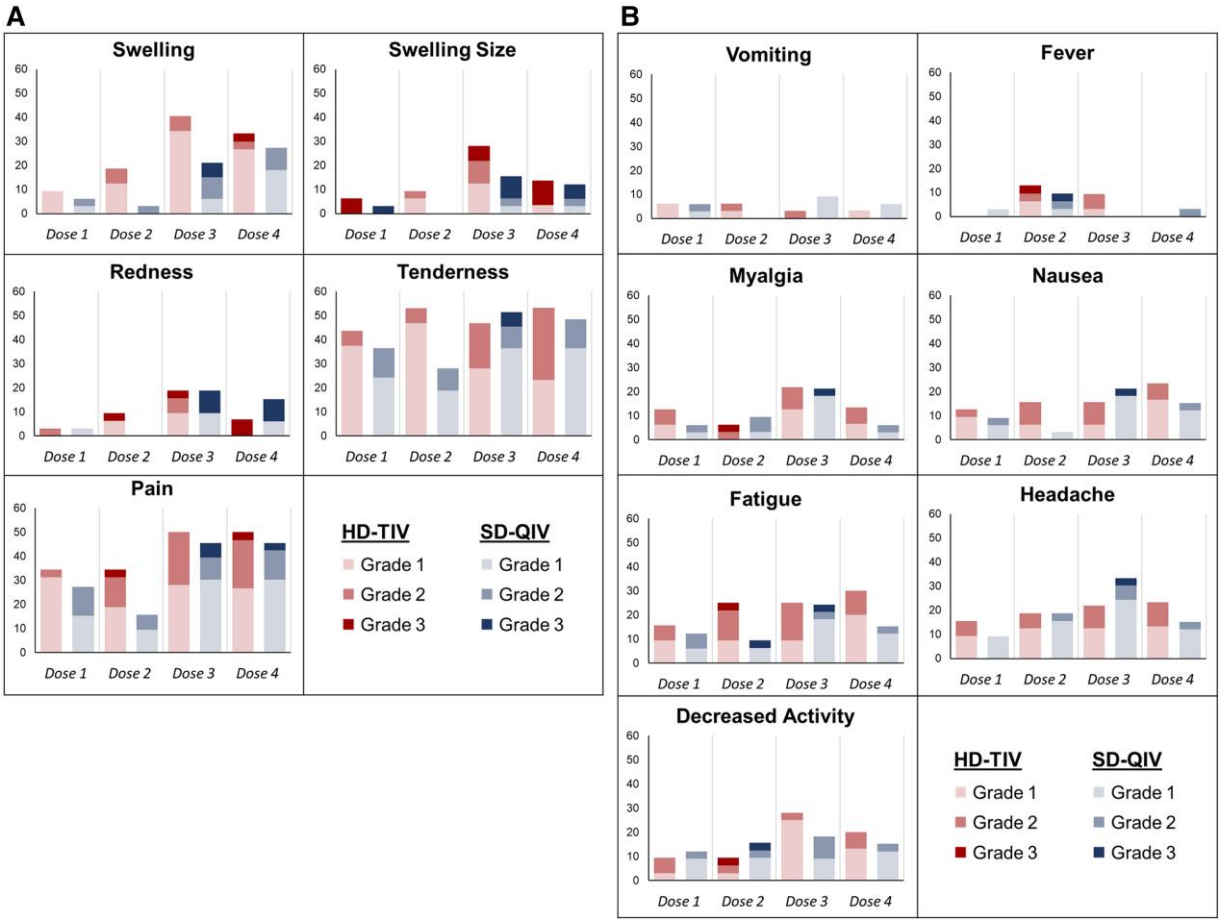

Figure 3. Relative frequency and severity of various reactions within each vaccine group after each of the 4 doses (doses 1 and 2 in year 1; doses 1R and 2R in year 2): *A*, systemic reactions; *B*, injection site reactions. Reaction severity was graded on a scale from 1 to 3 (mild, moderate, and severe, respectively). HD-TIV, high-dose trivalent influenza vaccine; SD-QIV, standard-dose quadrivalent influenza vaccine.

adjusted geometric mean ratios are not statistically significant. The groups had similar safety profiles, with limited injection site and systemic adverse reactions in year 2.

Our study represents the first evaluation of a 2-dose regimen of HD-TIV or SD-QIV in pediatric patients in consecutive influenza seasons post-HCT. Within the second season, we found that 1 vaccine dose of either formulation was sufficient to meet all 3 of the following WHO criteria for immunogenicity: >40% seroconversion (4-fold rise), GMT >2.5-fold increase, and >70% with a ≥1:40 HAI titer [3]. However, our original phase 2 trial (referred to as year 1 in this report) demonstrated that 2 doses of HD-TIV were required to achieve immunogenic superiority relative to 2 doses of SD-QIV. This study also revealed that a single dose of HD-TIV may be sufficient in the subsequent year for individuals receiving 2 doses of HD-TIV in the first influenza season post-HCT [6]. Additional studies are needed to determine if a single dose of SD inactivated influenza vaccine is sufficient following a 2-dose regimen of HD inactivated influenza vaccine.

This study demonstrated that 2 doses of HD-TIV were well tolerated in pediatric HCT recipients, even when administered in 2 consecutive influenza seasons. In the first year of this clinical trial, we had noted a higher frequency of injection site pain and tenderness in participants following the second HD-TIV dose, but these results were not reproduced in the second year of participation. Data from year 2 of our study showed a similar frequency and duration of injection site reactions and similar frequency of systemic adverse events after HD-TIV and SD-QIV. These findings contrast with previous studies in which 1 HD-TIV dose was associated with a higher frequency of injection site reactions as compared with 1 dose of SD-QIV [10, 13]. The majority of reactions in the second year were considered mild and resolved within 3 days. Our study supports the safety of the HD-TIV influenza vaccine and its repeated administration within the same season and in subsequent seasons within this population.

Several key limitations exist within this study. Although this is the largest pediatric HCT study comparing the safety and immunogenicity of 2 doses of HD-TIV and 2 doses of SD-QIV

over 2 influenza seasons, our study was sufficiently powered to detect differences between dose groups in only the initial influenza season. Furthermore, influenza vaccine composition varies annually depending on the prevalent strain circulating in the community, and improved immunogenicity in the second year may be attributable to modifications in the vaccine strain. This study excluded individuals with active, ongoing GVHD; as such, our findings may not be generalizable to all pediatric HCT recipients. Further investigation is required in patients with severe GVHD or those who have received rituximab to determine if a single dose in year 2 is adequate. Although we performed active influenza surveillance and noted a higher frequency of influenza virus infections among participants who received SD-QIV vaccine in the second year, this study was not powered to evaluate vaccine efficacy.

Our study demonstrated no safety concerns associated with the same vaccine dosing regimen in 2 consecutive influenza seasons. Additionally, 1 dose of either HD-TIV or SD-QIV in the subsequent year appears to be sufficient to achieve higher immunogenicity as compared with 2 doses of the same formulation in the initial year, as evidenced by meeting the WHO biological standards for vaccine response as well as achieving higher GMTs. However, whether the WHO thresholds are sufficient for protection in this high-risk population requires additional investigation, as does the potential impact of additional standard-dose influenza vaccine doses vs a high-dose vaccine in a single season. Inclusion of patients with ongoing immunosuppression, such as acute and chronic GVHD, is needed to further understand how to optimally protect this high-risk heterogenous population of pediatric patients after HCT.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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