Clinical Infectious Diseases

MAJOR ARTICLE

A Double-Blind, Randomized Trial of High-Dose vs Standard-Dose Influenza Vaccine in Adult Solid-Organ Transplant Recipients

Yoichiro Natori,[1] Mika Shiotsuka,[1] Jaclyn Slomovic,[1] Katja Hoschler,[2] Victor Ferreira,[1] Peter Ashton,[1] Coleman Rotstein,[1] Les Lilly,[1] Jeffrey Schiff,[1] Lianne Singer,[1] Atul Humar,[1,a] and Deepali Kumar[1,a]

[1]Multi Organ Transplant Program, University Health Network, University of Toronto, Ontario, Canada; and [2]Public Health England, London, United Kingdom

(See the Review Article by Chong et al on pages 1802–11.)

Background. The annual standard-dose (SD) influenza vaccine has suboptimal immunogenicity in solid organ transplant recipients (SOTRs). Influenza vaccine that contains higher doses of antigens may lead to greater immunogenicity in this population.

Methods. We conducted a randomized, double-blind trial to compare the safety and immunogenicity of the 2016–2017 high-dose (HD; FluzoneHD, Sanofi) vs SD (Fluviral, GSK) influenza vaccine in adult SOTRs. Preimmunization and 4-week postimmunization sera underwent strain-specific hemagglutination inhibition assay.

Results. We enrolled 172 patients who received study vaccine, and 161 (84 HD; 77 SD) were eligible for analysis. Seroconversion to at least 1 of 3 vaccine antigens was present in 78.6% vs 55.8% in HD vs SD vaccine groups ($P < .001$), respectively. Seroconversions to A/ H1N1, A/H3N2, and B strains were 40.5% vs 20.5%, 57.1% vs 32.5%, and 58.3% vs 41.6% in HD vs SD vaccine groups ($P = .006$, $P = .002$, $P = .028$, respectively). Post-immunization geometric mean titers of A/H1N1, A/H3N2, and B strains were significantly higher in the HD group ($P = .007$, $P = .002$, $P = .033$). Independent factors associated with seroconversion to at least 1 vaccine strain were the use of HD vaccine (odds ratio [OR], 3.23; 95% confidence interval [CI], 1.56–6.67) and use of mycophenolate doses <2 g daily (OR, 2.76; 95% CI, 1.12–6.76).

Conclusions. HD vaccine demonstrated significantly better immunogenicity than SD vaccine in adult transplant recipients and may be the preferred influenza vaccine for this population.

Clinical Trials Registration. NCT03139565.

Keywords. immunocompromised; immunogenicity; immunosuppression; seroconversion; seroprotection.

Organ transplantation is a curative and transformative therapy for patients with end-stage organ disease. The number of people living with organ transplants has grown significantly in the past decade, and it is estimated that there are approximately 200 000 patients living with kidney transplants in the United States alone [1]. All transplant recipients require life-long immunosuppression, which increases their risk of infection. Influenza virus infection is known to be an important cause of morbidity and mortality in organ transplant recipients [2]. Complications of influenza infection, including viral and bacterial pneumonia, appear to be common in this patient population, and prolonged shedding of virus may potentially lead to increased infectivity and spread during periods of heightened influenza activity [2–4].

Therefore, efforts aimed at the prevention of influenza in this uniquely susceptible population are of paramount importance. Although the annual influenza vaccine is suggested for all immunocompromised patients [5], the immunogenic response (seroconversion and seroprotection) to vaccine in transplant recipients is known to be suboptimal and ranges from 15% to 70% [6–9]. Several methods to improve vaccine immunogenicity in immunocompromised patients have been proposed. These include using booster doses, changing the method of delivery, using adjuvants, and increasing the dose of antigen delivered [7, 10, 11]. The majority of such measures have not resulted in clinically significant increases in immunogenicity, and currently no clear recommendations exist regarding the optimal influenza vaccine in transplant recipients. In addition, the use of boosters or multiple doses may be impractical since compliance with vaccination is already known to be challenging [12].

Inactivated standard-dose (SD) influenza vaccine contains 15 μg of each of 3 hemagglutinin proteins for 3–4 circulating strains. A high-dose (HD) influenza vaccine is also available that contains 60 μg from 3 circulating strains, which represents a 4-fold increase in dose compared to the standard vaccine [13]. In North America, the HD vaccine has been approved for use

Received 2 October 2017; editorial decision 24 November 2017; accepted 13 December 2017; published online December 14, 2017.

Correspondence: D. Kumar, Transplant Infectious Diseases & Multi Organ Transplant Program, University Health Network, 585 University Ave., 11-PMB-174, Toronto, Ontario M5G 2N2, Canada (deepali.kumar@uhn.ca).

[a]A. H. and D. K. contributed equally to the manuscript.

Clinical Infectious Diseases® 2018;66(11):1698–704

DOI: 10.1093/cid/cix1082

in the population aged ≥65 years, a subgroup with poor vaccine responses and increased complications of influenza due to immunosenescence [14, 15]. In this subgroup, studies with the HD vaccine have shown increased immunogenicity as well as a reduction in clinical influenza infections when compared to SD vaccine [13, 16–19]. We hypothesized that the HD vaccine may also be more immunogenic in organ transplant recipients. To assess this, we performed a randomized trial to compare the safety and immunogenicity of SD vs HD influenza vaccine in transplant patients during the 2016–2017 influenza season.

METHODS

Patient Population and Study Design

This study was conducted as part of a tertiary care organ transplant program and was a double-blind, randomized, controlled trial that compared the HD influenza vaccine vs the SD vaccine. We enrolled adult patients (aged ≥18 years) who had received an organ transplant (kidney, liver, heart, lung and pancreas, or combined organs) and had a functioning allograft. We excluded patients who were within 3 months post-transplant, had already received influenza vaccination for the 2016–2017 season, had an egg allergy or allergy to previous influenza vaccine, experienced febrile illness within 1 week prior, had an active cytomegalovirus infection, had a previous life-threatening reaction to influenza vaccine, or had received intravenous immunoglobulin in the past 30 days or was planning to receive intravenous immunoglobulin in the next 4 weeks. The institutional research ethics board approved the study. A letter of no objection to conduct the study was also obtained from Health Canada due to off-label use of HD vaccine.

After written informed consent was obtained from patients, participants were randomized to receive either HD or SD seasonal influenza vaccine in a 1:1 ratio. Both vaccines contained the same 3 influenza antigens in 0.5-mL volume: A/California/7/2009 (H1N1)pdm09, A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008. The HD vaccine was FluzoneHD (Sanofi, Canada), and the SD vaccine was Fluviral (GSK, Canada). Both vaccines are split-virus vaccines. Randomization was done using a computer-generated schedule in blocks of 4. The investigators, patients, and study team members who obtained consent and assessed adverse events were blinded to vaccine assignment. The study vaccine was prepared and administered to participants' nondominant arm by an unblinded physician not otherwise associated with the study. Sera were obtained before and 4 weeks after vaccination for strain-specific antibody testing. Study team members contacted participants at 2 and 7 days after vaccination to assess adverse events.

Outcomes

The primary outcome was vaccine immunogenicity by hemagglutination inhibition assay (HAI) based on an assessment of pre- and post-vaccine (4 weeks) antibody titer. The World Health Organization (WHO) recommends use of the HAI for validating annual vaccines [20–22]. Testing was performed at a WHO national influenza laboratory (Public Health England). Briefly, serum was incubated with an enzyme to remove any hemagglutinin inhibitors. Serum was then incubated with 0.7% turkey red blood cells (for A/H1N1 and B strains) and guinea pig red blood cells (for A/H3N2) and influenza virus. Titers were determined by doubling dilutions of antibody. Seroprotection was defined as a post-immunization titer of ≥1:40 to each of the 3 vaccine antigens. Seroconversion was defined as a ≥4-fold increase in titer compared to prevaccination as well as reaching a seroprotective titer. These definitions are based on standard criteria for influenza vaccine response. The primary outcome was seroconversion to at least 1 of the 3 vaccine antigens. HAI titers were also determined to a nonvaccine B strain (B/Phuket/3073/2013), which was contained in the 2016–2017 quadrivalent influenza vaccine but not in the study vaccines. Since quadrivalent vaccines are available, HAI titers to the additional B strain would provide information regarding differences in cross-protection between the study vaccines.

The secondary outcomes included local and systemic adverse events to vaccination. Adverse events were categorized as mild (no interference in daily activities), moderate (some interference in daily activities), and severe (participants unable to perform daily activities). We followed study participants for 6 months after vaccination for secondary outcomes including influenza infection, hospitalization, and biopsy-proven acute rejection episodes.

Statistical Analyses

The sample size was based on previous studies that used seasonal influenza vaccine in solid organ transplant recipients (SOTRs), which had indicated a response rate of approximately 50% to each of the 3 antigens in these vaccines. A 20%–25% percent increase in seroconversion rates would be recognized as a clinically significant difference to justify usage of HD vaccine. Therefore, for an alpha of 0.05 and a power of 80%, a sample size of 58 to 93 evaluable patients in each study group was required. The immunogenicity analysis was only performed in those who received a vaccine dose and returned for follow-up serum (per-protocol population). The safety analysis was performed in all patients who received the study vaccine regardless of whether they returned for follow-up serum. Demographics were analyzed using descriptive statistics. Differences in vaccine response rates between the 2 arms were compared using χ^2 or Fisher exact test. Pre- and post-vaccination titers were compared using Wilcoxon rank-sum test. Titers <10 were assigned a value of 5 for statistical analysis. Univariate analyses were performed to determine significant factors affecting seroconversion to at least 1 vaccine antigen using χ^2 test for categorical variables and Mann-Whitney U test for continuous variables. Mycophenolate mofetil (MMF) and mycophenolate sodium dose equivalencies

were calculated using previously published data [23]. For multivariate analysis, a model was developed using variables that had a P value < 0.2 on univariate analysis. Multivariate analysis was performed using binary logistic regression. Statistical significance was defined as a P value < 0.05. Statistical analysis was performed using IBM SPSS version 22.0 (Chicago).

RESULTS

Between 24 October 2016 and 27 January 2017, we screened 263 SOTRs (Figure 1). We excluded 91 patients for several reasons including refusal to participate (n = 74) and active participation in other interventional studies (n = 10). Therefore, we enrolled 172 SOTRs (87 HD, 85 SD), and all received study vaccine. Enrollment was completed once the minimum sample size target was reached and the influenza season was ending. Table 1 shows that the baseline characteristics of the cohorts from each group were well balanced. The overall median time from transplant to vaccination was 38 months (interquartile range, 12–89.5 months). Other demographic characteristics including influenza vaccination in the prior year, current immunosuppression, and type of organ transplanted were similar in the 2 groups.

Vaccine Immunogenicity: High Dose vs Standard Dose

Of the 172 enrolled patients, 10 did not provide post-vaccination sera and 1 patient developed influenza infection before providing follow-up serum. Those 11 patients were excluded from the immunogenicity analysis (Figure 1). Therefore, the immunogenicity analysis included 161 patients (84 HD, 77 SD).

Comparative seroconversion rates are shown in Table 2 and Figure 2. Seroconversion to at least 1 of 3 influenza antigens was 78.6% vs 55.8% in HD vs SD vaccine groups, respectively (P = .002; odds ratio [OR], 2.90; 95% confidence interval [95% CI], 1.46–5.77). Similarly, seroconversion to at least 2 and all 3 vaccine antigens was also greater for the HD vaccine group (Figure 2). Seroconversions to A/H1N1, A/H3N2, and B strains were 40.5% vs 20.8%, 57.1% vs 32.5%, and 58.3% vs 41.6% in HD vs SD vaccine groups (P = .007, P = .002, P = .033), respectively (Table 2). Geometric mean fold rise (GMFR; absolute fold-increase of titer from pre- to post-vaccination) for A/ H1N1, A/H3N2, and B/Brisbane strains was significantly greater in the HD vaccine group (P = .001, P = .005, P = .002, respectively; Table 2).

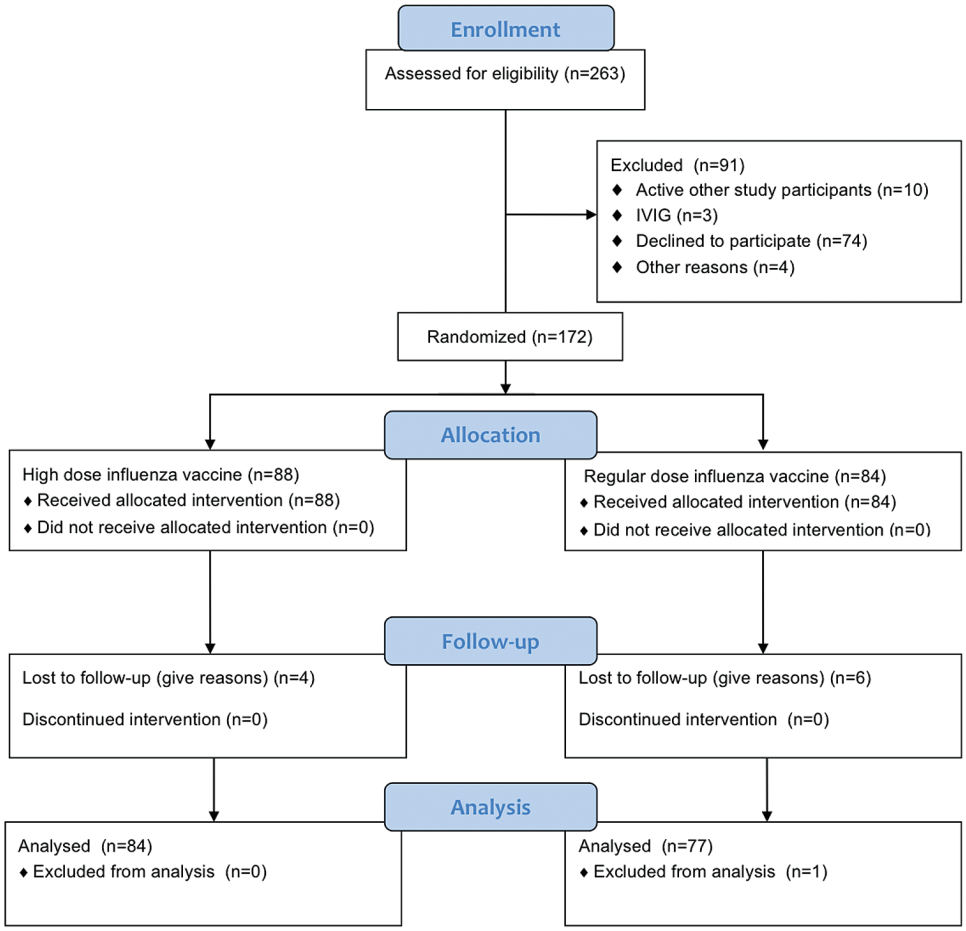

Figure 1. Study flow chart. Abbreviation: IVIG, intravenous immuneglobulin.

Table 1. Patient Characteristics at Enrollment

Characteristic	All (n = 172)	Standard Dose (n = 85)	High Dose (n = 87)	*P* Value
Age, median (range)	57 (18–86)	57(19–80)	57 (18–86)	.74
Male sex (%)	121 (70.3)	61 (71.8)	60 (69.0)	.69
Time from transplantation to vaccination (months), median (interquartile range)	38 (12–89.5)	33.5 (11–89.5)	48 (14–95)	.34
Within 1 year of transplantation (%)	40 (23.3)	22 (25.9)	18 (20.7)	.37
Previous year vaccination[a] (%)	116 (67.1)	59 (69.4)	64 (73.6)	.55
History of documented influenza[b] (%)	7 (4.1)	6 (7.1)	1 (1.1)	.06
Antithymocyte globulin within 6 months prior (%)	4 (2.3)	3 (3.5)	1 (1.1)	.37
Previous rejection (%)	4 (2.3)	3 (3.5)	1 (1.1)	.37
Type of transplant (%)				
Kidney	67 (39.0)	30 (35.3)	37 (42.5)	
Liver	38 (22.1)	19 (22.4)	19 (21.8)	
Lung	25 (14.5)	15 (17.6)	10 (11.5)	
Heart	23 (13.3)	12 (14.1)	11 (12.6)	
Combined	19 (11.0)	8 (9.4)	11 (12.6)	.77
Immunosuppression				
Prednisone (%)	131 (76.2)	64 (75.3)	67 (77.0)	.79
Prednisone dose, mg/day, median (range)	5 (2–40)	5 (2.5–40)	5 (2–30)	.60
Tacrolimus (%)	126 (73.3)	60 (70.6)	66 (75.9)	.44
Cyclosporine (%)	35 (20.3)	21 (24.7)	14 (16.1)	.16
Mycophenolate mofetil/mycophenolate sodium (%)	115 (66.9)	59 (69.4)	56 (64.4)	.48
Azathioprine (%)	11 (6.4)	8 (9.4)	3 (3.4)	.13
Sirolimus (%)	12 (7.0)	6 (7.1)	6 (6.9)	.99

Data apply to all patients who received study vaccine.

[a]Based on self report at the time of enrollment.

[b]Based on documentation in the transplant chart for the 2015–2016 influenza season.

Other Immunogenicity Parameters

Geometric mean titers (GMTs) before vaccination for A/H1N1, A/H3N2, and B/Brisbane strains were not significantly different in HD vs SD vaccine groups, respectively (Table 3). GMTs increased after vaccination for both vaccines ($P < .001$ for all strains and both study groups). GMTs after vaccination were significantly greater in the HD vaccine group compared to the SD group for A/ H1N1 and B/Brisbane (373.4 vs 227.3, 834.3 vs 446.4 in the HD group vs the SD group, $P = .014$, $P = <.001$, respectively; Supplementary Figure S1). For A/H3N2, there was a trend toward greater titers in the HD vaccine group (688.6 vs 453.1, $P = .053$). Preimmunization seroprotection rates ranged from 55.8% to 75.3% in the SD group and from 41.7% to 76.2% in the HD group. Post-immunization seroprotection rates ranged from 74% to 94% and were not significantly different between the vaccines (Table 3).

For B/Phuket, a strain not contained in the study vaccines, the HD vaccine group had a significantly greater seroconversion rate, GMFR, and post-vaccine GMT ($P = .004$, $P = .012$, and $P = .021$, respectively) compared to the SD vaccine group (Tables 2 and 3).

Factors that affected vaccine seroconversion to at least 1 antigen contained in the study vaccine were analyzed (Table 4). In univariate analysis, patients who received the equivalent of MMF <2 g/day and who received the HD vaccine had a greater likelihood of seroconversion ($P = .01$, $P = .003$, respectively). The multivariate model included all factors with *P* values < .2 in the univariate analysis. Receiving HD vaccine (compared to SD vaccine) and MMF equivalent <2 g/day (compared to ≥2 g/day) were associated with significantly greater seroconversion in the multivariate models; MMF equivalent <2 g (OR, 2.76; 95% CI, 1.12–6.76; $P = .027$) and HD vaccination (OR, 3.23; 95% CI, 1.56–6.67; $P = .002$; Table 4).

Table 2. Seroconversion to High-Dose vs Standard-Dose Influenza Vaccine, per-protocol Population

	Standard Dose (n = 77)	High Dose (n=84)	*P* Value
Seroconversion (%)			
A/H1N1	16 (20.8)	34 (40.5)	.007
A/H3N2	25 (32.5)	48 (57.1)	.002
B/Brisbane	32 (41.6)	49 (58.3)	.033
B/Phuket[a]	11 (14.3)	28 (33.3)	.005
Geometric mean fold rise			
A/H1N1	14.0	20.3	.001
A/H3N2	28.5	31.7	.005
B/Brisbane	5.4	20.4	.002
B/Phuket[a]	3.1	24.7	.011

[a]Influenza B strain not contained in study vaccines.

Vaccine Safety

Adverse events after vaccination were assessed in all 172 patients who received study vaccine. Within 7 days of vaccination, there

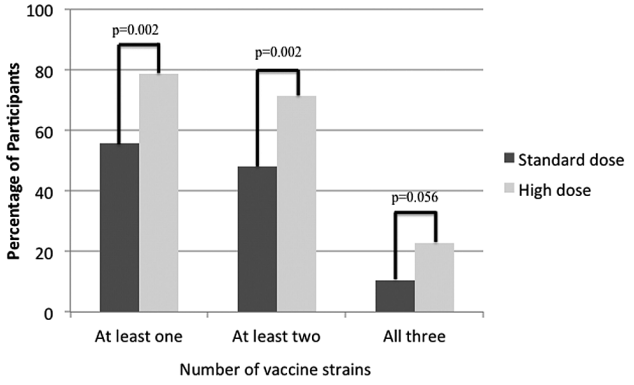

Figure 2. Seroconversion rates to at least 1, at least 2, or all 3 vaccine antigens based on vaccine type.

were no significant differences in local adverse events and fever after administration of HD and SD vaccines (Table 5). However, there was a trend toward greater overall systemic events with HD vaccine that predominantly included gastrointestinal complaints, arthralgias, and fatigue.

During the 6-month follow-up period, there were 23 hospitalizations; all were unrelated to immunization (15/85 in the SD vaccine group and 8/87 in the HD vaccine group; $P = .12$). Biopsy-proven rejection was noted in 4 patients.

Microbiologically confirmed influenza infection was diagnosed in 2 (2.4%) patients who received SD vaccine and 1 (1.1%) who received HD vaccine ($P = .62$). Two patients developed influenza A/H3N2 infection. This occurred in a study participant who received HD vaccine and developed infection 67 days after immunization despite having achieved seroprotective titers to A/H3N2 at 4 weeks. Another study participant developed A/H3N2 infection 8 days after receiving SD vaccine and required hospitalization. The third patient with influenza had received SD vaccine and developed an A/H1N1 infection 87 days after immunization. This patient had not achieved a seroprotective titer to A/H1N1 at 4 weeks.

Table 3. Geometric Mean Titers and Seroprotection Rates of High-Dose vs Standard-Dose Influenza Vaccine, per-protocol Population

	Standard Dose (n = 77)	High Dose (n = 84)	*P* Value
Geometric mean titer			
A/H1N1 (pre)	123.0	121.3	.20
A/H1N1 (post)	227.3	373.4	.014
A/H3N2 (pre)	69.0	95.7	.28
A/H3N2 (post)	453.1	688.6	.053
B/Brisbane (pre)	174.9	206.2	.53
B/Brisbane (post)	446.4	834.3	<.001
B/Phuket[a] (pre)	140.8	148.0	.88
B/Phuket[a] (post)	199.1	523.0	.023
Seroprotection post-vaccine (%)			
A/H1N1	64 (83.1)	70 (83.3)	.97
A/H3N2	57 (74.0)	67 (79.8)	.39
B/Brisbane	70 (90.9)	79 (94.0)	.55
B/Phuket[a]	51 (66.2)	67 (79.8)	.053

[a]Influenza B strain not contained in study vaccines.

DISCUSSION

We conducted a double-blind, randomized, controlled trial to compare HD vs SD influenza vaccines in a cohort of SOTRs. We found that HD vaccine had better immunogenicity as determined by the primary endpoint of seroconversion and a similar safety profile compared to SD vaccine. The increased rate of seroconversion was consistent across all 3 subtypes within the vaccine, as well as the nonvaccine B subtype tested. In the multivariate analysis, the HD vaccine was independently associated with seroconversion to at least 1 vaccine antigen. In addition, receipt of lower doses of mycophenolate were also significantly associated with seroconversion rates.

The HD influenza vaccine was approved by the US Food and Drug Administration in 2009 and recently was authorized by Health Canada for use in those aged ≥ 65 years. Studies with HD influenza vaccine in this age group have shown that HD vaccine has a relative efficacy of 24% in reducing the incidence of laboratory-confirmed influenza infection compared to SD vaccine [18]. In addition, immunogenicity studies have shown greater GMTs and seroconversion rates for HD vaccine compared to SD vaccine [16, 17, 19]. For example, Falsey et al showed that seroconversion rates were 11.8%–25.4% greater with HD vaccine compared to SD vaccine in persons aged ≥65 years [16]. Similarly, our study showed an absolute difference between HD and SD vaccine of 19.7% for A/H1N1, 24.6% for A/H3N2, and 16.7% for B. Both pre- and post-vaccination seroprotection rates were high with either vaccine, and no significant differences were observed. This is based on a conventional seroprotective titer of 1:40 as defined for the general adult population; it is not known whether this titer is protective for an immunosuppressed population. The protective titer may vary depending on the population studied. For example, Black et al showed that an HAI titer of 1:110 is required to protect 50% of children from influenza [24]. Therefore, we chose to use seroconversion as our primary outcome. No significant differences in adverse events were seen.

Organ transplant recipients are on life-long immunosuppression and generally have poor responses to influenza vaccine [6]. Mycophenolate has been shown in previous studies to be an especially potent inhibitor of vaccine immunogenicity likely because it inhibits B-cell function [7, 25]. Egli et al showed that high doses of MMF/mycophenolic acid inhibit influenza-induced CD86 and human leucocyte antigen-DR expression on B cells [25]. We made a similar finding in the current study. Other factors that influence vaccine response in transplant recipients include type of transplant, with lung transplant recipients having lower titers. In addition, time from transplant has been shown to be important, with lower immunogenicity in those within 6 months of transplant [26]. In the

Table 4. Factors Associated With Seroconversion to at Least 1 Influenza Antigen

	No Seroconversion (n = 52) (%)	Seroconversion (n = 109) (%)	Univariate *P* Value	Multivariate *P* Value	Odds Ratio
Female sex	15 (28.8)	33 (30.3)	.85		
Previous rejection	2 (3.8)	1 (0.9)	.24		
Previous vaccination	38 (73.1)	79 (72.5)	.94		
Azathioprine	4 (7.7)	7 (6.4)	.75		
Sirolimus	2 (3.8)	9 (8.3)	.51		
Prednisone	43 (82.7)	79 (72.5)	.17	.21	0.57 (0.24–1.37)
Calcineurin inhibitor	49 (94.2)	101 (92.7)	.99		
Mycophenolate mofetil equivalent <2 g/day (%)	**36 (69.2)**	**95 (87.2)**	**.009**	**.027**	**2.76 (1.12–6.76)**
Lung transplantation (%)	4 (7.7)	19 (17.4)	.15	.093	2.79 (0.84–9.26)
Within 6 months of transplantation	8 (15.4)	8 (7.3)	.16	.43	0.62 (0.19–2.04)
Aged >65 years (%)	7 (13.5)	23 (21.1)	.29		
High-dose vaccine (%)	**18 (34.6)**	**66 (60.0)**	**.003**	**.002**	**3.23 (1.56–6.67)**
Antithymocyte globulin within 6 months **(%)**	2 (3.8)	2 (1.8)	.60		
Age	57 (19–79)	57 (18–76)	.26		
Time from transplantation	36.5 (3–1402)	42.0 (3–288)	.76		

current study, we did not show these factors to be significant potentially since lung transplant recipients made up only 14.5% of the overall group and only 9.3% of patients were within 6 months of transplant. Previous studies in transplant recipients that have evaluated intradermal influenza vaccine preparations or adjuvanted influenza vaccines have not shown a significant benefit over standard intramuscular unadjuvanted preparations [7]. Recently, Cordero et al performed a randomized trial of 1 vs 2 doses of influenza vaccine in the same season [12]. They showed that in the per-protocol population, there was improved seroconversion and seroprotection for all 3 strains in the group that received 2 doses compared to 1 dose of vaccine. However, this strategy requires a second visit to a vaccine provider, and patient compliance with multidose vaccines is known to be low [27, 28]. To our knowledge, there is only 1 prior study in organ transplant recipients that used the HD influenza vaccine. This was a randomized trial in the pediatric organ transplant population (n = 38) that showed greater seroconversion rates in the A/H3N2 group with HD vaccine compared to SD vaccine, although this study was likely underpowered to detect differences across all vaccine-included serotypes [29].

Table 5. Adverse Events After Vaccination

	Standard Dose (n = 85)	High Dose (n = 87)	*P* Value
Adverse events within 7 days (%)			
Local	21(24.7)	23(26.4)	.80
Erythema	2(2.4)	2(2.3)	.99
Induration	2(2.4)	4(4.6)	.68
Tenderness	20(23.5)	23(26.4)	.66
Systemic	5(5.9)	13(14.9)	.079
Fever	4(4.7)	3(3.4)	.72
Gastrointestinal	0(0)	3(3.4)	.25
Arthralgia	0(0)	3(3.4)	.25
Fatigue	2(2.4)	7(8.0)	.17
Adverse events within 6 months (%)			
Hospitalization[a]	15(17.6)	8(9.2)	.12
Influenza	2(2.4)	1(1.1)	.62
Rejection	1(1.2)	3(3.4)	.62

Data apply to all patients who received study vaccine.

[a]Causes of hospitalization were as follows: influenza (n = 1), noninfluenza respiratory virus infection (n = 4), pneumonia (n = 1), pulmonary aspergillosis (n = 1), pulmonary embolism (n = 1), carbon dioxide retention (n = 1), diverticulitis (n = 1), pancreatitis (n = 1), cholangitis (n = 1), gastrointestinal bleeding (n = 1), gastritis (n = 2), confusion (n = 1), depression (n = 1), planned surgery (n = 4), cellulitis secondary to cat bite (n = 1), and rejection (n = 1).

Another novel finding in our study is that HD vaccine demonstrated significantly better immunogenicity for a non-vaccine antigen (ie, B/Phuket). Similar to a previous study by our group, this suggests that transplant recipients can develop heterologous immunity (ie, cross-reactive antibodies to antigens not included in the vaccine preparation) [30]. Our results further suggest that HD vaccines may be significantly better at generating heterologous immunity compared with SD vaccines.

Our study had some limitations. We did not conduct an efficacy study as influenza attack rates vary and this would require a prohibitively large sample size with possible evaluation over multiple seasons. However, immunogenicity is an accepted surrogate marker of protection and immunogenicity endpoints are frequently used to license seasonal influenza vaccines [13].

In conclusion, the HD vaccine had significantly better immunogenicity and similar safety compared to SD vaccine in adult organ transplant recipients. Therefore, our study suggests that HD vaccine should be used as the preferential vaccine in SOTRs to prevent influenza infection.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Author contributions. Y. N., A. H., and D. K participated in research design, writing of the paper, and performance of research and data analysis. L. S., C. R., and J. K. participated in writing of the paper and data

analysis. M. S., J. S., P. A., V. F., and K. H. participated in performance of research.

Disclaimer. Sanofi had no role in the design, conduct, analysis, or publication of the study.

Financial support. The study was partially funded by the Multi-Organ Transplant Program. FluzoneHD was purchased from Sanofi, Canada. Fluviral was obtained from the Ontario public health supply.

Potential conflicts of interest. D. K has received research funding from Roche and GSK and honoraria from GSK and Sanofi. A. H. has received research funding from Roche. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. United States Renal Data System. Annual Data Report. **2017**. Available at: https://www.usrds.org/2017/view/v2_06.aspx. Accessed 9 November 2017.
2. Kumar D, Michaels MG, Morris MI, et al; American Society of Transplantation H1N1 Collaborative Study Group. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis **2010**; 10:521–6.
3. Vilchez RA, Fung J, Kusne S. The pathogenesis and management of influenza virus infection in organ transplant recipients. Transpl Infect Dis **2002**; 4:177–82.
4. Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. Clin Infect Dis **2014**; 58:214–24.
5. Rubin LG, Levin MJ, Ljungman P, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis **2014**; 58:e44–100.
6. Kumar D, Blumberg EA, Danziger-Isakov L, et al; AST Infectious Diseases Community of Practice. Influenza vaccination in the organ transplant recipient: review and summary recommendations. Am J Transplant **2011**; 11:2020–30.
7. Baluch A, Humar A, Eurich D, et al. Randomized controlled trial of high-dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. Am J Transplant **2013**; 13:1026–33.
8. Candon S, Thervet E, Lebon P, et al. Humoral and cellular immune responses after influenza vaccination in kidney transplant recipients. Am J Transplant **2009**; 9:2346–54.
9. Scharpé J, Evenepoel P, Maes B, et al. Influenza vaccination is efficacious and safe in renal transplant recipients. Am J Transplant **2008**; 8:332–7.
10. Kumar D, Campbell P, Hoschler K, et al. Randomized controlled trial of adjuvanted versus nonadjuvanted influenza vaccine in kidney transplant recipients. Transplantation **2016**; 100:662–9.
11. Manuel O, Humar A, Chen MH, et al. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. Am J Transplant **2007**; 7:2567–72.
12. Cordero E, Roca-Oporto C, Bulnes-Ramos A, et al; TRANSGRIPE 1–2 Study Group. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1–2, a randomized controlled clinical trial. Clin Infect Dis **2017**; 64:829–38.
13. Centers for Disease Control and Prevention. Licensure of a high-dose inactivated influenza vaccine for persons aged >or=65 years (Fluzone High-Dose) and guidance for use—United States, 2010. Morb Mortal Wkly Rep **2010**; 59:485–6.
14. McElhaney JE. Influenza vaccine responses in older adults. Ageing Res Rev **2011**; 10:379–88.
15. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices—United States, 2017–18 influenza season. MMWR Recomm Rep **2017**; 66:1–20.
16. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis **2009**; 200:172–80.
17. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine **2007**; 25:7656–63.
18. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med **2014**; 371: 635–45.
19. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med **2006**; 166:1121–7.
20. Prince HE, Leber AL. Comparison of complement fixation and hemagglutination inhibition assays for detecting antibody responses following influenza virus vaccination. Clin Diagn Lab Immunol **2003**; 10:481–2.
21. Ellis JS, Zambon MC. Molecular analysis of an outbreak of influenza in the United Kingdom. Eur J Epidemiol **1997**; 13:369–72.
22. World Health Organization. Manual for the laboratory diagnosis and virological surveillance of influenza. **2011**. Available at: http://whqlibdoc.who.int/publications/2011/9789241548090_eng.pdf. Accessed 5 November 2017.
23. Salvadori M, Holzer H, de Mattos A, et al; ERL B301 Study Groups. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. Am J Transplant **2004**; 4:231–6.
24. Black S, Nicolay U, Vesikari T, et al. Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. Pediatr Infect Dis J **2011**; 30:1081–5.
25. Egli A, Humar A, Widmer LA, et al. Effect of immunosuppression on T-helper 2 and B-cell responses to influenza vaccination. J Infect Dis **2015**; 212:137–46.
26. Birdwell KA, Ikizler MR, Sannella EC, et al. Decreased antibody response to influenza vaccination in kidney transplant recipients: a prospective cohort study. Am J Kidney Dis **2009**; 54:112–21.
27. Nelson JC, Bittner RC, Bounds L, et al. Compliance with multiple-dose vaccine schedules among older children, adolescents, and adults: results from a vaccine safety datalink study. Am J Public Health **2009**; 99(Suppl 2):S389–97.
28. Gallagher KE, Kadokura E, Eckert LO, et al. Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review. BMC Public Health **2016**; 16:172.
29. GiaQuinta S, Michaels MG, McCullers JA, et al. Randomized, double-blind comparison of standard-dose vs. high-dose trivalent inactivated influenza vaccine in pediatric solid organ transplant patients. Pediatr Transplant **2015**; 19:219–28.
30. Kumar D, Ferreira VH, Campbell P, Hoschler K, Humar A. Heterologous immune responses to influenza vaccine in kidney transplant recipients. Am J Transplant **2017**; 17:281–6.