# A Systematic Review of Safety and Immunogenicity of Influenza Vaccination Strategies in Solid Organ Transplant Recipients

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**(See the Major Article by Natori et al on pages 1698–704.)**

Immunogenicity from seasonal inactivated influenza vaccine (IIV) remains suboptimal in solid organ transplant recipients (SOTRs). We conducted a systematic review that compared the safety and immunogenicity of nonstandard influenza vaccination strategies with single-dose IIV in SOTRs. Booster doses and possibly high-dose (HD) influenza vaccination strategies seem to hold promise for improving vaccination immunogenicity in SOTRs. Administration of intradermal and MF59-adjuvanted trivalent IIV (IIV3) did not improve vaccine immunogenicity compared with single-dose intramuscular IIV. Alternative vaccine strategies were generally well tolerated; SOTRs who received HD, intradermal or adjuvanted IIV3 had a higher frequency of infection site reactions, while systemic adverse events were more frequent in SOTRs who received HD IIV3. Allograft rejection rates were similar in both groups. SOTRs should continue to receive standard-dose IIV annually in accordance with current recommendations, pending future studies to determine the optimal timing, frequency, and dosage of IIV using the booster-dose strategy.

**Keywords.** influenza vaccination; solid organ transplants; immunogenicity; immunization.

Influenza is an acute respiratory infection with a disease spectrum that ranges from a self-limited febrile illness to a highly severe disease, accounting for up to 49 000 deaths annually in the United States [1]. Immunocompromised individuals, including solid organ transplant recipients (SOTRs), are among those at highest risk for influenza-associated complications, such as allograft rejection and secondary bacterial pneumonia [2, 3].

The Centers for Disease Control and Prevention recommends use of annual influenza vaccination to reduce influenza-associated complications [4]. In SOTRs, immunological responses to influenza vaccination tend to be lower and more heterogeneous than in immunocompetent hosts, with seroprotection rates ranging from 15% to 90% [5–8]. Owing to the high likelihood of inadequate seroresponse secondary to intensified immunosuppression in the early posttransplantation period, the 2013 Infectious Diseases Society of America Clinical Practice guideline vaccinating immunocompromised hosts recommends annual administration of inactivated influenza vaccine (IIV) >2 months after transplantation (strong, low recommendation), except when influenza outbreaks occur, during which IIV should be offered and administered as early as 1 month after transplantation (weak, very low) [9].

Because influenza-associated complications continue to be an important cause of hospitalizations and deaths in SOTRs [10], various strategies such as high-dose (HD) influenza vaccines, a booster-dose (BD) strategy, intradermal vaccination, and adjuvanted vaccines have been used. However, it remains unclear whether these alternative strategies improve immunogenicity over the standard approach (single standard dose [SD], intramuscularly administered IIV) in SOTRs. Understanding available data on the safety and immunogenicity of these nonstandard influenza vaccination strategies may help clinicians make informed decisions about which strategy to undertake. We conducted this systematic review to evaluate and synthesize current evidence to address our primary question of whether alternative influenza vaccination strategies are (1) more immunogenic and (2) as safe as the standard single-dose intramuscular IIV in SOTRs.

## METHODS

### Search Strategy

With the assistance of an experienced medical librarian, MEDLINE (1946 through June 2017) and EMBASE (1947 through June 2017) were searched, using a combination of search terms that included "influenza vaccine(s)," "flu shot,"

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"flu vaccine," "influenza vaccination," and "flu vaccination," combined with "transplants," "transplant," "graft(s)," "transplant recipients," and "organ transplantation." The reference lists of selected articles were also searched for potentially eligible studies.

### Study Selection and Extraction

Two investigators (P .P. C and D. J. W) developed eligibility criteria a priori using PICOTS (population, intervention, comparison, outcome[s], and study design) criteria. Our study population consisted of adult and pediatric SOTRs, defined as recipients of heart, lung, liver, kidney, pancreas, intestinal, or multivisceral transplants, alone or in combination. Studies performed in hematopoietic stem cell transplant recipients and other immunocompromised hosts, such as patients with rheumatologic diseases and human immunodeficiency virus infection, were excluded. Any alternative (nonstandard) influenza vaccination approach, predefined as use of intradermal or HD influenza vaccine, SD influenza vaccine administered more than once per season (BD strategy), and/or use of adjuvanted influenza vaccine was considered an intervention.

Studies were included only if they compared the safety and immunogenicity of alternative influenza vaccination approaches with that of single SD intramuscular trivalent IIV (IIV3) in adult and/or pediatric SOTRs. All studies that included a comparator group were eligible for inclusion, regardless of whether they were randomized controlled trials. Vaccine immunogenicity was defined based on the international European Agency for the Evaluation of Medicinal Products/Committee for Proprietary Medicinal Products 1997 criteria [11] and may include ≥1 of the following: (1) seroprotection rate, defined as the proportion of individuals achieving titers ≥1:40; (2) seroconversion rate, defined as postvaccination titers >1:40 if prevaccination serum was negative or ≥4-fold increase in antibody titers if it was positive; and (3) geometric mean titer (GMT), defined as the mean postvaccination antibody titer. Studies published in non-English languages and those with only abstracts available were excluded.

Two independent reviewers (P. P. C and D. J. W) reviewed the title and abstract search, with inclusion decisions for each article made independently based on inclusion and exclusion criteria. Any discrepancies were resolved by consensus after a full-text review by both reviewers. Data extraction for eligible studies was conducted independently, focusing on the safety and immunogenicity of various alternative influenza vaccination strategies.

## RESULTS

### Study Range and Characteristics

The initial search yielded 1950 articles/abstracts (1372 articles/abstracts from EMBASE and 578 articles/abstracts from MEDLINE) (Figure 1). Of those, 428 were duplicates and

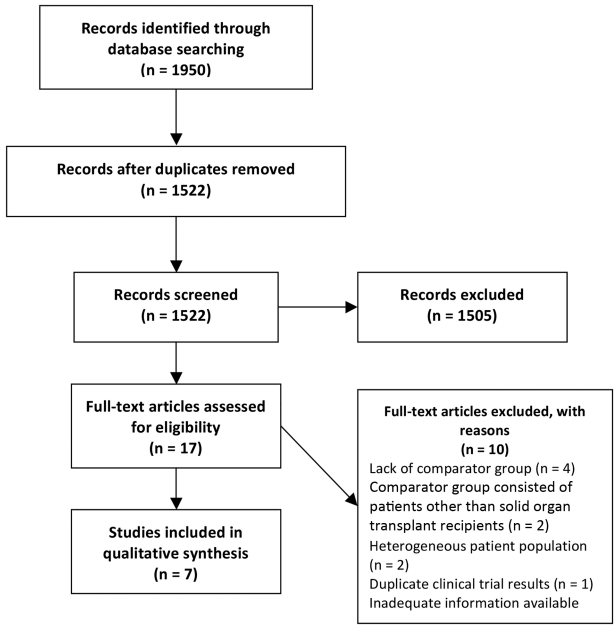


**Figure 1.** Flow chart of search.

excluded. After titles and abstracts of the remaining 1522 publications were screened, 17 articles were retrieved in full text and 7 studies met eligibility criteria. Reasons for exclusion include lack of (n = 4) [12–15] or non-SOTR (n = 2) [16, 17] comparator group, heterogeneous patient population including patients with rheumatologic disease and human immunodeficiency virus infection (n = 2) [18, 19], concerns regarding study methods (n = 1) [20], and duplicate trial results (n = 1) [21] (Figure 1).

Table 1 summarizes characteristics of the 7 selected studies, including 6 randomized controlled trials [22–27] and 1 prospective cohort study [28]. Alternative influenza vaccination strategies evaluated in these studies included HD IIV3 [23] (n = 1), BD intramuscular IIV3 [24, 28] (n = 2), intradermal IIV3 [22, 26, 27] (n = 3), and adjuvanted IIV3 [25] (n = 1). All studies included SOTRs who received SD intramuscular IIV3 as a comparator group.

### Patient Demographics and Inclusion/Exclusion Criteria

The 7 selected studies yielded a total of 943 patients (Table 1). Of these, 92% (868 of 943) were adult SOTRs, and 30% (279 of 943) were female. Transplant types included kidney (n = 422), liver (n = 229), lung (n = 181), heart (n = 89), intestinal (n = 1), and multiorgan transplants (n = 21). Most studies included SOTRs ≥3 months after transplantation (5 of 7 studies) and excluded those with a recent history of allograft rejection (5 of 7 studies) and those with a documented history of severe adverse reactions to influenza vaccination (4 of 7 studies).

### Influenza Vaccine Characteristics and Vaccination Strategy

The alternative influenza vaccination strategy used differed across all 7 studies. GiaQuinta et al [23] investigated the effects

**Table 1. Characteristics of Assessed Studies**

| Reference | Study Design | Study Population (Sample Size) | Dose, Route, and No. of Doses | | End Points | |
|---|---|---|---|---|---|---|
| | | | Intervention Group[a] | Comparator Group[a] | Effectiveness | Safety |
| Baluch et al [22] | RCT, blocked randomization, outcome assessor blinded | Adults and children Age and type of transplants N=229 | HD, intradermal, 2 doses in succession; Intanza; A/California/7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, B/Brisbane/60/2008; 9 μg of antigen per strain in 0.1 mL | SD IIV3, intramuscular, 1 dose; Vaxigrip | Seroconversion[b] to ≥1 influenza vaccine antigen | Anti-human leukocyte antigen antibodies; local and systemic AEs; allograft rejection and graft function |
| GiaQuinta et al [23] | RCT, double-blind phase 1 safety and efficacy study | Children (aged 3–17 y) (N = 38) | HD (60 μg), intramuscular, 1 or 2 doses[c]; HD Fluzone; A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), B/Brisbane/60/2008 60 μg per 0.5 mL | SD (15 μg) IIV3, intramuscular 1 or 2 doses[c]; Fluzone | Seroconversion rates[d]; seroprotection rates[e]; differences between pre- and postdose GMTs | Local and systemic AEs; allograft rejection |
| Cordero et al [24] | RCT, stratified randomization, phase 3, open label | Adults (aged ≥16 y) (N = 424) | SD IIV3, intramuscular, 5 wk after 1st dose; Mutagrip; A/California/7/2009 (H1N1), A/Victoria/361/2011(H3N2), B/Wisconsin/1/2010 | SD IIV3, intramuscular, 1 dose; Mutagrip | Seroconversion rates Seroprotection rates, postvaccination GMT; microbiologically confirmed influenza cases during follow-up | AEs; allograft rejection |
| Hojsak et al [28] | Prospective cohort study | Children, LT recipients (N = 37) | SD IIV3, intramuscular, 4–6 wk after 1st dose; Vaxigrip; A/H1N1 New Caledonia/20/99, A/H3N2 Wisconsin/67/05, B/Malaysia/2506/04 | SD IIV3, intramuscular, 1 dose[f]; Vaxigrip; A/H1N1 New Caledonia/20/99, A/H3N2 New York/55/04, B/Shanghai/361/02 | Seroconversion rates[d]; seroprotection rates[e]; differences between pre- and postdose GMTs | AEs |
| Kumar et al [25] | RCT | Adult KT recipients (N = 68) | Adjuvanted IIV3 with MF59, intramuscular, 1 dose; Fluad A/California/7/2009 (H1N1), A/Victoria/361/2011(H3N2), B/Wisconsin/1/2010; 15 μg of antigen per strain in 0.5 mL | Nonadjuvanted IIV3, intramuscular, 1 dose; Agriflu A/California/7/2009 (H1N1), A/Victoria/361/2011(H3N2), B/Wisconsin/1/2010; 15 μg of antigen per strain in 0.5 mL | Seroconversion[b] to ≥1 influenza vaccine antigen | Local and systemic AEs; allograft rejection |
| Morelon et al [26] | RCT, phase 2, open label with screening step | Adult (aged 18–60 y) KT recipients (N = 62) | SD, intradermal, 1 dose; Vaxigrip; A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004; 15 μg of antigen per strain in 0.5 mL | SD IIV3, intramuscular or SC, 1 dose; Vaxigrip; A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004; 15 μg of antigen per strain in 0.5 mL | Seroconversion rates; seroprotection rates; GMT; GMTR[g] 21 d after vaccination | Local and systemic AEs |
| Manuel et al [27] | RCT, investigator-blinded | Adult lung transplant recipients (N = 85) | SD, intradermal, 2 simultaneous doses; Fluviral or Mutagrip; A/Brisbane/59/2007(H1N1), A/Brisbane/10/2007(H3N2), B/Florida/4/2006; 6 μg of antigen per strain in 0.1 mL | SD IIV3, intramuscular, 1 dose; Fluviral or Mutagrip; A/Brisbane/59/2007(H1N1), A/Brisbane/10/2007(H3N2), B/Florida/4/2006; 15 μg of antigen per strain in 0.5 mL | Seroconversion rates; seroprotection rates[h]; seroconversion factor[i]; vaccine response[j] | Acute allograft rejection |

Abbreviations: AEs, adverse events; GMT, geometric mean titer; GMTR, GMT ratio; HD, high dose; IIV3, inactivated trivalent influenza vaccine; KT, kidney transplant; LT, liver transplant; RCT, randomized controlled trial; SD, standard dose.

[a]Influenza vaccines were nonadjuvanted unless listed otherwise.

[b]Defined as ≥4-fold rise in titer from baseline.

[c]Subjects aged <9 years received either 1 or 2 doses of vaccine based on Advisory Committee on Immunization Practices recommendations.

[d]Percentage of subjects achieving a ≥4-fold increase in hemagglutination inhibition (HAI) titers from a seropositive prevaccination titer (≥10) or a rise from <10 to ≥40 in those who are seronegative.

[e]Percentage of subjects achieving an HAI titer ≥1:40.

[f]Historical controls (previous influenza season of 2004–2005).

[g]Defined as ratio of GMT between post- and prevaccination titers.

[h]Percentage of subjects achieving a HAI titer ≥1:32.

[i]Ratio of hemagglutination inhibition titer before and after vaccination.

[j]Defined as seroconversion to ≥1 of the 3 vaccine antigens.

of HD IIV3 containing 60 μg of antigen per influenza virus strain; Kumar et al [25] evaluated an MF59-adjuvanted vaccine that contained 15 μg of antigen per strain. Studies that investigated the use of intradermal IIV3 used 6 μg of antigen per strain administered simultaneously in 2 doses (cumulatively, 12 μg of antigen per strain) [27], 9 μg of antigen per strain administered simultaneously in 2 doses (cumulatively, 18 μg of antigen per strain) [22] and 15 μg of antigen per strain in a single dose [26]. Cordero et al [24]. and Hojsak et al [28] evaluated BD strategies in which 2 sequential doses of SD IIV3 were administered 5 or 4–6 weeks apart, respectively.

The comparator group in all studies consisted of SOTRs who received SD IIV3 containing 15 μg of antigen of each of 2 A (H1N1 and H3N2) strains and 1 B strain of influenza given as a single 0.5-mL intramuscular dose. Selection of vaccine strains was dependent on the annual recommendations by the World Health Organization based on circulating influenza strains (Table 1).

#### Vaccination Immunogenicity

All 7 studies assessed for vaccination immunogenicity by measuring pre- and postvaccination strain-specific influenza antigen titers using hemagglutination inhibition assay (Table 2). The timing of serum sample collection varied, most commonly 4 weeks after vaccination but ranging between 3 [26] to 6 weeks after vaccination [23, 28]. Most studies (86%; 6 of 7) included seroconversion rate, seroprotection rate and differences in pre- and postvaccination GMT as measures of vaccine immunogenicity. Short-term immunogenicity was assessed in all studies; long-term immunogenicity at 12 months after vaccination was evaluated in 1 study [24].

##### *Intradermal Influenza Vaccine*

Using a 2-dose simultaneous administration strategy, seroconversion rates to ≥1 influenza antigen did not differ between intradermal and intramuscular groups (48.2% [55 of 114] vs 42.6% [49 of 115; $P$ = .47] [22] and 14.6% [6 of 41] vs 18.6% [8 of 43; $P$ = .77] [27]). In addition, pre- and postvaccination GMT and seroprotection rates were also not different [22, 27]. Baluch et al [22] noted a trend toward higher postvaccination GMT (41.31 vs 29.1; $P$ = .07) and seroprotection rate (63.6% vs 52.4%; $P$ = .10) for influenza B in the intradermal group, but the differences was not significant. Manuel et al [27] reported significantly lower seroprotection rates for A/H3N2 (83% vs 98%; $P$ = .02) and influenza B (29% vs 58%; $P$ < .01) in the intradermal group compared with the comparator group.

Morelon et al [26] reported higher seroconversion rates for influenza A/H1N1 (35% [11 of 31] vs 19% [6 of 31]) and A/H3N2 (35% [11 of 31] vs 19% [6 of 31]) but not influenza B (19% [6 of 31 vs 19% [6 of 31]) in the intradermal group. Similarly, seroprotection rates were higher for influenza A/H1N1 (71% [22 of 31] vs 52% [16 of 31]), A/H3N2 (52% [16 of 31] vs 36% [11 of 31]) and similar for influenza B (71% [22 of 31] vs 61% [19 of 31]) in the intradermal group. Postvaccination GMT was higher for influenza A/H1N1 in the intradermal group than in the comparator group (95.7% vs 44.7%); these values were similar in the 2 groups for A/H3N2 (38.3% vs 25.3%, respectively) and influenza B (48.4% vs 41.4%) [26].

Baluch et al [22] analyzed factors that influenced seroprotection. SOTRs receiving ≥2 g/d of mycophenolate mofetil (MMF) (37.3% vs 62.7%; $P$ = .02), lung transplant recipients (28% vs 72%; $P$ = .02), and those <6 months after transplantation (8.7% vs 91.3%; $P$ = .01) had a significantly lower seroprotection rate for A/H1N1. Patients receiving ≥2 g/d of MMF (36.6% vs 63.4%; $P$ = .04) and those <6 months after transplantation (6.5% vs 93.5%; $P$ < .01) also had lower seroprotection rates for influenza B [22].

##### *HD Influenza Vaccine*

In the study by GiaQuinta et al [23], 38 pediatric SOTRs were randomized to either HD or SD IIV3. Seroconversion for A/H3N2 occurred in a higher proportion of the HD group compared with the SD group (54% vs 13%; $P$ = .01) [23], but the seroprotection rate for A/H1N1 (95% vs 80%; $P$ = .14) and influenza B (46% vs 47%; $P$ = .94) and postvaccination GMTs for A/H1N1 (GMT difference, 462.9; 95% confidence interval [CI], −85.9 to 1112.4) did not differ between the 2 groups [23].

##### *BD Influenza Vaccine*

Cordero et al [24] reported the results of the TRANSGRIPE 1-2 study, an open-label, phase 3, parallel-group, randomized controlled clinical trial that evaluated the safety and efficacy of a BD administered 5 weeks after an initial dose of IIV3 compared with the single SD intramuscular nonajuvanted IIV3 in SOTRs. Using modified intention-to-treat (mITT) analysis, 2 doses of influenza vaccine was associated with a higher seroconversion rate for influenza A(H1N1)pdm at 10 weeks using bivariable analyses (46.7% vs 32.7%; odds ratio [OR], 1.81; 95% CI, 1.01–3.24; $P$ = .05) but not to other influenza strains, or after adjustment for potential confounders in multivariable analyses. In the per-protocol analysis, a BD of IIV3 was independently associated with a higher likelihood of seroconversion at 10 weeks for all influenza strains, with the number needed to treat to achieve seroconversion being 7 [24].

Seroprotection rate was higher in the BD than in the control group using mITT, for the 3 types of influenza virus: 54% versus 43.2% (OR, 1.54; 95% CI, 1.05–2.27; $P$ = .03) for A(H1N1)pdm; 56.9% versus 45.5% (OR, 1.58; 95% CI, 1.08–2.31; $P$ = .02) for A(H3N2); and 83.4% versus 71.8% (OR, 1.97; 95% CI, 1.23–3.16; $P$ < .01) for influenza B. A booster IIV3 dose was independently associated with higher seroprotection rates, with the number needed to treat to achieve seroprotection being ≤10 for all 3 strains. Short-term postvaccination GMTs were significantly higher in the BD group than in the control group, an effect observed only in bivariable analysis in both the mITT and per-protocol analyses but not the multivariable analyses and only for influenza A/H3N2 and influenza B. At 1 year after

**Table 2. Summary of Vaccine Immunogenicity**

| Study | Immunogenicity Marker | Intervention Group[a] | Comparator Group[a] | *P* Value[b] |
|---|---|---|---|---|
| Baluch et al [22] | *A/H1N1* | *HD* | *SD* | |
| | Seroprotection rate[c] | 71 (76/107) | 70.5 (74/105) | .93 |
| | Seroconversion rate[d] | 37.4 (40/107) | 34.3 (36/105) | .64 |
| | Prevaccination GMT | 24.0 (18.2–31.6) | 22.1 (16.7–29.3) | .61 |
| | Postvaccination GMT | 68.9 (50.4–94.3) | 62.2 (45.7–84.9) | |
| | Geometric mean seroconversion factor[e] | 2.87 | 2.81 | .64 |
| | *A/H3N2* | *HD* | *SD* | |
| | Seroprotection rate | 70.1 (75/107) | 63.8 (67/105) | .33 |
| | Seroconversion rate | 29 (31/107) | 30.5 (32/105) | .81 |
| | Prevaccination GMT | 21.9 (17–26.7) | 19.7 (15.9–24.6) | .48 |
| | Postvaccination GMT | 51.1 (40.2–64.8) | 43.6 (33.5–56.7) | |
| | Geometric mean seroconversion factor[e] | 2.35 | 2.19 | .81 |
| | *B* | *HD* | *SD* | |
| | Seroprotection rate | 63.6 (68/107) | 52.4 (55/105) | .10 |
| | Seroconversion rate | 21.5 (23/107) | 17.1 (18/105) | .42 |
| | Prevaccination GMT | 18.6 (14.4–24) | 17.0 (13.4–21.5) | .07 |
| | Postvaccination GMT | 41.41 (31.8–53.6) | 29.1 (22.3–38) | |
| | Geometric mean seroconversion factor[e] | 2.22 | 1.72 | .42 |
| GiaQuinta et al [23] | *A/H1N1* | *HD* | *SD* | |
| | Seroprotection rate | 95.5 (21/22) | 80 (12/15) | .14 |
| | Seroconversion rate | 68 (15/22) | 47 (7/15) | .19 |
| | Prevaccination GMT | 77.5 (35.2–170.5) | 62 (20.9–155.1) | NA |
| | Postvaccination GMT | 773.2 (374.6–1363.3) | 310.3 (124–718.4) | NA |
| | GMT difference estimate | 695.7 (305.3–1299.2) | 248.3 (32.9–681.9) | NA |
| | *A/H3N2* | *HD* | *SD* | |
| | Seroprotection rate | 86 (19/22) | 80 (12/15) | .61 |
| | Seroconversion rate | 54 (12/22) | 13 (2/15) | .01 |
| | Prevaccination GMT | 34.7 (21–55.7) | 93.3 (47.4–195.5) | NA |
| | Postvaccination GMT | 131.7 (76.7–233.5) | 136.1 (71.8–254) | NA |
| | GMT difference estimate | 97 (35.8–194) | 42.8 (−64.4 to 170.5) | NA |
| | *B* | *HD* | *SD* | |
| | Seroprotection rate | 46 (10/22) | 47 (7/15) | .94 |
| | Seroconversion rate | 18 (4/22) | 33 (5/15) | .29 |
| | Prevaccination GMT | 19.6 (14.2–26.8) | 21.1 (11.4–48.9) | NA |
| | Postvaccination GMT | 36.8 (23.3–60.6) | 36.2 (18.9–83.2) | NA |
| | GMT difference estimate | 17.2 (1.9–42.4) | 15.1 (−15.4 to 62.1) | NA |
| Cordero et al [24] | Short-term[f] | | | |
| | *A/H1N1* | *BD* | *Single SD* | *OR (95% CI)* |
| | Seroprotection rate | 54 (114/211) | 43.2 (92/213) | 1.54 (1.05–2.27) |
| | Seroconversion rate | 46.7 (43/211) | 32.7 (33/213) | 1.81 (1.009–3.24) |
| | Postvaccination GMT | 41.61 (32.90–52.61) | 33.34 (25.45–43.67) | 0.06 (−.01 to 0.04) |
| | *A/H3N2* | *BD* | *Single SD* | *OR (95% CI)* |
| | Seroprotection rate | 56.9 (120/211) | 45.5 (97/213) | 1.58 (1.08–2.31) |
| | Seroconversion rate | 39.1 (45/211) | 30.2 (38/213) | 1.49 (.87–2.54) |
| | Postvaccination GMT | 44.73 (35.16–56.85) | 27.16 (21.43–34.41) | 0.14 (.01–.07) |
| | *B* | *BD* | *Single SD* | |
| | Seroprotection rate | 83.4 (176/211) | 71.8 (153/213) | 1.97 (1.23–3.16) |
| | Seroconversion rate | 75.9 (63/211) | 63.9 (53/213) | 1.78 (.91–3.50) |
| | Postvaccination GMT | 180.08 (139.45–232.57) | 95.31 (71.91–126.32) | 0.16 (.02–.06) |
| | Long-term[f] | | | |
| | *A/H1N1* | *BD* | *Single SD* | *OR (95% CI)* |
| | Seroprotection rate | 27 (57/211) | 33.3 (71/213) | 0.74 (.49–1.12) |
| | Seroconversion rate | 20.7 (19/211) | 19.8 (20/213) | 1.05 (.52–2.13) |

**Table 2. Continued**

| Study | Immunogenicity Marker | Intervention Group[a] | Comparator Group[a] | *P* Value[b] |
|---|---|---|---|---|
| | Postvaccination GMT | 15.94 (13.33–19.07) | 17.48 (14.40–21.22) | −0.03 (−.05 to .02) |
| | *A/H3N2* | *BD* | *Single SD* | *OR (95% CI)* |
| | Seroprotection rate | 48.3 (102/211) | 53.5 (114/213) | 0.81 (.56–1.19) |
| | Seroconversion rate | 40.9 (47/211) | 45.2 (57/213) | 0.84 (.50–1.40) |
| | Postvaccination GMT | 42.58 (32.69–55.45) | 46.46 (35.61–60.62) | −0.02 (−.03 to .02) |
| | *B* | *BD* | *Single SD* | *OR (95% CI)* |
| | Seroprotection rate | 73.5 (155/211) | 69 (135/213) | 1.24 (.89–1.89) |
| | Seroconversion rate | 63.9 (53/211) | 50.6 (42/213) | 1.73 (.91–3.50) |
| | Postvaccination GMT | 77.67 (61.09–98.75) | 69.55 (54.53–88.71) | 0.03 (−.02 to .04) |
| Hojsak et al [28] | *A/H1N1* | *BD* | *Single SD* | … |
| | Seroprotection rate (baseline) | 48 (18/37) | 58.8 (10/17) | |
| | Seroprotection rate (1 dose) | 64.9 (24/37) (*P* = .08)[g] | 64.7 (11/17) (*P* = .33) | |
| | Seroprotection rate (2 doses) | 75 (27/32) (*P* = .005) | NA | |
| | Seroconversion rate (1 dose) | 40.5 (15/37) | 17.6 (3/17) | |
| | Seroconversion rate (2 doses) | 54.0 (20/37) | NA | |
| | GMT (t1) | 31.35 | 47.08 | |
| | GMT (t2) | 67.59 (*P* = .37) | 65.25 (*P* = .09) | |
| | GMT (t3) | 80.00 (*P* = .001) | NA | |
| | *A/H3N2* | | | |
| | Seroprotection rate (baseline) | 43.2 (16/37) | 16.7 (3/18) | |
| | Seroprotection rate (1 dose) | 70.3 (26/37) (*P* = .003) | 47.1 (8/17) (*P* = .06) | |
| | Seroprotection rate (2 doses) | 84.4 (27/32) (*P* ≤ .001) | NA | |
| | Seroconversion rate (1 dose) | 35.1 (13/37) | 42.2 (7/17) | |
| | Seroconversion rate (2 doses) | 56.7 (21/37) | NA | |
| | GMT (t1) | 39.26 | 12.6 | |
| | GMT (t2) | 89.52 (*P* = .028) | 33.00 (*P* = .03) | |
| | GMT (t3) | 103.75 (*P* = .001) | NA | |
| | *B* | | | |
| | Seroprotection rate (baseline) | 8.1 (3/37) | 50 (9/18) | |
| | Seroprotection rate (1 dose) | 35.1 (13/37) (*P* = .003) | 58.8 (10/17) (*P* = .58) | |
| | Seroprotection rate (2 doses) | 35.5 (11/32) (*P* = .009) | NA | |
| | Seroconversion rate (1 dose) | 40.5 (15/37) | 16.7 (3/18) | |
| | Seroconversion rate (2 doses) | 48.6 (18/37) | NA | |
| | GMT (t1) | 7.99 | 46.6 | |
| | GMT (t2) | 24.12 (*P* < .001) | 69.48 (*P* = .13) | |
| | GMT (t3) | 21.3 (*P* < .001) | NA | |
| Kumar et al [25][h] | *A/H1N1* | *MF59-adjuvanted IIV3, intramuscular, 1 dose* | *Nonadjuvanted IIV3, intramuscular, 1 dose* | |
| | Seroprotection rate | 83.9% | 86.2% | .80 |
| | Seroconversion rate | 45.2% | 48.3% | .28 |
| | Prevaccination GMT | 31.3 | 28.6 | .77 |
| | Postvaccination GMT | 136.8 | 123.0 | .65 |
| | Seroconversion factor | 4.37 | 4.30 | .73 |
| | *A/H3N2* | | | |
| | Seroprotection rate | 100% | 93.1% | .23 |
| | Seroconversion rate | 48.4% | 34.5% | .28 |
| | Prevaccination GMT | 62.6 | 71.0 | .86 |
| | Postvaccination GMT | 209.2 | 184.7 | .96 |
| | Seroconversion factor | 3.34 | 2.60 | .56 |
| | *B* | | | |
| | Seroprotection rate | 61.3% | 65.5% | .73 |
| | Seroconversion rate | 32.3% | 24.1% | .49 |
| | Prevaccination GMT | 28.6 | 22.0 | .36 |
| | Postvaccination GMT | 71.5 | 48.4 | .33 |
| | Seroconversion factor | 2.50 | 2.20 | .98 |

**Table 2. Continued**

| Study | Immunogenicity Marker | Intervention Group[a] | Comparator Group[a] | *P* Value[b] |
|---|---|---|---|---|
| Morelon et al [26] | *A/H1N1* | *SD, intradermal, 1 dose* | *SD IIV3, intramuscular or subcutaneous, 1 dose* | NA[i] |
| | Seroprotection rate | 71 (22/31) | 52 (16/31) | |
| | Seroconversion rate | 35 (11/31) | 19 (6/31) | |
| | Prevaccination GMT | 30.9 (18.9–50.6) | 23.1 (13.5–39.7) | |
| | Postvaccination GMT | 95.7 (55.1–166) | 44.7 (24.3–82.4) | |
| | GMTR | 3.09 (2.17–4.40) | 1.93 (1.30–2.88) | |
| | *A/H3N2* | | | |
| | Seroprotection rate | 52 (16/31) | 36 (11/31) | |
| | Seroconversion rate | 35 (11/31) | 19 (6/31) | |
| | Prevaccination GMT | 10.9 (0.8–21.4) | 10.8 (8.66–13.5) | |
| | Postvaccination GMT | 38.3 (25–58.5) | 25.3 (15.8–40.4) | |
| | GMTR | 3.50 (2.29–5.34) | 2.34 (1.56–3.51) | |
| | *B* | | | |
| | Seroprotection rate | 71 (22/31) | 61 (19/31) | |
| | Seroconversion rate | 19 (6/31) | 19 (6/31) | |
| | Prevaccination GMT | 24.7 (18.5–33.0) | 23.4 (16.1–33.9) | |
| | Postvaccination GMT | 48.4 (34.7–67.4) | 41.4 (27.8–61.4) | |
| | GMTR | 1.96 (1.57–2.44) | 1.77 (1.38–2.27) | |
| Manuel et al [27] | *A/H1N1* | *SD, intradermal, 2 simultaneous doses* | *SD IIV3, intramuscular, 1 dose* | |
| | Seroprotection rate | 39 (16/41) | 28 (12/43) | .36 |
| | Seroconversion rate | 7.3 (3/41) | 7 (3/43) | >.99 |
| | Prevaccination GMT | 12.3 (8.8–17.1) | 12.0 (8.8–16.4) | .91 |
| | Postvaccination GMT | 15.7 (11.1–22.3) | 17.5 (11.8–25.9) | |
| | Seroconversion factor | 1.3 (1.0–1.6) | 1.5 (1.2–1.9) | .15 |
| | *A/H3N2* | | | |
| | Seroprotection rate | 83 (16/41) | 98 (42/43) | .02 |
| | Seroconversion rate | 4.9 (2/41) | 7 (3/43) | >.99 |
| | Prevaccination GMT | 74.6 (47.3–117.6) | 83.0 (61.8–111.6) | .60 |
| | Postvaccination GMT | 84.0 (52.0–135.7) | 108.9 (77.5–153.2) | |
| | Seroconversion factor | 1.1 (0.98–1.3) | 1.3 (1.1–1.6) | .24 |
| | *B* | | | |
| | Seroprotection rate | 29 (12/41) | 58 (12/43) | .36 |
| | Seroconversion rate | 7.3 (3/41) | 11.6 (5/43) | .71 |
| | Prevaccination GMT | 11.5 (7.6–17.4) | 14.1 (9.3–21.3) | .28 |
| | Postvaccination GMT | 14.5 (9.6–21.8) | 20.2 (12.8–31.9) | |
| | Seroconversion factor | 1.3 (1.1–1.5) | 1.4 (1.0–1.9) | .65 |

Abbreviations: BD, booster dose; CI, confidence interval; GMT, geometric mean titer; GMT (t1), GMT at baseline,; GMT (t2), GMT after single-dose influenza vaccine; GMT (t3), GMT after 2 doses of influenza vaccine; GMTR, GMT ratio; HD, high dose; IIV3, inactivated trivalent influenza vaccine; NA, not applicable; OR, odds ratio; SD, standard dose.

[a]Unless otherwise specified, values represent % (proportion) of patients for seroprotection and seroconversion rates and [mean? median?] (95% CI) for GMT, GMTR, and GMT difference.

[b]Values represent *P* values unless otherwise specified.

[c]Seroprotection rates are defined as the percentage of subjects achieving a hemagglutination inhibition titer ≥1:40.

[d]Seroconversion rates are defined as the percentage of subjects achieving ≥4-fold rise in titer from baseline.

[e]The geometric mean seroconversion factor is defined as the ratio of GMT between post- and prevaccination titers.

[f]Results presented are from intention-to-treat analysis.

[g]*P* values for Hojsak et al represent difference between immunogenicity marker after a single dose (or 2 doses) of influenza vaccine compared with baseline in the same study subject.

[h]Proportions for rates and confidence intervals for GMTs were not provided by Kumar et al.

[i]Morelon et al used descriptive statistics; statistical testing not done, and *P* values were not available.

vaccination, no differences in rates of seroconversion, seroprotection, and GMTs were observed between treatment groups.

In a prospective cohort study performed in pediatric liver transplant recipients (n = 37), Hojsak et al [28] reported higher seroprotection rates after 2 sequential SDs of the intramuscular IIV3, 4–6 weeks apart during the 2005–2006 influenza season for all 3 strains compared with baseline, as follows: A/H1N1, 75% versus 48.6% ($P = .005$); A/H3N2, 84.4% versus 43.2% ($P \leq .001$); and B, 35.5% versus 8.1% ($P < .01$). Seroprotection rates for the group that received single SD intramuscular IIV3 during the 2004–2005 influenza season were as follows, again compared with baseline seroprotection rates: A/H1N1, 64.7% versus 58.8% ($P = .33$); A/H3N2, 47.1% versus 16.7% ($P = .06$); and B, 58.8% versus 50% ($P = .58$).

*Adjuvanted SD Influenza Vaccine*

In a clinical trial of adult kidney transplant recipients randomized to receive either MF59-adjuvanted IIV3 or nonadjuvanted IIV3, the seroprotection and seroconversion rates and postvaccination GMTs did not differ between the 2 groups [25]. A subgroup analysis demonstrated that MF59-adjuvanted IIV3 was the only factor significantly associated with seroconversion (OR, 6.10; 95% CI, 1.2 –28.6) [25]. Use of MMF at ≥2 g/d (44.4% vs 71.4%; $P = .05$) and older age (OR per year of increasing age, 0.95; 95% CI, .90–.99) were significantly associated with lower seroconversion rates [25].

### Vaccine Safety

*Intradermal Influenza Vaccine*

The proportion of local adverse events (AEs), such as erythema ($P < .001$), induration ($P < .001$), tenderness ($P < .001$), and pruritus ($P = .005$), were significantly higher with intradermal IIV3 [22, 26] (Table 3). Although Manuel et al [27] reported a higher percentage of local AEs, this difference was not statistically significant (41% vs 25%; $P = .16$). Local AEs were mild or moderate in severity, and their severity and duration did not different between the 2 groups.

Systemic AEs did not differ between the intradermal and comparator groups in the studies by Morelon et al (55% vs 52%) [26] and Manuel et al [27] (7% vs 16%; $P = .31$). Baluch et al [22] reported a higher frequency of nausea and diarrhea in the intradermal group. Allograft rejection rates within 6 months after vaccination also did not differ between the intradermal and comparator groups; graft function was stable in all patients at the time of follow-up in this study, and confirmed development of de novo anti-human leukocyte antigen antibody was reported in only 1.4% (3 of 212) [22].

*HD Influenza Vaccine*

SOTRs who received HD IIV reported more injection site tenderness (73% vs 40%; $P = .05$), erythema (82% vs 47%; $P = .02$), myalgias (27% vs 0%; $P = .03$), and fatigue (23% vs 0%; $P = .05$) [23]. Allograft rejection occurred in 2.6% (1 of 38) 6 months after influenza vaccination in the SD group and thus was deemed unrelated [23].

*BD Strategy*

Rates of allograft rejection rates and local and systemic AEs did not differ significantly between the BD and comparator groups ($P > .05$) [24]. Most AEs reported were mild or moderate in severity.

*Adjuvanted SD Influenza Vaccine*

SOTRs who received the MF59-adjuvanted IIV3 were significantly more likely to develop injection site tenderness than those who received nonadjuvanted intramuscular IIV3 (77.4% vs 51.6%; $P = .03$); other local and systemic AEs did not differ between the 2 groups. Only 1 episode of acute allograft rejection was reported 3 weeks after vaccination during the 6-month follow-up period, and this occurred in the nonadjuvanted vaccine group.

## DISCUSSION

Despite alternative influenza vaccination strategies, seroconversion and seroprotection rates for influenza antigens were low in SOTRs. Neither intradermal [22, 26, 27] nor adjuvanted [25] influenza vaccine strategies improved immunogenicity compared with single SD intramuscular IIV3. Whereas HD and BD IIV3 conferred better seroprotection, antigen-specific immunogenicity varied substantially across studies. Pediatric SOTRs who received HD IIV3 were more likely than those in the SD IIV3 group to seroconvert for A/H3N2, but not for A/H1N1 or influenza B. In the TRANSGRIPE 1-2 study, a booster IIV3 dose administered 5 weeks after the first dose was significantly associated with a higher seroconversion rate for A/H1N1 but not for other strains [24]. The heterogeneity in influenza antigen-specific immunogenicity seems unpredictable and independent of the vaccination strategy. A prospective cohort study performed in pediatric liver transplant recipients reported significantly higher seroprotection rates for all 3 influenza strains after 2 sequential SDs of the intramuscular IIV3, 4–6 weeks apart [28].

Among transplant types, lung transplant recipients had the lowest seroresponse rates to influenza vaccination. In addition to ≥2 g/d of MMF and vaccination within 6 months after transplantation, Baluch et al [22] found that lung transplant recipients had lower seroprotection rates to A/H1N1 and that intradermal influenza vaccine had greater immunogenicity in recipients of non-lung transplants in a subgroup analysis. In another study by Manuel et al [27], seroconversion rates to each of the IIV3 influenza antigens in lung transplant recipients ranged from 5% to 12% . Limited data are available regarding long-term immunogenicity of alternative influenza vaccination strategies. In the TRANSGRIPE 1-2 study, the 1-year postvaccination seroconversion, seroprotection rates and GMTs did not differ between the BD and SD groups. A decrease in the 1-year GMT was noted in both groups [24].

These nonstandard influenza vaccination strategies seem to be safe and generally well tolerated. SOTRs who received HD, intradermal, and adjuvanted IIV were more likely to experience local AEs, which were mild or moderate and transient injection site reactions. Systemic AEs were more frequent in SOTRs who received HD IIV3. Allograft rejection rates did not differ between the alternative and standard influenza vaccine groups.

There was substantial heterogeneity in the design, protocols, and data analyses of the included studies, some of which could have introduced bias. Morelon et al [26] prescreened and enrolled only adult renal transplant recipients who were vaccinated in the previous influenza season but failed to serorespond to A/H3N2. Enrolled patients were thus less likely to serorespond, possibly accounting for low seroconversion and seroprotection rates. This same study reported only descriptive statistics and did not perform statistical comparisons, so differences in vaccine immunogenicity for each antigen are highly subject to interpretation.

**Table 3. Adverse Events Attributed Attributed to Influenza Vaccination**

| AEs by Study[a] | Patients, % (Proportion) | | *P* Value[b] |
|---|---|---|---|
| | Intervention Group | Comparator group | |
| Baluch et al [22] | Intradermal | Intramuscular | |
| Local[c] | | | |
| Erythema | 55.3 (63/114) | 7 (8/114) | <.001 |
| Induration | 30.7 (35/114) | 7 (8/114) | <.001 |
| Pruritus | 18.4 (21/114) | 1.8 (2/114) | <.001 |
| Tenderness | 57.9 (66/114) | 24.6 (28/114) | <.001 |
| Systemic[c] | | | |
| Fatigue | 10.6 (12/114) | 8.8 (10/114) | .13 |
| GI symptoms | 15.8 (18/114) | 5.2 (6/114) | .016 |
| Subjective fever | 4.4 (5/114) | 1.8 (2/114) | .45 |
| GiaQuinta et al [23][d] | High dose | Standard dose | |
| Local | | | |
| Overall | 82 | 47 | .03 |
| Tenderness | 73 | 40 | .05 |
| Systemic | | | |
| Fatigue | 23 | 0 | .05 |
| Myalgias | 27 | 0 | .03 |
| Cordero et al [24] | | | |
| Severity of AEs | Booster dose | Standard dose | OR (95% CI)[e] |
| Mild | 68 | 82.5 | 0.82 (.74–.91) |
| Moderate | 30 | 31.7 | 0.94 (.73–1.23) |
| Severe[f] | 8.3 | 8.6 | 1.07 (.61–1.89) |
| Serious AEs[f] | 6.4 | 7.5 | 0.86 (.45–1.63) |
| Graft rejection | 0.8 | 1.2 | 0.68 (.11–4.09) |
| Kumar et al [25] | | | |
| Local | Adjuvanted | Nonadjuvanted | |
| Erythema | 9.7 (3/31) | 3.2 (1/31) | .61 |
| Induration | 6.5 (2/31) | 6.5 (2/31) | .99 |
| Tenderness | 77.4 (24/31) | 51.6 (16/31) | .03 |
| Systemic | | | |
| Fever (>38°C) | 0 | 0 | |
| Subjective fever | 6.5 (2/31) | 9.7 (3/31) | .99 |
| GI intolerance | 6.5 (2/31) | 9.7 (3/31) | .99 |
| Fatigue | 32.3 (10/31) | 22.6 (7/31) | .39 |
| Other | 3.2 (1/31) | 6.5 (2/31) | .99 |
| Morelon et al [26] | Intradermal | Intramuscular | NA[g] |
| Local | | | |
| Overall | 81 (25/31) | 48 (15/31) | |
| Erythema | 71 (22/31) | 16 (5/31) | |
| Induration | 36 (11/31) | 19 (6/31) | |
| Pruritus | 29 (9/31) | 10 (3/31) | |
| Swelling | 36 (11/31) | 10 (3/31) | |
| Tenderness | 32 (10/31) | 39 (12/31) | |
| Systemic | | | |
| Overall | 55 (17/31) | 52 (16/31) | |
| Fever | 3 (1/31) | 0 (0/31) | |
| Headache | 39 (12/31) | 36 (11/31) | |
| Malaise | 13 (4/31) | 13 (4/31) | |
| Myalgia | 19 (6/31) | 16 (5/31) | |
| Shivering | 16 (5/31) | 10 (3/31) | |
| Manuel et al [27] | Intradermal | Intramuscular | |
| Overall | 44 (18/41) | 34 (15/44) | .38 |
| Local AEs | 41 (17/41) | 25 (11/44) | .16 |
| Systemic AEs | 7 (3/41) | 16 (7/44) | .31 |

Abbreviations: AEs, adverse events; CI, confidence interval; GI, gastrointestinal; NA, not available; OR, odds ratio.

[a]Proportions and percentages were unavailable for the published article by Hojsak et al, despite personal communication with the corresponding author.

[b]Values represent *P* values unless otherwise specified.

[c]Percentages and proportions obtained via personal communication with the corresponding author.

[d]The proportions were not provided in the original paper (GiaQuinta et al). For the paper by Manuel et al, please refer to proportions that are provided below.

[e]Cordero et al reported 95% confidence intervals for the odds of developing AEs in the booster dose group compared to standard dose group. P-values were not reported in the original paper.

[f]Severe AEs were defined by Cordero et al as the inability to participate in daily activities. Serious AEs were defined as graft rejection or loss, events leading to death or hospitalization or its prolongation, considered as life-threatening or medically important, or resulting in disability.

[g]Statistical testing was not performed by the authors owing to small sample size in each group.

Hojsak et al [28] aimed to compare a 2-dose standard intramus-cular IIV3 with findings in pediatric liver transplant recipients who received single-dose intramuscular IIV3 in the previous influenza season, but statistical comparisons were not performed between the 2 groups, limiting interpretation of the results. Finally, there was variability in postvaccination serum sample collection (ranging from 3 to 6 weeks after vaccination); it is unclear whether this variability contributed to vaccine immunogenicity differences across studies.

In conclusion, BD and HD influenza vaccination strategies seem to hold promise for improving vaccination immunogenicity and were generally well tolerated in SOTRs. Future studies should focus on clarifying the optimal timing, frequency, and dose and in assessing whether these strategies improve vaccine immunogenicity. In the interim, SOTRs should continue to receive the SD IIV annually in accordance with current Infectious Diseases Society of America and Centers for Disease Control and Prevention recommendations.

## Notes

***Author contributions.*** Research idea and study design: P. P. C and D. J. W; data acquisition: L. H.; data analysis/interpretation: P. P. C and D. J. W; supervision or mentorship: D. J. W; drafting of manuscript: P. P. C. Each author critically revised and approved of the final version of the manuscript.

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