Comparative Immunogenicity of Enhanced Seasonal Influenza Vaccines in Older Adults: A Systematic Review and Meta-analysis

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Background. A number of enhanced influenza vaccines have been developed for use in older adults, including high-dose, MF59-adjuvanted, and intradermal vaccines.

Methods. We conducted a systematic review examining the improvements in antibody responses measured by the hemagglutination inhibition assay associated with these enhanced vaccines, compared with each other and with the standard-dose (SD) vaccine using random effects models.

Results. Thirty-nine trials were included. Compared with adults aged ≥ 60 years receiving SD vaccines, those receiving enhanced vaccines had significantly higher postvaccination titers (for all vaccine strains) and higher proportions with elevated titers ≥ 40 (for most vaccine strains). High-dose vaccine elicited 82% higher postvaccination titer to A(H3N2) compared with SD vaccine; this was significantly higher than the 52% estimated for MF59-adjuvanted versus SD vaccines ($P = .04$), which was higher than the 32% estimated for intradermal versus SD vaccines ($P < .01$).

Conclusions. Overall, by summarizing current evidence, we found that enhanced vaccines had greater antibody responses than the SD vaccine. Indications of differences among enhanced vaccines highlight the fact that further research is needed to compare new vaccine options, especially during seasons with mismatched circulating strains and for immune outcomes other than hemagglutination inhibition titers as well as vaccine efficacy.

Keywords. Immunogenicity; influenza; vaccine.

Inactivated influenza virus vaccines were first developed in the 1940s and are now widely used in the control of influenza and reduction of disease burden [1]. Although school-age children generally have the greatest risk of influenza virus infections each year [2], the burden of severe influenza disease is greatest in older adults. For example, in the United States, adults aged ≥ 65 years comprise 14.5% of the population but account for 60% of hospitalizations and $>90\%$ of deaths associated with respiratory complications of influenza [3, 4]. Older adults are therefore a priority group for influenza vaccination [5].

The most commonly used influenza vaccines worldwide for older adults today are inactivated, split-virus influenza vaccines prepared from influenza viruses inoculated in fertilized chicken eggs. These vaccines have 15 μg of hemagglutinin (HA) antigen per 0.5-mL dose; thus, a trivalent vaccine has a total of 45 μg of antigen, and quadrivalent vaccines that include an additional B

strain have 60 μg of total antigen [5]. However, the clinical effectiveness of these “standard-dose” (SD) vaccines to prevent influenza illness among older adults (37%) may be slightly lower than among younger adults (51%) [6], and this difference has been linked to poorer immunogenicity [5]. Although poorer immunogenicity among older adults may be due in part to immunosenescence, a recent study showed that more historical exposures to natural infections and vaccinations may also impair vaccine response independent of older chronological age per se [7].

To address the poorer immunogenicity of influenza vaccines in older adults, a number of new and potentially enhanced vaccines have been developed in recent years. These include the addition of adjuvants to vaccines, the inclusion of higher antigen content, and administration of intradermal vaccines [8–11]. The MF59-adjuvanted vaccine is an inactivated subunit vaccine containing 15 μg of each HA in a 0.5-mL dose and an oil-in-water emulsion of squalene [10]. The high-dose (HD) vaccine is an inactivated split-virus vaccine containing 60 μg of each HA in a 0.5-mL dose [12], and the intradermal vaccine is an inactivated split-virus vaccine containing 15 μg of each HA in a 0.1-mL dose [8]. With few exceptions, these enhanced vaccines have been examined in comparison with SD vaccines, and there has been little attention to the potential differences among these

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new vaccine options. The objective of the current review was to examine the improvements in vaccine-induced humoral immunity associated with these enhanced vaccines, compared with each other and with SD vaccines.

MATERIALS AND METHODS

We conducted this systematic review and meta-analysis in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (Supplementary Table 1) [13].

Literature Search Strategy and Study Selection

We searched the online databases of PubMed, MEDLINE, and EMBASE to identify potential studies using a combination of all 5 of the following search terms in “all fields”: (1) *influenza*, (2) *vaccine* or *vaccination*, (3) *elderly* or *older adults*, (4) *immune* or *immunogenicity*, and (5) *adjuvanted* or *high dose* or *high-dose* or *MF59* or *intradermal*.

The databases were searched for any trials published through 31 December 2017. Additional relevant studies were retrieved manually from reference lists of identified articles.

Two reviewers (T. W. Y. N. and H. Z. G.) independently screened and determined inclusion of identified articles. Discrepancies were resolved through discussion between the 2 reviewers until a consensus was reached. Eligible studies met the following inclusion criteria: (1) randomized controlled trials (RCTs) that investigated any of the 3 enhanced influenza vaccines: MF59-adjuvanted, HD, or intradermal seasonal influenza vaccine; (2) publication in English or Chinese; (3) study participants aged ≥ 60 years; (4) antibody response assessed with the hemagglutination inhibition (HAI) assay; (5) results reported as the geometric mean titer (GMT) and/or proportions of participants with HAI titers ≥ 40 at 1 month after vaccination (because this threshold is sometimes cited as a level that provides some degree of clinical protection) [14, 15]. Trials without an SD vaccine were included because they can contribute to effect estimates, except for comparisons between enhanced and SD vaccines (as described below). We excluded studies focused on immunocompromised patients.

Outcome Assessment

To overcome the issue of high variability in the quantification of antibody titers across reagents, laboratories, and methods [16], we measured immune responses in ratios or differences between two time points or two vaccines in each trial. Immunogenicity was assessed using 3 measurements: (1) the mean fold rise (MFR) in GMT from before vaccination (day 0) to after vaccination (day 30) in vaccine recipients; (2) the ratio of postvaccination GMTs (day 30) in the enhanced vaccine group to those in the SD vaccine group; and (3) the absolute difference in the proportion of participants with elevated titers ≥ 40 at 1 month after vaccination, comparing

recipients of the intervention vaccine with the SD control group. Outcomes were assessed for A(H1N1), A(H3N2), B/Victoria, and B/Yamagata.

Assessment of Risk of Bias

The Cochrane Collaboration tool was used to assess risk of bias for each included trial [17]. The assessment was independently performed by 2 reviewers (T. W. Y. N. and H. Z. G.). Disagreements were resolved through discussion between them. A judgment of low, high, or unclear risk of bias was made for each of the 7 domains in the tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Potential publication bias was also evaluated using funnel plots for each outcome measurement.

Data Synthesis and Statistical Analysis

Data on the 3 measurements were extracted from the full articles on all included trials or retrieved from other review articles [8, 9]. From these trials, we extracted the reported GMT before and after vaccination and corresponding standard errors or 95% confidence intervals (CIs) for each vaccination group, and the proportions of participants with elevated HAI titers ≥ 40 among the enhanced and SD vaccine groups.

We used random effect models in our meta-analysis, which assumed the effect sizes were similar but not identical across trials, to derive the pooled estimates and 95% CI of the three immunogenicity outcomes for each enhanced vaccine type against each vaccine strain. MFR and postvaccination titer ratios were estimated on a base 2 logarithmic scale from reported GMT and variances in both enhanced and SD vaccine groups. The MFR was calculated by dividing the reported GMT values after vaccination by the values immediately before vaccination. For the ratio of postvaccination titers, in trials that included the SD vaccine as a comparator, we calculated the ratio of the reported GMT values after vaccination in the enhanced vaccine group with those after vaccination in the SD control group. For each comparison of enhanced and SD vaccines, we subtracted the proportion with HAI titer ≥ 40 in the SD group from the respective proportion in the enhanced vaccine group and presented the difference as a percentage. We assessed heterogeneity in meta-analysis using the I^2 statistic.

To investigate the differences between vaccine types in terms of each immunogenicity outcome, we performed a post hoc analysis using meta-regression to test for differences in effect size between these vaccines. For each outcome and strain, we tested for between-group difference among the enhanced influenza vaccines using meta-regression. For significant results, we further investigate the magnitude of the difference by comparing the pooled estimates of each vaccine against each other (ie, outcome for HD vs ID, HD vs MF59, and ID vs MF59). Sensitivity analysis was also performed by meta-regression to compare outcomes between vaccines that

contained A(H1N1) prepandemic strain and A(H1N1)pdm09 strain. The statistical analyses were performed using R software, version 3.3.0 (R Foundation for Statistical Computing).

RESULTS

Summary of Trials

The literature search yielded 862 records, from which 509 were screened for title and abstract after duplicates were

removed. After excluding 421 records during title or abstract screening, we retrieved full articles of the remaining 88 studies for further eligibility screening, from which 49 were excluded (Figure 1). A total of 39 RCTs were included in this systematic review; 1 trial studied both HD and intradermal vaccines and 5 included both MF59-adjuvanted and intradermal vaccines [18–23]. Summary characteristics of the included trials are shown in Table 1. The majority of trials (33/39; 84.6%) focused exclusively on healthy,

Figure 1. Flow chart of study selection in the systematic review. Outcome 1 was mean fold rise; outcome 2, postvaccination titers ratios of enhanced versus standard-dose vaccines; outcome 3, absolute differences in proportion with elevated titers between enhanced and standard-dose vaccines. Abbreviation: HAI, hemagglutination inhibition.

Table 1. Summary Characteristics of the Included Trials

Study	Year	Sample Size, No. of Participants	Participant Age, y ^a	Setting	Country	Outcome 1: Mean Fold Rise	Outcome 2: Ratio of Postvaccination Titers ^b	Outcome 3: Absolute Difference in Proportions With Elevated Titers ^b	Comparison With Standard-Dose Vaccine
High-dose vaccine									
Keitel 2006 [47]	2001–2002	50	65–88	Community	United States	X	X	X	X
Couch 2007 [48] ^c	2004–2005	206	65–95	Community	United States	X	X	X	X
Falsey 2009 [49]	2006–2007	2576	65–97	Community	United States	X	X	X	X
Tsang et al (2014) [18]	2007–2008	317	65–93	Community	United States	X	X	X	X
DiazGranados et al (2013) [12]	2009–2010	2000	64.3–99.9	Community	United States	X	X	X	X
DiazGranados et al (2014) [39]	2011–2012 and 2012–2013	2375 and 2879	73.3 (5.8)	Community	United States and Canada	X	X	X	X
Nace et al (2015) [26]	2011–2012 and 2012–2013	31 and 58	87 (6)	Nursing home	United States	X	X	X	X
Intradermal vaccine (15 µg)									
Holland 2008 [50]	2005–2006	359	60–84	Community	New Zealand	X	X	X	X
Arnou 2009 [51]	2006–2007	2604	60–94	Community	Belgium	X	X	X	X
Tsang et al (2014) [18]	2007–2008	633	65–94	Community	United States	X	X	X	X
Van Damme et al (2010) [19]	2007–2008	390	73.9 (6.3)	Community	Belgium and France	X	X	X	X
Ansaldo 2013 [52]	2010–2011	24	>60	Community	Italy	X	X	X	X
Hoon Han 2013 [53]	2010–2011	60	64.9 (3.6)	Community	Korea	X	X	X	X
Camilloni et al (2014) [22]	2011–2012	40	64–100	Nursing home	Italy	X	X	X	X
Hung 2014 [54]	2011–2012	31	64–79	Community	Hong Kong	X	X	X	X
Scheifele et al (2013) [21]	2011–2012	301	73.7	Community	Canada	X	X	X	X
Seo et al (2014) [20]	2011–2012	111	65–86	Community	Korea	X	X	X	X
Levin et al (2016) [23]	2012–2013	60	70.6 (4.0)	Community	Belgium and Germany	X	X	X	X
Boonnak 2017 [55]	2012–2013	111	60–84	Community	Thailand	X	X	X	X
Arakane 2015 [56]	2013–2014	50	65–79	Community	Japan	X	X	X	X
Arakane 2015 [57]	2013–2014	450	65–88	Community	Japan	X	X	X	X
Chan 2014 [58]	2013–2014	50	81.7 (4.8)	Nursing home	Hong Kong	X	X	X	X
MF59-adjuvanted vaccine									
Minutello et al (1999) [27]	1992–1993, 1993–1994, and 1994–1995	46, 39, and 35	65–81	Community	Italy	X	X	X	X
MF59-adjuvanted vaccine									
De Donato 1999 [59]	1993–1994	94	65–87	Community	Italy	X	X	X	X
Gasparini 2001 [60]	1994–1995	192	75.9	Community	Italy	X	X	X	X
Baldo 2001 [61]	1998–1999	99	65–100	Nursing home	Italy	X	X	X	X
Pregliasco 2001 [62]	1998–1999	41	Age criterion: >64	Nursing home	Italy	X	X	X	X
Squarcione 2003 [63]	1998–1999	595	73.4 (5.9)	Community	Italy	X	X	X	X
Sindoni 2009 [64]	2002–2003	96	79.0 (8.3)	Community	Italy	X	X	X	X
Ruf 2004 [65]	2002–2003	275	67.9 (6.3)	Community	Germany	X	X	X	X
Iorio 2006 [66] ^{c,d}	2004–2005	104	71.3 (9.2)	Community	Italy	X	X	X	X
De Bruijn 2007 [67]	2004–2005	126	61–98	Community	Germany, Sweden, Lithuania, and Bulgaria	X	X	X	X

Ansaldi et al (2008) [24]	2004–2005	25	Age criterion: ≥65	-	Italy	X	X	X	X
Ansaldi et al (2010) [25]	2005–2006	25	72.1 (4.4)	Community	Italy	X	X	X	X
Li 2008 [68]	2005–2006	367	Age criterion: ≥60	Community	China	X	X	X	X
Van Damme et al (2010) [19]	2007–2008	385	74.7 (6.6)	Community	Belgium and France	X	X	X	X
Della Cioppa 2014 [69]	2008–2009	45	68.5 (3.1)	Community	Germany, Poland, and Belgium	X	X	X	X
Song 2013 [70]	2009–2010	47	71.2 (4.5)	Community	Korea	X	X	X	X
Frey 2014 [71]	2010–2011	3479	71.9 (5.3)	Community	Columbia, Panama, Philippines, and United States	X	X	X	X
Camilloni et al (2014) [22]	2011–2012	40	72–98	Nursing home	Italy	X	X	X	X
Scheifele et al (2013) [21]	2011–2012	299	73.8	Community	Canada	X	X	X	X
Seo et al (2014) [20]	2011–2012	111	65–88	Community	Korea	X	X	X	X
Song 2015 [72]	2013–2014	56	71.0 (4.2)	Community	Korea	X	X	X	X
Levin et al (2016) [23]	2012–2013	63	69.6 (3.9)	Community	Belgium and Germany	X	X	X	X
Song 2017 [73]	2014–2015	382	65.5–66.4	Community	Korea	X	X	X	X

*Age is presented either as a range or as a mean (with parenthetical standard deviation if available). If neither was reported, the study age criterion is provided.

^bOutcome 3 should be the absolute difference in proportions with elevated titers for enhanced versus standard-dose vaccines.

^cStudy retrieved from reference lists.

^dStudy targets were patients with chronic cardiocerebrovascular conditions but on stabilized long-term therapy with oral anticoagulant.

community-dwelling older adults aged 60–100 years. Trials typically excluded persons with an allergy to the components of the vaccines, history of Guillain-Barré syndrome, known or suspected immunodeficiency, receipt of immunosuppressive therapy, ongoing or recent acute febrile illness before vaccination, current alcohol abuse or drug addiction, or receipt of blood or blood-derived products within 3 months.

Seven trials were included for the HD vaccine, accounting for a total of 10 492 vaccine recipients. All HD trials evaluated the postvaccination GMTs for all 3 strains and compared these with the SD vaccine. The MFR could be calculated for 5 of the HD trials and ratio of proportions with elevated titers could be calculated for 6 of them.

Fifteen trials, with a total of 5274 recipients, were included for the intradermal vaccine, and all trials examined antibody responses against all 3 strains. Ten trials compared responses with SD vaccine in proportions with elevated titers. The MFR could be calculated for 13 of the trials of intradermal vaccine, and ratios of postvaccination GMTs compared with SD vaccine could be measured for 8 of them.

Finally, for the MF59-adjuvanted vaccine, 23 trials, with a total of 7066 recipients, were included in this systematic review; 2 trials examined antibody responses against A(H3N2) strain only [24, 25]. Eighteen of the trials compared responses with SD vaccine in proportions with elevated titers. The MFR could be calculated for 21 of the MF59-adjuvanted trials and the ratios of postvaccination GMTs could be measured for 17 of them.

Risk of Bias Within Trials

All 39 trials were considered at low risk of selection bias, reporting bias, incomplete outcome data, and other sources of bias (Supplementary Table 2). All trials reported random assignment of participants to vaccine groups, though 18 did not report their allocation concealment methods. All trials clearly reported the specified outcomes. The number of dropouts was small from day 0 to day 30 in the trials. Dropout reasons were clearly listed, with baseline characteristics similar between dropouts and those who remained in the vaccine groups, showing that the dropout was nondifferential. Twelve trials were conducted as open label, 6 as observer blind, 1 as single blind, 2 as double blind for dose but open-label for route, and 12 as double blind. Six trials did not report their methods of blinding. In addition, 29 trials were considered at low risk for detection bias during outcome assessment, and for 10 the risk was unclear.

MFR After Vaccination

There were high levels of between-studies variance of $I^2 > 90\%$, precluding pooled estimates of the MFR in the meta-analysis (Table 2). Therefore, measured MFRs in each study are displayed in Supplementary Figure 1, and the wide range of observed MFRs across trials is summarized in Table 2. For all enhanced vaccines across all trials, the MFR in titers from

Table 2. Range of Estimates of Mean Fold Rise in Standard-Dose and Enhanced Vaccine Groups^a

Vaccine Strain	Estimated Mean Fold Rise by Vaccine Type, Range [n of studies; I^2 Statistic ^b as %]			
	Standard Dose	High Dose	Intradermal	MF59 Adjuvanted
A(H1N1)	1.36–17.14 [29; 97]	1.93–13.28 [6; 97]	2.84–12.98 [11; 97]	2.25–13.66 [21; 97]
A(H3N2)	1.40–14.36 [32; 95]	2.36–8.16 [6; 96]	1.82–13.77 [11; 99]	1.19–27.00 [23; 96]
B/Yamagata	1.49–14.68 [14; 95]	2.43–3.29 [3; 32]	2.78–4.71 [3; 71]	2.02–16.24 [13; 96]
B/Victoria	1.04–12.94 [15; 98]	1.67–3.58 [3; 94]	1.40–5.45 [8; 99]	1.57–15.11 [8; 98]

^aThe variability between estimates was substantial and prohibited estimation of pooled mean fold rises.

^bThe I^2 statistic is a measure of heterogeneity.

Blank cells indicate post hoc test was not performed because the test for between vaccine differences showed insignificant result.

before vaccination to 1 month after vaccination was significantly greater than 1 against A(H1N1), A(H3N2), and B/Yamagata (ie, lower limit of 95% CI of all estimates are >1). However, significant MFR was less consistent across the large number of observations for SD vaccine ([Supplementary Figure 1](#)).

Ratio of Postvaccination Titers for Enhanced Versus SD Vaccines

The magnitude of HAI antibody response after vaccination was higher among those who received enhanced vaccines than among those who received SD vaccine; the pooled ratio of postvaccination (day 30) GMT after enhanced vaccines to postvaccination GMT after SD vaccine was significantly greater than 1 for HD, intradermal, and MF59-adjuvanted vaccine groups against all strains that we could examine ([Table 3](#) and [Supplementary Figure 2](#)). We were not able to generate a pooled estimate for intradermal vaccine against B/Yamagata because only 1 trial was included in the analysis.

In post hoc analyses, we compared the magnitude of the effects between the enhanced vaccines ([Table 3](#)). The ratio of postvaccination GMTs for HD versus SD vaccine groups was significantly larger than the ratio for MF59-adjuvant versus SD vaccine group across all strains except B/Yamagata and was significantly larger than the ratio for intradermal versus SD vaccine groups for all strains except B/Yamagata, which we were not able to examine.

The magnitude of differences between enhanced and SD vaccines in postvaccination GMT against A(H3N2) was highest for HD (82%; 95% CI, 73%–91%), followed by MF59-adjuvanted (52%; 35%–72%) and intradermal (32%; 10%–59%) vaccines. Compared with SD vaccine, HD vaccine elicited higher postvaccination GMT than both MF59-adjuvanted and intradermal vaccines for A(H1N1), A(H3N2), and B/Victoria viruses.

Difference in Proportion with Elevated Postvaccination Titers ≥ 40 Between Enhanced and SD

The enhanced vaccine groups had a significantly larger pooled proportion of recipients with postvaccination HAI titers ≥ 40 than the SD vaccine group for almost all influenza A subtypes (range in absolute differences, 3.0%–8.1%) and B lineages (4.1%–13.5%) ([Table 4](#) and [Supplementary Figure 3](#)), with the exception of intradermal vaccine against B/Yamagata, for which the difference was not significant. The magnitude of these differences was similar across the enhanced vaccine types, exception for the responses to B/Victoria ([Table 4](#)). In pooled analyses, the absolute difference of participants with postvaccination titers ≥ 40 was 10.4% for HD recipients compared with SD recipients, whereas the difference was 4.1% for both intradermal and MF59-adjuvanted vaccines.

Table 3. Pooled Estimates of Postvaccination Titer Ratio to Standard-Dose Vaccine by Enhanced Vaccine Type

Vaccine Strains	Pooled Estimate (95% CI) of Postvaccination Titer Ratio by Vaccine Type [n of studies; I^2 Statistic ^a as %]			P Value for Between-Vaccine Differences ^b	P Value for Post Hoc Comparison Between Vaccine Types ^b		
	High Dose	Intradermal	MF59 Adjuvanted		High Dose vs Intradermal	High Dose vs MF59 Adjuvanted	Intradermal vs MF59 Adjuvanted
A(H1N1)	1.72 (1.61–1.84) [9; 60]	1.22 (1.03–1.43) [8; 75]	1.28 (1.12–1.46) [16; 80]	<.01	<.01	<.01	.59
A(H3N2)	1.82 (1.73–1.91) [9; 25]	1.32 (1.10–1.59) [8; 84]	1.52 (1.35–1.72) [19; 75]	.01	<.01	.04	<.01
B/Yamagata	1.49 (1.29–1.72) [4; 46]	... ^c	1.33 (1.22–1.45) [10; 10]	.20 ^d	... ^c	.10	... ^c
B/Victoria	1.44 (1.32–1.56) [5; 73]	1.18 (1.06–1.30) [7; 66]	1.21 (1.11–1.33) [6; 40]	<.01	<.01	.01	.64

Abbreviation: CI, confidence interval.

^aThe I^2 statistic is a measure of heterogeneity.

^bMeta-regression on vaccine types was used to identify associated differences, in terms of the pooled estimates of postvaccination titer ratio to SD vaccine, between enhanced vaccines, along with P values.

^cPooled estimates were not available because only 1 trial was included in the analysis.

^dComparison was performed between high-dose and MF59-adjuvanted vaccines only.

Table 4. Pooled Estimates of Absolute Difference Between Enhanced and Standard-Dose Vaccines in Percentage of Vaccinees with Postvaccination Titer ≥ 40 , by Vaccine Type

Vaccine strains	Pooled Estimate (95% CI) of Absolute Difference by Vaccine Type, % [n of studies; I^2 Statistic ^a as %]			PValue for Between-Vaccine Differences ^b	PValue for Post Hoc Comparison Between Vaccine Types ^b		
	High Dose	Intradermal	MF59 Adjuvanted		High Dose vs Intradermal	High Dose vs MF59 Adjuvanted	Intradermal vs MF59 Adjuvanted
A(H1N1)	8.07 (5.16–10.98) [8; 88]	5.86 (3.80–7.93) [10; 0]	4.59 (1.55–7.63) [17; 73]	.17	...	...	...
A(H3N2)	2.99 (2.17–3.81) [8; 39]	3.39 (1.78–5.00) [10; 16]	7.02 (4.08–9.96) [20; 79]	.11	...	...	...
B/Yamagata	13.48 (11.45–15.52) [3; 0]	11.83 (–5.38 to 29.04) [3; 81]	10.63 (5.51–15.75) [11; 54]	.79	...	...	...
B/Victoria	10.40 (7.65–13.15) [5; 66]	4.12 (0.58–7.65) [7; 51]	4.12 (0.98–7.27) [6; 43]	<.01	<.01	<.01	.91

Abbreviation: CI, confidence interval.

^aThe I^2 statistic is a measure of heterogeneity.

^bMeta-regression on vaccine types was used to identify associated differences between enhanced vaccines, in terms of the pooled estimates of absolute differences in proportions with postvaccination titer ≥ 40 compared with standard-dose vaccine, along with P values.

Blank cells indicate post hoc test was not performed because the test for between vaccine differences showed insignificant result.

Risk of Bias Between Trials

Despite substantial heterogeneity between trials identified in the estimation of pooled MFRs, the measure of heterogeneity was lower for the other 2 outcomes. No asymmetry was detected from funnel plots for ratios of postvaccination GMT between enhanced and SD vaccines for any of the strains (Supplementary Figure 4). Asymmetry was evident for absolute differences in proportions with postvaccination titers ≥ 40 between enhanced and SD vaccines (Supplementary Figure 5). This asymmetry came mainly from 2 trials by Nace et al [26] and Minutello et al [27] with data points of larger absolute difference against A(H1N1) and A(H3N2) [23].

Sensitivity Analysis

No significant differences were noted between vaccines that contained A(H1N1) prepandemic strain and A(H1N1)pdm09 strain for the MFR from before to after vaccination ($P = .12$), postvaccination titers ratios of enhanced versus SD vaccines ($P = .78$), and absolute differences in proportion with elevated titers between enhanced and SD vaccines ($P = .97$).

DISCUSSION

In our review of 39 vaccine trials among older adults, we found comparable immunogenicity profiles among all of the enhanced seasonal influenza vaccines against vaccine strains or lineages, based on HAI titers at 30 days after vaccination. Postvaccination GMTs were significantly higher for enhanced vaccines than for SD vaccine for all vaccine strains we could examine. Notably, HD vaccine elicited 82% higher postvaccination GMT to A(H3N2) compared with SD; MF59 and intradermal vaccines elicited 52% and 32% higher GMTs, respectively. HD vaccine elicited higher postvaccination GMTs than both MF59-adjuvanted and intradermal vaccines for A(H1N1) and B/Victoria viruses. Similarly, a higher proportion of older adults receiving enhanced vaccines had postvaccination titers ≥ 40

compared with those receiving SD vaccine for all strains, except for intradermal vaccine against B/Yamagata. However, the magnitude of these differences was modest. The only significant difference in elevated titers between the enhanced vaccines was the higher proportion of HD vaccine recipients with titers ≥ 40 against B/Victoria viruses compared with intradermal and MF59-adjuvanted vaccine recipients.

Our findings were consistent with those of previous reviews that focused on specific vaccine types and reported improved immunogenicity of MF59-adjuvanted [8] and intradermal [8, 9, 28] compared with SD vaccines. By simultaneously mapping the response to different vaccine options, our review highlights that the magnitude of this improved response against A(H3N2) vaccine components was larger for HD vaccine, in terms of the ratio of postvaccination GMT to that of SD vaccine, compared with intradermal and MF59-adjuvanted vaccines. Given that current SD vaccines provide markedly lower clinical protection among older adults against A(H3N2)-associated hospitalization [6], indications of differences among enhanced vaccines on A(H3N2) immunogenicity highlight the importance of future head-to-head comparisons between vaccine options.

However, our focus on HAI against single vaccine components is admittedly limited; we did not examine some of the hypothesized unique advantages associated with specific vaccines. For example, some have argued that MF59-adjuvanted vaccines may provide a broader response across vaccine targets in part by reducing or eliminating the blunting of antibody response to recent antigens and the preferential response to earlier historical antigens [10, 29]. There were also insufficient data on the immunogenicity of enhanced vaccines against circulating strains that are drifted from the vaccine strain.

Head-to-head comparative trials of the efficacy of enhanced vaccines against clinical outcomes would be very informative, preferably across multiple years to capture epidemics of vaccine matched as well as mismatched strains. All 3 enhanced vaccines

were judged in previous reviews to be well tolerated. Although all enhanced vaccines were reported to have higher incidence of solicited local adverse events compared with SD vaccine, they have similar profile of solicited systemic events, except for the MF59-adjuvanted vaccine, for which such events were more common [9, 11, 28, 30, 31]. Overall, no serious adverse events were reported and these enhanced vaccines were considered to be safe for use in older adults [9, 30, 32].

The improvements in immunogenicity for each of the enhanced vaccines described here (Tables 2 and 3) correspond to findings of reduced risk of influenza virus infections reported in RCTs and observational studies among older adults [30, 31, 33–36]. Meta-analyses reported significantly lower risk of developing laboratory-confirmed influenza virus infections and significantly higher relative vaccine efficacy against influenzalike illness, hospital admissions from several causes, and postinfluenza death in HD compared with vaccine recipients SD [30, 34]. Case-control studies of MF59-adjuvanted vaccine also estimated significantly higher relative effectiveness than for SD vaccine, against both laboratory-confirmed influenza and hospitalization for influenza or pneumonia [35, 36], but effectiveness was reportedly similar to that of intradermal vaccine against hospitalizations with clinical diagnoses of influenza or pneumonia [31].

Although there is growing consensus that under some circumstances repeated annual influenza vaccination can blunt antibody response to vaccine and possibly reduce clinical vaccine efficacy in some seasons [37], the mechanisms underlying this effect are less clear. Disentangling the role of immune aging (or immunosenescence) from the role of repeated vaccination in blunting antibody response and/or vaccine efficacy is particularly challenging [7, 38]. It is possible that enhanced vaccines could overcome both of these challenges. However, with few exceptions [27, 39], vaccine trials typically follow up participants for only 1 year, and prior influenza vaccination history is often not reported. One trial that followed up older adults for 2 years observed lower antibody response to a second annual dose of HD vaccine [39].

Our review has additional limitations. First, most of the B influenza findings were limited to B/Victoria, given the absence of B/Yamagata strains from most of the trivalent vaccines examined. Forthcoming research using quadrivalent vaccines should expand information on the impact of enhanced vaccines on B influenza immunogenicity, although among older adults the largest disease burden seems to be due to A(H3N2) strains [6]. Second, immunogenicity is generally measured against egg-adapted vaccine viruses that may not fully represent protection against circulating strains, especially for A(H3N2) viruses, which are prone to egg-adapted changes [40].

Third, we could only examine humoral immune response measured using the HAI assay, given that it is the most frequently used method to assess vaccine performance during licensing [16]. Although HAI is the established correlate of protection for

influenza vaccines, information on other immune responses, such as the neuraminidase-inhibiting response [41] and cell-mediated immune (CMI) responses [42], could also offer insight into the relative value of enhanced vaccines. Indeed, CMI may be especially relevant to vaccine protection among older adults [42]. CMI assays may also help distinguish the impact of viral proteins that differ between subunit and split-virus vaccines.

Fourth, we could not compare MFRs between vaccines owing to high variability between trials. This variability may be due to the differences in prevaccination titers across seasons, which may be affected by influenza vaccination history and exposure to the circulating strains in previous seasons. Perhaps MFR is a less relevant measure to evaluate vaccine responses across studies, because it is also prone to the ceiling effect of antibody response that reduces the antibody rise after vaccination.

Fifth, owing to limited data, we pooled results for prepandemic H1N1 and A(H1N1)pdm09, although sensitivity analyses indicated similar results when they were examined separately, which may be expected because of the exposure of this cohort to similar historical A(H1N1) strains during childhood [43, 44].

Sixth, we did not evaluate differences in vaccine response in older adults with different conditions, because we aimed to focus on older adults in general. Finally, we did not include the latest vaccine options, such as FluBlok (Sanofi Pasteur) [45] and Flucelvax (Seqirus Inc.) [46], that are also promising options for improving vaccine protection.

In conclusion, we found that all enhanced vaccines resulted in greater immune responses that may improve effectiveness. Head-to-head immunogenicity and efficacy trials of these enhanced vaccines would be very informative, particularly if conducted across multiple years to provide data on efficacy against a variety of circulating strains and to provide data on immune responses to repeated vaccinations with enhanced vaccines.

Supplementary Data

Supplementary materials are available at *The Journal of 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

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