Immunogenicity of high-dose, MF59-adjuvanted, and intradermal seasonal influenza vaccines in older adults: a systematic review and meta-analysis

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Background

A number of alternative influenza vaccination strategies have been developed for use in older adults, including the use of higher antigen content, the addition of adjuvants to vaccines, and intradermal rather than intramuscular administration of antigen. We reviewed the improvements in vaccine-induced antibody responses associated with these enhanced vaccines, compared to each other, and compared to conventional standard-dose (SD) vaccine.

Methods

We conducted a systematic review and meta-analysis of randomized controlled trials on the high-dose (HD), MF59-adjuvanted, and intradermal (ID) seasonal influenza vaccines. Electronic databases were searched systematically from 1 January 1995 to 18 August 2016, for trials conducted in participants aged ≥60 years that assessed antibody responses by the hemagglutinin inhibition (HI) assay. We extracted data including geometric mean HI titers (GMTs) at pre-vaccination (day0) and post-vaccination (day30), and proportions of participants with elevated HAI titers of ≥40 among the alternative and SD vaccine groups. Two immunogenicity outcomes were assessed using random effects models: (i) the ratio of post-vaccination log_2GMT of the alternative vaccine groups versus the post-vaccination log_2GMT of the SD comparator; and (ii) the absolute difference in the proportion of participants with elevated titers in alternative vaccine groups compared to the SD group. Outcomes were assessed for A(H1N1), A(H3N2), B/Victoria and B/Yamagata. Heterogeneity in meta-analysis was assessed using the I-squared statistic. The pooled effects for the vaccine groups were compared using meta-regression and post-hoc tests were done between each vaccine group. Sensitivity analysis was performed by meta-regression to compare outcomes between A(H1N1) pre-pandemic and A(H1N1)pdm09 strains.

Conclusions

We found comparable immunogenicity for the HD and MF59-adjuvanted vaccines, both of which were superior to the ID vaccine, and all three alternative vaccines were superior to SD vaccine. We only considered protection against vaccine strains, and an extension of this analysis to mismatched circulating strains would also be of interest. While immunogenicity is only a rough correlate of clinical effectiveness, these alternative vaccines could contribute to appropriate strategies to address the challenge of the relatively poorer immune response and effectiveness of SD vaccine among older adults.

Results

A total of 28 trials were included. The magnitude of post-vaccination response was significantly higher among alternative vaccine recipients against all strains except B/Yamagata (Table 1). Compared to ID ($p<0.01$) and MF59-adjuvanted ($p<0.01$), HD vaccine had significantly higher ratio to SD against A(H1N1). For A(H3N2), HD had significantly higher ratio than ID ($p=0.01$) but the comparison with MF59-adjuvanted was not significant ($p=0.11$). Lastly, significantly higher ratio of HD was found compared to ID ($p<0.01$) and MF59-adjuvanted ($p=0.02$) against B/Victoria. In regards to the difference in proportion with elevated titer, alternative vaccines had a significantly higher outcome compared to SD for all strains, with the exception of B/Yamagata (Table 2). Among alternative vaccines, significant between-group difference was only observed in B/Victoria ($p<0.01$), where HD had significantly higher outcome compared to ID ($p=0.01$) and MF59-adjuvanted vaccine ($p<0.01$). No significant differences were found between A(H1N1) pre-pandemic and A(H1N1)pdm09 strains for both outcomes ($p=0.48$ and 0.79, respectively).

Table 1. Pooled estimates of log_2(geometric mean titer ratio) vs. standard-dose vaccine and 95% confidence intervals by vaccine type

Vaccine strains	Vaccine type			
	High-dose	Intradermal	MF59-adjuvanted	Between vaccine differences, p-value
A(H1N1)	1.11 (1.10, 1.13)	1.04 (1.01, 1.08)	1.05(1.02, 1.08)	<0.01
	n=8; I^2=67%	*n=8; I^2=76%*	*n=16; I^2=81%*	
A(H3N2)	1.11(1.10, 1.12)	1.06 (1.02, 1.09)	1.09 (1.06, 1.11)	0.02
	n=8; I^2=21%	*n=8; I^2=80%*	*n=19; I^2=75%*	
B/Yamagata	1.11(1.10, 1.13)	1.10 (1.01, 1.20)	1.08 (1.05, 1.10)	0.16
	n=3; I^2=0%	*n=1; I^2=N/A*	*n=10; I^2=32%*	
B/Victoria	1.08 (1.07, 1.10)	1.04 (1.02, 1.06)	1.05 (1.02, 1.08)	0.01
	n=5; I^2=60%	*n=7; I^2=60%*	*n=6; I^2=70%*	

Table 2. Pooled estimates of absolute difference in percentage points with post-vaccination geometric mean titer ≥40 vs. standard-dose vaccine, and 95% confidence intervals, by vaccine type

Vaccine strains	Vaccine type			
	High-dose	Intradermal	MF59-adjuvanted	Between vaccine differences, p-value
A(H1N1)	8.11 (5.21, 11.01)	5.82 (3.68, 7.97)	4.59 (1.42, 7.76)	0.17
	n=8; I^2=88%	*n=8; I^2=0%*	*n=16; I^2=75%*	
A(H3N2)	2.99 (2.17, 3.81)	3.11 (1.14, 5.07)	7.09 (4.02, 10.17)	0.11
	n=8; I^2=40%	*n=8; I^2=32%*	*n=19; I^2=80%*	
B/Yamagata	13.48(11.45, 15.52)	4.00 (-9.79, 17.79)	10.66(5.16, 16.16)	0.54
	n=3; I^2=0%	*n=1; I^2=N/A*	*n=10; I^2=59%*	
B/Victoria	10.40 (7.65, 13.16)	4.11 (0.58, 7.65)	4.12 (0.97, 7.27)	<0.01
	n=5; I^2=66%	*n=7; I^2=51%*	*n=6; I^2=43%*	