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Original Article

A Meta-analysis of intradermal versus intramuscular influenza vaccines: Immunogenicity and Adverse Events

Fawziah Marra,[a,b] Flora Young,[c] Kathryn Richardson,[a] Carlo A. Marra[a]

[a]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada. [b]BC Centre for Disease Control, Vancouver, BC, Canada. [c]Fraser Health Authority, Vancouver, BC, Canada.
Correspondence: Dr Fawziah Marra, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, BC V6T 1Z3, Canada.
E-mail: fawziah.marra@ubc.ca

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Objective To determine immunogenicity and safety of intradermal (ID) influenza vaccines compared with intramuscular (IM) administration and effect of dose and age.

Design Meta-anlysis.

Setting Systematic review and meta-analysis of randomized controlled trials on influenza vaccines.

Sample Randomized, controlled trials comparing ID seasonal split-virus influenza vaccines with 15 μg IM control in subjects 18 years of age or older and assessed antibody response at 21–28 days post-vaccination were considered for inclusion.

Results A total of 13 trials were included. The pooled immunogenicity outcomes did not differ significantly between the IM and ID vaccine groups for the H1N1 (ratio of GMTR: 0·92, 95% confidence interval 0·77–1·09; seroconversion: 0·94, 0·86–1·02; seroprotection: 0·97, 0·94–1·00) and B strains (GMTR: 0·93, 0·80–1·08; seroconversion: 0·91, 0·80–1·04; seroprotection: 0·97, 0·91–1·03). For the H3N2 strain, there was no significant difference in GMTR (0·97, 0·80–1·18); however, there was a lower pooled seroconversion (0·89, 0·80–0·99) and seroprotection rate (0·98, 0·96–0·99) for ID recipients. There was a statistically significant association between increasing doses of the ID vaccination with increasing immunogenicity response ($P = 0·01$). There were no differences in adverse event rates within 3 days post-vaccination for ID versus IM. But for adverse events occurring 7 days post-vaccination, ID vaccination was associated with a greater incidence of local events but not systemic events.

Conclusions There was no significant difference in immunologic response when comparing ID with IM administration of the influenza vaccination in the overall population, but higher doses of ID vaccine in the older adult population produced a better response.

Keywords Influenza vaccine, intradermal, meta-analysis, route of administration.

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Introduction

The global burden of influenza is enormous as in a typical year 20% of the world's population is infected and about half million individuals are associated with significant morbidity and mortality.[1] Older adults are at a higher risk of developing complications because of an influenza infection, with a mortality rate of 22 per 100 000 person-years in those older than 65 years of age compared with three per 100 000 person-years in those who are younger.[2]

Influenza vaccines are very effective at preventing influenza infections with an efficacy rate of 80% (95% confidence interval 56–91) in healthy adults 65 years of age or younger reported in a meta-analysis.[3] Unfortunately, vaccines are less effective in older adults because of immunosenescence, whereby there is deterioration in immune function secondary to aging, especially in the ability to mount a primary immune response to new antigens.[4] Antibody responses to influenza vaccines in older adults were found to be less than in younger adults, with odds ratios for seroconversion and seroprotection rates ranging from 0·24 to 0·59.[5]

Because of the vulnerability of older adults to complications secondary to influenza infections and the lower efficacy of vaccines in older adults, several innovative methods of vaccination have been investigated to improve immune response.[6,7] Some of these strategies include vaccines that are adjuvanted, live attenuated, intranasal, virosomal, administered at a higher dose, and administered intradermally (ID).[6] ID vaccines are theorized to improve immune response because of the abundance of immunostimulatory cells such as dendritic cells in the dermis.[7,8]

This is a promising mode of administration and has been studied in various populations, including both older adults and younger adults. We have previously published a qualitative systematic review on this topic,[9] but the objective of this study was to conduct a quantitative approach and perform a meta-analysis of studies that compared ID vaccines with traditional methods of administration in adults to determine their immunogenicity and safety and also to determine the effect of dose and age on immunogenicity.

Materials and methods

Literature search strategy and study selection

The online databases of Embase, MEDLINE, and PubMed were searched to identify potential studies using the following search strategy: 'influenza vaccine,' 'intradermal drug administration,' 'injections, intradermal,' 'intradermal influenza vaccine.' Articles were limited to English only. The databases were searched from January 1, 1996 to February 10, 2012.

Two investigators searched the literature and extracted data independently. Inclusion criteria were the same as those used for our systematic review and were as follows: (i) randomized trials comparing ID administration of seasonal split-virus influenza vaccines with intramuscular (IM) control; (ii) study participants were 18 years of age or older; (iii) studies assessed antibody response by the hemagglutinin (HA) inhibition method; (iv) studies reported results as the geometric mean titer (GMT), the geometric mean titer ratio (GMTR), seroprotection rate, and seroconversion or significant increase rate assessed at 21–28 days post-vaccination. Finally, if multiple doses were evaluated in a study as well as the single dose, we only included the results associated with the single-dose administration. The following studies were excluded: (i) those that investigated pandemic influenza vaccines; (ii) those that evaluated whole-virus vaccines; and (iii) those that included immunocompromised subjects.

Outcome assessment

Immunogenicity was assessed using geometric mean titer ratio (i.e., mean fold increase in GMT from pre-vaccination to post-vaccination), seroprotection rate (i.e., % with anti-HA titer ≥40), and seroconversion (i.e., post-vaccination titers ≥40 for those with pre-vaccination titer <10) as these are the immunogenicity criteria used by the European Medicines Agency (EMA) to assess influenza vaccines.[10] The EMA criteria state that for those 18–60 years of age, one of the following criteria needs to be satisfied: GMTR > 2·5, seroconversion rate > 40%, or seroprotection rate > 70%. However, for those >60 years of age, the criteria are as follows: GMTR > 2·0, seroconversion rate > 30%, or seroprotection rate > 60%.[10] For the meta-analysis, our pooled outcomes included GMTR, seroprotection rate, and seroconversion rate at days 21–28 post-vaccination for each of the three strains included in the seasonal influenza vaccine. Outcomes up to 12 months post-vaccination were also assessed, if data were available. Safety outcomes included systemic and local adverse events within 3 days post-vaccination and within 7 days post-vaccination as per EMA standard.[10]

Data synthesis and statistical analysis

Data from RCTs were extracted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 5 statement.[11] The methodological quality of the RCTs, including risk of bias assessment, was assessed according to Cochrane Collaboration recommendations[12] and the Jadad score[13] for consideration of random sequence generation, allocation concealment, blinding procedures, address of incomplete outcome data, and unselective reporting. This scoring tool is appropriate to use despite the fact that some studies were not double-blinded and different routes of administration are used.

The ratio was used as the effect measure for comparing the GMTR from the ID and IM vaccination groups. For each study, the logarithm of the ratio of GMTR and corresponding SEs was estimated from the reported GMTR and 95% confidence interval (CI) in both groups. For all other outcomes, the risk ratio (RR) was calculated from the proportions reported in each study. Risk ratios from different studies were combined and weighted by the inverse of their variances using a random-effects model to obtain a pooled RR with 95% CI.[14]

An estimate of the between-study variance was provided, and meta-regression was used to examine the extent to which study-level variables explained heterogeneity in the treatment effects. The following variables were considered: age (≤60, >60 years), sex ratio, dose, proportion with influenza vaccination history in previous year, and number of years study was conducted. Random-effects meta-analysis was stratified by the study-level variable that explained the most heterogeneity between studies.

A sensitivity analysis was performed excluding the first-year results from one study[15] whose results had been overly influential in the immunogenicity meta-analyses. Analyses were performed using cochrane revman version 5 and stata version 9 (www.cochrane.org).

Results

The literature search yielded 245 citations, from which 210 were excluded because the title or abstract revealed them to be not related to influenza vaccination or they were duplications. Full articles of the remaining 35 studies were

Table 1. Pooled risk ratios for intradermal compared with intramuscular influenza vaccine for efficacy

Vaccine Strain	Author	Dose used in study (μg)	Total number of patients	Ratio of GMTR, [95% CI]	Seroconversion, RR [95% CI]	Seroprotection, RR [95% CI]
H1N1	Auewarakul *et al.* [20]	ID 3	400	–	0·90 [0·85, 0·95]	0·95 [0·92, 0·99]
		IM 15	100			
	Belshe *et al.*[19]	ID 3	29	0·75 [0·62, 0·90]	0·87 [0·59, 1·28]	0·85 [0·61, 1·17]
		IM 15	31			
	Beran *et al.*[15] (Year 1)	ID 3	378	0·42 [0·42, 0·43]	0·71 [0·63, 0·79]	0·84 [0·78, 0·90]
		IM 15	376			
	Kenney *et al.*[21]	ID 3	50	1·02 [0·94, 1·11]	1·05 [0·86, 1·28]	0·89 [0·78, 1·03]
		IM 15	50			
	Van Damme *et al.*[17]	ID 3	60	0·92 [0·88, 1·09]	1·17 [0·95, 1·43]	0·97 [0·89, 1·05]
		IM 15	60			
	Subtotal			0·75 [0·42, 1·34]	0·92 [0·78, 1·08]	0·91 [0·85, 0·97]
	Belshe *et al.*[26] (>60 years)	ID 6	56	0·79 [0·76, 0·83]	0·68 [0·33, 1·44]	1·00 [0·96, 1·04]
		IM 15	46			
	Belshe *et al.*[26] (≤60 years)	ID 6	60	1·03 [0·97, 1·09]	0·74 [0·46, 1·18]	1·00 [0·97, 1·03]
		IM 15	63			
	Belshe *et al.*[19]	ID 6	28	0·90 [0·74, 1·11]	0·92 [0·63, 1·33]	1·07 [0·83, 1·38]
		IM 15	31			
	Beran *et al.*[15] (Year 1)	ID 6	375	0·48 [0·48, 0·49)]	0·74 [0·66, 0·82]	0·82 [0·76, 0·88]
		IM 15	376			
	Chuaychoo *et al.*[27]	ID 6	81	0·93 [0·87, 1·00]	0·90 [0·75, 1·07]	0·99 [0·91, 1·08]
		IM 15	75			
	Van Damme *et al.*[17]	ID 6	60	0·81 [0·72, 0·91]	1·07 [0·86, 1·34]	0·97 [0·89, 1·05]
		IM 15	60			
	Subtotal			0·80 [0·57, 1·12]	0·85 [0·73, 1·00]	0·96 [0·97, 1·02]
	Arnou *et al.*[16]	ID 9	1255	0·94 [0·94, 0·95]	1·02 [0·93, 1·13]	1·01 [0·97, 1·06]
		IM 15	421			
	Belshe *et al.*[19]	ID 9	27	0·66 [0·54, 0·80]	0·79 [0·52, 1·21]	0·97 [0·73, 1·29]
		IM 15	31			
	Beran *et al.*[15] (Year 2)	ID 9	544	0·91 [0·91, 0·92]	0·94 [0·82, 1·08]	0·96 [0·93, 1·00]
		IM 15	547			
	Beran *et al.*[15] (Year 3)	ID 9	417	0·95 [0·94, 0·96]	0·81 [0·60, 1·11]	0·99 [0·95, 1·04]
		IM 15	411			
	Chi *et al.*[23]	ID 9	63	0·81 [0·76, 0·87]	–	1·03 [0·80, 1·33]
		IM 15	65			
	Leroux-Roel *et al.*[18]	ID 9	383	1·17 [1·16, 1·19]	1·05 [0·97, 1·15]	1·04 [0·99, 1·09]
		IM 15	385			
	Subtotal			0·92 [0·85, 1·01]	1·00 [0·93, 1·07]	1·00 [0·97, 1·02]
	Arnou *et al.*[24] (Year 2)	ID 15	262	1·36 [1·33, 1·39]	1·20 [1·04, 1·38]	1·14 [1·05, 1·24]
		IM 15	143			
	Arnou *et al.*[24] (Year 3)	ID 15	298	1·00 [0·97, 1·03]	1·12 [0·76, 1·65]	1·08 [0·93, 1·25]
		IM 15	67			
	Holland *et al.*,[25]	ID 15	359	1·58 [1·56, 1·60]	–	–
		IM 15	358			
	Van Damme *et al.*[22]	ID 15	395	0·90 [0·89, 0·91]	–	0·93 [0·88, 0·99]
		IM 15	395			
	Subtotal			1·18 [0·85, 1·63]	1·19 [1·04, 1·36]	1·04 [0·90, 1·20]
	Holland *et al.*[25]	ID 21	359	1·80 [1·78, 1·82]	–	–
		IM 15	358			
	Subtotal			1·80 [1·78, 1·82]	–	–
	Total			0·92 [0·77, 1·09]	0·94 [0·86, 1·02]	0·97 [0·94, 1·00]

Table 1. (Continued)

Vaccine Strain	Author	Dose used in study (μg)	Total number of patients	Ratio of GMTR, [95% CI]	Seroconversion, RR [95% CI]	Seroprotection, RR [95% CI]
H3N2	Auewarakul *et al.*[20]	ID 3	400	–	0·86 [0·78–0·95)	0·91 [0·86–0·96)
		IM 15	100			
	Belshe *et al.*[19]	ID 3	29	1·86 [1·57, 2·21]	0·74 [0·57, 0·96]	0·83 [0·70, 0·99]
		IM 15	31			
	Beran *et al.*[15] (Year 1)	ID 3	378	0·38 [0·38, 0·39]	0·56 [0·48, 0·65]	0·92 [0·88, 0·95]
		IM 15	376			
	Kenney *et al.*[21]	ID 3	50	2·68 [2·44, 2·93]	1·18 [0·92, 1·51]	0·98 [0·91, 1·05]
		IM 15	50			
	Van Damme *et al.*[17]	ID 3	60	0·54 [0·49, 0·60]	0·74 [0·57, 0·96]	1·00 [0·95, 1·05]
		IM 15	60			
	Subtotal			1·01 [0·36, 2·80]	0·79 [0·62, 1·00]	0·94 [0·90, 0·99]
	Belshe *et al.*[26] (>60 years)	ID 6	56	0·57 [0·52, 0·61]	0·41 [0·20, 0·83]	0·93 [0·86, 1·01]
		IM 15	46			
	Belshe *et al.*[26] (≤60 years)	ID 6	60	1·12 [1·05, 1·18]	0·80 [0·64, 1·01]	1·00 [0·97, 1·03]
		IM 15	63			
	Belshe *et al.*[19]	ID 6	28	1·33 [1·12, 1·59]	0·81 [0·65, 1·02]	0·90 [0·78, 1·03]
		IM 15	31			
	Beran *et al.*[15] (Year 1)	ID 6	375	0·46 [0·45, 0·47]	0·67 [0·59, 0·77]	0·91 [0·87, 0·95]
		IM 15	376			
	Chuaychoo *et al.*[27]	ID 6	81	0·72 [0·67, 0·78]	0·83 [0·68, 1·02]	0·97 [0·83, 1·14]
		IM 15	75			
	Van Damme *et al.*[17]	ID 6	60	0·58 [0·53, 0·64]	0·89 [0·71, 1·11]	0·98 [0·93, 1·04]
		IM 15	60			
	Subtotal			0·74 [0·51, 1·06]	0·77 [0·68, 0·87]	0·95 [0·91, 1·00]
	Arnou *et al.*[16]	ID 9	1255	1·03 [1·02, 1·04]	0·96 [0·89, 1·03]	0·98 [0·95, 1·00]
		IM 15	421			
	Belshe *et al.*[19]	ID 9	27	0·71 [0·61, 0·83]	0·80 [0·64, 1·01]	0·95 [0·78, 1·15]
		IM 15	31			
	Beran *et al.*[15] (Year 2)	ID 9	544	1·00 [0·99, 1·01]	1·05 [0·93, 1·17]	0·98 [0·96, 0·99]
		IM 15	547			
	Beran *et al.*[15] (Year 3)	ID 9	417	1·31 [1·30, 1·33]	1·33 [1·17, 1·52]	1·01 [1·00, 1·02]
		IM 15	411			
	Chi *et al.*[23]	ID 9	63	0·84 [0·77, 0·90]	–	0·97 [0·79, 1·19]
		IM 15	65			
	Leroux-Roel *et al.*[18]	ID 9	383	1·36 [1·35, 1·38]	1·07 [1·00, 1·14]	1·01 [1·00, 1·02]
		IM 15	385			
	Subtotal			1·03 [0·91, 1·17]	1·04 [0·93, 1·17]	1·00 [0·98, 1·01]
	Arnou *et al.*[24] (Year 2)	ID 15	262	1·19 [1·17, 1·21]	1·16 [0·91, 1·47]	1·02 [0·99, 1·06]
		IM 15	143			
	Arnou *et al.*[24] (Year 3)	ID 15	298	1·12 [1·07, 1·16]	1·17 [0·96, 1·44]	1·15 [1·01, 1·32]
		IM 15	67			
	Holland *et al.*[25]	ID 15	359	1·54 [1·52, 1·56]	–	–
		IM 15	358			
	Van Damme *et al.*[22]	ID 15	395	0·88 [0·87, 0·89]	–	–
		IM 15	395			
	Subtotal			1·16 [0·86, 1·56]	1·17 [1·00, 1·36]	1·07 [0·95, 1·19]
	Holland *et al.*[25]	ID 21	359	1·75 [1·73, 1·78]	–	–
		IM 15	358			
	Subtotal			1·75 [1·73, 1·78]	–	–
	Total			0·97 [0·80, 1·18]	0·89 [0·80, 0·99]	0·98 [0·96, 0·99]

Table 1. (Continued)

Vaccine Strain	Author	Dose used in study (μg)	Total number of patients	Ratio of GMTR, [95% CI]	Seroconversion, RR [95% CI]	Seroprotection, RR [95% CI]
B Strain	Auewarakul *et al.*[20]	ID 3	400	–	0·60 [0·46, 0·77]	0·76 [0·62, 0·94]
		IM 15	100			
	Belshe *et al.*[19]	ID 3	29	1·30 [1·10, 1·54]	0·81 [0·54, 1·23]	0·88 [0·71, 1·09]
		IM 15	31			
	Beran *et al.*[15] (Year 1)	ID 3	378	0·48 [0·47, 0·48]	0·44 [0·35, 0·55]	0·51 [0·43, 0·62]
		IM 15	376			
	Kenney *et al.*[21]	ID 3	50	0·81 [0·75, 0·88]	1·00 [0·83, 1·20]	1·00 [0·96, 1·04]
		IM 15	50			
	Van Damme *et al.*[17]	ID 3	60	0·89 [0·81, 0·97]	1·08 [0·83, 1·40]	1·07 [0·89, 1·28]
		IM 15	60			
	Subtotal			0·81 [0·52, 1·26]	0·74 [0·52, 1·07]	0·82 [0·64, 1·05]
	Belshe *et al.*[26] (>60 years)	ID 6	56	0·81 [0·78, 0·84]	0·75 [0·35, 1·60]	1·00 [0·96, 1·04]
		IM 15	46			
	Belshe *et al.*[26] (≤60 years)	ID 6	60	0·70 [0·66, 0·75]	0·60 [0·36, 0·99]	1·00 [0·97, 1·03]
		IM 15	63			
	Belshe *et al.*[19]	ID 6	28	1·30 [1·09, 1·55]	0·97 [0·68, 1·38]	1·03 [0·89, 1·20]
		IM 15	31			
	Beran *et al.*[15] (Year 1)	ID 6	375	0·55 [0·54, 0·55]	0·57 [0·47, 0·70]	0·59 [0·50, 0·70]
		IM 15	376			
	Chuaychoo *et al.*[27]	ID 6	81	0·50 [0·46, 0·54]	0·90 [0·67, 1·22]	0·94 [0·77, 1·16]
		IM 15	75			
	Van Damme *et al.*[17]	ID 6	60	1·24 [1·13, 1·36]	1·08 [0·83, 1·40]	1·11 [0·93, 1·32]
		IM 15	60			
	Subtotal			0·79 [0·62, 1·01]	0·80 [0·61, 1·04]	0·94 [0·86, 1·03]
	Arnou*et al.*[16]	ID 9	1255	0·96 [0·96, 0·97]	0·93 [0·85, 1·02]	0·97 [0·91, 1·04]
		IM 15	421			
	Belshe *et al.*[19]	ID 9	27	0·80 [0·68, 0·94]	0·90 [0·61, 1·32]	0·95 [0·78, 1·15]
		IM 15	31			
	Beran *et al.*[15] (Year 2)	ID 9	544	0·94 [0·93, 0·95]	0·95 [0·87, 1·04]	0·98 [0·91, 1·05]
		IM 15	547			
	Beran *et al.*[15] (Year 3)	ID 9	417	1·00 [0·99, 1·01]	1·23 [0·95, 1·59]	1·02 [0·96, 1·09]
		IM 15	411			
	Chi *et al.* [23]	ID 9	63	0·71 [0·67, 0·76]	–	0·61 [0·30, 1·22]
		IM 15	65			
	Leroux-Roel *et al.*[18]	ID 9	383	1·12 [1·11, 1·13]	1·04 [0·96, 1·13]	1·06 [1·00, 1·11]
		IM 15	385			
	Subtotal			0·93 [0·87, 0·99]	0·99 [0·92, 1·06]	1·01 [0·97, 1·05]
	Arnou *et al.*[24] (Year 2)	ID 15	262	1·14 [1·13, 1·15]	2·87 [1·86, 4·42]	1·71 [1·48, 1·98]
		IM 15	143			
	Arnou *et al.*[24] (Year 3)	ID 15	298	1·32 [1·28, 1·36]	1·27 [0·97, 1·66]	1·11 [0·93, 1·31]
		IM 15	67			
	Holland *et al.*[25]	ID 15	359	1·36 [1·35, 1·38]	–	–
		IM 15	358			
	Van Damme *et al.*[22]	ID 15	395	1·02 [1·01, 1·03]	–	–
		IM 15	395			
	Subtotal			1·20 [1·04, 1·39]	1·87 [0·85, 4·15]	1·38 [0·90, 2·12]
	Holland *et al.*[25]	ID 21	359	1·59 [1·57, 1·61]	–	–
		IM 15	358			
	Subtotal			1·59 [1·57, 1·61]	–	–
	Total			0·93 [0·80, 1·08]	0·91 [0·80, 1·04]	0·97 [0·91, 1·03]

A GMTR

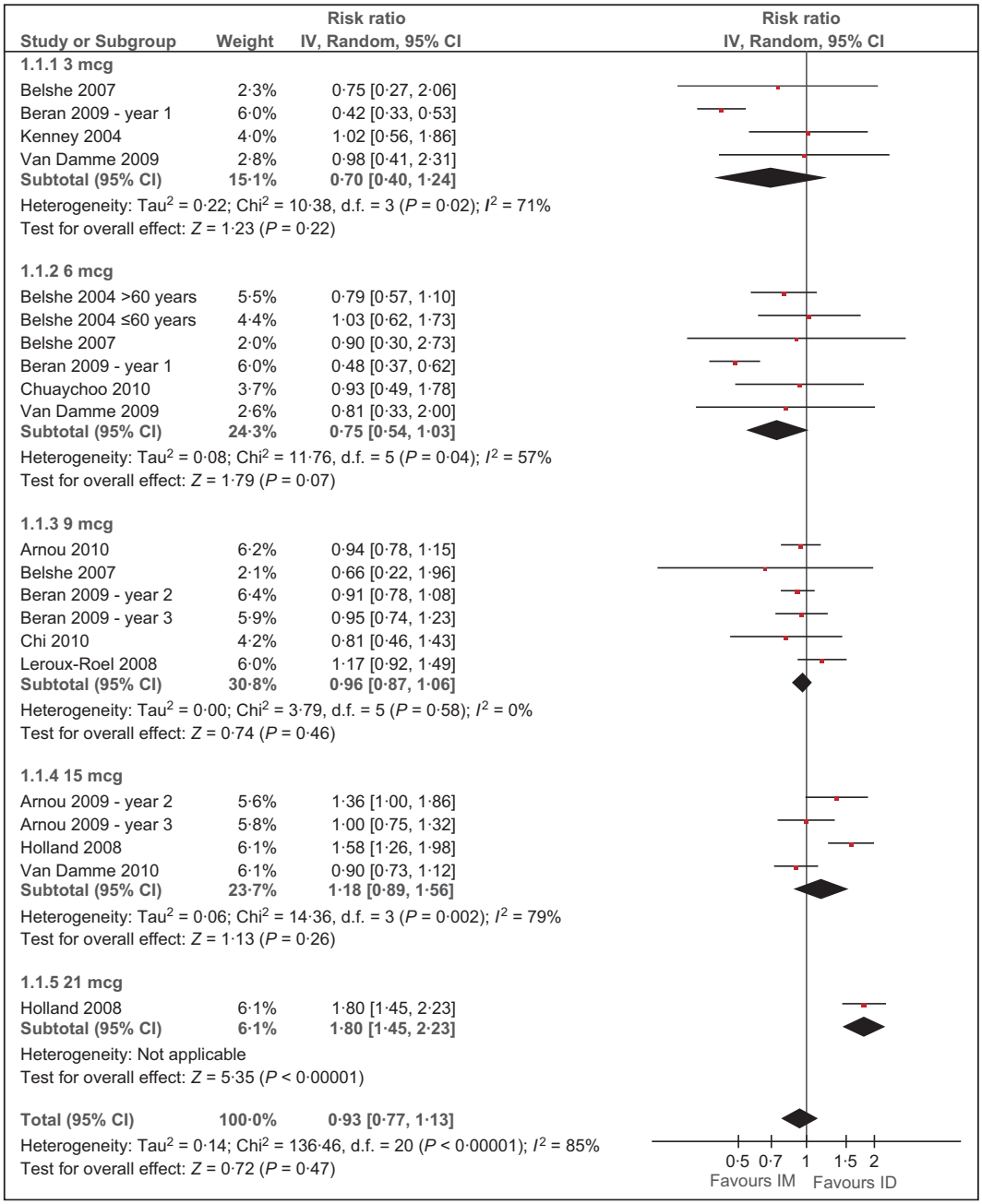
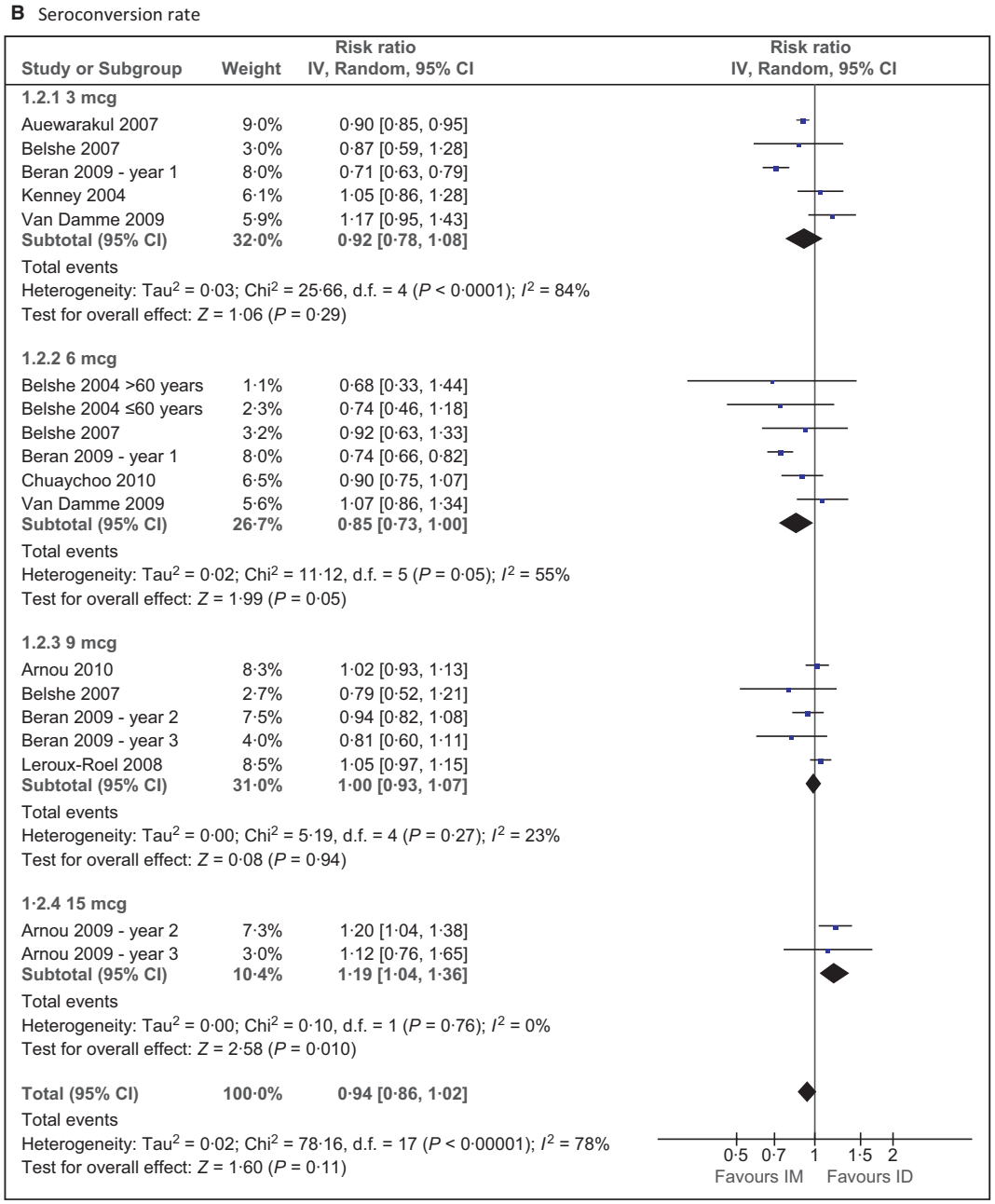


Figure 1. Pooled immunogenicity for (a) ratio of GMTR, (b) risk ratio of seroconversion, (c) risk ratio of seroprotection for intradermal compared with intramuscular influenza vaccine for H1N1 strain.

retrieved for further evaluation, from which a further 22 studies were excluded because of various reasons (i.e. animal studies, non-randomized, use of whole-virus vaccine, assessment of titers not within 21–28 days).

Thirteen randomized, controlled, open-label trials[15–27] were included in this meta-analysis, and these were also included in our systematic review.[8] Seven trials[15–21] were performed in young adults 18–60 years of age, four trials[22–25] were performed in elderly subjects >60 years, and two trials[26,27] included both young adults and elderly participants, of which one[26] performed separate analyses for both groups and one[27] provided a separate analysis for the elderly population only. Nine trials[15,16,20–26] had a Jadad score of 3, and four trials[17–19,27] had a score of 1.

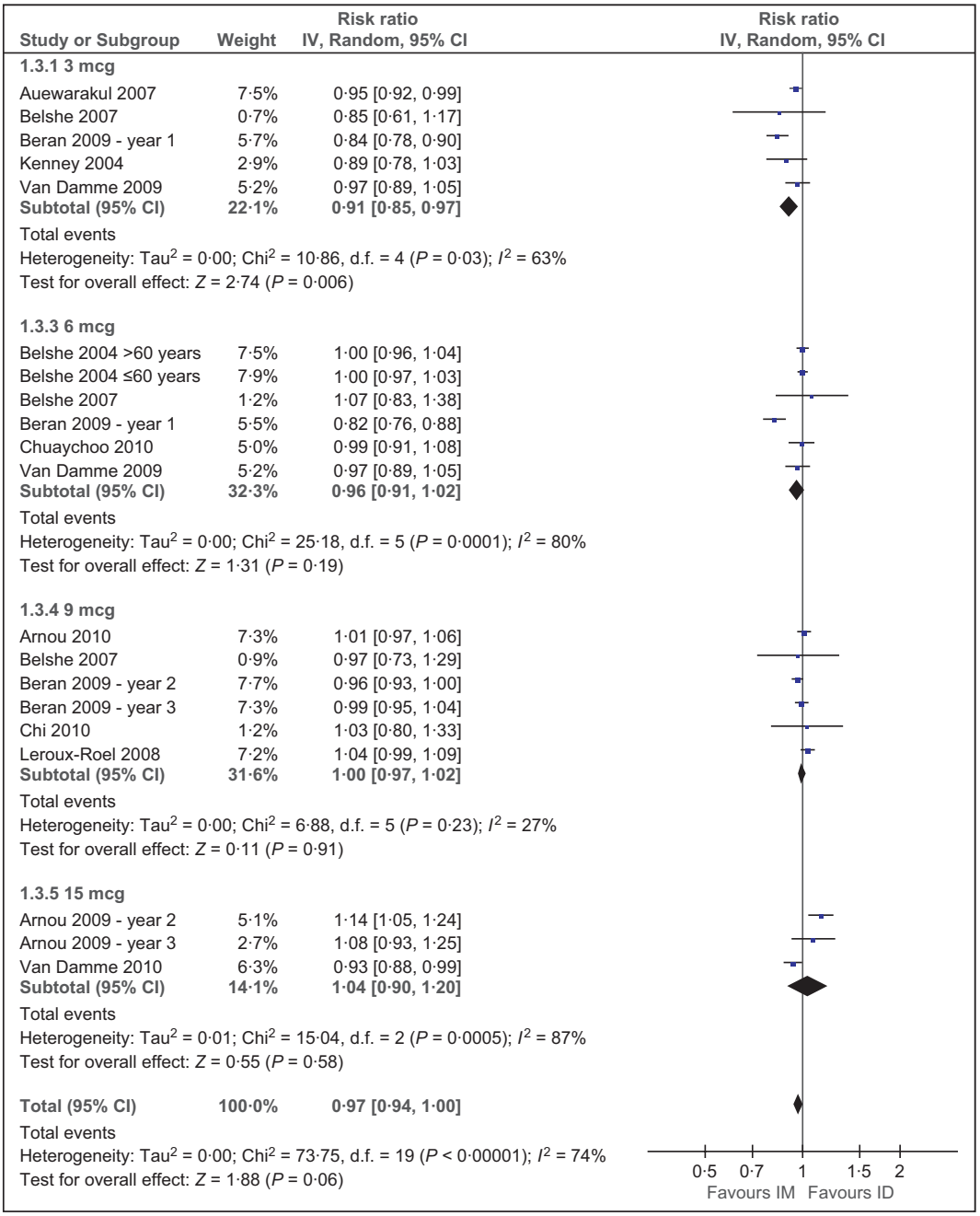


Immunogenicity

The immunogenicity outcomes (i.e., GMTR, seroprotection, and seroconversion) for the H1N1, H3N2, and B strains did not differ significantly across the intramuscular and intradermal vaccine groups, except for the H3N2 strain, where there was a lower pooled seroconversion (RR 0·89, 95% CI 0·80–0·99) and seroprotection rate (RR 0·98, 95% CI, 0·96–0·99) for ID recipients. This is shown in Table 1.

Meta-analyses of studies stratified by ID dose are shown in Figures 1–3. For H1N1 at a dose of 15 μg, the seroconversion RR was 1·19 (95% CI, 1·04–1·36), while at 6 μg, it was 0·85 (95% CI, 0·73–1·00), and also at 3 μg, the seroprotection rate was significantly lowered for ID recipients with a RR of 0·91 (95% CI, 0·85–0·97) compared with IM recipients (Figure 1). For H3N2 at 15 μg, the seroconversion RR was 1·17 (1·00–1·36), while at 3 μg, it was 0·79 (0·62–1·00) compared with IM groups. Also at 3 μg, the seroprotection RR was 0·94 (0·90–0·99) (Figure 2). For B at 15 μg, the GMTR RR was 1·20 (1·04–1·39), while at 9 μg, it was 0·93 (0·87–0·99) (Figure 3).

C Seroprotection rate



Generally for ID at the same dose as control (15 μg), there were no significant differences between the outcomes, apart from the fact that ID was superior to IM vaccination for H1N1 and H3N2 seroconversion and for B GMTR. In the meta-regression, age had *P*-values of <0·1 for H1N1 GMTR ($P = 0·05$) and B seroconversion ($P = 0·01$). No other study-level variables were significantly associated with more than one immunogenicity outcome in the meta-regression for H1N1, H3N2, or B influenza strains.

Adverse events within 3 days post-vaccination

There were no differences in adverse event rates within 3 days post-vaccination for ID versus IM vaccination. There was little evidence of heterogeneity (only ≥1 ADR had $P < 0·05$). In meta-regression, age was the strongest predictor

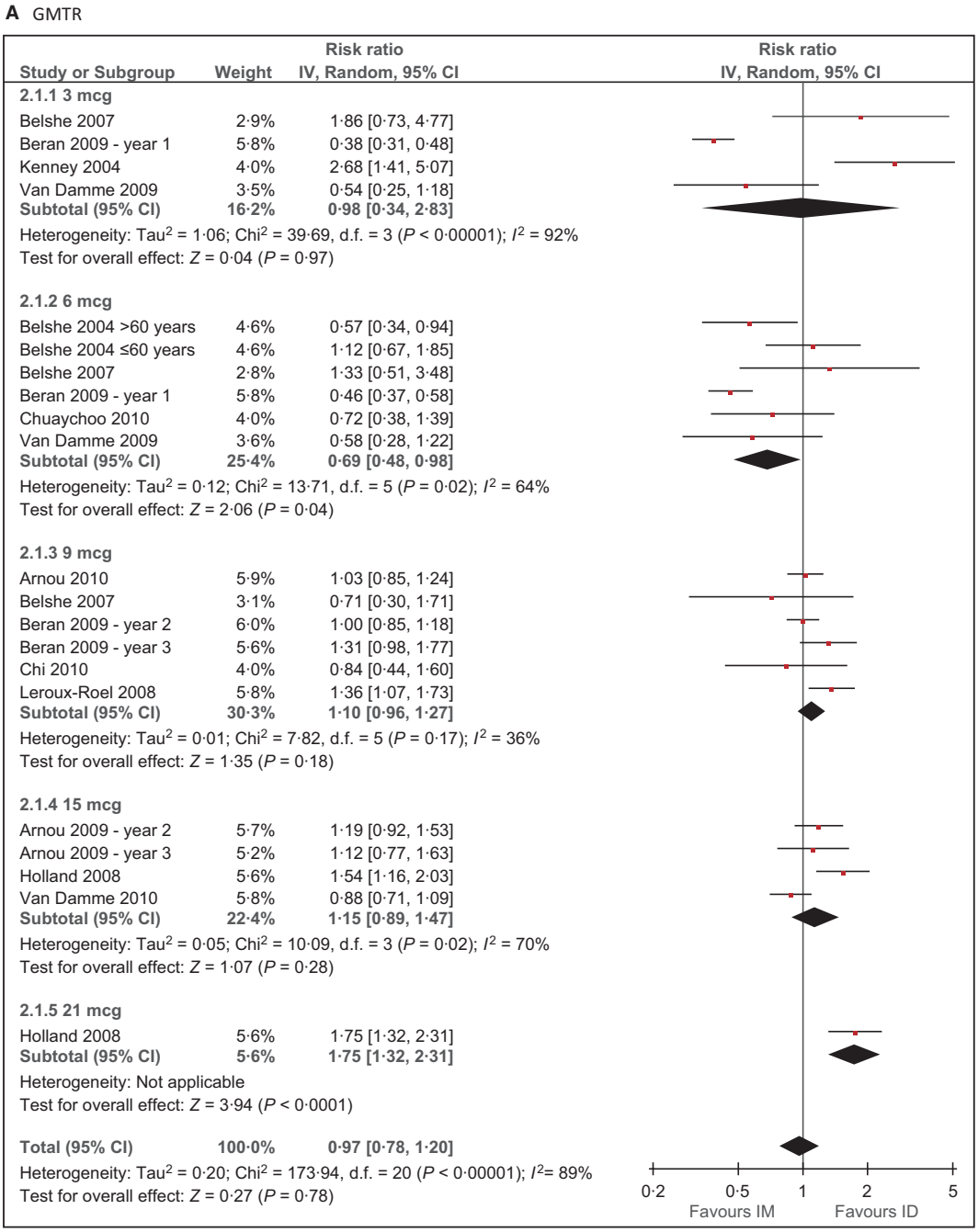


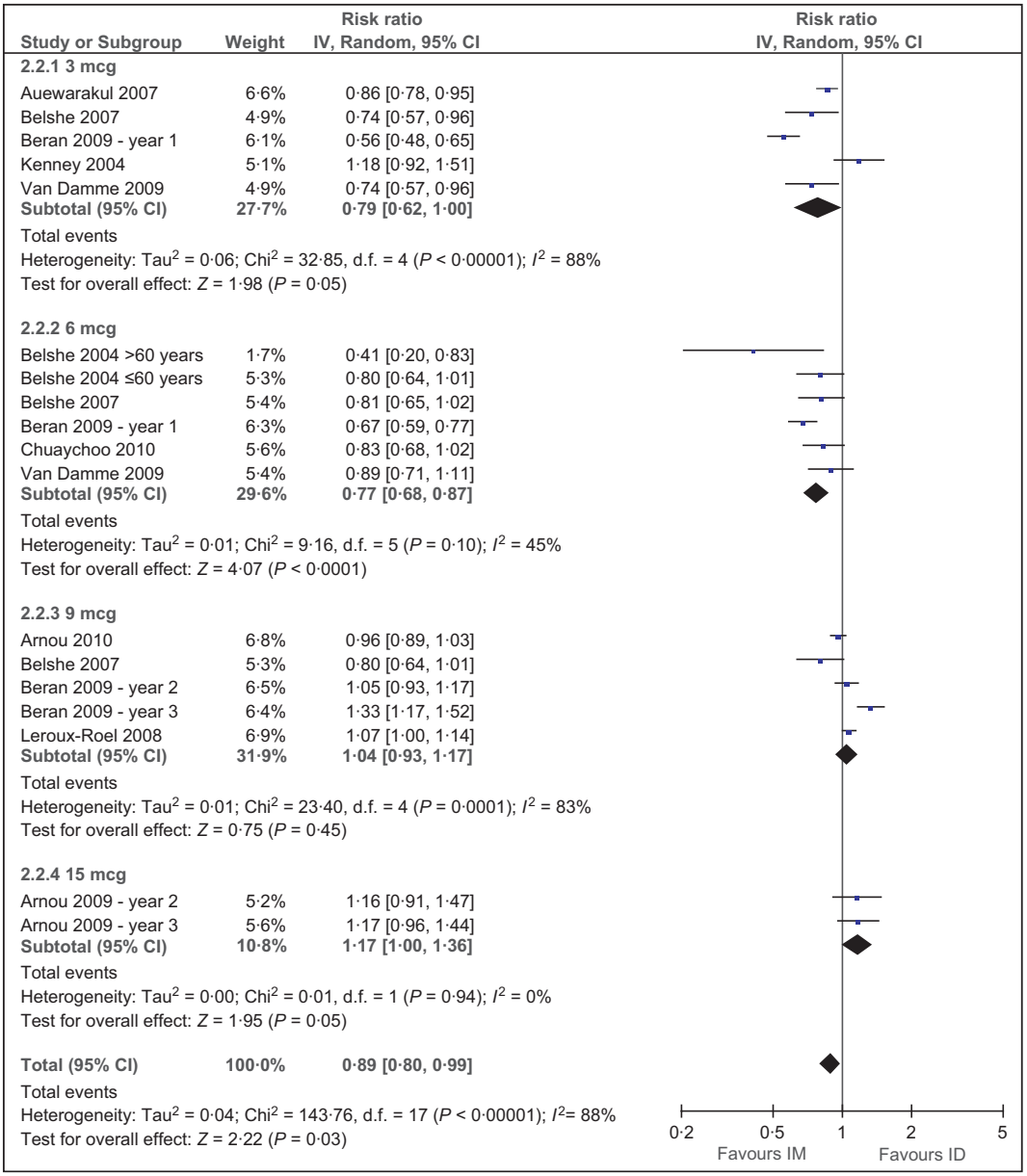
Figure 2. Pooled immunogenicity for (a) ratio of GMTR, (b) risk ratio of seroconversion, (c) risk ratio of seroprotection for intradermal compared with intramuscular influenza vaccine for H3N2 strain.

of the results, so meta-analyses of studies stratified by age (≤60, >60 years) are shown in Table 2. However, no consistent patterns between age and the RR for adverse events were observed. Age was only significantly associated with malaise (P = 0·03), with a RR of 0·84 (95% CI 0·71–0·98) for those aged ≤60 when comparing ID versus IM groups.

Adverse events within 7 days post-vaccination

Intradermal vaccination was associated with a greater incidence of local adverse events (Table 3) when compared with IM administration. This was particularly true for the categories of ≥1 ADR (RR 1·94, 95% CI 1·60–2·35), erythema (5·34, 4·35–6·55), swelling (4·65, 3·70–5·85), induration (4·41,

B Seroconversion rate

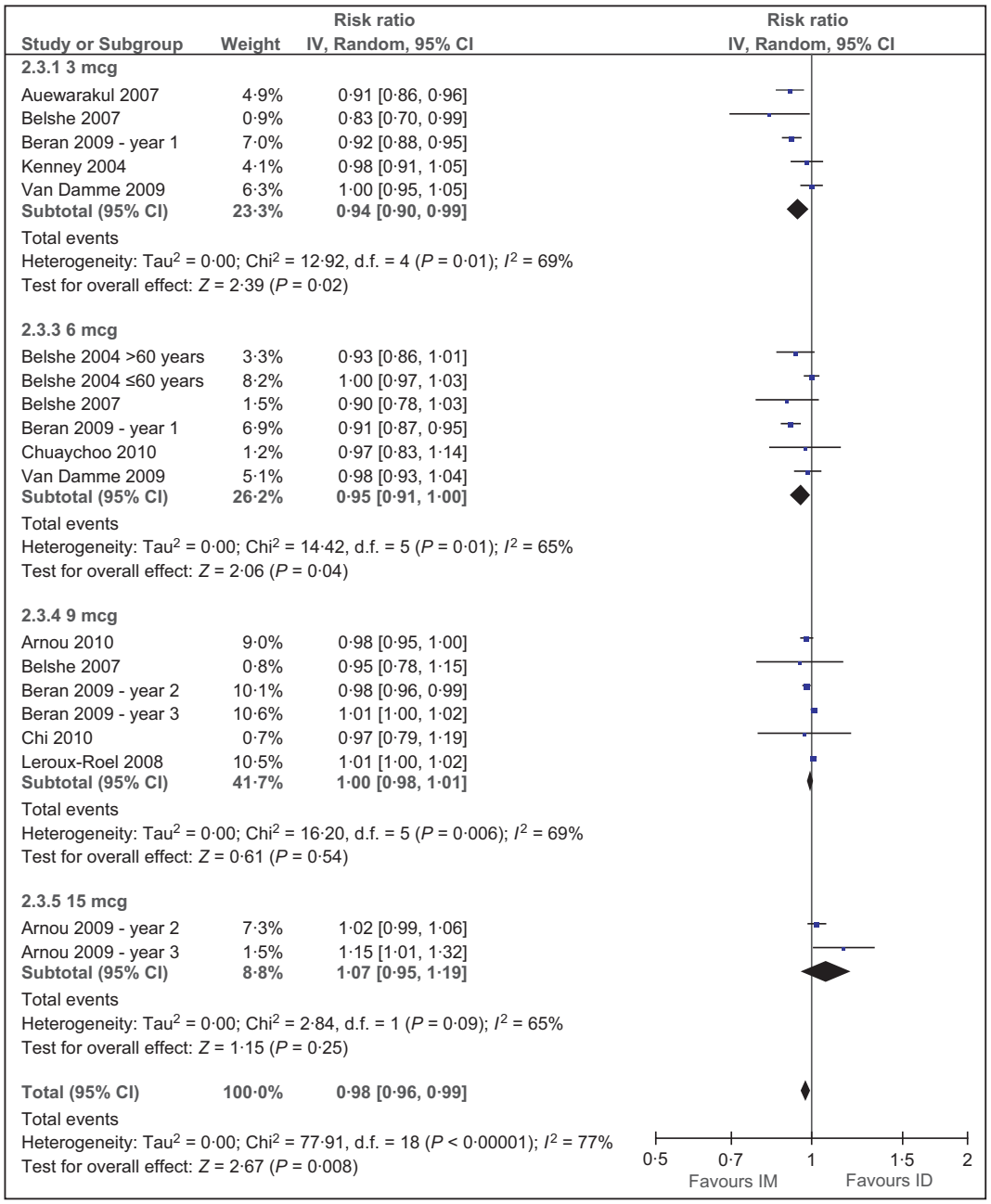


3·38–5·75), and pruritis (4·09, 3·55–4·72). However ID vaccination was not associated with a greater incidence of any systemic adverse events examined (Table 4) and was associated with a lower incidence of myalgia (0·80, 0·66–0·97). There was evidence of heterogeneity for most adverse events. In the meta-regression, age was weakly associated with adverse events. However, no consistent pattern between age and the RR for adverse events was observed in the meta-analyses of studies stratified by age (≤60, >60 years), specifically with local events ≥1 ADR ($P = 0·08$) and pruritis ($P = 0·06$), and for systemic events fever ($P = 0·08$), malaise ($P = 0·08$), and myalgia ($P = 0·06$).

Sensitivity analysis

The adverse event results remained unchanged when excluding the first-year data from one study,[15] whose results had been overly influential in the immunogenicity meta-analyses. However, in the sensitivity analysis, none of the immunogenicity outcomes remained significantly different overall across ID and IM recipients. Although the strong associations with dose remained (all $P < 0·05$), the pooled RRs in those dose subgroups with significant results in the main analysis were still comparable. Also other results from the meta-regressions were consistent with conclusions made in the main analysis.

C Seroprotection rate



Discussion

The results of this meta-analysis suggest there is no difference in overall immunogenicity outcomes when comparing ID with conventional IM influenza vaccine administration. However, our meta-analysis did see a significant dose–response relationship in favor of ID administration. This is consistent with the results of the Keitel *et al.*[28] study where higher doses of IM influenza vaccines in older adults (60 μg HA/strain) had 44–71% higher HA inhibition antibody titers compared with those who received the standard 15 μg HA/strain. In fact, of the three trials included in this meta-analysis that compared the 15 μg dose ID with 15 μg IM[22,24,25] in older adults, two showed superiority of ID over IM[24,25] and one of the trials showed non-inferiority between ID and IM.[22] ID administration of influenza vaccine therefore promises as a potential strategy to improve the immunogenicity response in

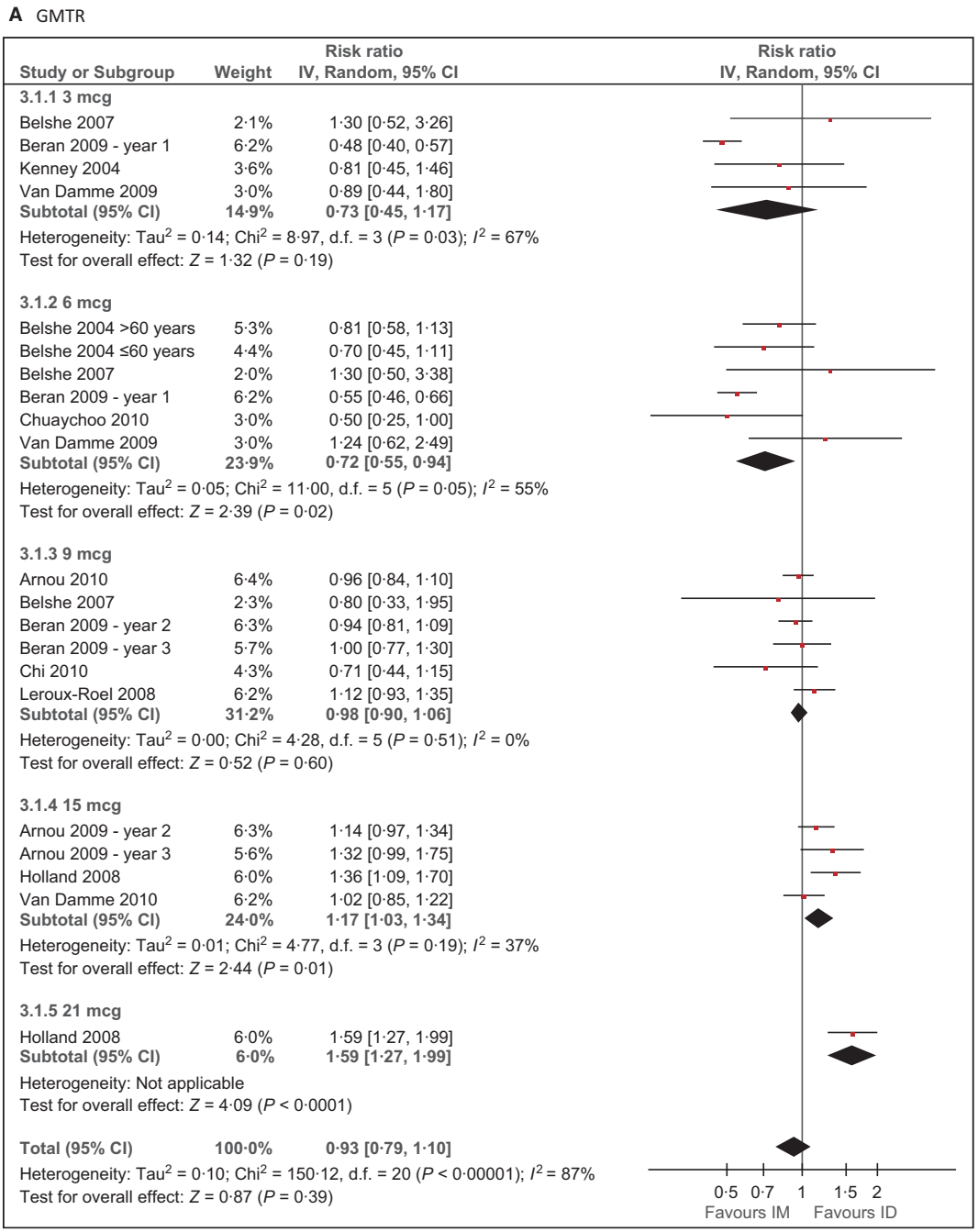
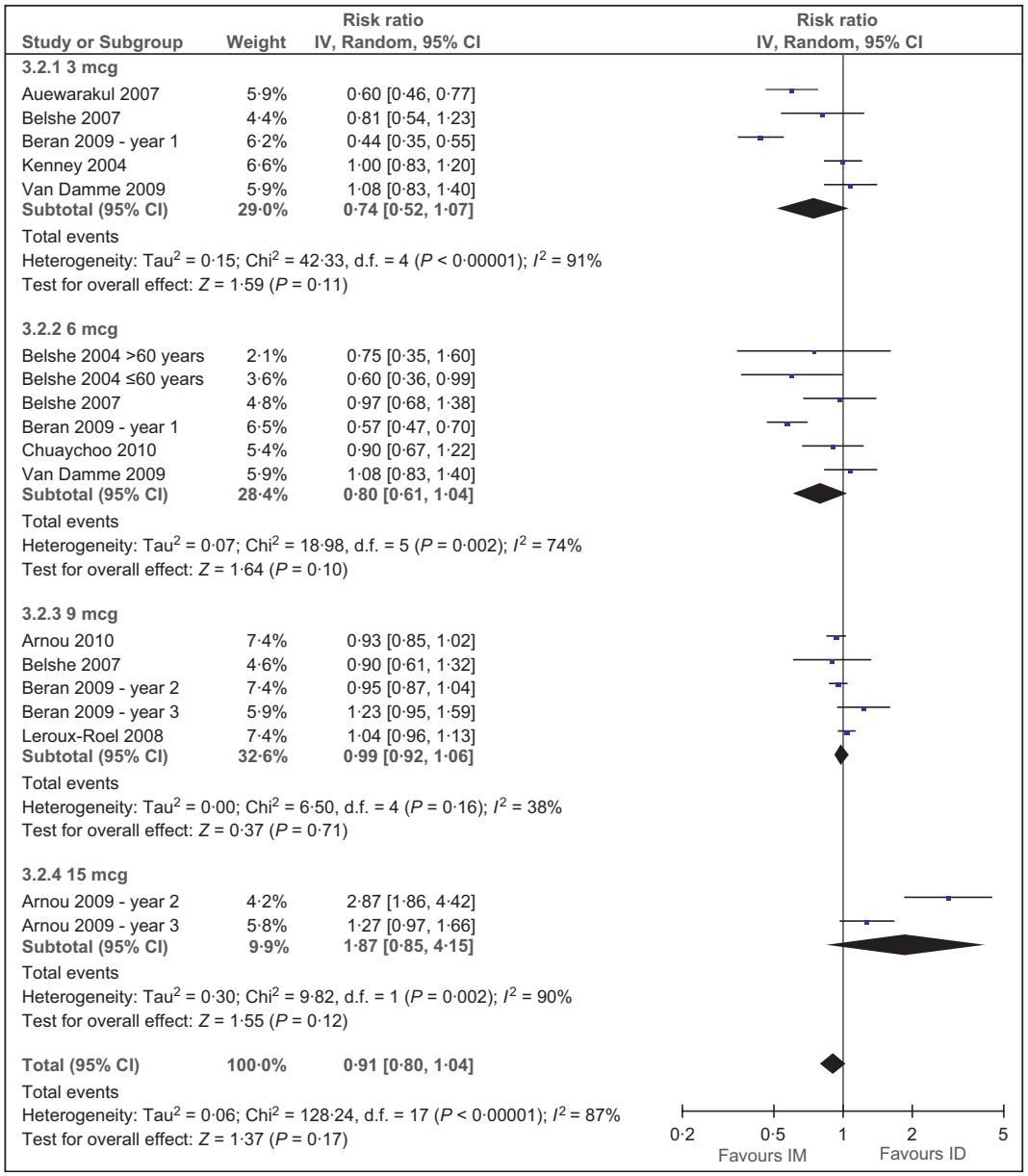


Figure 3. Pooled immunogenicity for (a) ratio of GMTR, (b) risk ratio of seroconversion, (c) risk ratio of seroprotection for intradermal compared with intramuscular influenza vaccine for B strain.

older adults as they are at higher risk of morbidity and mortality because of influenza illness.[2,29] Thus, a higher dose of influenza vaccine administered ID may be a good option in the older adult population to improve their immunogenicity response.

The meta-analysis was performed on both adults and elderly. As the licensed vaccines are two separate formulations, one for adults (9 μg) and another for the elderly (15 μg), analyses were also performed within the separate age groups, but findings were similar for most outcomes. Because of the large number of results presented, we decided not to also present the results separately by the two age groups. However, age group (<60 and >60 years) was examined as a possible explanatory factor for

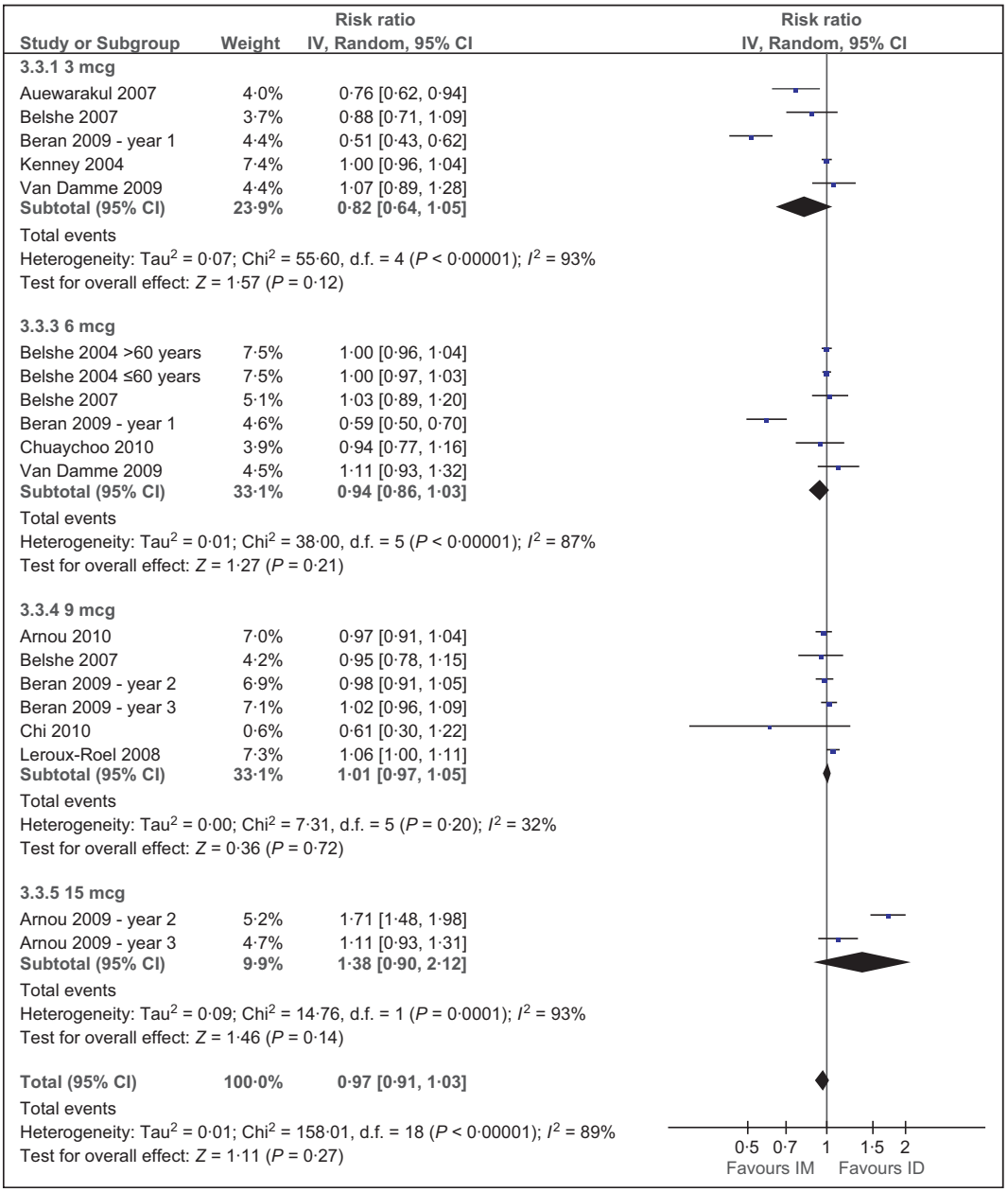
B Seroconversion rate



heterogeneity seen within the results, and those with significant differences between the groups are reported in the results. In the meta-regression, age had *P*-values of <0·1 for H1N1 GMTR ($P = 0{\cdot}05$) and B seroconversion ($P = 0{\cdot}01$). No statistically significant differences in adverse events in the first 3 days were found between the two groups. For adverse events in the first 7 days, there were no differences in systemic adverse events; however, there was a higher incidence of local adverse events, specifically erythema, swelling, induration, and pruritis in the ID group when compared with the IM group.

There are several limitations in this meta-analysis. There was significant heterogeneity across studies for the immunogenicity outcomes. This finding may be due to differences between studies such as ages of the study population and doses used. However, the differences in dosing across studies permitted a dose–response analysis (data not supplied). Furthermore, we were not able to include all the data from the included studies into the meta-analysis because some of the data were either not included in the study article or were presented as figures. Authors of the studies were contacted for additional information, but we

C Seroprotection rate



were unsuccessful in obtaining the necessary data. Another limitation in this meta-analysis is that none of the included trials were double-blinded. However, as the outcomes assessed are objective laboratory values, this is unlikely to affect results. Additionally, we excluded trials that included immunocompromised patients, who are likely to have different immune responses from those who are immunocompetent. As such, these results cannot be extrapolated to those who are immunocompromised. Finally, none of the included trials assessed clinical outcomes, such as occurrence of influenza illness, hospitalizations, and mortality. This is a significant limitation, given that antibody response is not necessarily the best predictor of clinical efficacy in older adults. Recent studies demonstrate that serum HA antibody titers may not be associated with the development of influenza.[30] Because of this possible lack of correlation, there is still much to be done in this area to evaluate cell-mediated immunity and its association with clinical efficacy, especially in older individuals and those with chronic illness.

Table 2. Pooled risk ratios for intradermal compared with intramuscular influenza vaccine for adverse events within 3 days post-vaccination

ADR	Age group	Author	Risk ratio (95% CI)	*P*-Value	I^2 (%)
≥1 local ADR	18–60 years	Arnou *et al.*[16]	0·91 [0·77, 1·07]		
		Belshe *et al.*[19]	1·48 [1·16, 1·89]		
		Beran *et al.*[15] (Year 1)	0·77 [0·55, 1·07]		
		Beran *et al.*[15] (Year 2)	0·92 [0·66, 1·27]		
		Beran *et al.*[15] (Year 3)	1·13 [0·78, 1·63]		
		Leroux-Roel *et al.*[18]	0·73 [0·55, 0·98]		
		Subtotal	0·96 [0·78, 1·20]	0·74	73
	>60 years	Arnou *et al.*[24] (Year 1)	0·99 [0·82, 1·19]		
		Holland *et al.*[25]	1·16 [0·86, 1·58]		
		Van Damme *et al.*[22]	0·92 [0·65, 1·32]		
		Subtotal	1·01 [0·88, 1·17]	0·86	0
	Total		0·98 [0·85, 1·13]	0·82	60
Induration	18–60 years	Arnou *et al.*[16]	1·26 [0·06, 26·12]		
		Beran *et al.*[15] (Year 1)	0·17 [0·01, 4·07]		
		Leroux-Roel *et al.*[18]	1·99 [0·08, 48·76]		
		Subtotal	0·76 [0·12, 4·66]	0·77	0
	>60 years	Arnou *et al.*[24] (Year 1)	2·93 [0·15, 56·61]		
		Subtotal	2·93 [0·15, 56·61]	0·48	N/A
	Total		1·10 [0·23, 5·16]	0·91	0
Pyrexia	18–60 years	Arnou *et al.*[16]	2·01 [0·86, 4·66]		
		Beran *et al.*[15] (Year 1)	0·75 [0·27, 2·08]		
		Beran *et al.*[15] (Year 2)	1·68 [0·40, 6·98]		
		Beran *et al.*[15] (Year 3)	3·43 [0·72, 16·43]		
		Leroux-Roel *et al.*[18]	1·99 [0·54, 7·30]		
		Subtotal	1·62 [0·98, 2·70]	0·06	0
	>60 years	Arnou *et al.*[24] (Year 1)	0·81 [0·43, 1·50]		
		Holland *et al.*[25]	0·89 [0·40, 2·00]		
		Van Damme *et al.*[22]	0·50 [0·19, 1·32]		
		Subtotal	0·75 [0·49, 1·17]	0·21	0
	Total		1·08 [0·73, 1·61]	0·70	25
Malaise	18–60 years	Arnou *et al.*[16]	0·87 [0·69, 1·09]		
		Beran *et al.*[15] (Year 1)	0·76 [0·43, 1·34]		
		Beran *et al.*[15] (Year 2)	0·85 [0·52, 1·40]		
		Beran *et al.*[15] (Year 3)	0·78 [0·41, 1·49]		
		Leroux-Roel *et al.*[18]	0·81 [0·58, 1·12]		
		Subtotal	0·84 [0·71, 0·98]	0·03	0
	>60 years	Arnou *et al.*[24] (Year 1)	1·12 [0·86, 1·45]		
		Holland *et al.*[25]	1·19 [0·78, 1·81]		
		Van Damme *et al.*[22]	0·95 [0·51, 1·75]		
		Subtotal	1·11 [0·90, 1·37]	0·31	0
	Total		0·93 [0·82, 1·06]	0·28	0
Shivering	18–60 years	Arnou *et al.*[16]	1·15 [0·79, 1·69]		
		Beran *et al.*[15] (Year 1)	1·23 [0·75, 2·02]		
		Beran *et al.*[15] (Year 2)	0·88 [0·57, 1·36]		
		Beran *et al.*[15] (Year 3)	1·17 [0·71, 1·93]		
		Leroux-Roel *et al.*[18]	0·80 [0·50, 1·29]		
		Subtotal	1·03 [0·85, 1·26]	0·75	0
	>60 years	Arnou *et al.*[24] (Year 1)	0·84 [0·61, 1·18]		
		Holland *et al.*[25]	3·52 [0·43, 28·50]		
		Van Damme *et al.*[22]	1·04 [0·60, 1·81]		
		Subtotal	0·92 [0·69, 1·22]	0·55	1
	Total		0·99 [0·84, 1·17]	0·92	0

Table 3. Pooled risk ratios for intradermal compared with intramuscular influenza vaccine for local adverse events within 7 days post-vaccination

ADR	Age group	Author	Risk ratio (95% CI)	*P*-Value	I^2 (%)
≥1 local ADR	18–60 years	Arnou *et al.*[16]	1·39 [1·30, 1·49]		
		Belshe *et al.*[19]	1·48 [1·16, 1·89]		
		Beran *et al.*[15](Year 2)	1·67 [1·51, 1·85]		
		Beran *et al.*[15] (Year 3)	1·67 [1·48, 1·88]		
		Van Damme *et al.*[17]	6·43 [3·18, 13·0]		
		Subtotal	1·66 [1·40, 1·96]	<0·00001	86
	>60 years	Arnou *et al.*[24] (Year 1)	2·46 [2·24, 2·69]		
		Holland *et al.*[25]	2·24 [1·97, 2·55]		
		Van Damme *et al.*[22]	2·08 [1·78, 2·42]		
		Subtotal	2·29 [2·07, 2·52]	<0·00001	48
	Total		1·94 [1·60, 2·35]	<0·00001	95
Erythema	18–60 years	Arnou *et al.*[16]	1·26 [0·06, 26·12]		
		Auewarakul *et al.*[20]	46·12 [11·69, 181·89]		
		Belshe *et al.*[26]	15·24 [5·86, 39·62]		
		Belshe *et al.*[19]	3·75 [2·06, 6·81]		
		Beran *et al.*[15] (Year 2)	7·31 [5·68, 9·41]		
		Beran *et al.*[15] (Year 3)	5·64 [4·34, 7·32]		
		Kenny *et al.*[21]	12·0 [4·68, 30·77]		
		Van Damme *et al.*[17]	3·92 [2·55, 6·03]		
		Subtotal	6·31 [4·29, 9·27]	<0·00001	87
	>60 years	Arnou *et al.*[24] (Year 1)	4·73 [4·10, 5·46]		
		Belshe *et al.*[26]	9·70 [3·75, 25·08]		
		Chi *et al.*[23]	5·08 [2·72, 9·49]		
		Holland *et al.*[25]	4·12 [3·32, 5·10]		
		Van Damme *et al.*[22]	4·72 [3·64, 6·14]		
		Subtotal	2·93 [0·15, 56·61]	<0·00001	0
	Total		5·34 [4·35, 6·55]	<0·00001	79
Swelling	18–60 years	Arnou *et al.*[16]	2·99 [2·48, 3·60]		
		Belshe *et al.*[26]	5·94 [2·66, 13·26]		
		Belshe *et al.*[19]	4·24 [2·27, 7·94]		
		Kenney *et al.*[21]	8·40 [3·63, 19·46]		
		Van Damme *et al.*[17]	8·10 [4·14, 15·83]		
		Subtotal	5·12 [3·13, 8·38]	<0·00001	73
	>60 years	Arnou *et al.*[24] (Year 1)	4·28 [3·49, 5·24]		
		Belshe *et al.*[26]	14·66 [3·71, 57·96]		
		Holland *et al.*[25]	4·51 [3·46, 5·90]		
		Van Damme *et al.*[22]	4·52 [3·12, 6·55]		
		Subtotal	4·45 [3·83, 5·17]	<0·00001	2
	Total		4·65 [3·70, 5·85]	<0·00001	65
Induration	18–60 years	Arnou *et al.*[16]	2·33 [1·98, 2·74]		
		Auewarakul *et al.*[20]	17·11 [6·53, 44·79]		
		Belshe *et al.*[26]	12·94 [4·94, 33·87]		
		Beran *et al.*[15] (Year 2)	4·49 [3·38, 5·98]		
		Beran *et al.*[15] (Year 3)	3·23 [2·44, 4·28]		
		Kenny*et al.*[2]	4·25 [1·54, 11·74]		
		Van Damme *et al.*[17]	4·91 [2·87, 8·40]		
		Subtotal	4·71 [3·13, 7·09]	<0·00001	86
	>60 years	Arnou *et al.*[24] (Year 1)	4·65 [3·78, 5·71]		
		Belshe *et al.*[26]	16·81 [4·27, 66·14]		
		Holland *et al.*[25]	3·91 [3·09, 4·95]		
		Van Damme *et al.*[22]	3·11 [2·26, 4·28]		
		Subtotal	4·12 [3·14, 5·40]	<0·00001	65
	Total		4·41 [3·38, 5·75]	<0·00001	84

Table 3. (Continued)

ADR	Age group	Author	Risk ratio (95% CI)	*P*-Value	I^2 (%)
Ecchymosis	18–60 years	Arnou *et al.*[16]	1·01 [0·74, 1·38]		
		Beran *et al.*[15] (Year 2)	0·91 [0·39, 2·13]		
		Beran *et al.*[15] (Year 3)	0·98 [0·49, 1·98]		
		Van Damme *et al.*[17]	1·50 [0·16, 14·12]		
		Subtotal	1·00 [0·76, 1·31]	1·00	0
	>60 years	Arnou *et al.*[24] (Year 1)	0·92 [0·64, 1·33]		
		Holland *et al.*[25]	1·44 [0·90, 2·30]		
		Van Damme *et al.*[22]	1·58 [0·78, 3·21]		
		Subtotal	1·19 [0·84, 1·69]	0·32	35
	Total		1·07 [0·89, 1·30]	0·47	0
Pruritis	18–60 years	Arnou *et al.*[16]	3·44 [2·69, 4·40]		
		Beran *et al.*[15] (Year 2)	4·43 [3·20, 6·15]		
		Beran *et al.*[15] (Year 3)	3·83 [2·64, 5·54]		
		Kenny *et al.*[21]	10·50 [2·60, 42·43]		
		Van Damme *et al*[17]	39·83 [2·49, 637·02]		
		Subtotal	4·04 [3·14, 5·20]	<0·00001	36
	>60 years	Arnou *et al.*[24] (Year 1)	4·85 [3·81, 6·17]		
		Chi *et al.*[23]	3·81 [1·34, 10·85]		
		Holland *et al.*[25]	3·44 [2·43, 4·88]		
		Van Damme *et al.*[22]	4·30 [2·87, 6·43]		
		Subtotal	4·32 [3·62, 5·14]	<0·00001	0
	Total		4·09 [3·55, 4·72]	<0·00001	16
Pain	18–60 years	Arnou *et al.*[16]	0·89 [0·80, 1·00]		
		Auewarakul *et al.*[20]	0·80 [0·62, 1·03]		
		Belshe *et al.*[19]	0·77 [0·49, 1·21]		
		Beran *et al.*[15] (Year 2)	0·96 [0·82, 1·11]		
		Beran *et al.*[15] (Year 3)	1·16 [0·98, 1·37]		
		Van Damme *et al.*[17]	0·89 [0·72, 1·11]		
		Subtotal	0·94 [0·84, 1·04]	0·22	48
	>60 years	Arnou *et al.*[24] (Year 1)	1·33 [1·14, 1·54]		
		Chi *et al.*[23]	1·02 [0·38, 2·73]		
		Holland *et al.*[25]	1·03 [0·78, 1·36]		
		Van Damme *et al.*[22]	0·95 [0·72, 1·25]		
		Subtotal	1·12 [0·92, 1·37]	0·26	48
	Total		0·99 [0·88, 1·11]	0·82	67

Conclusion

In conclusion, there were no differences in immunogenicity outcomes when comparing ID with conventional IM administration of influenza vaccination in all patients. But in older adults, administration of the ID influenza vaccine at a higher dose elicited a better immune response. Rates of adverse events were comparable between ID and IM administration, but ID influenza vaccines were associated with a greater incidence of local adverse events in the first 7 days.

Authors' contributions

FM and FY designed the study, extracted the data, and reviewed the selected papers. KR did the statistical analyses. FY, KR, and FM drafted the manuscript and approved the final manuscript. CM assisted with the statistical analysis and reviewed final draft.

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Conflict of interest

FY, FM, and KR have no relationships with Sanofi Pasteur, GlaxoKlineSmith and Novartis that might have an interest in the submitted work in the previous 3 years. Also, their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and FY, FM, and KR have no non-financial interests that may be relevant to the submitted work.

Table 4. Pooled risk ratios for intradermal compared with intramuscular influenza vaccine for systemic adverse events within 7 days post-vaccination

ADR	Age group	Author	Risk ratio (95% CI)	*P*-Value	I^2 (%)
≥1 systemic ADR	18–60 years	Arnou *et al.*[16]	0·93 [0·83, 1·04]		
		Belshe *et al.*[19]	0·87 [0·63, 1·19]		
		Beran *et al.*[15] (Year 2)	0·86 [0·72, 1·03]		
		Beran *et al.*[15] (Year 3)	1·19 [0·95, 1·50]		
		Subtotal	0·95 [0·84, 1·08]	0·44	46
	>60 years	Arnou *et al.*[24] (Year 1)	1·04 [0·91, 1·18]		
		Holland *et al.*[25]	2·24 [1·97, 2·55]		
		Van Damme[22]	2·14 [1·77, 2·59]		
		Subtotal	1·70 [1·00, 2·89]	0·05	97
	Total				
Fever	18–60 years	Arnou *et al.*[16]	1·15 [0·67, 2·00]		
		Auewarakul *et al.*[20]	0·75 [0·31, 1·84]		
		Belshe *et al.*[19]	0·12 [0·00, 2·77]		
		Beran *et al.*[15] (Year 2)	1·61 [0·53, 4·89]		
		Beran *et al.*[15] (Year 3)	4·90 [1·08, 22·25]		
		Subtotal	1·23 [0·65, 2·31]	0·52	41
	>60 years	Arnou *et al.*[24] (Year 1)	0·72 [0·49, 1·08]		
		Holland *et al.*[25]	0·97 [0·53, 1·79]		
		Van Damme *et al.*[22]	0·69 [0·37, 1·29]		
		Subtotal	0·77 [0·57, 1·03]	0·08	0
	Total		0·93 [0·67, 1·28]	0·66	32
Headache	18–60 years	Arnou *et al.*[16]	0·98 [0·83, 1·14]		
		Auewarakul *et al.*[20]	0·71 [0·46, 1·08]		
		Belshe *et al.*[19]	0·75 [0·48, 1·18]		
		Beran *et al.*[15] (Year 2)	1·08 [0·82, 1·42]		
		Beran *et al.*[15] (Year 3)	1·19 [0·86, 1·64]		
		Van Damme *et al.*[17]	1·21 [0·75, 1·93]		
		Subtotal	0·99 [0·86, 1·13]	0·87	19
	>60 years	Arnou *et al.*[24] (Year 1)	1·03 [0·85, 1·23]		
		Chi *et al.*.[23]	0·41 [0·13, 1·23]		
		Holland *et al.*.[25]	0·98 [0·75, 1·29]		
		Subtotal	0·98 [0·80, 1·20]	0·85	24
	Total		0·99 [0·90, 1·09]	0·84	9
Malaise	18–60 years	Arnou *et al.*[16]	0·94 [0·76, 1·17]		
		Auewarakul *et al.*[20]	0·54 [0·35, 0·84]		
		Belshe *et al.*[19]	1·28 [0·66, 2·48]		
		Van Damme *et al.*[17]	0·91 [0·47, 1·77]		
		Subtotal	0·85 [0·61, 1·18]	0·33	53
	>60 years	Arnou *et al.*[24] (Year 1)	1·08 [0·85, 1·38]		
		Holland *et al.*[25]	1·15 [0·80, 1·66]		
		Subtotal	1·10 [0·90, 1·35]	0·34	0
	Total		0·95 [0·78, 1·17]	0·65	47
Mylagia	18–60 years	Arnou *et al.*[16]	0·80 [0·68, 0·94]		
		Auewarakul *et al.*[20]	0·60 [0·42, 0·87]		
		Belshe *et al.*[19]	0·95 [0·53, 1·73]		
		Beran *et al.*[15] (Year 2)	0·48 [0·33, 0·68]		
		Beran *et al.*[15] (Year 3)	1·12 [0·76, 1·67]		
		Van Damme *et al.*[17]	0·55 [0·25, 1·22]		
		Subtotal	0·72 [0·56, 0·93]	0·01	62
	>60 years	Arnou *et al.*[24] (Year 1)	0·98 [0·80, 1·20]		
		Holland *et al.*[25]	1·01 [0·72, 1·41]		
		Subtotal	0·98 [0·83, 1·17]	0·86	0
	Total		0·80 [0·66, 0·97]	0·03	64

Table 4. (Continued)

ADR	Age group	Author	Risk ratio (95% CI)	*P*-Value	I^2 (%)
Shivering	18–60 years	Arnou *et al.*[16]	1·27 [0·89, 1·82]		
		Subtotal	1·27 [0·89, 1·82]	0·19	N/A
	>60 years	Arnou *et al.*[24] (Year 1)	0·76 [0·57, 1·02]		
		Holland *et al.*[25]	1·68 [0·46, 6·05]		
		Subtotal	0·87 [0·48, 1·57]	0·65	28
	Total		1·03 [0·65, 1·61]	0·91	64
Arthralgia	18–60 years	Auewarakul *et al.*[20]	0·98 [0·51, 1·89]		
		Beran *et al.*[15] (Year 2)	0·94 [0·59, 1·52]		
		Beran *et al.*[15] (Year 3)	3·19 [1·46, 6·96]		
		Subtotal	1·36 [0·68, 2·74]	0·38	73
	Total		1·36 [0·68, 2·74	0·38	73
Chills	18–60 years	Auewarakul *et al.*[20]	0·61 [0·26, 1·43]		
		Subtotal	0·61 [0·26, 1·43]	0·25	N/A
	>60 years	Chi *et al.*[23]	1·02 [0·06, 15·89]		
		Subtotal	1·02 [0·06, 15·89]	0·99	N/A
	Total		0·64 [0·28, 1·44]	0·28	0
Nausea	18–60 years	Auewarakul *et al.*[20]	0·69 [0·22, 2·12]		
		Subtotal	0·69 [0·22, 2·12]	0·52	N/A
	>60 years	Chi *et al.*[23]	0·68 [0·12, 3·92]		
		Subtotal	0·68 [0·12, 3·92]	0·66	N/A
	Total		0·69 [0·27, 1·77]	0·43	0
Arthralgia	18–60 years	Auewarakul *et al.*[20]	0·98 [0·51, 1·89]		
		Beran *et al.*[15] (Year 2)	0·94 [0·59, 1·52]		
		Beran *et al.*[15] (Year 3)	3·19 [1·46, 6·96]		
		Subtotal	1·36 [0·68, 2·74]	0·38	73
	Total		1·36 [0·68, 2·74]	0·38	73

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