Appendix Supplementary Content

Appendix 1: Protocol amendments

Comparative effectiveness of influenza vaccines in adults 60 years of age and older: a systematic review and network meta-analysis

Section	Previous protocol criteria	Changed criteria/deviations	Justification
Review question	Which influenza vaccine available for adults 65 years of age and older is the most effective?	Which influenza vaccine available for adults 60 years of age and older is the most effective?	Some studies include data on older adults by referring to 60+. Therefore, to capture a broader sample of studies, we have updated the age to include 60+ instead of 65+.
Types of study to be included	Randomised controlled trials (RCTs), case test-negative studies, NRCTs (e.g., such as quasi-RCTs, non-randomised trials, interrupted time series, controlled before after), and observational studies (e.g., cohort, case control) will be included. Studies must have a control or comparator in order to be eligible for inclusion and as such, cross-sectional, case series, case reports, and qualitative studies will be excluded.	Randomised controlled trials (RCTs) will be included. Case test-negative studies, NRCTs (e.g., such as quasi-RCTs, non-randomised trials, interrupted time series, controlled before after), and observational studies (e.g., cohort, case control) will be excluded. Studies must have a control or comparator in order to be eligible for inclusion and as such, cross-sectional, case series, case reports, and qualitative studies will be excluded.	Due to feasibility reasons and resource concerns, case test-negative studies, NRCTs, and observational studies (e.g., cohort, case control) were excluded.
Participants/ population	All adults aged 65 years and older (studies with a median age of participants of 60 years will be included).	All adults aged 60 years and older will be included.	Some studies include data on older adults by referring to 60+. Therefore, to capture a broader sample of studies, we have updated the age to include 60+ instead of 65+.
Intervention(s), exposure(s)	Any influenza vaccines for adults 65 years of age and older (e.g. trivalent standard dose influenza vaccine, quadrivalent standard dose influenza vaccine, adjuvanted trivalent influenza vaccine, trivalent high dose influenza vaccine, egg-based vaccines). Both pandemic and seasonal influenza vaccines will be considered for inclusion.	Any influenza vaccines for adults 60 years of age and older licensed for use in Canada and/or the United States (e.g. trivalent standard dose influenza vaccine, quadrivalent standard dose influenza vaccine, adjuvanted trivalent influenza vaccine, trivalent high dose influenza vaccine, egg-based vaccines).	Pandemic vaccines were not considered in this review as they are not relevant to the main objective of this research, as per the guidance received from stakeholders and subject matter experts.

Main outcome	Cases of laboratory confirmed influenza and cases of influenza like illness (ILI).	Vaccine efficacy against infection. Both laboratory confirmed symptomatic infection (LCI) as well as influenza like illness (ILI) will be considered for inclusion and analysed separately.	Main outcome defined as vaccine efficacy will be explored.
Secondary outcomes	Secondary outcomes include: • All cause hospitalization • Hospitalization due to influenza infection • Hospitalization due to pneumonia infection • Adverse vascular events (non-fatal myocardial infarction, stroke, cardiovascular death, hospitalization for heart failure) • Mortality from influenza infection	Secondary outcomes include: • Acute respiratory illness (ARI) cases • Laboratory confirmed-ARI • Hospitalization for ILI • Emergency room (ER) visit for ILI • Hospitalization for ARI • ER visit for ARI • Hospitalization for LCI • ER visit for LCI • Hospitalization for pneumonia due to ILI • Hospitalization for pneumonia due to ARI • Hospitalization for pneumonia due to LCI • ER visit for pneumonia • Hospitalization/inpatient for any cause • ER Visit (any cause) • Inpatient/outpatient visit • Outpatient visit • LCI-related healthcare interactions • Number of vascular adverse events (AEs) • Number of participants with vascular AEs • Hospitalizations due to cardiovascular events • LCI-related mortality • All-cause mortality	Additional outcomes of interest were identified collaboratively with stakeholders and subject matter experts.
Strategy for data synthesis	Random-effects network meta-analysis (NMA) will be conducted, by vaccine type, to compare the effectiveness of available vaccines for seasonal and pandemic influenza separately.	The NMA will be conducted in R using the netmeta package. We assessed small-study effects and publication bias in the outcomes with at least 10 studies and using the comparison-adjusted funnel plot and the following chronological order of the interventions and based on Barberis et al., 2016[1] • IIV4 Adjuvanted	Random-effects meta-analysis was conducted, by vaccine type due to the reduced scope of the project.

		• IIV4 High Dose • IIV4 Standard dose (2012) • IIV3 Adjuvanted (1997) • IIV3 High dose (2009) • IIV3 Standard dose • Recombinant Trivalent (RIV3) (2013) • Recombinant Quadrivalent (RIV4) • Tdap (Tetanus, diphtheria, and pertussis) • Placebo	
Analysis of subgroups or subsets	If feasible (i.e., sufficient amount of studies and data), the following sub-group analyses will be considered: • Age: 65-79 years of age vs. ≥80 years of age • Healthy vs. individuals with comorbid conditions (defined as conditions that last for one or more years, require ongoing medical attention and/or limit activities of daily living) • Sex (female vs. male) • Previous vaccination with any influenza vaccine vs. vaccine-naïve • Individuals who are frail vs. those who are not • Vaccines with matched vs. unmatched strains	We conducted the following analyses: a. LCI (NMA): sex b. Outpatient visits (NMA): none c. All-cause mortality (NMA): sex, rob d. Vascular events (NMA): none e. Pairwise meta-analysis: LCI (none), outpatient (none), all-cause mortality (rob, age>80 vs age<80), inpatient hospitalizations any cause (low rob, age> 80 vs <80)	We were unable to assess transitivity using healthy versus chronic disease (comorbidities) and previous vaccination, since this was rarely reported in the publications. We were only able to explore sex (% of females below and above 50%), age (below and above 80 years) and risk of bias (restricting to low risk of bias studies) in pairwise and network meta-analysis. We also conducted network meta-analyses as a sensitivity analysis for the primary outcomes using a revised categorization of the nodes. Specifically: IIV3-SD and IIV4-SD were defined as SD IIV3-HD and IIV4-HD were defined as HD RIV3 and RIV4 were defined as RIV IIV3-Adj and IIV4-Adj were defined as Adj
Risk of bias (quality) assessment	Risk of bias appraisal will be carried out independently and in duplicate by 2 reviewers using the Cochrane Risk of Bias tool RCTs, the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for non-randomised intervention studies.	Risk of bias appraisal will be carried out independently and in duplicate by 2 reviewers using the Cochrane Risk of Bias tool RCTs.	Due to the exclusion of NCRTs and observational studies, no risk of bias assessments will be completed using the ROBINS-I tool.

Summary of Findings	NA	We assessed credibility of evidence using CINeMA in the outcomes that NMA was possible and GRADE in the outcomes where a pairwise meta-analysis was conducted but no NMA was conducted.	For completeness and to inform decision making we assessed certainty and quality of evidence.

1. Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. J Prev Med Hyg. 2016 Sep;57(3):E115-E120. PMID: 27980374; PMCID: PMC5139605.

Appendix 2: Methods on selection process, data extraction, and credibility of results

Selection process

A screening form for the title and abstract stage was developed in collaboration with Public Health Agency of Canada and the research team based on pre-defined eligibility criteria. Screening was conducted in two stages using Synthesi.SR[1]: level one screening of titles and abstracts and level two screening of full-text articles (Appendices 2A and 2B). First, the team conducted one pilot-test at level one of 50 random titles/abstracts resulting in 74% agreement, and another at level two of 25 random full-texts resulting in 70% agreement among the team. Next, two reviewers (MG, PAK, VN, MC, AP) independently screened the identified citations for study eligibility. Conflicts at both screening levels were resolved by a third reviewer (MG).

Data items and data extraction

A data abstraction form (Appendix 2C) was created to capture data on the study characteristics (e.g. duration of follow-up, study design, country of conduct, multi-center vs. single site), patient characteristics (e.g., mean age, age range, co-morbidities, frailty), intervention characteristics (e.g., type of vaccine, dose, unadjuvanted versus adjuvanted), and outcome characteristics (e.g., number of patients with influenza, acute respiratory infection, vascular adverse events, hospitalizations, and mortality at the longest duration of follow-up). Prior to data abstraction, the form was piloted on a random sample of five included articles. When a high level of agreement was reached, two reviewers SST, MG, PAK, VN, MC, RR, AP, CS) independently abstracted data from each study. Conflicts were resolved by a third reviewer (SST, MG, VN).

Assessment of the confidence in the evidence

Confidence in NMA estimates was assessed for each outcome using CINeMA (Confidence in Network meta-analysis)[2] as very low, low, moderate or high on the basis of six domains (within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence). Each domain was evaluated as 'no concerns', 'some concerns' or 'major concerns'. We used the overall risk of bias per study, and for each treatment comparison we applied the average risk of bias over the studies. Similarly, for all treatment comparisons we used the average for indirectness. We assessed reporting bias based on the comparison-adjusted funnel plot, where possible. Downgrading of the confidence rating was conducted whenever any of the domains except for reporting bias was rated as 'some concerns' or 'major concerns'.

For imprecision, we considered the null effect (e.g., OR=1) for the evaluation of the clinically important size of effect, where statistical significance and clinical importance would coincide. Heterogeneity and incoherence (i.e., inconsistency) were assessed by following the standard CINeMA approach[2]. As a complimentary approach in the NMA outcomes, and based on previous publications and content expert advice, we considered the following to be clinically important effect sizes: risk ratio at 67% in LCI (or OR at 63.5%), risk ratio at 85% in vascular adverse events[3] (or IRR at 85%), risk ratio at 75% in outpatient visits (or OR at 72%), risk ratio at 5% in all-cause mortality[4] (or OR at 34%).

Confidence in pairwise meta-analysis estimates for which a NMA could not be performed was assessed by two reviewers (IVF, JJYN) independently using the GRADE approach[5]. Disagreements were resolved by discussion.

Appendix 2A: Level 1 screening guidelines

Question 1: Does this study examine a relevant influenza vaccine? [Mandatory]	
Response Options:	□ Yes □ No □ Unclear
Notes:	**INCLUDE** the citation if the study mentions influenza vaccines licensed in Canada/United States for adults 60 years of age and older or similar, which may include but is not limited to the following relevant vaccines and associated acronyms: • Afluria Tetra (Afluria Quadrivalent) • Agriflu/Agrippal • ccIIV3/IIV3-cc - Cell-Culture Inactivated Influenza Vaccine, Trivalent (Flucelvax) • ccIIV4/IIV4-cc - Cell-cultured inactivated quadrivalent vaccine • Fluad • Fluad Quadrivalent • Flucelvax Tetra (Flucelvax Quadrivalent) • Flulaval Tetra • Fluviral • Fluvirin • Fluzone High-Dose • Fluzone High-Dose Quadrivalent • Fluzone Quadrivalent • IIV3- Adj - Inactivated trivalent influenza vaccine - adjuvanted • IIV3 - Inactivated Influenza Vaccine, Trivalent • IIV4 – SD - Inactivated quadravalent influenza vaccine - standard dose • IIV4 –HD - Inactivated quadravalent influenza vaccine - high dose • IIV4-Adj - Inactivated quadravalent influenca vaccine - adjuvanted • IIV3-HD - Inactivated trivalent influenza vaccine - high dose • IIV3-SD - Inactivated trivalent influenza vaccine - standard dose • Influvac • Influvac Tetra • QIV - quadravalent inactivated vaccine • RIV3 - Recombinant Influenza Vaccine, Trivalent (Flublok) • TIV - Trivalent (Inactivated) Influenza Vaccine (replaced by the term IIV) • Recombinant influenza vaccine (RIV) • RIV4 – Recombinant Influenza Vaccine, Quadrivalent (Flublok quadrivalent) • Supemtek • 2009 H1N1 pandemic vaccine **EXCLUDE** the citation if the following vaccines are mentioned: • Live attenuated influenza vaccine (LAIV) • Virosomal, ASO3-adjuvanted, and intradermal vaccines • Monovalent influenza vaccines **UNLESS** it is the H1N1 pandemic vaccine from 2009 • Bivalent influenza vaccines • Experimental vaccines that have not yet moved to development or ever been approved • Any other influenza vaccine not licensed in Canada/United States (e.g. Vaxigrip)

Question 2: Does this study include adult patients aged 60 years and older?	
Response Options:	□ Yes □ No □ Unclear
Notes:	**INCLUDE** the citation if: • A range is given with only the minimum, e.g., '18 and over' or it says only 'adults' • Only the mean or median age is given and it is >60 years **EXCLUDE** the citation if: • A range is given where the maximum age is less than 60 years, e.g., '18-45 years'

Question 3: Is this an eligible study design?	
Response Options:	□ Yes □ No □ Unclear

Notes:	**INCLUDE** all primary research studies. Study designs include:
	• Experimental studies such as
	  ○ Randomized controlled trials (RCTs), including patient randomized, cluster-randomized, and cross-over randomized trials
	  ○ Quasi-randomized clinical trial
	
	EXCLUDE citations with the following study designs
	• Cross-sectional
	• Case series
	• Case reports
	• Registry reports without comparator or denominator info
	• Qualitative studies
	• Opinion pieces (editorials, commentaries, letters)
	• Economic evaluations (cost-effectiveness, cost benefit analysis, etc.)
	• Clinical practice guideline
	• Consensus conference paper
	• Health technology assessment report
	• Non-RCTs (non-randomized controlled studies)*
	• Quasi-experimental studies* such as
	  ○ Interrupted time series
	  ○ Controlled before after studies
	• Observational studies*
	  ○ Cohort studies (both retrospective and prospective)
	  ○ Case control studies (traditional and test-negative designs)

*Study designs were excluded in a post-protocol decision	

Question 4: Is this a potentially relevant study with the following formats? [Flagging question	
Response Options:	□ Conference Abstract □ Non-English article □ Protocol □ Systematic Review □ Unclear

Appendix 2B: Level 2 screening guidelines

Question 1: Does this study examine a relevant influenza vaccine? [Mandatory]	
Response Options:	□ Yes □ No □ Unclear
Notes:	**INCLUDE** the citation if the study mentions influenza vaccines licensed in Canada/United States for adults 65 years of age and older or similar, which may include but is not limited to the following relevant vaccines and associated acronyms: • Afluria Tetra (Afluria Quadrivalent) • Agriflu/Agrippal • ccIIV3/IIV3-cc - Cell-Culture Inactivated Influenza Vaccine, Trivalent (Flucelvax) • ccIIV4/IIV4-cc - Cell-cultured inactivated quadrivalent vaccine • Fluad • Fluad Quadrivalent • Flucelvax Tetra (Flucelvax Quadrivalent) • Flulaval Tetra • Fluviral • Fluvirin • Fluzone High-Dose • Fluzone High-Dose Quadrivalent • Fluzone Quadrivalent • IIV3- Adj - Inactivated trivalent influenza vaccine - adjuvanted • IIV3 - Inactivated Influenza Vaccine, Trivalent • IIV4 – SD - Inactivated quadravalent influenza vaccine - standard dose • IIV4 –HD - Inactivated quadravalent influenza vaccine - high dose • IIV4-Adj - Inactivated quadravalent influenca vaccine - adjuvanted • IIV3-HD - Inactivated trivalent influenza vaccine - high dose • IIV3-SD - Inactivated trivalent influenza vaccine - standard dose • Influvac • Influvac Tetra • QIV - quadravalent inactivated vaccine • RIV3 - Recombinant Influenza Vaccine, Trivalent (Flublok) • TIV - Trivalent (Inactivated) Influenza Vaccine (replaced by the term IIV) • Recombinant influenza vaccine (RIV) • RIV4 – Recombinant Influenza Vaccine, Quadrivalent (Flublok quadrivalent) • Supemtek **EXCLUDE** the citation if the following vaccines are mentioned: • Live attenuated influenza vaccine (LAIV) • Virosomal, ASO3-adjuvanted, and intradermal vaccines • Monovalent influenza vaccines • Bivalent influenza vaccines • Experimental vaccines that have not yet moved to development or ever been approved • Any other influenza vaccine not licensed in Canada/United States (e.g. Vaxigrip) • Intradermal vaccines

Question 2: Does this study include adult patients aged 60 years and older?	
Response Options:	□ Yes □ No □ Unclear
Notes:	**INCLUDE** the citation if: • A range is given with only the minimum, e.g., '18 and over' or it says only 'adults' • Only the mean or median age is given and it is >60 years **EXCLUDE** the citation if: • A range is given where the maximum age is less than 60 years, e.g., '18-45 years'

Question 3: Does this study include an eligible comparator group?	
Response Options:	□ Yes □ No □ Unclear
Notes:	**INCLUDE** the citation if the comparator is: • Any trivalent or quadrivalent influenza vaccines licensed in Canada/United States for adults ages 60 years and over • May consider comparisons of products similar to a Canadian or US-licensed vaccine in terms of dosage, formulation, and route of administration (e.g. Vaxigrip is similar to Fluzone) • Any vaccine for influenza or non-influenza control vaccines for any other condition (i.e., meningococcal or pneumococcal vaccines) • The same vaccine as the treatment arm but with a different dose and/or formulation • Placebo or no vaccine

Question 4: Is this an eligible study design?	
Response Options:	□ Yes □ No □ Unclear

Notes:	**INCLUDE** all primary research studies. Study designs include:
	• Experimental studies such as
	  ○ Randomized controlled trials (RCTs), including patient randomized, cluster-randomized, and cross-over randomized trials
	  ○ Quasi-randomized clinical trial
	
	EXCLUDE citations with the following study designs
	• Cross-sectional
	• Case series
	• Case reports
	• Registry reports without comparator or denominator info
	• Qualitative studies
	• Opinion pieces (editorials, commentaries, letters)
	• Economic evaluations (cost-effectiveness, cost benefit analysis, etc.)
	• Clinical practice guideline
	• Consensus conference paper
	• Health technology assessment report
	• Non-RCTs (non-randomized controlled studies)*
	• Quasi-experimental studies* such as
	• Interrupted time series
	• Controlled before after studies
	• Observational studies*
	• Cohort studies (both retrospective and prospective)

	• Case control studies (traditional and test-negative designs)
*Study designs were excluded in a post-protocol decision	

Question 5: Does this study include relevant outcomes?	
Response Options:	□ Yes □ No □ Unclear
Notes:	Relevant outcomes include: **Laboratory confirmed influenza** –Incidence (Newly diagnosed cases) of laboratory confirmed influenza with or without symptoms. **Influenza-like-Illness (ILI)** - Incidence (Newly diagnosed cases) of influenza like illness diagnosed based on symptoms only or based on symptoms + laboratory confirmed. **Hospitalization**- All causes of hospitalization, including but not limited to laboratory-confirmed influenza, influenza like illness, pneumonia etc. **Mortality**- Deaths recorded due to influenza, influenza like illness, cardiovascular disease or all-cause mortality **Adverse vascular events**- Adverse events include non-fatal myocardial infarction, stroke, cardiovascular death and heart failure

Question 6: Is this a potentially relevant study with the following formats? [Flagging question] *Only flag studies if the responses to Q1-Q4 are YES or UNCLEAR	
Response Options:	□ Conference Abstract □ Non-English article □ Protocol □ Systematic Review □ Unclear

Appendix 2C: Data abstraction form guidelines

NOTES

Please enter not applicable (NA) or not reported (NR) as needed instead of leaving cells blank.
The form has been designed to accommodate six arm studies, for studies with 7 or more arms copy and paste additional columns as needed. Please ensure they are numbered properly.

Tab 1. Study Characteristics

STUDY CHARACTERISTICS	
Excel column	**Description**
RefID	[Will already be filled in]
Reviewer	[Will already be filled in]
Last name of first author	Enter the last name of the first author. **Example:** Smith
Year of publication	Enter the year the study was published. **Example:** 2015
Publishing source name	Enter the journal name or name of the publishing source (if the journal name is not available).
Publication type	Select the publication type. ☐ Journal article ☐ Report ☐ Conference abstract ☐ Results from trial registry ☐ Dissertation/Thesis
Funding source name	Enter the source of funding support for the research. **Example:** CIHR; Bayer. Enter 'None' for no funding source.
Funding source type	Select the category of the research sponsor type. ☐ Public ☐ Industry ☐ Public & Industry ☐ NR ☐ Unclear
Trial/Study name	Enter the name of the trial or study. **Example:** Flublok Study
Trial identifier	Enter the clinicaltrials.gov trial number or any other trial identification number if applicable. If details of linked trials are provided please indicate this in the **Comment** column. **Example:** NCT00007501, EudraCT Number: 2007-000744-28

Study design*	Select the study design from the dropdown. ☐ Randomized controlled trials (RCTs) ☐ Cluster RCTs ☐ Cross-over RCTs ☐ Quasi-RCTs ☐ Unclear **Note:** Studies might not always explicitly state the design in which case select the best option based on the methods section. If unclear, please include any relevant information in the comment column at the end of the tab. *****The following study designs were excluded in a post-protocol decision: Non-RCTs, Interrupted time series, Controlled before after, Prospective cohort, Retrospective cohort, Case control, Case test-negative, Nested case- control, Case-cohort
Country	Enter the country of conduct. If the trial is a multi-site trial, ensure all the countries are listed (separated by commas). If the country of conduct is not clear, use the country from the first author's affiliation. If the study doesn't mention the country but mentions a region, enter the region (e.g., Sub-Saharan Africa). **Example:** USA, Canada, Netherlands
Single or multicenter	From the dropdown, select whether the study is single center, multicenter, unclear or NR (not reported).
No. of centers in total	Enter the total number of centers partaking in the study.
Influenza season	Enter the relevant influenza season(s) during which the study was conducted. If multiple seasons are reported, separate using a semicolon. Specify northern or southern hemisphere **Example: N** 2017/2018 or **S** 2018
Companion report	Please select from the dropdown the following options: ☐ YES ☐ NO ☐ Unclear ☐ NR
Industry conflict declared?	Please indicate if authors declare any industry conflict using the dropdown options. ☐ YES ☐ NO ☐ Unclear ☐ NR Example of declaration statement: *Employees may hold stock and/or stock options in the company.*
Conflict details	Copy-paste the description of the conflict.
Comment	Please enter any comments.

Tab 2. Participant Characteristics

PARTICIPANT CHARACTERISTICS	
Excel column	**Description**
RefID	[Auto-populated based on previous entry]
Reviewer	[Auto-populated based on previous entry]
Patient inclusion criteria	Copy-paste the patient inclusion criteria for the study.
Patient exclusion criteria	Copy-paste the patient exclusion criteria for the study.
Setting	Copy and paste the description of the study setting. **Example:** Long term care home, Family doctor, Flu clinic
Overall sample size	Enter the total number of participants enrolled in the study forrandomization.
% Female	Enter in the overall percent of females in the study (in all treatment groups). If necessary, calculate using the following: Calculation: [(#Tx1Females+#Tx2Females)/(Tx1Sample+Tx2Sample)]*100
% Male	Enter in the overall percent of males in the study (in all treatment groups). If necessary, calculate using the following:
	Calculation: [(#Tx1Males+#Tx2Males)/(Tx1Sample+Tx2Sample)]*100
% Other	Enter the overall percent of participants with other specified gender or no specified gender in the study (in all treatment groups). If multiple other genders are reported, separate using a semicolon. If necessary, calculate using the following: Calculation: [(#Tx1Other+#Tx2Other)/(Tx1Sample+Tx2Sample)]*100
Race	Copy and paste the breakdown of participants' race if provided.
Age value	Enter the age of the overall sample. If age is reported as a bracket (e.g., 65- 70 years), enter the relevant bracket and accompanying value with a colon in between (e.g., 65-75: 50%). If there are multiple brackets, separate using a semicolon (e.g., 65-75: 50%; 76-85: 50%).
Age measure	Select how age is reported for the overall sample: ☐Mean ☐Median ☐Range ☐Bracket ☐Unclear ☐NR
Age variance value	Enter the value of the variance reported. **Example:** SD: 14.3; Range: 59-85

Age variance type	Select from the dropdown menu: ☐ Standard deviation (SD) ☐ Standard error (SE) ☐ Range ☐ Interquartile range (IQR) ☐ 95% CI ☐ Unclear ☐ NR
Comorbidities	Enter details of any comorbid conditions present in the entire study sample. If a comorbidity scale/index was used report the results. If comorbid conditions are presented per treatment group, enter NA here, and abstract per treatment group below. **Example:** Heart disease (45%), COPD (13%), Cancer (8%); Charlson Comorbidity Index (1.2)
Vaccination history	Copy and paste any information about the participants' history of influenza vaccination for the entire sample.
Frailty (%)	Enter the percentage of participants who are described as frail for the entire sample.
Frailty Definition	Enter or copy and paste how frailty was defined for the entire sample.
Frailty Scale	Enter the name of the scale used to measure frailty for the entire sample.
Frailty Score	Enter the participants' score on the frailty scale along with the variance forthe entire sample.
Tx1_Name	Enter the name of the intervention allocated to the treatment arm. Be sure to include mention of type (monovalent, trivalent, tetravalent) and whetherit is adjuvanted. **Example:** Agriflu (tetravalent adjuvanted); Flublok (trivalent)
Tx1_Comorbidities	Enter details of any comorbid conditions present in the treatment group. If a comorbidity scale/index was used report the results. **Example:** Heart disease (45%), COPD (13%), Cancer (8%); Charlson Comorbidity Index (1.2)
Tx1_Vaccination history	Copy and paste any information about the participants' history of influenza vaccination.
Tx1_Frailty (%)	Enter the percentage of participants who are described as frail.
Tx1_Frailty Definition	Enter or copy and paste how frailty was defined.
Tx1_Frailty Scale	Enter the name of the scale used to measure frailty.
Tx1_Place ofresidence	Copy and paste the breakdown of places of residence (e.g., rural, urban, suburban, long-term care, congregate setting etc).
Tx1_Race	Copy and paste the breakdown of races.
Tx1_Occupation	Copy and paste the breakdown of occupations.
Tx1_% Female	Enter the percent of females.

Tx1_% Male	Enter the percent of males.
Tx1_% Other gender	Enter the percent of other specified gender or no specified gender. If there are multiple genders reported, separate using a semicolon.
Tx1_ Religion	Copy and paste the breakdown of religious backgrounds.
Tx1_Education	Copy and paste the breakdown of educational backgrounds.
Tx1_ Socioeconomic status	Copy and paste the breakdown of participants' socioeconomic status.
Tx1_Social capital	Copy and paste the breakdown of participants' social capital categories.
Tx1_Disability	Copy and paste the breakdown of participants' disability categories.
Tx1_Features ofrelationships	Copy and paste any information on the participants' features of relationships(e.g., smoking parents, excluded from school).
Tx1_Time dependent relationships	Copy and paste any information on the participants' time dependent relationships (e.g., leaving the hospital, respite care, other instances where aperson may be temporarily at a disadvantage).
Comment	Enter any relevant comments for the patient characteristics that are not captured elsewhere.
Please add more columns if there are additional arms.	

Tab 3. Intervention Characteristics

INTERVENTION CHARACTERISTICS	
Excel column	**Description**
RefID	[Auto-populated based on previous entry]
Reviewer	[Auto-populated based on previous entry]
Description of treatment arms	Enter or copy and paste the description of the treatment arms in the study. **Example:** Patients randomized into following groups: Aged 65-75 years to placebo, aged 65-75 years to Flublok
Tx1_name	Enter the name of the intervention allocated to the treatment arm. Be sure to include mention of type (monovalent, trivalent, tetravalent) and whether it is adjuvanted. NOTE: For observational studies, Tx1_name would be those vaccinated or unvaccinated, and NOT cases or controls. Cases/controls should be noted in the outcomes tab as appropriate (e.g., cases are LCI). **Example:** Agriflu (tetravalent adjuvanted); Flublok (trivalent)
Tx1_Vaccine	From the dropdown indicate at what level vaccines were assigned: ☐ Clinic/facility

assignment	☐ Patient ☐ Other ☐ UNCLEAR ☐ NR
Tx1_platform	Copy and paste any description of the platform used for virus growth (e.g. mammalian cell culture based, egg based, plant based, recombinant, etc.). **Select from the drop-down:** ☐ Egg-based ☐ Cell-based ☐ Recombinant ☐ NR
Tx1_virus strains	Enter the virus strains contained in the intervention for this treatment arm. If there are multiple years with different strains, enter the year first, colon and strains. Use a semicolon to separate years. The virus strains are limited to the following: A/H1N1, A/H3N2, B/Yam, B/Vic
Tx1_concentration	Enter the concentration of Hemagglutinin per strain in the intervention for this treatment arm. **Example:** 15 microgram/strain
Tx1_adjuvant	Enter the name and composition of the adjuvant used in the intervention for this treatment arm. If the vaccine is unadjuvanted enter 'NA'. **Example:** MF59 formulated with 9.75 mg squalene, 1.18 mg polysorbate 80, 1.18 mg sorbitan trioleate, 0.66 mg sodium citrate dihydrate, and 0.04 mgcitricacid monohydrate
Tx1_volume	Enter the volume of the injection for this treatment arm. **Example:** 0.5mL
Tx1_administration	Enter the route of administration and location of the intervention. **Example:** Intramuscular, deltoid
Tx1_frequency	Enter number of doses administered. **Example:** single dose
Tx1_duration	Enter the duration between doses if applicable. If a single dose was given enter 'NA'.
Tx1_sample size	Enter the number of patients randomized to this study arm that received the intervention.
Tx1_lost to follow up	Enter the number of participants lost to follow up in this study arm
Tx1_age value	Enter the overall age of participants in this intervention arm. If age is reported as a bracket (e.g., 65-70 years), enter the relevant bracket and accompanying value with a colon in between (e.g., 65-75: 50%). If there are multiple brackets, separate using a semicolon (e.g., 65-75: 50%; 76-85: 50%))

Tx1_age measure	Select how age is reported: ☐Mean ☐Median ☐Range ☐Bracket ☐Unclear ☐NR
Tx1_ age variancevalue	Enter the value of the variance reported. **Example:** SD: 14.3; Range: 59-85
Tx1_ age variancetype	Select from the dropdown menu: ☐ Standard deviation (SD) ☐ Standard error (SE) ☐ Range ☐ Interquartile range (IQR) ☐ 95% CI ☐NR
Predominant circulating strain	Enter the name(s) of the predominant circulating strain(s). **Example:** A/Victoria/7/83 (H1N1), B/USSR/100/83
Other circulating strain	Enter the name(s) of the other circulating strain(s).
Mismatched strain?	Enter whether the study reported a mismatch between the strains included inthe vaccine and the circulating strains for the given time period (s).
Comments	Enter any relevant comments that are not captured elsewhere.
Please add more columns if there are additional arms.	

Tab 4. Outcomes

OUTCOMES	
Excel column	**Description**
RefID	[Auto-populated based on previous entry]
Reviewer	[Auto-populated based on previous entry]
Incidence of ILI and Influenza	
ILI without testing	Enter or copy and paste how cases of Influenza-like-illness (ILI) without testing were defined in the study. **Example:** ILI was defined as temperature of ≥37.2◦C or feverishness and atleast two of the following symptoms: headache, myalgia, cough, or sore throat.

Acute respiratory illness	Enter or copy and paste how cases of acute respiratory illness (ARI) were diagnosed and/or confirmed in the study.
Laboratory confirmed-ARI	Enter or copy and paste how cases of laboratory confirmed-ARI were diagnosed and/or confirmed in the study.
Laboratory confirmed influenza	Enter or copy and paste how laboratory confirmed influenza (LCI) infections were diagnosed and/or confirmed in the study. Make sure to report the methods used to confirm LCI. **Example:** Respiratory illnesses detected by active and passive surveillance triggered the collection of nasopharyngeal swab for influenza confirmation…Laboratory confirmation of influenza in nasopharyngeal specimens was defined as a positive result on tissue culture and/or polymerase chain reaction (PCR).
Duration of follow-up	Enter the duration of follow-up for the outcome measure using the unit reported in the paper. **Example:** 3 years, 24 months, 365 days, etc.
Timing of assessment	Enter the timing of outcome assessment using the unit reported in the paper. Also, indicate if timing of assessment was part of eligibility criteria. **Example:** started 2 weeks post vaccination and throughout the winter
Tx1_name	Name is pre-populated using entry from the intervention characteristics tab.
Tx1_sample size	Enter the number of participants included in the outcome analysis (e.g., ITT, Per Protocol, or LOCF).
Tx1_lost to follow up	Enter the number of patients lost to follow up in this study arm.
Tx1_reasons for lost to follow up	Copy-paste the reasons participants were lost to follow up.
Tx1_method for dealing with missing data	Enter the method authors used to deal with missing data (e.g., Intention-to-treat, last observation carried forward, per protocol).
Tx1_ILI cases	Enter the number of or percentage of ILI cases reported (if reported as a proportion make sure you include the % symbol).
Tx1_ARI cases	Enter the number of or percentage of acute respiratory infection (ARI) cases reported (if reported as a proportion make sure you include the % symbol).
Tx1_LC-ARI cases	Enter the number of or percentage of LC-ARI cases reported (if reported as a proportion make sure you include the % symbol).
Tx1_LCI cases	Enter the number of or percentage of confirmed influenza infections (if reported as a proportion make sure you include the % symbol).
HOSPITALIZATIONS	
Tx1_Hospitalization for ILI	Enter the number of or percentage of hospitalizations due to ILI (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization/ER visit for ILI	Enter the number of or percentage of composite hospitalizations/emergency room (ER) visits due to ILI (if reported as a proportion make sure you include the % symbol).

Tx1_Hospitalization for ARI	Enter the number of or percentage of hospitalizations due to acute respiratory infections (ARI) (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization/ER for ARI	Enter the number of or percentage of composite hospitalizations/ER visits due to ARI (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization for LCI	Enter the number of or percentage of hospitalizations due to LCI (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization/ER for LCI	Enter the number of or percentage of composite hospitalizations/ER visits due to LCI (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization for pneumonia due to ILI	Enter the number of or percentage of hospitalizations due to ILI-related pneumonia (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization for pneumonia due to ARI	Enter the number of or percentage of hospitalizations due to ARI-related pneumonia (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization for pneumonia due to LCI	Enter the number of or percentage of hospitalizations due to LCI-related pneumonia (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization/ER for pneumonia	Enter the number of or percentage of composite hospitalizations/ER visits due to ILI/ARI- or LCI-related pneumonia (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization/ Inpatient visit for any cause	Enter the number of or percentage of hospitalizations due to any cause (if reported as a proportion make sure you include the % symbol).
Tx1_Hospitalization/ER for any cause	Enter the number of or percentage of composite hospitalizations/ER visits due to any cause (if reported as a proportion make sure you include the % symbol).
Tx1_Inpatient/outpatient visit	Enter the number of or percentage of composite inpatient/outpatient visits (if reported as a proportion make sure you include the % symbol).
Tx1_Reasons for hospitalization	Enter or copy and paste the reasons for hospitalization as reported in the study.
Tx1_Outpatient visit	Enter the number of or percentage of outpatient visits (if reported as a proportion make sure you include the % symbol).
Tx1_ LCI-related health careinteractions	Enter the number of or percentage of LCI-related health care interactions (if reported as a proportion make sure you include the % symbol).
ADVERSE VASCULAR EVENTS AND MORTALITY	
Definition of Vascular AEs	Enter or copy and paste the types of vascular adverse events reported in the study (e.g., non-fatal myocardial infarction, stroke, cardiovascular death, heart failure).
Tx1_# of Vascular adverseevents	Enter the count of adverse vascular events including non-fatal myocardial infarction, stroke, cardiovascular death, and heart failure.

Tx1_# participants with Vascular adverse events	Enter the count of participants with adverse vascular events including non-fatal myocardial infarction, stroke, cardiovascular death, and heart failure.
Tx1_# of Hospitalizations due to cardiovascular events	Enter the count of hospitalizations due to cardiovascular events.
Tx1_# of participants hospitalized due to cardiovascular events	Enter the count of participants hospitalized due to cardiovascular events.
Tx1_# of LCI-related deaths	Enter the count of LCI-related deaths.
Tx1_ # of All-cause deaths	Enter the count of all-cause deaths during the course of the study
Vaccine Related?	Enter or copy and paste whether any adverse vascular events or deaths were assessed as vaccine related.
Comments	Enter any relevant comments for the outcomes that are not captured elsewhere.
Please add more columns if there are additional arms.	

Tab 5. Statistical Model Data

Notes: This tab is only for non-randomized studies.

Excel column	Description
RefID	Enter the refID of the study being abstracted
Reviewer	Enter your initials
Tx Comparison 1	Enter the name of the treatment group/vaccine being compared. Be sure to include the type (monovalent, trivalent, tetravalent) and whether it is adjuvanted. **Example**: Agriflu (tetravalent adjuvanted); Flublok (trivalent)
Tx Comparison 2	Enter the name of the treatment group/vaccine being compared to "Tx Comparison 1". Be sure to include the type (monovalent, trivalent, tetravalent) and whether it is adjuvanted. For additional comparisons, insert data in rows below. Ensure to include the refid and reviewer name.
Outcome measure	Enter the relevant outcomes **Example:** ILI, hospitalization
Measure of effect/association	Enter the name of the measure of effect/association (e.g., adjusted odds ratio, adjusted rate ratio). If adjusted values are not reported, then enter the unadjusted effect size.

Adjusted?	Select if the measure of effect was adjusted or not from the dropdown menu: ☐ Yes ☐ No ☐ Unclear ☐ Not reported
Measure of effect/association value	Enter the value for the measure of effect/association.
95% CI	Enter the 95% CI.
Analysis method	Enter in the analysis methods used. **Example:** Multiple logistic/log binomial/Cox proportional hazards regression
Confounders / variables controlled for in model	List any confounders or variables which were controlled for in the model. Copy and paste any description of confounders/controls from the paper.
Number of participants	Enter the total number of participants included in the model.
Description of propensity scores or other advanced analysis	Please provide a description of propensity scores or any other advanced analysis that was used.
Qualitative Evidence	Report any results collected narratively.
Comments	Enter any relevant comments that are not captured elsewhere. For example, if matching was used instead of adjustment.

Appendix 3: Database search strategies

March 30, 2022

Ovid MEDLINE(R) ALL <1946 to March 22, 2022>

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1 influenza, human/ or exp influenzavirus a/ or exp influenzavirus b/ or influenzavirus c/ or Hemagglutinin Glycoproteins, Influenza Virus/
2 (flu or flue or influenza* or grippe).tw,kf.
3 1 or 2
4 exp Vaccines/ or Immunization/
5 (vaccin* or immuni* or inocula* or shot or jab).tw,kf.
6 4 or 5
7 3 and 6
8 exp Adjuvants, Immunologic/
9 exp Antibodies, Viral/
10 Hemagglutination Inhibition Tests/ or Plant Proteins/im or (adjuvant* or squalene* or emulsion*).mp.
11 or/8-10
12 3 and 11
13 influenza vaccines/
14 influenza vaccine*.tw,kf.
15 13 or 14
16 7 or 12 or 15

Core set 1
17 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw,kf.
18 16 and 17

Core set 2 (limited to trivalent or quadrivalent)
19 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok).tw,kf,rn.
20 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw,kf.
21 19 or 20
22 18 or 21

Core set 3 (core set 3 plus all known drug names)
23 limit 22 to "all aged (65 and over)"
24 exp Aged/ or geriatrics/ or aging/
25 (geriatric* or elder* or old* or ageing or aging or senior* or older adult* or retired or retiree* or elder* or pensioner* or nursing home* or older people or older patient* or gerontology or Sexagenarian*OR septuagenarian* or octogenarian or nonagenarian*OR centenarian* or sixties or seventies or eighties or nineties).tw,kf.
26 22 and (24 or 25)
27 23 or 26
28 animals/ not humans/
29 27 not 28
30 21 not 28
31 29 or 30 – Final set with all named drug articles

Database: Embase Classic+Embase <1947 to 2022 March 29>

---

1 exp Influenza virus/ or exp influenza/ or exp influenzavirus a/ or Hemagglutinin Glycoproteins, Influenza Virus/
2 (flu or flue or influenza*or grippe).tw.

3 1 or 2
4 exp vaccine/ or exp immunization/
5 (vaccin* or immuni* or inocula* or shot or jab).tw.
6 4 or 5
7 3 and 6
8 immunological adjuvant/
9 exp virus antibody/
10 hemagglutination inhibition test/ or exp plant protein/ or (adjuvant* or squalene* or emulsion*).mp.
11 or/8-10
12 3 and 11
13 influenza vaccine/
14 influenza vaccine*.tw.
15 13 or 14
16 7 or 12 or 15
17 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
18 16 and 17
19 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok).tw.
20 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
21 19 or 20
22 18 or 21
23 limit 22 to aged <65+ years>
24 exp aged/ or exp aging/ or exp geriatrics/
25 (geriatric* or elder* or old* or ageing or aging or senior* or older adult* or retired or retiree* or elder* or pensioner* or nursing home* or older people or older patient* or gerontology or Sexagenarian*OR septuagenarian* or octogenarian or nonagenarian*OR centenarian* or sixties or seventies or eighties or nineties).tw.
26 22 and (24 or 25)
27 23 or 26
28 animals/ not humans/
29 27 not 28
30 21 not 28
31 29 or 30

Database: JBI EBP Database <Current to March 23, 2022>
Search Strategy:

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1 (flu or flue or influenza* or grippe or hemagglutinin).tw.
2 (vaccin* or immuni* or inocula* or shot or jab).tw.
3 (adjuvant* or squalene* or emulsion*).mp.
4 1 and (2 or 3)
5 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
6 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok).tw.
7 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
8 or/4-7
*Note: no age limit

Database: APA PsycInfo <1806 to March Week 3 2022>

---

1 exp influenza/
2 (flu or flue or influenza*or grippe or Hemagglutinin).tw.
3 1 or 2
4 immunization/

5 (vaccin* or immuni* or inocula* or shot or jab).tw.
6 (adjuvant* or squalene* or emulsion*).tw.
7 or/4-6
8 3 and 7
9 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
10 8 and 9
11 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok).tw.
12 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
13 10 or 11 or 12
14 animals/ not humans/
15 13 not 14
*Note: no age limit

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 24, 2022>, EBM Reviews - ACP Journal Club <1991 to March 2022>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <March 2022>, EBM Reviews - Cochrane Central Register of Controlled Trials <January 2022>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>
Search Strategy:
---
1 (flu or flue or influenza* or grippe or hemagglutinin).tw.
2 (vaccin* or immuni* or inocula* or shot or jab).tw.
3 (adjuvant* or squalene* or emulsion*).mp.
4 1 and (2 or 3)
5 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
6 4 and 5
7 (geriatric* or elder* or old* or ageing or aging or senior* or older adult* or retired or retiree* or elder* or pensioner* or nursing home* or older people or older patient* or gerontology or Sexagenarian*OR septuagenarian* or octogenarian or nonagenarian*OR centenarian* or sixties or seventies or eighties or nineties).tw.
8 6 and 7
9 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok).tw.
10 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
11 9 or 10
12 8 or 11
*Note: no need to exclude animals

UPDATED SEARCHES - June 17, 2022

Database: Ovid MEDLINE(R) ALL <1946 to June 16, 2022>
---
1 influenza, human/ or exp influenzavirus a/ or exp influenzavirus b/ or influenzavirus c/ or Hemagglutinin Glycoproteins, Influenza Virus/
2 (flu or flue or influenza* or grippe).tw,kf.
3 1 or 2
4 exp Vaccines/ or Immunization/
5 (vaccin* or immuni* or inocula* or shot or jab).tw,kf.
6 4 or 5
7 3 and 6
8 exp Adjuvants, Immunologic/
9 exp Antibodies, Viral/

10 Hemagglutination Inhibition Tests/ or Plant Proteins/im or exp Recombinant Proteins/ or (adjuvant* or squalene* or emulsion*).mp.
11 or/8-10
12 3 and 11
13 influenza vaccines/
14 influenza vaccine*.tw,kf.
15 13 or 14
16 7 or 12 or 15

Core set 1
17 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).mp.
18 16 and 17

Core set 2 (limited to trivalent or quadrivalent)
19 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok or Supemtek).tw,kf,rn.
20 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or "Influpozzi Adiuvato" or aIIV3* or aIIV4*).tw,kf.
21 (RIV or RIV3 or RIV4 or IIV3* or SD-IIV3 or HD-IIV3 or ccIIV3 or cc-IIV3 or cIIV3 or eIIV4 or IIV4* or SD-IIV4 or HD-IIV4 or ccIIV4 or cc-IIV4 or cIIV4 or eIIV4).tw,kf.
22 or/19-21
23 18 or 22

Core set 3: core set 3 PLUS all known drug names and abbreviations – Note that the known drug names and abbreviations have NOT been combined with terms for influenza or vaccines
24 limit 23 to "all aged (65 and over)"
25 exp Aged/ or geriatrics/ or aging/
26 (geriatric* or elder* or old* or ageing or aging or senior* or "older adult*" or retired or retiree* or elder* or pensioner* or "nursing home*" or "older people" or "older patient*" or gerontology or Sexagenarian*OR septuagenarian* or octogenarian or nonagenarian* or centenarian* or sixties or seventies or eighties or nineties).tw,kf.
27 23 and (25 or 26)
28 24 or 27
29 animals/ not humans/
30 28 not 29
31 22 not 29
32 30 or 31 * **– Final set with all named drugs/abbreviations**

*RIV abbreviation includes rivaroxaban, so these articles were removed using “NOT rivaroxaban.tw,kf.”

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 15, 2022>, EBM Reviews - ACP Journal Club <1991 to May 2022>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <May 2022>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2022>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

---

1 (flu or flue or influenza* or grippe).tw.
2 (vaccin* or immuni* or inocula* or shot or jab).tw.
3 (adjuvant* or squalene* or emulsion*).mp.
4 1 and (2 or 3)
5 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
6 4 and 5
7 (geriatric* or elder* or old* or ageing or aging or senior* or older adult* or retired or retiree* or elder* or pensioner* or nursing home* or older people or older patient* or gerontology or Sexagenarian*OR

septuagenarian* or octogenarian or nonagenarian*OR centenarian* or sixties or seventies or eighties or nineties).tw.
8 6 and 7
9 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok or Supemtek).tw.
10 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
11 (RIV or RIV3 or RIV4 or IIV3* or SD-IIV3 or HD-IIV3 or ccIIV3 or cc-IIV3 or cIIV3 or eIIV4 or IIV4* or SD-IIV4 or HD-IIV4 or ccIIV4 or cc-IIV4 or cIIV4 or eIIV4).tw.
12 or/9-11
13 7 and 12
14 8 or 13

Database: JBI EBP Database <Current to June 08, 2022>

---

1 (flu or flue or influenza* or grippe).tw.
2 (vaccin* or immuni* or inocula* or shot or jab).tw.
3 (adjuvant* or squalene* or emulsion*).mp.
4 1 and (2 or 3)
5 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
6 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok).tw.
7 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
8 (RIV or RIV3 or RIV4 or IIV3* or SD-IIV3 or HD-IIV3 or ccIIV3 or cc-IIV3 or cIIV3 or eIIV4 or IIV4* or SD-IIV4 or HD-IIV4 or ccIIV4 or cc-IIV4 or cIIV4 or eIIV4).tw.
9 or/4-8

Database: APA PsycInfo <1806 to June Week 2 2022>

---

1 exp influenza/
2 (flu or flue or influenza*or grippe or Hemagglutinin).tw.
3 1 or 2
4 immunization/
5 (vaccin* or immuni* or inocula* or shot or jab).tw.
6 (adjuvant* or squalene* or emulsion*).tw.
7 or/4-6
8 3 and 7
9 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
10 8 and 9
11 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok or Supemtek).tw.
12 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or Influpozzi Adiuvato or aIIV3* or aIIV4*).tw.
13 (RIV or RIV3 or RIV4 or IIV3* or SD-IIV3 or HD-IIV3 or ccIIV3 or cc-IIV3 or cIIV3 or eIIV4 or IIV4* or SD-IIV4 or HD-IIV4 or ccIIV4 or cc-IIV4 or cIIV4 or eIIV4).tw.
14 or/10-13
15 animals/ not humans/
16 14 not 15

Database: Embase Classic+Embase <1947 to 2022 June 16>

---

1 exp Influenza virus/ or exp influenza/ or exp influenzavirus a/ or Hemagglutinin Glycoproteins, Influenza Virus/
2 (flu or flue or influenza*or grippe).tw.
3 1 or 2

4 exp vaccine/ or exp immunization/
5 (vaccin* or immuni* or inocula* or shot or jab).tw.
6 4 or 5
7 3 and 6
8 immunological adjuvant/
9 exp virus antibody/
10 hemagglutination inhibition test/ or exp plant protein/ or exp recombinant protein/ or (adjuvant* or squalene* or emulsion*).mp.
11 or/8-10
12 3 and 11
13 influenza vaccine/
14 influenza vaccine*.tw.
15 13 or 14
16 7 or 12 or 15
17 (trivalent or quadrivalent or TIV or aTIV or QIV or aQIV).tw.
18 16 and 17
19 (flulaval or fluzone or fluad* or fluzone or agriflu or fluviral or influvac or alfuria or fluarix or flucelvax or flublok or Supemtek).tw.
20 (MF59* or MF?59* or aTIV or aQIV or chiromas or gripguard or "Influpozzi Adiuvato" or aIIV3* or aIIV4*).tw.
21 (RIV or RIV3 or RIV4 or IIV3* or SD-IIV3 or HD-IIV3 or ccIIV3 or cc-IIV3 or cIIV3 or eIIV4 or IIV4* or SD-IIV4 or HD-IIV4 or ccIIV4 or cc-IIV4 or cIIV4 or eIIV4).tw.
22 or/19-21
23 18 or 22
24 limit 23 to aged <65+ years>
25 exp aged/ or exp aging/ or exp geriatrics/
26 (geriatric* or elder* or old* or ageing or aging or senior* or older adult* or retired or retiree* or elder* or pensioner* or nursing home* or older people or older patient* or gerontology or Sexagenarian*OR septuagenarian* or octogenarian or nonagenarian*OR centenarian* or sixties or seventies or eighties or nineties).tw.
27 23 and (25 or 26)
28 24 or 27
29 animals/ not humans/
30 28 not 29
31 22 not 29
32 30 or 31*

*RIV abbreviation includes rivaroxaban, so these articles were removed using “NOT rivaroxaban.tw.”

Appendix 4: Grey literature sources

Trial registries

- CenterWatch Clinical Trials Listing Service: https://www.centerwatch.com/clinical-trials/listings/
- Clinicaltrials.gov: https://clinicaltrials.gov/ct/screen/AdvancedSearch
    - New trial in 2022 - Flublok or Fluzone With Advax-CpG55.2 or AF03 https://clinicaltrials.gov/ct2/show/NCT03945825
- EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/ctr-search/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html
- ISRCTN: http://www.isrctn.com
- UKCRN: http://www.ukcrc.org/research-infrastructure/clinical-research-networks/uk-clinical-research-network-ukcrn/
- WHO: https://www.who.int/ictrp/en/

COVID databases

- Cochrane: https://covid-19.cochrane.org
- CAMRADES COVID-19-SOLES: https://camarades.shinyapps.io/COVID-19-SOLES/
- COVID-NMA: https://covid-nma.com
- COVID-19 L*ove:
- https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5e7fce7e3d05156b5f5e032a&intervention_variable=603b9fe03d05151f35cf13dc&classification=all
- LitCOVID: https://www.ncbi.nlm.nih.gov/research/coronavirus/
- WHO COVID-19: https://covid19.who.int

Pre-print databases

- bioRxiv (biology): www.biorxiv.org
- JMIR Publications: https://preprints.jmir.org/
- medRxiv: https://www.medrxiv.org/
- Open Science Framework: https://osf.io
- Preprints.org: https://www.preprints.org
- Research Square: https://www.researchsquare.com

CDC

- Quadrivalent Influenza Vaccine: https://www.cdc.gov/flu/prevent/quadrivalent.htm
  Brand names: AFLURIA Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, Flucelvax Quadrivalent and Fluzone Quadrivalent, FluMist Quadrivalent
- TABLE. Influenza vaccines — United States, 2021–22 influenza season* - https://www.cdc.gov/flu/professionals/acip/2021-2022/acip-table.htm
- Summary: 'Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2021-22' - https://www.cdc.gov/flu/professionals/acip/summary/summary-recommendations.htm

Alfuria

- BCCDC: http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%202%20-%20Imms/Part4/Influenza_AfluriaTetra.pdf
- FDA: https://www.fda.gov/vaccines-blood-biologics/vaccines/afluria-afluria-southern-hemisphere
- Government of Canada: https://www.canada.ca/en/public-health/services/publications/healthy-living/supplemental-statement-afluria-tetra.html
- Public Health ON: https://www.publichealthontario.ca/-/media/documents/f/2020/fact-sheet-influenza-vaccine-2020-2021.pdf?la=en
- Seqirus: https://www.seqirus.ca/-/media/seqirus-canada/docs-en/afluria-tetra-product-monograph--februray-19th-2021.pdf

Adiuvato

- Sequirus: https://www.seqirus.it/notizie/approvato-dall-unione-europea-il-primo-vaccino-antinfluenzale-quadrivalente-adiuvato
- https://www.ema.europa.eu/en/documents/product-information/fluad-tetra-epar-product-information_it.pdf
- https://www.aulss2.veneto.it/documents/6017636/7745924/Fluad/10cad3c6-abc9-4ed6-991c-6bd0eddf6e63

Agriflu

- FDA: https://www.fda.gov/vaccines-blood-biologics/vaccines/agriflu AND related: https://www.drugs.com/history/agriflu.html
- Government of Canada: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/15577a-eng.php
- Government of Canada:https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2017-2018.html
- Novartis:https://www.novartis.ca/sites/www.novartis.ca/files/agriflu_patient_e_0.pdf
- NPOA: https://npao.org/health-canada-suspends-use-of-novartis-flu-vaccine-agriflu-fluad/
- ON public drug programs: http://www.health.gov.on.ca/en/pro/programs/drugs/opdp_eo/notices/exec_office_20171117.pdf
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- Sequirus: https://www.seqirus.ca/products/AGRIFLU

Flulaval / **Fluviral**

- BCCDC: http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%202%20-%20Imms/Part4/Influenza_FluLavalTetra.pdf - updated
- FDA: https://www.fda.gov/media/74537/download
- GSK: https://ca.gsk.com/media/590283/flulaval-tetra.pdf
- GSK: https://ca.gsk.com/media/1352353/fluviral.pdf
- NLM: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a9806027-8323-4abf-849f-46fb10984f13

Fluzone

- BCCDC:http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Immunization/Vaccine%20Info/FluzoneHD_QandA.pdf
- Fluzone.ca: https://www.fluzone.ca/
- CDC: https://www.cdc.gov/flu/prevent/qa_fluzone.htm
- FDA: https://www.fda.gov/vaccines-blood-biologics/vaccines/fluzone-fluzone-high-dose-and-fluzone-intradermal
- Fluzone® High-Dose Influenza Vaccine with a Booster Is Associated with Low Rates of Influenza Infection in Patients with Plasma Cell Disorders - http://www.bloodjournal.org/content/126/23/3058?sso-checked=true
- Sanofi: http://products.sanofi.ca/en/fluzone-qiv.pdf
- Sanofiflu: https://sanofiflu.com/fluzone-quadrivalent-influenza-vaccine.html

Fluad

- CDC: https://www.cdc.gov/flu/prevent/adjuvant.htm
- CentreWatch: https://www.centerwatch.com/clinical-trials/listings/213945/flu-fluad-vs-fluzone-hd/
- Fluad.com: https://flu.seqirus.com/Formulation/Fluad/p/FluadIn?seasonCategoryCode=Seqirus_InSeason
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- Novartis: file:///Users/jessiemcgowan/Downloads/Fluad%20Slide%20Deck_E_Sep2014.pdf
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- PubMED CENTRAL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3780956/
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- https://www.precisionvaccinations.com/vaccines/fluarix-quadrivalent-influenza-vaccine

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- FDA: https://www.fda.gov/vaccines-blood-biologics/vaccines/flucelvax-quadrivalent
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Flublok
- CDC: Recombinant Influenza (Flu) Vaccine - https://www.cdc.gov/flu/prevent/qa_flublok-vaccine.htm
- FDA: https://www.fda.gov/vaccines-blood-biologics/vaccines/flublok-quadrivalent https://www.fluzone.com/flu-vaccines/flublok-quadrivalent
- https://www.sanofiflu.com/flublok-quadrivalent-influenza-vaccine/
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- BGP Pharma: https://www.mylan.ca/-/media/mylanca/documents/english/product-pdf/influvac-pm-2017-05-30.pdf
- https://pdf.hres.ca/dpd_pm/00045022.PDF
- https://www.scribd.com/document/347239541/Influvac-Insert-2017

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Alberta: https://www.albertahealthservices.ca/assets/info/hp/cdc/if-hp-cdc-influenza-qiv-fluzone-bio-pg-07-265.pdf

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British Columbia:
- https://www.healthlinkbc.ca/health-feature/flu-season

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- http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Immunization/Vaccine%20Info/Archived_Quadrivalent_Influenza_Vaccine_Q_A_2015-16.pdf
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- Healthy Aging Interventions, Programs, and Initiatives: An Environmental Scan - https://www.cadth.ca/healthy-aging-interventions-programs-and-initiatives-environmental-scan
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- Point-of-Care Testing for Influenza - https://www.cadth.ca/point-care-testing-influenza

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- MMWR Reports: https://www.cdc.gov/mmwr/index.html
- FastStats: https://www.cdc.gov/nchs/fastats/
- National Centre for Health Statistics: https://www.cdc.gov/nchs/

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CMA Infobase: https://joulecma.ca/cpg/homepage

CMS.gov: https://www.cms.gov/medicare-coverage-database/indexes/technology-assessments-index.aspx?TAId=85&bc=AAAQAAAAAAAA&

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- https://www.prevention.va.gov/flu/

ECRI: https://www.ecri.org

FDA:

- https://www.fda.gov/vaccines-blood-biologics/vaccines/influenza-virus-vaccine-quadrivalent-types-and-types-b
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- https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance/weekly-influenza-reports.html
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Johns Hopkins:
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PEI:
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PHAC:
- https://www.canada.ca/en/public-health.html
- https://www.canada.ca/en/public-health/services/reports-publications/disease-prevention-control-guidelines.html
- Notifiable disease online: https://dsol-smed.phac-aspc.gc.ca/notifiable/
- Reports and publication: https://www.canada.ca/en/public-health/services/reports-publications.html
- Surveillance: https://www.canada.ca/en/public-health/services/surveillance.html

Manitoba:
- https://www.gov.mb.ca/health/publichealth/cdc/div/manual/docs/msiipp.pdf
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National guidelines clearinghouse: https://www.ahrq.gov/gam/index.html

New Brunswick: https://www.nbms.nb.ca/flu-shot/ - updated

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- https://www.gov.nl.ca/hcs/publichealth/cdc/flu-information/ - updated
- NLCAHR: https://www.nlcahr.mun.ca/CHRSP/CompletedCHRSP.php'

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Ontario
- http://www.health.gov.on.ca/en/pro/programs/publichealth/flu/uiip/default.aspx
- http://www.health.gov.on.ca/en/pro/programs/publichealth/flu/uiip/default09212017.aspx
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- PATH HTA: https://www.path-hta.ca

Quebec:
- INESSS - https://www.inesss.qc.ca/en/about-us/about-the-institut.html
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Saskatchewan:

- Influenza reports: https://www.saskatchewan.ca/government/government-structure/ministries/health/other-reports/influenza-reports
- Rxfiles: https://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx
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- https://publications.saskatchewan.ca/#/home

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- https://www150.statcan.gc.ca/n1/pub/82-624-x/2015001/article/14218-eng.htm
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Yukon: http://www.hss.gov.yk.ca/2599.php

International

WHO:

- https://www.who.int/health-topics/influenza-seasonal#tab=tab_1 - Updated

INAHTA: http://www.inahta.org/publications/

General Grey

- GreyNet International: http://www.greylit.org
- National Technical Information Service (NTIS): http://www.ntis.gov/

Search engines

- TRIP database: http://www.tripdatabase.com/
- Google: https://www.google.ca/advanced_search
- Google Scholar: https://scholar.google.com/intl/en/scholar/about.html

Thesis

- Center for Research Libraries Foreign Dissertation: https://www.crl.edu/collections/topics/dissertations
- DART-Europe E-theses Portal: http://www.dart-europe.eu/basic-search.php
- Electronic Theses Online Service (ETHOS) | British Library: http://ethos.bl.uk/Home.do;jsessionid=D96E9CF245B0FE0199DDDB94FF4BD2A7
- Open access dissertations: https://oatd.org
- Thesis Canada Portal: http://www.bac-lac.gc.ca/eng/services/theses/Pages/theses-canada.aspx

Specific articles

- Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8542957/
- Recombinant HA-based vaccine outperforms split and subunit vaccines in elicitation of influenza-specific CD4 T cells and CD4 T cell-dependent antibody responses in humans - https://www.nature.com/articles/s41541-020-00227-

Clinical Trial Databases – full list - new

- AMIS (German): https://www.dimdi.de/dynamic/de/arzneimittel/arzneimittel-recherchieren/amis/
- Australian New Zealand Clinical Trials Registry (ANZCTR): http://www.anzctr.org.au
- Be Part of Research (UK Clinical Trials): https://sites.google.com/a/york.ac.uk/yhectrialsregisters/home/clinicaltrials/uk-clinical-trials
- Brazilian Clinical Trials Registry: http://www.ensaiosclinicos.gov.br/

- China Drug Trials (in Chinese only): http://www.chinadrugtrials.org.cn/eap/main
- Chinese Clinical Trial Registry (ChiCTR): http://www.chictr.org.cn/enIndex.aspx
- ClinicalStudyDataRequest: https://clinicalstudydatarequest.com
- ClinicalTrials.gov: https://www.clinicaltrials.gov
- CentreWatch: https://www.centerwatch.com/clinical-trials/listings/
- Chinese Clinical Trial Registry (ChiCTR): http://www.chictr.org.cn/abouten.aspx
- Clinical Research Information Service (CRiS) (Korea): https://cris.nih.go.kr/cris/en/
- Cuban Registry of Clinical Trials: http://registroclinico.sld.cu/en/home
- DRKS - German Clinical Trials Register: https://www.drks.de/drks_web/
- Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/
- EORTC Clinical Trials Database: https://www.eortc.org/clinical-trials/
- EORTC Clinical Trials tools: https://www.eortc.org/tools/
- EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/ctr-search/
- EudraCT (European Union Drug Regulating Authorities Clinical Trials Database): https://eudract.ema.europa.eu
- Health Canada Clinical Trials Database: https://health-products.canada.ca/ctdb-bdec/index-eng.jsp
- Hong Kong UCT Register: http://www.hkuctr.com
- ISRCTN (UK): http://www.isrctn.com/page/about
- India (Clinical Trials Registry India): http://ctri.nic.in/Clinicaltrials/pubview.php
- Iranian Registry of Clinical Trials (IRCT): https://www.irct.ir
- Italian Medicines Agency - AIFA – Agenzia Italiaiana del Farmaco: https://www.aifa.gov.it
- OpenTrialsFDA: https://opentrials.net/opentrialsfda.1.html
- Philippine Health Research Registry: http://registry.healthresearch.ph/
- Japan Primary Registries Network (JPRN): https://rctportal.niph.go.jp/en/
- Netherland Trial Register: https://www.trialregister.nl/trialreg/index.asp
- Pan African Clinical Trials Registry: https://pactr.samrc.ac.za/
- PharmNet.Bund Clinical Trials: https://www.pharmnet-bund.de/static/en/clinical-trials/index.html
- Peruvian Registry of Clinical Trials: https://www.ins.gob.pe/ensayosclinicos/
- Research Registry: https://www.researchregistry.com
- South African National Clinical Trials Register: http://www.sanctr.gov.za/
- Spanish Registry of Clinical Studies (REec): https://reec.aemps.es/reec/public/web.html
- SNCTP (Swiss National Clinical Trials Portal): https://www.kofam.ch/en/snctp-portal/searching-for-a-clinical-trial/
- Sri Lanka Clinical Trials Registry: https://slctr.lk/
- Tanzania Clinical Trial Registry: https://www.trialassure.com/resources/blog/registry-snapshot-tanzania-clinical-trials-registry-tzctr/
- Thai Clinical Trials Registry: http://www.clinicaltrials.in.th/
- Trials tracker: https://fdaaa.trialstracker.net
- University hospital Medical Information Network (UMIN) Clinical Trials Registry (for Japan): https://www.umin.ac.jp/ctr/
- WHO: WHO International Clinical Trials Registry Platform
- YODA Yale University Open Data Access: https://yoda.yale.edu

Appendix 5: Vaccine composition and circulating strains

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
Studies included in quantitative and descriptive analysis (n = 26)							
Rudenko, 2001[6]	Nursing home	N 1996/1997	Tx1	IIV3-SD	Trivalent inactivated, split virus influenza vaccine	A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), B/Harbin/07/94	Other circulating strains: A/H1N1 and influenza B
			Tx2	Placebo	Placebo	NA	
Wongsurakiat, 2004[7]	Clinic	S 1997/1998	Tx1	IIV3-SD	Trivalent inactivated, split virus influenza vaccine SD	A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), B/Harbin/07/94	Predominant circulating strain: A/Sydney/5/97 (H3N2)
			Tx2	Placebo	Placebo (Vitamin B1)	NA	
Allsup, 2004[8]	Community	N 1999/2000	Tx1	IIV3-SD	Trivalent inactivated, split virion influenza vaccine SD	A/Beijing/262/95(H1N1), A/Sydney/5/97 (H3N2), B/Beijing/184/93	Predominant circulating strain: A/H3N2
			Tx2	Placebo	Placebo	NA	
Falsey, 2009[9]	Community	N 2006/2007	Tx1	IIV3-HD	Fluzone HD	A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/04	Predominant circulating strain: A/H1 Other circulating strain: A/H3
			Tx2	IIV3-SD	Fluzone SD	A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/04	
Keitel, 2010[10]	Community	N 2006/2007	Tx1	RIV3	FluBlok	A/Wisconsin (H3N2); A/New Caledonia (H1N1), B/Ohio	Predominant circulating strain: A/H1 Other circulating strain: A/H3
			Tx2	IIV3-SD	Fluzone SD	A/Wisconsin (H3N2); A/New Caledonia (H1N1), B/Malaysia	
DiazGranados, 2013[11]	Clinic	N 2009/2010	Tx1	IIV3-HD	Fluzone HD	A/Brisbane/59/07 (H1N1), A/Uruguay/716/2007 X-175C (H3N2), and B/Brisbane/60/2008 strains	Predominant circulating strain: H1N1
			Tx2	IIV3-SD	Fluzone SD	A/Brisbane/59/07 (H1N1), A/Uruguay/716/2007 X-175C (H3N2), B/Brisbane/60/2008	
Scheifele, 2013[12]	Community or living assistance facility	N 2011/2012	Tx1	IIV3-Adj	Fluad, adjuvanted	A/ California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like and B/Brisbane/60/2008	Circulating strains: A/H3N2, pH1N1 and influenza B
			Tx2	IIV3-SD	Agriflu SD	A/ California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like and B/Brisbane/60/2008	
Pepin, 2013[13]	Community	N 2011/2012	Tx1	IIV4-SD	Quadrivalent inactivated influenza vaccine SD	A/California/07/2009(H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage) strains	Predominant circulating Strain: A/H3N2

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
			Tx2	IIV3-SD	Trivalent inactivated influenza vaccine SD (pooled)	A/California/07/2009 (H1N1),A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage) strains OR B/Florida/04/2006 (Yamagata lineage) strains	Other circulating strains: B viruses and A/H1N1pdm09
Tsang, 2014[14]	NR	N 2007/2008	Tx1	IIV3-SD	Fluzone SD	A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004	Circulating strains: A/H1N1, A/H3N2 and B viruses
			Tx2	IIV3-HD	Fluzone HD	A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004	
Frey, 2014[15]	NR	N 2010/2011 and S 2010/2011 *Note: This study was conducted in 4 different countries in different hemisphere but in methods they only mention northern hemisphere vaccine	Tx1	IIV3-Adj	Fluad, adjuvanted	A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), B/Brisbane/60/2008	Predominant circulating strain: A/H3N2 Other circulating strain: A/H1N1
			Tx2	IIV3-SD	Agriflu SD	A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), B/Brisbane/60/2008	
DiazGranados, 2014[16]	Research centers	N 2011/2012 and N 2012/2013	Tx1	IIV3-HD	Fluzone HD	2011/2012: A/California/ 7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008; 2012/2013: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), B/Texas/6/2011 (B/Wisconsin/1/2010-like virus)	Predominating circulating strain: A/H3N2
			Tx2	IIV3-SD	Fluzone SD	2011/2012: A/California/ 7/2009 (H1N1),A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008; 2012/2013: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2),	

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						B/Texas/6/2011 (B/Wisconsin/1/2010-like virus)	
Nace, 2014[17]	Long term care home	N 2011/2012 and N 2012/2013	Tx1	IIV3-HD	Fluzone HD	2011/2012: A/California/7/2009(H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008; 2012/2013: A/California/7/2009(H1N1), A/Victoria/361/2011(H3N2), B/Texas/6/2011	Predominant circulating strain: A/H3N2
			Tx2	IIV3-SD	Fluzone SD	2011/2012: A/California/7/2009(H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008; 2012/2013: A/California/7/2009(H1N1), A/Victoria/361/2011(H3N2), B/Texas/6/2011	
Bart, 2016[18]	Community	N 2013/2014	Tx1	IIV3-CC-SD	Flucelvax/Optaflu SD	A/Brisbane/10/2010 (H1N1); A/Texas/50/2012 (H3N2); B/Massachusetts/2/2012 (Yamagata lineage) OR B/Brisbane/60/2008 (Victoria lineage)	Predominant circulating strain: A/H1N1pdm09
			Tx2	IIV4-CC-SD	Quadrivalent inactivated influenza vaccine, cell-cultured, SD	A/Brisbane/10/2010 (H1N1); A/Texas/50/2012 (H3N2); B/Massachusetts/2/2012; B/Brisbane/60/2008	
Gravenstein, 2017[19]	Nursing home	N 2013/2014	Tx1	IIV3-HD	Fluzone HD	A/California/7/2009 (H1N1)pdm09-like virus; A/Victoria/361/2011 (H3N2); B/Massachusetts/2/2012-like virus	Predominant circulating strain: A/H1N1pdm09
			Tx2	IIV3-SD	Fluzone SD	A/California/7/2009 (H1N1)pdm09-like virus; A/Victoria/361/2011 (H3N2); B/Massachusetts/2/2012-like virus	
Dunkle, 2017[20]	Outpatient centers	N 2014/2015	Tx1	RIV4	Flublok	A/California/7/2009 (H1N1)-like, A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012, B/Brisbane/60/2008	Predominant circulating strain: A/H3N2
			Tx2	IIV4-SD	Fluarix SD	A/California/7/2009 (H1N1)-like, A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012, B/Brisbane/60/2008	
Treanor, 2017[21]	NR	N 2014/2015	Tx1	IIV4-SD	Afluria Quadrivalent SD	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, B/Massachusetts/2/2012-	Predominant circulating strain: A/H3N2

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						like virus (B/Yamagata lineage), B/Brisbane/60/2008-like virus (B/Victoria lineage)	
			Tx2	IIV3-SD	Trivalent inactivated influenza vaccine (pooled) SD	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, B/Massachusetts/2/2012-like virus (B/Yamagata lineage) A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, B/Brisbane/ 60/ 2008-like virus (B/Victoria lineage)	
Gravenstein, 2018[22]	Nursing home	N 2012/2013	Tx1	IIV3-HD	Fluzone HD	A/California/7/2009-like (pH1N1), A/Victoria/361/2011-like (H3N2), and B/Wisconsin/1/2010-like (B/Yamagata lineage)	Predominant circulating strain: A/H3N2 for the 2012–2013 season
			Tx2	IIV3-SD	Fluzone SD	A/California/7/2009-like (pH1N1), A/Victoria/361/2011-like (H3N2), and B/Wisconsin/1/2010-like (B/Yamagata lineage)	
Chang, 2019[23]	Community	N 2017/2018	Tx1	IIV4-HD	Quadrivalent inactivated split virion influenza vaccine HD	A/Michigan/45/2015 X-275, A/Hong Kong/4801/2014 [NYMC X-263B], B/Brisbane/60/2008, B/Phuket/3073/2013	Predominant circulating strain: A/H3N2
			Tx2	IIV3-HD	Fluzone (pooled) HD	A/Michigan/45/2015 X-275, A/Hong Kong/4801/2014 [NYMC X-263B], B/Brisbane/60/2008 OR B/Phuket/3073/2013	
Loeb, 2020[24]	Community	N 2014/2015, N 2015/2016, N 2016/2017 and N 2017/2018	Tx1	IIV3-SD	Fluzone SD	2014/2015: A/California/7/2009-like (2009 H1N1) virus, an A/Texas/50/2012-like (H3N2) virus, and a B/Massachusetts/2/2012-like (B/Yamagata lineage) virus 2015/2016: A/California/7/2009 (H1N1)pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like (B/Yamagata lineage) virus 2016/2017: A/California/7/2009 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus (B/Victoria lineage)	Predominant circulating strains in USA: 2014/2015: A/H3N2; 2015/2016: A/H1N1pdm09; 2016/2017: A/H3N2; 2017/2018: A/H3N2

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						2017/2018: A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus	
			Tx2	IIV3-HD	Fluzone HD	2014/2015: A/California/7/2009-like (2009 H1N1) virus, an A/Texas/50/2012-like (H3N2) virus, and a B/Massachusetts/2/2012-like (B/Yamagata lineage) virus 2015/2016: A/California/7/2009 (H1N1)pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like (B/Yamagata lineage) virus 2016/2017: A/California/7/2009 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus (B/Victoria lineage) 2017/2018: A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus	
Belongia, 2020[25]	Clinic	N 2017/2018	Tx1	IIV3-HD	Fluzone HD	Not fully defined: "The A(H3N2) recommended vaccine component was identical in 2016–17 and 2017/18: A/Hong Kong/4801/2014–like (clade 3C.2a)."	Predominant circulating strain: circulating A(H3N2) viruses: (A/Singapore/INFIMH-16–0019/2016 and A/Kentucky/29/2017) Other circulating strain: A/Kansas/14/2017 (KS14), an antigenically advanced virus that circulated at a low level during 2017–18.
			Tx2	IIV3-Adj	Fluad, adjuvanted	Not fully defined: "The A(H3N2) recommended vaccine component was identical in 2016–17 and 2017/18: A/Hong Kong/4801/2014–like (clade 3C.2a)."	
			Tx3	RIV4	FluBlok	Not fully defined: "The A(H3N2) recommended vaccine component was identical in 2016–17 and 2017/18: A/Hong Kong/4801/2014–like (clade 3C.2a)."	
Cowling, 2020[26]	Community	N 2017/2018	Tx1	IIV4-SD	FluQuadri SD	A/Michigan/45/2015(H1N1)-like virus (clade 6B.1), A/Hong	Predominant circulating strain:

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						Kong/4801/2014(H3N2)-like virus (clade 3C.2a), B/Brisbane/60/2008-like virus (Victoria lineage; clade 1A), B/Phuket/3073/2013-like virus (Yamagata lineage; clade 3)	A(H1N1)pdm09
			Tx2	IIV3-Adj	Fluad, adjuvanted	A/Michigan/45/2015(H1N1)-like virus (clade 6B.1), A/Hong Kong/4801/2014(H3N2)-like virus (clade 3C.2a), B/Brisbane/60/2008-like virus (Victoria lineage; clade 1A)	
			Tx3	IIV3-HD	Fluzone HD	A/Michigan/45/2015(H1N1)-like virus (clade 6B.1), A/Hong Kong/4801/2014(H3N2)-like virus (clade 3C.2a), B/Brisbane/60/2008-like virus (Victoria lineage; clade 1A)	
			Tx4	RIV4	Flublok	A/Michigan/45/2015(H1N1)-like virus (clade 6B.1), A/Hong Kong/4801/2014(H3N2)-like virus (clade 3C.2a), B/Brisbane/60/2008-like virus (Victoria lineage; clade 1A), B/Phuket/3073/2013-like virus (Yamagata lineage; clade 3)	
Essink, 2020[27]	NR	N 2017/2018	Tx1	IIV4-Adj	Quadrivalent inactivated influenza vaccine, adjuvanted	A/Michigan/45/2015 (H1N1)-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, B/Phuket/3073/2013-like virus (Yamagata lineage), B/Brisbane/60/2008-like virus (Victoria lineage)	Predominant circulating strain: A/H3N2
			Tx2	IIV3-Adj	Fluad (pooled), adjuvanted	A/Michigan/45/2015 (H1N1)-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, B/Brisbane/60/2008-like virus (Victoria lineage) OR B/Phuket/3073/2013-like virus (Yamagata lineage)	
Beran, 2021[28]	Community	N 2016/2017 and S 2017	Tx1	IIV4-Adj	Quadrivalent inactivated influenza vaccine, adjuvanted	N 2016/17: A California/7/2009pdm NYMCX-181 (A H1N1), A Hong Kong/4801/2014 NYMCX-263B (A H3N2), B Brisbane/9/2014 (B Yamagata), B Brisbane/60/2008 (B Victoria) S 2017: A Singapore/GP1908/2015 IVR-180 (A H1N1), A Hong Kong/4801/2014 NYMCX-263B (A H3N2), B	Unspecified A/H3N2 strains

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						Brisbane/9/2014 (B Yamagata), B Brisbane/60/2008 (B Victoria)	
			Tx2	Tdap	Boostrix	NA	
Schmader, 2021[29]	Community	N 2017/2018 and N 2018/2019	Tx1	IIV3-Adj	Fluad,, adjuvanted	2017/2018: A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus 2018/2019: A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus (updated), B/Colorado/06/2017-like (Victoria lineage) virus (updated)	Predominant circulating strains: A/H3N2 and A/H1N1pdm09, A/H3N2
			Tx2	IIV3-HD	Fluzone HD	2017/2018: A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus 2018/2019: A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus (updated), B/Colorado/06/2017-like (Victoria lineage) virus (updated)	
Teh, 2021[30]	Community	S 2019	Tx1	IIV3-HD	Fluzone HD	A/Michigan/45/2015 (H1N1)pdm09–like virus, A/Switzerland/8060/2017 (H3N2)–like virus, B/Phuket/3073/2013-like virus (Yamagata lineage)	Circulating strains: Influenza A viruses (A/H3N2, A/H1N1) and Influenza B viruses
			Tx2	IIV4-SD	FluQuadri SD	A/Michigan/45/2015 (H1N1)pdm09–like virus, A/Switzerland/8060/2017 (H3N2)–like virus, B/Phuket/3073/2013-like virus (Yamagata lineage), B/Colorado/06/2017-like virus (Victoria lineage)	
Vardeny, 2021[31]	NR	N 2016/2017, N 2017/2018, and N 2018/2019	Tx1	IIV3-HD	Fluzone HD	2017/2018: A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus 2018/2019: A/Michigan/45/2015 (H1N1)pdm09-like virus,	Predominant circulating strain: influenza A strain viruses (specifically influenza A/New York/55/2004 [H3N2] and novel influenza A [H1N1])

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus (updated), B/Colorado/06/2017-like (Victoria lineage) virus (updated)	Other circulating strain: B/Yamagata strain
			Tx2	IIV4-SD	Fluzone Quadrivalent SD	2017/2018: A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus 2018/2019: A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus (updated), B/Colorado/06/2017-like (Victoria lineage) virus (updated)	
Studies included only in descriptive analysis (n= 15)							
Treanor, 1994[32]	Community	NR	Tx1	IIV3-SD	Trivalent inactivated influenza vaccine SD	A/H1N1; A/H3N2; B/Ann Arbor/86 strain (1989 to 1990 flu vaccine) OR B/Yamgata/88	NR
			Tx3	Placebo	Placebo	NA	
de Bruijn, 2006[33]	Community	N 2004/2005	Tx1	IIV3-Adj	Fluad, adjuvanted	A/New Caledonia/20/99(H1N1)-like virus, an A/Fujian/411/2002(H3N2)-like virus and a B/Shanghai/361/2002-like virus	Predominant circulating strain: A/H3N2
			Tx2	IIV3-SD	Influvac subunit vaccine SD	A/New Caledonia/20/99(H1N1)-like virus, an A/Fujian/411/2002(H3N2)-like virus and a B/Shanghai/361/2002-like virus	
Szymczakiewicz-Multanowska, 2009[34]	Community	N 2004/2005	Tx1	IIV3-SD	Agrippal SD	A/New Caledonia/20/99(H1N1)-like, A/Fujian/411/2002(H3N2)-like, and B/Shanghai/361/2002(B)-like	Predominant circulating strain: A/H3N2
			Tx2	IIV3-SD-CC	Trivalent inactivated influenza vaccine, cell-cultured, SD	A/New Caledonia/20/99(H1N1)-like, A/Fujian/411/2002(H3N2)-like, and B/Shanghai/361/2002(B)-like	
Szymczakiewicz-Multanowska, 2012 (a)[35]	Community	N 2005/2006	Tx1	IIV3-SD-CC	Optaflu, cell-cultured SD	A/New Caledonia/20/99-like, A/California/7/2004-like, B/Shanghai/361/2002-like	Predominant circulating strain: Influenza B viruses Other circulating strains: A/H1N1 and A/H3N2
			Tx2	IIV3-SD	Agrippal SD	A/Solomon Islands/3/2006-like, A/Wisconsin/67/2005-like, B/Malaysia/2506/2004-like	
Szymczakiewicz-Multanowska, 2012 (b)[36]	Community	N 2007/2008	Tx1	IIV3-SD-CC	Optaflu, cell-cultured, SD	A/Solomon Islands/3/2006-like, A/Wisconsin/67/2005-like, B/Malaysia/2506/2004-like	Predominant circulating strain: A/H1N1

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
			Tx2	IIV3-SD	Agrippal SD	A/Solomon Islands/3/2006-like, A/Wisconsin/67/2005-like, B/Malaysia/2506/2004-like	Other circulating strains: A/H3N2, and B viruses
Della Cioppa, 2012[37]	NR	N 2008/2009	Tx1	IIV3-Adj	Trivalent inactivated influenza vaccine, adjuvanted	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/ 2007 (H3N2) and B/Florida/4/2006	Predominant circulating strain: A/H3 and A/H3N2 Other circulating strains: Type B viruses
			Tx2	IIV3-Other-Adj	Trivalent inactivated influenza vaccine, adjuvanted	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/ 2007 (H3N2) and B/Florida/4/2006	
			Tx3	IIV3-Adj	Trivalent inactivated influenza vaccine, adjuvanted	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/ 2007 (H3N2) and B/Florida/4/2006	
			Tx4	IIV3-Other-Adj	Trivalent inactivated influenza vaccine, adjuvanted	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/ 2007 (H3N2) and B/Florida/4/2006	
Della Cioppa, 2014[38]	NR	N 2008/2009	Tx1	IIV3-SD	Trivalent inactivated influenza vaccine SD	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Florida/4/2006	Predominant circulating strain: A/H3 and A/H3N2 Other circulating strains: Type B viruses
			Tx2	IIV3-Other	Trivalent inactivated influenza vaccine	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Florida/4/2006	
			Tx3	IIV3-Adj	Trivalent inactivated influenza vaccine, adjuvanted	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Florida/4/2006	
			Tx4	IIV3-Other-Adj	Trivalent inactivated influenza vaccine, adjuvanted	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Florida/4/2006	
Izikson, 2015[39]	NR	N 2012/2013	Tx1	RIV3	Flublok	A/H1N1:A/California/07/2009, A/H3N2:A/Victoria/361/2011, B/Wisconsin/1/2010	Predominant circulating strain: A/H3N2
			Tx2	IIV3-SD	Afluria SD	A/H1N1:A/California/07/2009, A/H3N2:A/Victoria/361/2011, B/Wisconsin/1/2010	
Novartis Vaccines and Diagnostics, 2016[40]	NR	NR	Tx1	IIV3-SD	Agriflu SD	NR	NR
			Tx2	IIV3-SD	Fluvirin SD	NR	
Trial registry, 2017[41]	NR	N 2011/2012	Tx1	IIV3-SD	Fluzone SD	A/California/7/2009-like (H1N1), A/Perth/16/2009-like (H3N2), and B/Brisbane/60/2008-like viruses	Predominant circulating strain: A/H3N2
			Tx2	IIV3-HD	Fluzone HD	A/California/7/2009-like (H1N1), A/Perth/16/2009-like (H3N2), and B/Brisbane/60/2008-like viruses	
Otten, 2020[42]	Community	N 2014/2015	Tx1	IIV3-Adj	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	Predominant circulating strain: A/H3N2

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
			Tx2	IIV3-Adj	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	
			Tx3	IIV3-Other-Adj	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	
			Tx4	IIV3-Other-Adj – bilateral	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	
			Tx5	IIV3-Adj-bilataeral + saline	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	
			Tx6	IIV3-Adj-bilateral + saline	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	
			Tx7	IIV3-Adj-bilateral	Agrippal/Fluad, adjuvanted	A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus	
McConeghy, 2020[43]	Nursing home	N 2016/2017	Tx1	IIV3-Adj	Fluad, adjuvanted	A/California/7/2009 (H1N1)–like virus, an A/Hong Kong/ 4801/2014 (H3N2)–like virus, and a B/Brisbane/60/2008–like virus (Victoria lineage)	Predominant circulating strain: A/H3N2
			Tx2	IIV3-SD	Fluvirin SD	A/California/7/2009 (H1N1)–like virus, an A/Hong Kong/ 4801/2014 (H3N2)–like virus, and a B/Brisbane/60/2008–like virus (Victoria lineage)	
Sanchez, 2020[44]	Clinic	N 2017/2018	Tx1	IIV4-HD	Quadrivalent inactivated influenza vaccine HD	A/Michigan/45/2015 (NYMC X-275), A/Hong Kong/4801/2014 (NYMC X-263B), B/Phuket/3073/2013, B/Brisbane/60/2008	Predominant circulating strain: A/H3N2
			Tx2	IIV4-HD	Quadrivalent inactivated influenza vaccine HD	A/Michigan/45/2015 (NYMC X-275), A/Hong Kong/4801/2014 (NYMC X-263B), B/Phuket/3073/2013, B/Brisbane/60/2008	
			Tx3	IIV4-SD	Quadrivalent inactivated influenza vaccine SD	A/Singapore/GP1908/ 2015 (IVR-180) pdm09 (A/H1N1-like), A/Hong Kong/4801/2014 (NYMC X-263) (A/H3N2-like), B/Phuket/3073/2013, B/Texas/2/2013 (B/Victoria lineage-like)	

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
McLean, 2021[45]	Community	N 2016/2017 and N 2017/2018	Tx1	IIV3-HD (2015/2016, 2016/2017)	Fluzone HD in 2015/2016 and 2016/2017	2016/2017: A/California/7/2009(H1N1)-like, A/Hong Kong/4801/2014(H3N2)-like virus, B/Brisbane/60/2008(B/Victoria)-like virus. 2017/2018: A/Michigan/45/2015(H1N1)-like virus, A/Hong Kong/4801/2014(H3N2)-like virus, /Brisbane/60/2008(B/Victoria)-like virus	Predominant circulating strain: A/H3N2; B/Yamagata-lineage
			Tx2	IIV3-Adj (2015/2016, 2016/2017)	Fluad in 2015/2016 and 2016/2017	2016/2017: A/California/7/2009(H1N1)-like, A/Hong Kong/4801/2014(H3N2)-like virus, B/Brisbane/60/2008(B/Victoria)-like virus. 2017/2018: A/Michigan/45/2015(H1N1)-like virus, A/Hong Kong/4801/2014(H3N2)-like virus, /Brisbane/60/2008(B/Victoria)-like virus	
			Tx3	IIV3-SD (2015/2016) + IIV3-HD (2016/2017)	Fluvirin SD in 2015/2016 and Fluzone HD in 2016/2017	2016/2017: A/California/7/2009(H1N1)-like, A/Hong Kong/4801/2014(H3N2)-like virus, B/Brisbane/60/2008(B/Victoria)-like virus. 2017/2018: A/Michigan/45/2015(H1N1)-like virus, A/Hong Kong/4801/2014(H3N2)-like virus, /Brisbane/60/2008(B/Victoria)-like virus	
			Tx4	IIV3-SD (2015/2016) + IIV3-Adj (2016/2017)	Fluvirin SD in 2015/2016 and Fluad, adjuvanted in 2016/2017	2016/2017: A/California/7/2009(H1N1)-like, A/Hong Kong/4801/2014(H3N2)-like virus, B/Brisbane/60/2008(B/Victoria)-like virus. 2017/2018:	

Author, Year	Setting	Influenza season	Tx	Vaccine type	Vaccine name	Vaccine strain	Circulating strain
						A/Michigan/45/2015(H1N1)-like virus, A/Hong Kong/4801/2014(H3N2)-like virus, /Brisbane/60/2008(B/Victoria)-like virus	
Trial registry, 2021[46]	Community	N 2020/2021	Tx1	IIV4-HD	Quadrivalent inactivated influenza vaccine HD	A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1), A/Hong Kong/2671/2019 IVR-208 (H3N2), B/Washington/02/2019 wt, B/Phuket/3073/2013 wt	NR
			Tx2	IIV4-SD	Quadrivalent inactivated influenza vaccine SD	A/(H1N1)-like strain, A/(H3N2)-like strain, B/(Victoria lineage)-like strain, B/(Yamagata lineage)-like strain	

Note: The term "-Other" in the vaccine name indicates that there are varying dosages available for different strains. As such, it is not categorized as standard dose nor high dose as per guidelines.
Abbreviations- NR: Not reported; N: Northern hemisphere; S: Southern hemisphere; IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; CC: Cell-cultured; RIV: Recombinant influenza vaccine; LAIV: Live attenuated influenza vaccine

Appendix 6: Antigenic characterization of viral strains for studies reporting laboratory-confirmed influenza

Author, year	Vaccine type	Vaccine composition	Type of laboratory-confirmed influenza used in the analysis	Circulating strains	Antigenic characterization as per author	Classification of laboratory-confirmed influenza viral strains as being matched	Classification of laboratory-confirmed influenza viral strains as being mismatched
Rudenko, 2001[6]	IIV3-SD	LAIV: A/Leningrad/134/17/57 (H3N2) or A/Texas/36/91(H1N1), A/Nanchang/933/95 (H3N2), B/Harbin/07/94 (Yamagata) and B/Ann Arbor/1/86 (Victoria); TIV: A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), B/Harbin/07/94 (Yamagata)	Culture or HI assay (secondary analysis)	Viral isolates similar to A/Texas/36/91 (H1N1), or B/Harbin/07/94	Typed by HI (cut-off: fourfold rise) to vaccine strains	A/Texas/36/91 (H1N1), B/Harbin/07/94 (Yamagata) (reported as matched)	NA
Wongsurakiat, 2004[7]	IIV3-SD	A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), and B/Harbin/ 07/94	HI test	A/Sydney/5/97 (H3N2)	Typed by HI (cut-off: fourfold rise) to vaccine strains	A/Sydney/5/97 (H3N2) (closely related to the influenza A/Nanchang/933/96 (H3N2)) (reported as matched)	NA
Keitel, 2010[10]	IIV3-SD, RIV3	IIV3-SD: A/Wisconsin (H3N2); A/New Caledonia (H1N1) and B/Malaysia; RIV3: A/Wisconsin (H3N2); A/New Caledonia (H1N1) and B/Ohio	Culture	A/New Caledonia/20/99 (H1N1) (From CDC)	Typed by HI (cut-off: fourfold rise) to vaccine strains	A/New Caledonia/20/99 (Classified as matched)	NA
DiazGranados, 2013[11]	IIV3	A/Brisbane/59/07 (H1N1), A/Uruguay/716/2007 X-175C (H3N2), and B/Brisbane/60/2008 strains	PCR	A/California/7/2009 (H1N1)	Seroprotection was considered as a post-vaccination HAI titer ≥1:40	NA	A/California/7/2009 (H1N1) (reported as genetically or antigenically distant)
DiazGranados, 2014[16]	IIV3	2011/2012: A/California/ 7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008; 2012/2013: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), B/Texas/6/2011 (B/Wisconsin/1/2010-like virus)	Culture or PCR assay or both	2011/2012 and 2012/2013: A/H3N2 (From CDC)	Typed by HI (cut-off: fourfold rise) to vaccine strains (from appendix)	2011/2012: A/Perth/16/2009-like (Reported as matched)	2012/2013: A/Victoria/361/2011 (Reported as mismatch)

Author, year	Vaccine type	Vaccine composition	Type of laboratory-confirmed influenza used in the analysis	Circulating strains	Antigenic characterization as per author	Classification of laboratory-confirmed influenza viral strains as being matched	Classification of laboratory-confirmed influenza viral strains as being mismatched
Dunkle, 2017[20]	RIV4, IIV4	A/California/ 7/2009 (H1N1)-like, A/Texas/50/2012 (H3N2), B/ Massachusetts/2/2012, and B/Brisbane/60/2008	RT-PCR assay and culture	influenza A subtype H3N2 viruses	Antigenic characterization not actively performed; based on predominant epidemic viruses or HAI titers ≥40	NA	A/Switzerland/971529 3/2013 (Classified as mismatched)
Loeb, 2020[24]	IIV3	2014/2015: A/Texas/50/2012 (H3N2), A/California/7/2009 (H1N1), and B/Massachusetts/2/2012 2015/2016: A/Switzerland/9715292-2013, A/California/7/2009 (H1N1), and B/Phuket/3073/2013 2016/2017: A/Hong Kong/4801-2014 (H3N2), A/California/7/2009 NYNC X-179A (H1N1), and B/Brisbane/60/2008 2017/2018: A/HongKong/4801/2014 (H3N2), A/Michigan/45/2015 (H1N1), and B/Brisbane/60/2008	PCR	2014/2015: A/H3N2; 2015/2016: A/H1N1pdm09; 2016/2017: A/H3N2; 2017/2018: A/H3N2	Typed by HI (cut-off: fourfold rise) to vaccine strains	2015/2016: A/California/7/2009 (Classified as matched) 2016/2017: A/Hong Kong/4801/2014 (Classified as matched) 2017/2018: A/Hong Kong/4801/2014 (the A(H3N2) (Classified as matched)	2014/2015: A/Texas/50/2012-like (Classified as mismatched)
Belongia, 2020[25]	HD-IIV3, aIIV3, RIV4	The A(H3N2) recommended vaccine component was identical in 2016–17 and 2017–18: A/Hong Kong/4801/2014–like (clade 3C.2a)	RT-PCR	A/Singapore/INFIMH-16–0019/2016 and A/Kentucky/29/2017 and A/Kansas/14/2017 (KS14)	Typed by HI (cut-off: fourfold rise) to vaccine strains	Circulating A(H3N2) viruses were antigenically similar to the cell-grown vaccine reference virus. (reported as matched)	NA
Teh, 2021[30]	IIV3, IIV4	TIV: A/Michigan/45/2015 (H1N1)pdm09–like virus, A/Switzerland/8060/2017 (H3N2)–like virus and B/ Phuket/3073/2013-like virus (Yamagata lineage) QIV: A/Michigan/45/2015 (H1N1)pdm09–	PCR	A(H3N2)	Typed by HI (cut-off: fourfold rise) to vaccine strains	A(H1N1)pdm09 viruses and viruses from both influenza B lineages (Classified as matched)	NA

Author, year	Vaccine type	Vaccine composition	Type of laboratory-confirmed influenza used in the analysis	Circulating strains	Antigenic characterization as per author	Classification of laboratory-confirmed influenza viral strains as being matched	Classification of laboratory-confirmed influenza viral strains as being mismatched
		like virus, A/Switzerland/8060/2017 (H3N2)–like virus, B/ Phuket/3073/2013-like virus (Yamagata lineage) and B/Colorado/06/2017-like virus (Victoria lineage)					
McLean, 2021[45]	IIV3-HD, IIV3-SD, IIV3-Adj	2016/2017 A/California/7/2009(H1N1)-like, A/Hong Kong/4801/2014(H3N2)-like, and B/Brisbane/60/2008(B/Victoria)-like viruses 2017/2018 A/Michigan/45/2015(H1N1)-like virus, A/Hong Kong/4801/2014(H3N2)-like, and B/Brisbane/60/2008(B/Victoria)-like viruses	RT-PCR	A/H3N2; B/Yamagata-lineage	Typed by HI (cut-off: fourfold rise) to vaccine strains	NA	2016/2017 and 2017 and 2018 (reported as mismatch)

*The process of characterizing matched and mismatched vaccine strains involved two steps. In Step 1, viral strains from laboratory-confirmed influenza cases within the included RCTs were characterized using HI assays and reference vaccine strains. Strains were considered matched if they displayed antigenic similarity to the vaccine strain. In Step 2, when antigenic data was lacking, surveillance data from sources such as WHO and CDC were used to identify prevalent strains during the trial period. For multiple years, if there was a clear prevalence of matched over mismatched (or vice versa) - for instance a 3 year long study in which 1 year was mismatched and 2 years were matched, the study was characterized as matched. If a study where year 1 was mismatched and year 2 was matched, we characterized it as matched and mismatched in two separate analyses. When the matched or mismatched strains were presented in the study by the authors, they are listed as 'reported'. When the matched or mismatched strains were determined from surveillance data sources they are listed as 'classified'.

Abbreviations- NA: Not applicable; IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; Adj: Adjuvanted; RIV: Recombinant influenza vaccine; LAIV: Live attenuated influenza vaccine; HI: Hemagglutination-inhibition; PCR: Polymerase chain reaction; RT-PCR: Reverse transcription polymerase chain reaction; CDC: Centers for disease control and prevention

Appendix 7: Antigenic characterization of viral strains for studies reporting influenza-like illness

Author, year	Vaccine type	Vaccine composition	Influenza like illness definition	Circulating strains	Classification of influenza viral strains as being matched	Classification of viral strains as being mismatched
Wongsurakiat, 2004[7]	IIV3-SD	A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), and B/Harbin/ 07/94	Defined when the patients had symptoms of generalized aches, fever, and headache with or without upper respiratory tract symptoms.	A/Sydney/5/97 (H3N2)	A/Sydney/5/97 (H3N2) (closely related to the influenza A/Nanchang/933/96 (H3N2)) (reported as matched)	NA
Allsup, 2004[8]	IIV3	A/Beijing/262/95(H1N1), A/Sydney/5/97 (H3N2) and B/Beijing/184/93	Defined as an illness of sudden onset with features of cough, feverishness, prostration, myalgia and widespread aches and pains.	A/H3N2	A (H3N2) (Reported as match)	NA
Keitel, 2010[10]	IIV3-SD, RIV3	IIV3-SD: A/Wisconsin (H3N2); A/New Caledonia (H1N1) and B/Malaysia; RIV3: A/Wisconsin (H3N2); A/New Caledonia (H1N1) and B/Ohio	Subject met CDC-ILI definition (fever with cough and/or sore throat) and/or if the subject had sought medical care at another location (medically attended acute respiratory illness, or MAARI)	A/New Caledonia/20/99 (H1N1) (From CDC)	A/New Caledonia/20/99 (Classified as matched)	NA
DiazGranados, 2013[11]	IIV3	A/Brisbane/59/07 (H1N1), A/Uruguay/716/2007 X-175C (H3N2), and B/Brisbane/60/2008 strains	Defined as a new onset (or exacerbation of a pre-existing condition) of at least one of the following systemic symptoms: temperature >37.2 ◦C (>99.0 ◦F), feverishness (feeling of warmth), chills, tiredness, headaches or myalgia; and at least one of the following respiratory symptoms: nasal congestion or rhinorhea, sore throat, cough, sputum production, wheezing, chest tightness, shortness of breath, or chest pain with breathing.	A/California/7/2009 (H1N1)	NA	A/California/7/2009 (H1N1) (reported as genetically or antigenically distant)
Frey, 2014[15]	IIV3	A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008	Defined as temperature of ≥37.2 ◦C or feverishness and at least two of the following symptoms: headache, myalgia, cough, or sore throat	A/H3N2 and A/H1N1	A/California/7/2009-like and A/Perth/16/2009-like (Classified as matched)	NA
DiazGranados, 2014[16]	IIV3	2011/2012: A/California/ 7/2009 (H1N1), A/Victoria/210/2009 (H3N2) and B/Brisbane/60/2008; 2012/2013:	Defined as a respiratory illness with sore throat, cough, sputum production, wheezing, or difficulty breathing, concurrent with one or more of the following: temperature above 37.2°C, chills, tiredness, headaches, or myalgia.	2011/2012 and 2012/2013: A/H3N2 (From CDC)	2011/2012: A/Perth/16/2009-like (Reported as matched)	2012/2013: A/Victoria/361/2011 (Reported as mismatch)

		A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2) and B/Texas/6/2011 (B/Wisconsin/1/2010-like virus)				
Dunkle, 2017[20]	RIV4, IIV4	A/California/ 7/2009 (H1N1)-like, A/Texas/50/2012 (H3N2), B/ Massachusetts/2/2012, and B/Brisbane/60/2008	Defined in the protocol as at least one symptom in both the respiratory and systemic illness categories, regardless of severity.	influenza A subtype H3N2 viruses	NA	A/Switzerland/9715293/2013 (Classified as mismatched)
Teh, 2021[30]	IIV3, IIV4	TIV: A/Michigan/45/2015 (H1N1)pdm09–like virus, A/Switzerland/8060/2017 (H3N2)–like virus and B/ Phuket/3073/2013-like virus (Yamagata lineage) QIV: A/Michigan/45/2015 (H1N1)pdm09–like virus, A/Switzerland/8060/2017 (H3N2)–like virus, B/ Phuket/3073/2013-like virus (Yamagata lineage) and B/Colorado/06/2017-like virus (Victoria lineage)	Defined by the presence of fever (≥38°C) and at least 1 respiratory symptom.	A(H3N2)	A(H1N1)pdm09 viruses and viruses from both influenza B lineages (Classified as matched)	NA

*The process of characterizing matched and mismatched vaccine strains involved two steps. In Step 1, viral strains from influenza cases within the included RCTs were characterized using HI assays and reference vaccine strains. Strains were considered matched if they displayed antigenic similarity to the vaccine strain. In Step 2, when antigenic data was lacking, surveillance data from sources such as WHO and CDC were used to identify prevalent strains during the trial period. For multiple years, if there was a clear prevalence of matched over mismatched (or vice versa) - for instance a 3 year long study in which 1 year was mismatched and 2 years were matched, the study was characterized as matched. If a study where year 1 was mismatched and year 2 was matched, we characterized it as matched and mismatched in two separate analyses. When the matched or mismatched strains were presented in the study by the authors, they are listed as 'reported'. When the matched or mismatched strains were determined from surveillance data sources they are listed as 'classified'.

Abbreviations- NA: Not applicable; IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; Adj: Adjuvanted; RIV: Recombinant influenza vaccine; LAIV: Live attenuated influenza vaccine; HI: Hemagglutination-inhibition; PCR: Polymerase chain reaction; RT-PCR: Reverse transcription polymerase chain reaction; CDC: Centers for disease control and prevention; MAARI: medically attended acute respiratory illness

Appendix 8: List of Outcomes and Relevant Studies in the Review but Not in the Quantitative Synthesis

Outcome Name	Number of Studies	Intervention comparison	Number of Participants	References of Studies Not Included in the Analysis	Reasons for Exclusion from the Analysis
ARI Cases	1	IIV3-HD: IIV3-SD	31,983	DiazGranados, 2014[16]	This intervention comparison was informed by a single study. No pairwise or network meta-analysis was conducted for this outcome.
LC-ARI Cases	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
ER Visit for ARI	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
ER Visit for LCI	1	IIV3-HD: IIV3-SD	31,983	DiazGranados, 2014[16]	This intervention comparison was informed by a single study. No pairwise or network meta-analysis was conducted for this outcome.
Hospitalization for Pneumonia due to ILI	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
Hospitalization for Pneumonia due to ARI	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
Hospitalization for Pneumonia due to LCI	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
Inpatient or Outpatient Hospital Visit	2	IIV3-HD: IIV3-SD	9158	DiazGranados, 2013[11]	These intervention comparisons were each informed by a single study. No pairwise or network meta-analysis was conducted for this outcome.
		The study compared one intervention of interest (IIV3-Adj) with different adjuvant dosages (bilaterial, bilateral + saline).	238	Otten, 2020[42]	
Hospitalization due to Cardiovascular Events	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.

LCI Related Death	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
LCI Related Healthcare Interactions	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
Number of Hospitalization events due to cardiovascular events	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
Vascular AE related to influenza	0	-	-	-	No studies were identified in this outcome. No pairwise or network meta-analysis was conducted for this outcome.
ER Visit (any cause)	2	IIV3-HD: IIV3-SD	53,008	Gravenstein, 2017[19]	These intervention comparisons were each informed by a single study. Number of studies did not exceed number of interventions. No pairwise or network meta-analysis was conducted for this outcome.
		IIV3-Adj: IIV3-SD	50,012	McConeghy, 2020[43]	
ER Visit for Pneumonia (any cause)	2	IIV3-HD: IIV3-SD	556	Gravenstein, 2017[19]	These intervention comparisons were each informed by a single study. Number of studies did not exceed number of interventions. No pairwise or network meta-analysis was conducted for this outcome.
		IIV3-SD: Placebo	41	Treanor, 1994[32]	
Number of participants with vascular AE	3	IIV4-Adj:Tdap	6761	Beran, 2021[28]	These intervention comparisons were each informed by a single study. IIV4-Adj:Tdap was disconnected from the network to be considered in the analysis. Number of studies in the connected network did not exceed number of interventions. No pairwise or network meta-analysis was conducted for this outcome.
		IIV3-Adj: IIV3-HD	757	Schmader, 2021[29]	
		IIV3-Adj: IIV3-SD	616	Scheifele, 2013[12]	
Hospitalization for LCI	4	RIV: IIV4-SD	9003	Dunkle, 2017[20]	These intervention comparisons were each informed by a single study. Number of studies did not exceed number of interventions. No pairwise or network meta-analysis was conducted for this outcome.
		IIV3-SD: Placebo	125	Wongsurakiat, 2004[7]	
		IIV3-HD: IIV4-SD	68	Teh, 2021[30]	
		IIV3-HD: IIV3-SD	31,983	DiazGranados, 2014[16]	
	1	IIV4-SD: IIV3-Adj	1016	Cowling, 2020[26]	

Inpatient Hospitalization (any cause)		IIV4-SD*:* IIV3-*HD*	1018		These intervention comparisons were each informed by a single study. Number of studies did not exceed number of interventions. No network meta-analysis was conducted for this outcome.
		IIV4-SD*:* RIV	843		
		IIV3-Adj*:* IIV3-HD	1018		
		IIV3-Adj*:* RIV	843		
		IIV3-HD: RIV	845		
ILI Cases	5	IIV4-Adj: Tdap	6761	Beran, 2021[28]	These intervention comparisons were each informed by a single study. IIV4-Adj:Tdap was disconnected from the network to be considered in the analysis. Number of studies in the connected network did not exceed number of interventions. No network meta-analysis was conducted for this outcome.
		RIV: IIV4-SD	9003	Dunkle, 2017[20]	
		RIV: IIV3-SD	870	Keitel, 2009[10]	
		IIV3-HD: IIV4-SD	68	Teh, 2021[30]	
		IIV3-Adj: IIV3-SD	6961	Frey, 2014[15]	
Hospitalization for ARI	1	IIV3-Adj: IIV3-SD	50,012	McConeghy, 2020[43]	This intervention comparison was informed by a single study. No network meta-analysis was conducted for this outcome.
LCI Cases	2	IIV4-Adj: Tdap	6761	Beran, 2021[28]	These intervention comparisons were each informed by a single study. IIV4-Adj:Tdap was disconnected from the network to be considered in the analysis. We did not consider different vaccine formulations in the pairwise and network meta-analyses.
		The study compared three interventions of interest (IIV3-HD, IIV3-Adj, IIV3-SD) in different combinations (Fluvirin in one year followed by Fluzone) and with repeated interventions (one vaccine in 2015/16 and one in 2016/17).	152	McLean, 2021[45]	
All Cause Mortality	14	IIV3-Adj: IIV3-SD	9150	McConeghy, 2020[43]	No ICC or adjusted effect estimates were reported to be considered in the analyses.
		IIV3-Adj: IIV3-SD	386	de Bruijn, 2006[33]	The study included 0 events in all arms and was excluded from the analyses.
		The studies compared one intervention of interest (IIV3-SD) with different platforms (egg-based, cell-cultured).	2669	Szymczakiewicz-Multanowska, 2009[34]; Szymczakiewicz-Multanowska, 2012[35]; Szymczakiewicz-Multanowska, 2012[36]	We did not consider differences in vaccine platforms in the pairwise and network meta-analyses.
		The study compared one intervention of interest (IIV3-Adj) with different adjuvant dosages (25%, 50%).	180	Della Cioppa, 2012[37]	These intervention comparisons were each informed by a single study. We did not consider differences in adjuvant dosages in the pairwise and network meta-analyses.
		The study compared two interventions of interest	270	Della Cioppa, 2014[38]	These intervention comparisons were each

		(IIV3-SD, IIV3-Adj) with different dosage of HA (cumulative 60 µg) and was incompatible with our classification of dosage.			informed by a single study. We did not consider dosage classifications outside of the standard and high dose categories in the network meta-analyses.
		The studies compared one intervention of interest (IIV3-SD) with different licensing names (Fluvirin, Agriflu).	2902	Novartis Vaccines and Diagnostics, 2016[40]	We did not consider differences in licensing names in our pairwise and network meta-analyses.
		The study compared one intervention of interest (IIV3-Adj) with different adjuvant dosages (bilaterial, bilateral + saline).	238	Otten, 2020[42]	These intervention comparisons were informed by a single study. We did not consider differences in adjuvant dosages in the pairwise and network meta-analyses.
		IIV3-HD: IIV3-SD	10	Trial registry, 2017[41]	The study included 0 events in all arms and was excluded from the analysis.
		The study compared two interventions of interest (IIV3-HD, IIV4-SD) with different route of administration (intramuscular or subcutaneous injection)	175	Sanchez, 2020[44]	These intervention comparisons were each informed by a single study. We did not consider differences in route of administration in the pairwise and network meta-analyses.
		The study compared three interventions of interest (IIV3-HD, IIV3-Adj, IIV3-SD) in different combinations (Fluvirin in one year followed by Fluzone) and with repeated interventions (one vaccine in 2015/16 and one in 2016/17).	152	McLean, 2021[45]	These intervention comparisons were each informed by a single study. We did not consider differences in vaccine combinations or repeated vaccinations in the pairwise and network meta-analyses.
		IIV4-HD: IIV4-SD	2100	Trial Registry, 2021[46]	The study included 0 events in all arms and was excluded from the analysis.
Influenza-related Mortality	2	IIV3-Adj: IIV3-SD	6961	Frey, 2014[15]	These intervention comparisons were informed by a single study. No pairwise or network meta-analysis was conducted for this outcome.
		IIV4-SD: IIV3-SD	1741	Treanor, 2017[21]	
Number of Vascular Adverse Events	5	RIV: IIV4-SD	9003	Dunkle, 2017[20]	This intervention comparison was informed by a single study. RIV:IIV4-SD was disconnected from the network to be considered in the analysis.
		The studies compared one intervention of interest (IIV3-SD) with different platforms (egg-based, cell-cultured).	2669	Szymczakiewicz-Multanowska, 2009[34]; Szymczakiewicz-Multanowska, 2012[35], Szymczakiewicz-Multanowska, 2012[36]	We did not consider differences in vaccine platforms in the pairwise and network meta-analyses.

		The studies compared one intervention of interest (IIV3-SD) with different licensing names (Fluvirin, Agriflu).	2902	Novartis Vaccines and Diagnostics, 2016[40]	We did not consider differences in licensing names in our pairwise and network meta-analyses.

Abbreviations- CI: confidence intervals, ARI: acute respiratory infections, LC-ARI: laboratory-confirmed acute respiratory infections, ER: emergency room, ILI: influenza-like illness, LCI: laboratory-confirmed influenza, AE: adverse events
*Within the scope of the current review, these studies and their reported outcomes but were excluded from the analyses for the following reasons: 1) coding was not possible as it would result in pooling of the arms with no resultant comparator, 2) data was reported but no counts were present, 3) the study was disconnected from the network, and 4) the study did not contribute to any pairwise meta-analyses.

Appendix 9: List of 41 included studies and 15 companion reports

('*' denotes the studies included in quantitative synthesis)

Unique studies (n = 41)

1. *Allsup S, Haycox A, Regan M, Gosney M. Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial. Vaccine. Dec 16 2004;23(5):639-645.

2. *Bart S, Cannon K, Herrington D, Mills R, Forleo-Neto E, Lindert K, Abdul Mateen A. Immunogenicity and safety of a cell culture-based quadrivalent influenza vaccine in adults: a phase III, double-blind, multicenter, randomized, non-inferiority study. Human vaccines & immunotherapeutics. 2016 Sep 1;12(9):2278-88.

3. *Belongia EA, Levine MZ, Olaiya O, Gross FL, King JP, Flannery B, McLean HQ. Clinical trial to assess immunogenicity of high-dose, adjuvanted, and recombinant influenza vaccines against cell-grown A (H3N2) viruses in adults 65 to 74 years, 2017–2018. Vaccine. 2020 Mar 30;38(15):3121-8.

4. *Beran J, Reynales H, Poder A, Charles YY, Pitisuttithum P, Yuan LL, Vermeulen W, Verhoeven C, Leav B, Zhang B, Sawlwin D. Prevention of influenza during mismatched seasons in older adults with an MF59-adjuvanted quadrivalent influenza vaccine: a randomised, controlled, multicentre, phase 3 efficacy study. The Lancet Infectious Diseases. 2021 Jul 1;21(7):1027-37.

5. *Chang LJ, Meng Y, Janosczyk H, Landolfi V, Talbot HK. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: A phase 3 randomized clinical trial. Vaccine. 2019;37(39):5825-34.

6. *Cowling BJ, Perera RAPM, Valkenburg SA, Leung NHL, Iuliano AD, Tam YH, et al. Comparative immunogenicity of several enhanced influenza vaccine options for older adults: A randomized, controlled trial. Clinical Infectious Diseases. 2020;71(7):1704-14.

7. *David W. Scheifele, Shelly A. McNeil, Brian J. Ward, Marc Dionne, Curtis Cooper, Brenda Coleman, Mark Loeb, Ethan Rubinstein, Janet McElhaney, Todd Hatchette, Yan Li, Emanuele Montomoli, Amy Schneeberg, Julie A. Bettinger, Scott A. Halperin & PHAC/CIHR Influenza Research Network (2013) Safety, immunogenicity, and tolerability of three influenza vaccines in older adults, Human Vaccines & Immunotherapeutics, 9:11, 2460-2473, DOI: 10.4161/ hv.25580

8. De Bruijn IA, Nauta J, Gerez L, Palache AM. The virosomal influenza vaccine Invivac®: Immunogenicity and tolerability compared to an adjuvanted influenza vaccine (Fluad®) in elderly subjects. Vaccine. 2006 Nov 10;24(44-46):6629-31.

9. Della Cioppa G, Nicolay U, Lindert K, Leroux-Roels G, Clement F, Castellino F, Galli C, Groth N, Levin Y, Del Giudice G. A dose-ranging study in older adults to compare the safety and immunogenicity profiles of MF59®-adjuvanted and non-adjuvanted seasonal influenza

vaccines following intradermal and intramuscular administration. Human vaccines & immunotherapeutics. 2014 Jun 4;10(6):1701-10.

10. Della Cioppa G, Nicolay U, Lindert K, Leroux-Roels G, Clement F, Castellino F, Galli G, Groth N, Del Giudice G. Superior immunogenicity of seasonal influenza vaccines containing full dose of MF59® adjuvant: results from a dose-finding clinical trial in older adults. Human vaccines & immunotherapeutics. 2012 Feb 1;8(2):216-27.

11. *DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009–2010 season. Vaccine. 2013 Jan 30;31(6):861-6.

12. *DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, Pollak R, Christoff J, Earl J, Landolfi V, Martin E. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. New England Journal of Medicine. 2014 Aug 14;371(7):635-45.

13. *Dunkle, Lisa M.; Izikson, Ruvim; Patriarca, Peter; Goldenthal, Karen L.; Muse, Derek; Callahan, Janice; Cox, Manon M. J.; P. S. C. Study Team. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. The New England journal of medicine. 2017; 376(25):2427-2436.

14. *Essink B, Fierro C, Rosen J, Figueroa AL, Zhang B, Verhoeven C, et al. Immunogenicity and safety of MF59-adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-adjuvanted trivalent influenza vaccines in older adults. Vaccine. 2020;38(2):242-50.

15. Euctr, C. Z. Clinical trial to evaluate safety and immune response to flu vaccines in individuals 50 years of age and older.

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Appendix 10: List of excluded studies post-data abstraction

Reference (Author, Year)	Reason for Exclusion from Review (Post-Hoc Exclusions)
Chuaychoo, 2016	Intradermal doses were excluded from the study as they lack authorization in Canada. The study was excluded as there was no other relevant comparator available.
Levin, 2016	Inflexal V is not authorized for use in Canada. Additionally, Intradermal doses were excluded from the study as they lack authorization in Canada. No other relevant comparator, thus study was excluded. Thus, both study arms were excluded. The study was excluded as there was no other relevant comparator available.
Govaert, 1994	QIV (Evans Medical Ltd, UK) does not appear to be a vaccine authorized for use in US/Canada. The study was excluded as there was no other relevant comparator available.
Gravenstein, 1994	TIV conjugated with diphtheria toxoid is not licensed in Canada. The study was excluded as there was no other relevant comparator available.
Pregliasco, 2001	Inflexal V (virosomal adjuvanted influenza vaccine) and Inflexal (whole virus vaccine) are not available in Canada. The study was excluded as there was no other relevant comparator available.
Chi, 2010	ID doses are excluded since not authorized in Canada. The study was excluded as there was no other relevant comparator available.
Forrest, 2011	IIV3 from Aventis Pasteur not authorized for use in Canada nor US. The study was excluded as there was no other relevant comparator available.
McElhaney, 2013	The study arm utilizing AS03 is excluded, since it is not licensed in Canada. The study was excluded as there was no other relevant comparator available.
Greenberg, 2013	The candidate or investigational vaccine, which has not yet obtained licensure, is not deemed eligible for inclusion in this review. The study was excluded as there was no other relevant comparator available.
Rumke, 2013	AS03 is not licensed for use in Canada. The study was excluded as there was no other relevant comparator available.
Hung, 2013	Intradermal doses were excluded from the study as they lack authorization in Canada. The study was excluded as there was no other relevant comparator available.
Couch, 2014	AS03-adjuvanted A(H1N1) pandemic vaccine (not investigational) was not licensed for use in Canada. The study was excluded as there was no other relevant comparator available.
Greenberg, 2017	The candidate or investigational vaccine, which has not yet obtained licensure, is not deemed eligible for inclusion in this review. The study was excluded as there was no other relevant comparator available.
Choi, 2017	Canada has not authorized SK Chemicals vaccines. Therefore, both treatment arms were excluded. Due to the lack of a relevant vaccine, the study was excluded.
van de Witte, 2018	The candidate or investigational vaccine, which has not yet obtained licensure, is not deemed eligible for inclusion in this review. The study was excluded as there was no other relevant comparator available.
Young, 2019	The comparison between bi-annual and annual vaccination was not deemed relevant.
Ward, 2020	Plant-derived influenza vaccine not authorized in Canada or US. The study was excluded as there was no other relevant comparator available.
Izikson, 2022	Pandemic vaccines are not considered for inclusion in this review. The study was excluded as there was no other relevant comparator available.

Appendix 11: Study characteristics

Author, Year	Country	Publication details	Study design	Single or multicenter	Number of centers in total	Influenza season with Hemisphere	Intervention vs. comparator	Outcomes
Studies included in quantitative and descriptive analysis (n = 26)								
Rudenko, 2001[6]	Russia	Journal Name: Elsevier Vaccine Publication Type: Journal article Funding Source (Type): NR Conflict of Interest Declared: NR	RCT	Multicenter	9	N 1996/1997	IIV3-SD vs. Placebo	LCI Cases
Wongsurakiat, 2004[7]	Thailand	Journal Name: Chest Journal Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: No	RCT	Single	1	N 1997/1998	IIV3-SD vs. Placebo	Hospitalization for LCI, ILI Cases, Outpatient Visit, LCI Cases, All Cause Death
Allsup, 2004[8]	UK	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: NR	RCT	Multicenter	20	N 1999/2000	IIV3-SD vs. Placebo	ILI Cases, Outpatient Visit, All Cause Death
Falsey, 2009[9]	USA	Journal Name: Journal of Infectious Diseases Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	30	N 2006/2007	IIV3-HD vs. IIV3-SD	Inpatient Hospitalization (any cause), All Cause Death, Number of Vascular Adverse Events
Keitel, 2010[10]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): NR Conflict of Interest Declared: NR	RCT	Multicenter	NR	N 2006/2007	RIV3 vs. IIV3-SD	ILI Cases, LCI Cases, All Cause Death
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**

DiazGranados 2013[11]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	99	N 2009/2010	IIV3-HD vs. IIV3-SD	Inpatient or Outpatient Hospital Visit, ER Visit for ILI, ILI Cases, Outpatient Visit, LCI Cases, All Cause Death, Number of Vascular Adverse Events
Scheifele, 2013[12]	Canada	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Public and industry Conflict of Interest Declared: Yes	RCT	Multicenter	8	N 2011/2012	IIV3-Adj vs. IIV3-SD	Number of Participants with Vascular Adverse Events, All Cause Death, Number of Vascular Adverse Events
Pepin, 2013[13]	France, Germany	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Unclear	RCT	Multicenter	18	N 2011/2012	IIV4-SD vs. IIV3-SD	All Cause Death
Tsang, 2014[14]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	31	N 2007/2008	IIV3-SD vs. IIV3-HD	Number of Vascular Adverse Events
Frey, 2014[15]	Colombia, Panama, Philippines, USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	38	N 2010/2011	IIV3-Adj vs. IIV3-SD	ILI Cases, All Cause Death, Number of Vascular Adverse Events
DiazGranados, 2014[16]	USA, Canada	Journal Name: The New England Journal of Medicine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	126	N 2011/2012 and N 2012/2013	IIV3-HD vs. IIV3-SD	ARI Cases, ER Visit for LCI, Hospitalization for LCI, ER Visit for ILI, Hospitalization for ILI, Inpatient Hospitalization (any cause), ILI Cases, Hospitalization for ARI, Outpatient Visit, LCI Cases, All Cause Death, Number of Vascular Adverse Events
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**

Nace, 2014[17]	USA	Journal Name: The Journal of Infectious Diseases Publication Type: Journal article Funding Source (Type): Public and Industry Conflict of Interest Declared: Yes	RCT	Multicenter	15	N 2011/2012 and N 2012/2013	IIV3-HD vs. IIV3-SD	All Cause Death
Bart, 2016[18]	USA	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	40	N 2013/2014	IIV3-CC-SD vs. IIV4-CC-SD	All Cause Death
Gravenstein, 2017[19]	USA	Journal Name: Lancet Respiratory Medicine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	Cluster RCT	Multicenter	823	N 2013/2014	IIV3-HD vs. IIV3-SD	ER Visit (any cause), ER Visit for Pneumonia (any cause), Hospitalization for ARI, All Cause Death
Dunkle, 2017[20]	USA	Journal Name: The New England Journal of Medicine Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Multicenter	40	N 2014/2015	RIV4 vs. IIV4-SD	Hospitalization for LCI, ILI Cases, LCI Cases, All Cause Death, Number of Vascular Adverse Events
Treanor, 2017[21]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	31	N 2014/2015	IIV4-SD vs. IIV3-SD	All Cause Death
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**
Gravenstein, 2018[22]	USA	Journal Name: Human Vaccines & Immunotherapeutics	Cluster RCT	Multicenter	39	N 2012/2013	IIV3-HD vs. IIV3-SD	Inpatient Hospitalization (any cause), All Cause Death

		Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes						
Chang, 2019[23]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	35	N 2017/2018	IIV4-HD vs. IIV3-HD	All Cause Death, Number of Vascular Adverse Events
Loeb, 2020[24]	USA, Canada	Journal Name: Open Forum Infectious Diseases Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Multicenter	2	N 2014/2015, N 2015/2016, N 2016/2017 and N 2017/2018	IIV3-SD vs. IIV3-HD	LCI Cases
Belongia, 2020[25]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Single	1	N 2017/2018	IIV3-HD vs. IIV3-Adj vs.RIV4	LCI Cases
Cowling, 2020[26]	China	Journal Name: Clinical Infectious Diseases Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Multicenter	NR	N 2017/2018	IIV4-SD vs. IIV3-Adj vs. IIV3-HD vs. RIV4	Inpatient Hospitalization (any cause)
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**
Essink, 2020[27]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	20	N 2017/2018	IIV4-Adj vs. IIV3-Adj	All Cause Death, Number of Vascular Adverse Events

Beran, 2021[28]	Bulgaria, Colombia, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Philippines, Poland, Romania, Thailand, and Turkey	Journal Name: Lancet Infectious Diseases Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	89	N 2016/2017 and S 2017	IIV4-Adj vs. Tdap	Number of Participants with Vascular Adverse Events, All Cause Death
Schmader, 2021[29]	USA	Journal Name: JAMA Network Open Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Multicenter	3	N 2017/2018 and N 2018/2019	IIV3-Adj vs IIV3-HD	Number of Participants with Vascular Adverse Events, All Cause Death
Teh, 2021[30]	Australia	Journal Name: Clinical Infectious Diseases Publication Type: Journal article Funding Source (Type): Public and Industry Conflict of Interest Declared: Yes	RCT	Single	1	S 2019	IIV3-HD vs. IIV4-SD	Hospitalization for LCI, ILI Cases, LCI Cases
Vardeny, 2021[31]	USA, Canada	Journal Name: Journal of the American Medical Association Publication Type: Journal article Funding Source (Type): Public & Industry Conflict of Interest Declared: Yes	RCT	Multicenter	157	N 2016/2017; N 2017/2018 and N 2018/2019	IIV3-HD vs.IIV4-SD	All Cause Death
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**
Studies included only in descriptive analysis (n= 15)								
Treanor, 1994[32]	USA	Journal Name: The Journal of Infectious Diseases Publication Type: Journal article Funding Source (Type): Public	RCT	Multicenter	2	NR	IIV3-SD + Placebo	ER Visit for Pneumonia (any cause)

		Conflict of Interest Declared: No						
de Bruijn, 2006[33]	Netherlands	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type):NR Conflict of Interest Declared: NR	RCT	NR	NR	N 2004/2005	IIV3-Adj vs. IIV3-SD	All Cause Death
Szymczakiewicz-Multanowska, 2009[34]	Poland	Journal Name: The Journal of Infectious Diseases Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	5	N 2004/2005	IIV3-SD vs. IIV3-SD-CC	All Cause Death, Number of Vascular Adverse Events
Szymczakiewicz-Multanowska, 2012[35]	Poland	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	5	N 2005/2006	IIV3-SD-CC vs. IIV3-SD	All Cause Death, Number of Vascular Adverse Events
Szymczakiewicz-Multanowska, 2012[36]	Poland	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	5	N 2007/2008	IIV3-SD-CC vs. IIV3-SD	All Cause Death, Number of Vascular Adverse Events
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**
Della Cioppa, 2012[37]	Poland, Belgium, Germany	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	6	N 2008/2009	IIV3-Adj vs. IIV3-Adj vs. IIV3-Adj vs IIV3-Adj	All Cause Death

Della Cioppa, 2014[38]	Germany, Poland, Belgium	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	6	N 2008/2009	IIV3-SD vs. IIV3-Other vs. IIV3-Adj vs. IIV3-Other-Adj	All Cause Death
Izikson, 2015[39]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Multicenter	NR	N 2012/2013	RIV3 vs. IIV3-SD	All Cause Death
Novartis Vaccines and Diagnostics, 2016[40]	Thailand, Philippines, South Africa, Czech Republic.	Journal Name: EU Clinical Trials Register Publication Type: Results from trial registry Funding Source (Type): Industry Conflict of Interest Declared: NR	RCT	Multicenter	24	NR	IIV3-SD vs. IIV3-SD	All Cause Death, Number of Vascular Adverse Events
Trial registry, 2017[41]	USA	Journal Name: ClinicalTrials.gov Publication Type: Results from trial registry Funding Source (Type): Public Conflict of Interest Declared: NR	RCT	NR	NR	N 2011	IIV3-SD vs. IIV3-HD	All Cause Death
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**
Otten, 2020[42]	Germany	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Single	1	N 2014/2015	IIV3-Adj vs. IIV3-Adj vs. IIV3-Other-Adj vs.IIV3-Other-Adj – bilateral vs. IIV3-Adj-bilataeral + saline vs. IIV3-Adj-bilateral + saline vs. IIV3-Adj-bilateral	All Cause Death, Inpatient or Outpatient Hospital Visit

McConeghy, 2020[43]	USA	Journal Name: Clinical Infectious Diseases Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	Cluster RCT	Multicenter	823	N 2016/2017	IIV3-Adj vs. IIV3-SD	ER Visit (any cause), Hospitalization for ARI
Sanchez, 2020[44]	Japan	Journal Name: Human Vaccines & Immunotherapeutics Publication Type: Journal article Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	2	N 2017/2018	IIV4-HD vs. IIV4-HD vs. IIV4-SD	All Cause Death
McLean, 2021[45]	USA	Journal Name: Vaccine Publication Type: Journal article Funding Source (Type): Public Conflict of Interest Declared: Yes	RCT	Single	1	N 2016/2017 and N 201 7/2018	IIV3-HD (2015/2016, 2016/2017) vs. IIV3-Adj (2015/2016, 2016/2017) vs. IIV3-SD (2015/2016) + IIV3-HD (2016/2017) vs. IIV3-SD (2015/2016) + IIV3-Adj (2016/2017)	All Cause Death, LCI Cases
Author, Year	**Country**	**Publication details**	**Study design**	**Single or multicenter**	**Number of centers in total**	**Influenza season with Hemisphere**	**Intervention vs. comparator**	**Outcomes**
Trial registry, 2021[46]	Japan	Journal Name: ClinicalTrials.gov Publication Type: Results from trial registry Funding Source (Type): Industry Conflict of Interest Declared: Yes	RCT	Multicenter	10	N 2020/2021	IIV4-SD vs. IIV4-HD	All Cause Death

Note: The term "-Other" in the vaccine name indicates that there are varying dosages available for different strains. As such, it is not categorized as standard dose nor high dose as per guidelines.

Abbreviations- NR: Not reported; N: Northern hemisphere; S: Southern hemisphere; IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; CC: Cell-cultured; RIV: Recombinant influenza vaccine; USA: United States of America; UK: United Kingdom; RCT: Randomized controlled trial; ARI: Acute respiratory infection; LC-ARI: Laboratory-confirmed acute respiratory infection; ER: Emergency room; LCI: Laboratory-confirmed influenza; ILI: Influenza-like illness; AE: Adverse event

Appendix 12: Participant characteristics

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
Studies included in quantitative and descriptive analysis (n = 26)											
Rudenko, 2001[6]	Nursing home	319	69.3	30.7	NR	72.5 (5.5)	NR	NR	NR	NR	NR
Wongsurakiat, 2004[7]	Clinic	125	5.6	94.4	NR	68.4 (7.5)	Chronic lung disease: 100%; Comorbid diseases (hypertension, coronary artery diseases, or diabetes): 32.8%	NR	NR	NR	NR
Allsup, 2004[8]	Community	729	46.8	53.2	NR	68.9 (NR)	NR	NR	NR	NR	NR
Falsey, 2009[9]	Community	3876	52.4	47.6	White (92%), Hispanic (4.4%), Black (2.7%), Asian (0.4%), American Indian or Alaskan Native (0.08%), Native Hawaiian or Pacific Islander (0.05%), Other (0.3%)	73.0 (5.6)	NR	81.9% had receipt of vaccination in 2005	NR	NR	NR
Keitel, 2010[10]	Community	870	53.2	46.8	White (98%); Black (1%); Hispanic (0.1%); Asian (0.2%); Other (0.6%).	72.9 (6.1)	NR	83.1% vaccinated in the previous season	NR	NR	NR
DiazGranados, 2013[11]	Clinic	9172	53.7	46.3	Asian (0.7%); Black:	72.8 (6)	Cardiac disorders: 24.2%; Eye disorders: 50.3%;	88.7% had a previous history of seasonal	NR	NR	NR

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
					(4.9%); Caucasian: (85%); Hispanic (8.7%); American Indian or Alaska native: (0.3%); Native Hawaiian or other Pacific Islander: (0.07%); Other: (0.25%)		Immune system disorders: 44.3%; Metabolic disorders: 62.5%; Musculoskeletal disorders: 54.8%; Neoplasms: 21.3%; Psychiatric disorders: 24.2%; Vascular disorders: 65.1%	influenza vaccination			
Scheifele, 2013[12]	Community or assisted living facility	616	59.0	41.0	White/ Caucasian (95%)	73.8 (NR)	Well with co-morbidity: 19%	86% vaccinated with IIV3 in the past 2 years	4%	NR	NR
Pepin, 2013[13]	Community	785	54	46	NR	NR**	NR	NR	NR	NR	NR
Tsang, 2014[14]	NR	1912	56.0	44.0	Asian (0.6%), Black (2.5%), Caucasian (93.9%), Hispanic (2.4%), Other (1%)	NR (NR)	NR	86.5% vaccinated in the past year	NR	NR	NR
Frey, 2014[15]	NR	7104	65.1	34.9	Asian (53%), Black (1%), Caucasian (28%), Hispanic (18%), Native American/Hawaii (<1%), Other (<1%)	71.9 (5.3)	NR	NR	NR	NR	NR
DiazGranados, 2014[16]	Research centers	31989	56.6	43.4	White (94.6%), Asian (0.7%), Black (4%), Hispanic	73.3 (5.8)	Diabetes: 22.6%; Hypothyroidism: 20.1%;	73.6	NR	NR	NR

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
					(6.1%), Other (0.6%)						
Nace, 2014[17]	Long term care home	205	68.0	32.0	White, Non-Hispanic (99%) Other (1%)	87.0 (6)	NR	NR	100%	The standard ADL and IADL assessed functional status using 7 items each, scored from 0 to 2. The maximum score is 14 per scale, with higher scores indicating better function. Gait speed is measured through a timed 4-meter walk, with scores ≥1 m/s considered normal and scores ≤0.8 m/s indicating significant frailty and higher risk of mortality.	Gait speed, m/s, mean (SD) = 0.7 (0.3); ADL score, mean (SD) = 11.4 (3.7); IADL score, mean (SD) = 7.9 (4.2)
Bart, 2016[18]	Community	1340	NR	NR	NR	NR (NR)	NR	NR	NR	NR	NR
Gravenstein, 2017[19]	Nursing home	53008	72.2	27.8	African American (14.8%) White (75.5%), Hispanic (5.1%)	83.6 (8.5)	Heart failure: 20.5%; Stroke/cerebrov-ascular accident: 20.0%; Hypertension: 79%; Diabetes mellitus: 34.4%: Chronic lung disease: 20.2%; Dementias: 64.0%	NR	NR	NR	NR
Dunkle, 2017[20]	Outpatient centers	9003	58.5	41.5	Black (17.6%), White (80.3%), Other	64.1 (NA)	Cardiovascular disease: 30.4%; Condition requiring statin	NR	NR	NR	NR

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
					(2.1%); Hispanic ethnic group (4.9%), non-Hispanic (95.1%), Other (<1%)		lipid-lowering therapy: 27.7%				
Treanor, 2017[21]	NR	1743	NR	NR	NR	NR (NR)	NR	NR	NR	NR	NR
Gravenstein, 2018[22]	Nursing Homes	2957	74.6	25.3	African American, (12.4%); White, (79.2%); Hispanic, (5.9%); Other (includes: American Indians, Alaskan Natives, Native Americans, Pacific Islanders, and Asians) (2.2%).	84.0 (8.6)	Hypertension: 74.8%; Diabetes: 29.3%; Chronic lung disease: 19.7%;	NR	NR	NR	NR
Chang, 2019[23]	Community	2670	54.9	39.9	American Indian or Alaska Native (0.6%), Asian (0.7%), Black or African American (7.2%), White (90.7%), Multiple (0.4%), Not reported (0.4%)	73.0 (5.6)	NR	78.2% vaccinated in the past year	NR	NR	NR
Loeb, 2020[24]	Community	612	67.0	33.0	NR	77.0 (7.5)	NR	100% vaccinated in the previous	9%	FI was determined based on 40	Robust: 50%; Pre-frail:

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
								influenza season		validated items related to influenza outcomes. Participants were classified as frail (FI > 0.21), pre-frail (0.1 < FI ≤ 0.21), or robust (FI ≤ 0.1) using established thresholds.	40.8%; Frail: 8.8%; Unknown: 0.3%
Belongia, 2020[25]	Clinic	89	56.2	43.8	White (100%)	70.0 (2.5)	NR	NR	NR	NR	NR
Cowling, 2020[26]	Community	1861	60.8	39.2	NR	71.6 (NR)	NR	66.5% vaccinated in the 2016/2017 season	NR	NR	NR
Essink, 2020[27]	NR	1778	56.6	43.4	White (91.6%), Black (7%), Native Hawaiian or Pacific Islander (0.7%), Native American (0.1%), Other (0.2%)	72.5 (5.5)	NR	86.7% vaccinated in the past 5 years	NR	NR	NR
Beran, 2021[28]	Community	6790	61.8	38.2	American Indian or Alaska Native, (1.8%); Asian, (33.8%); Black or African American, (0.01%); White, (48.2%); Other(16.2%)	71·9 (5.4)	NR	29.6% vaccinated in the past 5 year	NR	NR	NR

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
Schmader, 2021[29]	Community	757	55.5	44.5	White (77.8%), Black (17%), Asian (1.2%), Other (4%)	76.5 (4.6)	NR	NR	NR	NR	NR
Teh, 2021[30]	Community	68	32.0	68.0	NR	60.0 (11.1)	Myeloma: 74%; Lymphoma: 22%	NR	NR	NR	NR
Vardeny, 2021[31]	NR	5260	28.3	71.7	White (78%), Black (14.9%), Asian (2.9%), First Nations/ American Indian (0.9%), Other (3%)	65.5 (12.6)	Diabetes: 37.2%; Chronic kidney disease: 30.3%; Myocardial infarction: 14.2%; Ischemic stroke: 8.3%; Peripheral artery disease: 4.4%	NR	NR	NR	NR
Studies included only in descriptive analysis (n= 15)											
Treanor, 1994[32]	Community	41	65.4	34.6	NR	NR (NR)	Chronic pulmonary conditions: 18%;	NR	NR	NR	NR
de Bruijn, 2006[33]	Community	386	NR	NR	NR	70.1 (NR)	NR	NR	NR	NR	NR
Szymczakiewicz-Multanowska, 2009[34]	Community	1354	56.4	43.6	NR	69.0 (5.7)	NR	59% had a previous history of seasonal influenza vaccination	NR	NR	NR
Szymczakiewicz-Multanowska, 2012[35]	Community	1168	56.6	43.4	Caucasian (100%)	69.6 (5.7)	NR	NR	NR	NR	NR
Szymczakiewicz-Multanowska, 2012[36]	Community	147	51.1	42.9	Caucasian (100%)	71.5 (5.5)	NR	NR	NR	NR	NR
Della Cioppa, 2012[37]	NR	180	46.1	53.9	NR	69.2 (4.1)	NR	NR	NR	NR	NR
Della Cioppa, 2014[38]	NR	270	53.0	47.0	Caucasian (99.3%), Asian (0.7%)	69.0 (3.8)	NR	NR	NR	NR	NR
Izikson, 2015[39]	NR	1295	54.0	46.0	White (91%), Black/African American: (8%), Asian	71.5 (5.1)	NR	NR	NR	NR	NR

Author, Year	Setting	Overall sample size	% Female	% Male	Race	Mean age, years (SD)	Most Common Comorbidities*	Influenza Vaccination history	Frailty (%)	Frailty scale	Frailty score
					(1%), American Indian/Alaska a Native (<1%), Native Hawaiian/ Other Pacific Islander (<1%), Multiple (<1%)						
Novartis Vaccines and Diagnostics, 2016[40]	NR	2902	63.3	36.7	NR	64.2 (8.9)	NR	NR	NR	NR	NR
Trial registry, 2017[41]	NR	10	60	40	White/Not Hispanic or Latino (100%)	70.1 (3.8)	NR	NR	NR	NR	NR
Otten, 2020[42]	Community	196	46.7	53.3	White, non-Hispanic (100%)	70.5 (NR)	NR	NR	NR	NR	NR
McConeghy, 2020[43]	Nursing home	50012	69.8	30.2	White (72.3%), Black (16.7%), Hispanic (6.2%)	78.7 (5.3)	Dementia: 61.9%; Congestive heart failure: 19.7%; Chronic respiratory illness: 21.8%	NR	NR	NR	NR
Sanchez, 2020[44]	Clinic	175	45.7	54.3	Asian (100%)	70.3 (3.6)	NR	NR	NR	NR	NR
McLean, 2021[45]	Community	152	53.3	46.7	White (100%)	69.8 (2.7)	NR	NR	NR	NR	NR
Trial registry, 2021[46]	Community	2100	47.1	52.9	Asian (100%)	68.3 (4.9)	NR	NR	NR	NR	NR

**For brevity, the most common comorbidities are listed in the summary table.*
** Enrollment in Pepin, 2013 was stratified by age at each site into adults 18–60 and >60 years of age. However, only data from the >60 age group was included in our review.
Abbreviations- LAIV: live attenuated influenza vaccine; FI: frailty index; ADL: activities of daily living; IADL: instrumental activities of daily living; m/s: meters/second; NR: not reported; SD: standard deviation

Appendix 13: Intervention characteristics

Author, Year	Setting	Tx	Vaccine Type	Platform	Dosage of HA/ strain	Adjuvant	Administration	Frequency
Studies included in quantitative and descriptive analysis (n = 26)								
Rudenko, 2001[6]	Nursing home	Tx1	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	Placebo	NA	NA	NA	Intramuscular; intranasal	Two doses
Wongsurakiat, 2004[7]	Clinic	Tx1	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular	Two doses
		Tx2	Placebo	NA	NA	NA	Intramuscular	Two doses
Allsup, 2004[8]	Community	Tx1	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	Placebo	NA	NA	NA	Intramuscular	NA
Falsey, 2009[9]	Community	Tx1	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Keitel, 2010[10]	Community	Tx1	RIV3	Egg-based	45 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
DiazGranados, 2013[11]	Clinic	Tx1	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-sD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Scheifele, 2013[12]	Community or assisted living facility	Tx1	IIV3-Adj	Egg-based	15 µg/ strain	MF59	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Pepin, 2013[13]	Community	Tx1	IIV4-SD	NR	15 µg/ strain	NA	Intramuscular injection into deltoid muscle or deep SC tissue	Single dose
		Tx2	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular injection into deltoid muscle or SC tissue	Single dose
Tsang, 2014[14]	NR	Tx1	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-HD	NR	60 µg/ strain	NA	Intramuscular	Single dose
Frey, 2014[15]	NR	Tx1	IIV3-Adj	Egg-based	15 µg/ strain	MF59 formulated with 9.75 mg squalene, 1.18 mg polysorbate	Intramuscular	Single dose

Author, Year	Setting	Tx	Vaccine Type	Platform	Dosage of HA/ strain	Adjuvant	Administration	Frequency
						80, 1.18 mg sorbitan trioleate, 0.66 mg sodium citrate dihydrate, and 0.04 mg citric acid monohydrate.		
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
DiazGranados, 2014[16]	Research centers	Tx1	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Nace, 2014[17]	Long term care home	Tx1	IIV3-HD	NR	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Bart, 2016[18]	Community	Tx1	IIV3-CC-SD	Cell-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV4-CC-SD	Cell-based	15 µg/ strain	NA	Intramuscular	Single dose
Gravenstein, 2017[19]	Nursing home	Tx1	IIV3-HD	NR	60 µg/ strain	NA	NR	Single dose
		Tx2	IIV3-SD	NR	15 µg/ strain	NA	NR	Single dose
Dunkle, 2017[20]	Outpatient centers	Tx1	RIV4	Recombinant	45 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV4-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Treanor, 2017[21]	NR	Tx1	IIV4-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Gravenstein, 2018[22]	Nursing homes	Tx1	IIV3-HD	NR	60 µg/ strain	NA	NR	NR
		Tx2	IIV3-SD	NR	15 µg/ strain	NA	NR	NR
Chang, 2019[23]	Community	Tx1	IIV4-HD	NR	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-HD	NR	60 µg/ strain	NA	Intramuscular	Single dose
Loeb, 2020[24]	Community	Tx1	IIV3-SD	NR	15 µg/ strain	NA	NR	NR
		Tx2	IIV3-HD	NR	60 µg/ strain	NA	NR	NR
Belongia, 2020[25]	Clinic	Tx1	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-Adj	Egg-based	15 µg/ strain	MF59	Intramuscular	Single dose
		Tx3	RIV4	Recombinant	45 µg/ strain	NA	Intramuscular	Single dose
	Community	Tx1	IIV4-SD	NR	15 µg/ strain	NA	Intramuscular	Single dose

Author, Year	Setting	Tx	Vaccine Type	Platform	Dosage of HA/ strain	Adjuvant	Administration	Frequency
Cowling, 2020[26]		Tx2	IIV3-Adj	NR	15 µg/ strain	MF59, a squalene-based emulsion	Intramuscular	Single dose
		Tx3	IIV3-HD	NR	60 µg/ strain	NA	Intramuscular	Single dose
		Tx4	RIV4	Recombinant	45 µg/ strain	NA	Intramuscular	Single dose
Essink, 2020[27]	NR	Tx1	IIV4-Adj	Egg-based	15 µg/ strain	MF59, squalene based	Intramuscular	Single dose
		Tx2	IIV3-Adj	Egg-based	15 µg/ strain	MF59, squalene based	Intramuscular	Single dose
Beran, 2021[28]	Community	Tx1	IIV4-Adj	Egg-based	15 µg/ strain	MF59	Intramuscular	Single dose
		Tx2	Tdap	NA	NA	NA	Intramuscular	Single dose
Schmader, 2021[29]	Community	Tx1	IIV3-Adj	Egg-based	15 µg/ strain	MF59 squalane adjuvant	Intramuscular	Single dose
		Tx2	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
Teh, 2021[30]	Community	Tx1	IIV3-HD	Egg-based	60 µg/ strain	NA	NR	Single dose
		Tx2	IIV4-SD	Egg-based	15 µg/ strain	NA	NR	Single dose
Vardeny, 2021[31]	NR	Tx1	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV4-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Studies included only in descriptive analysis (n= 15)								
Treanor, 1994[32]	Community	Tx1	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2Tx2	Placebo	NA	NA	NA	Intramuscular, intranasal	Single dose
de Bruijn, 2006[33]	Community	Tx1	IIV3-Adj	NR	15 µg/ strain	Yes - but adjuvant is not described in this report	Intramuscular	Single dose
		Tx2	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular	Single dose
Szymczakiewicz-Multanowska, 2009[34]	Community	Tx1	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD-CC	Cell-based	15 µg/ strain	NA	Intramuscular	Single dose
Szymczakiewicz-Multanowska, 2012 (a)[35]	Community	Tx1	IIV3-SD-CC	Cell-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose

Author, Year	Setting	Tx	Vaccine Type	Platform	Dosage of HA/ strain	Adjuvant	Administration	Frequency
Szymczakiewicz-Multanowska, 2012 (b)[36]	Community	Tx1	IIV3-SD-CC	Cell-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Della Cioppa, 2012[37]	NR	Tx1	IIV3-Adj	NR	15 µg/ strain	MF59 (25%)	Intramuscular	Single dose
		Tx2	IIV3-Other-Adj	NR	15 µg/ A/H1N1 strain; 30 µg/ H3N2 strain; 15 µg/ B strain (total HA is 60µg)	MF59 (25%)	Intramuscular	Single dose
		Tx3	IIV3-Adj	NR	15 µg/ strain	MF59 (50%)	Intramuscular	Single dose
		Tx4	IIV3-Other-Adj	NR	15 µg A/H1N1 strain; 30 µg/ H3N2 strain; 15 µg HA for B strain (total HA is 60µg)	MF59 (50%)	Intramuscular	Single dose
Della Cioppa, 2014[38]	NR	Tx1	IIV3-SD	NR	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-Other	NR	15 µg/ A/H1N1 strain; 30 µg/ H3N2 strain; 15 µg/ B strain (total HA is 60 µg)	NA	Intramuscular	Single dose
		Tx3	IIV3-Adj	NR	15 µg/ strain	MF59 - A standard/full dose (100%)	Intramuscular	Single dose
		Tx4	IIV3-Other-Adj	NR	15 µg/ A/H1N1 strain; 30 µg/ H3N2 strain; 15 µg/ for B strain (total HA is 60 µg)	MF59 - A standard/full dose (100%)	Intramuscular	Single dose
Izikson, 2015[39]	NR	Tx1	RIV3	Recombinant	45 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
Novartis Vaccines and Diagnostics, 2016[40]	NR	Tx1	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose
	NR	Tx1	IIV3-SD	Egg-based	15 µg/ strain	NA	Intramuscular	Single dose

Author, Year	Setting	Tx	Vaccine Type	Platform	Dosage of HA/ strain	Adjuvant	Administration	Frequency
Trial registry, 2017[41]		Tx2	IIV3-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
Otten, 2020[42]	Community	Tx1	IIV3-Adj	NR	15 µg/ strain	9.75 µg MF59	Intramuscular	Single dose
		Tx2	IIV3-Adj	NR	15 µg/ strain	19.5 µg MF59	Intramuscular	Single dose
		Tx3	IIV3-Other-Adj	NR	30 µg/ strain	9.75 µg MF59	Intramuscular	Single dose
		Tx4	IIV3-Other-Adj – bilateral	NR	30 µg/ strain	19.5 µg MF59	Two bilateral intramuscular injections in left (active vaccine) and right (saline) deltoid	Single dose
		Tx5	IIV3-Adj-bilataeral + saline	NR	15 µg/ strain	9.75 µg MF59	Two bilateral intramuscular injections in left (active vaccine) and right (saline) deltoid	Single dose
		Tx6	IIV3-Adj-bilateral + saline	NR	15 µg/ strain	29.25 µg MF59	Two bilateral intramuscular injections in left (active vaccine) and right (saline) deltoid	Single dose
		Tx7	IIV3-Adj-bilateral	NR	15 µg/ strain	9.75 µg MF59/ arm	Two bilateral intramuscular injections in left (active vaccine) and right (saline) deltoid	Single dose
McConeghy, 2020[43]	Nursing home	Tx1	IIV3-Adj	NR	15 µg/ strain	MF59	NR	Single dose
		Tx2	IIV3-SD	Egg-based	15 µg/ strain	NA	NR	Single dose
Sanchez, 2020[44]	Clinic	Tx1	IIV4-HD	NR	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV4-HD	NR	60 µg/ strain	NA	Subcutaneous	NR
		Tx3	IIV4-SD	NR	15 µg/ strain	NA	Subcutaneous	Single dose
McLean, 2021[45]	Community	Tx1	IIV3-HD (2015/2016, 2016/2017)	Egg-based	Year 1+2: 60 µg/ strain	NA	NR	Single dose

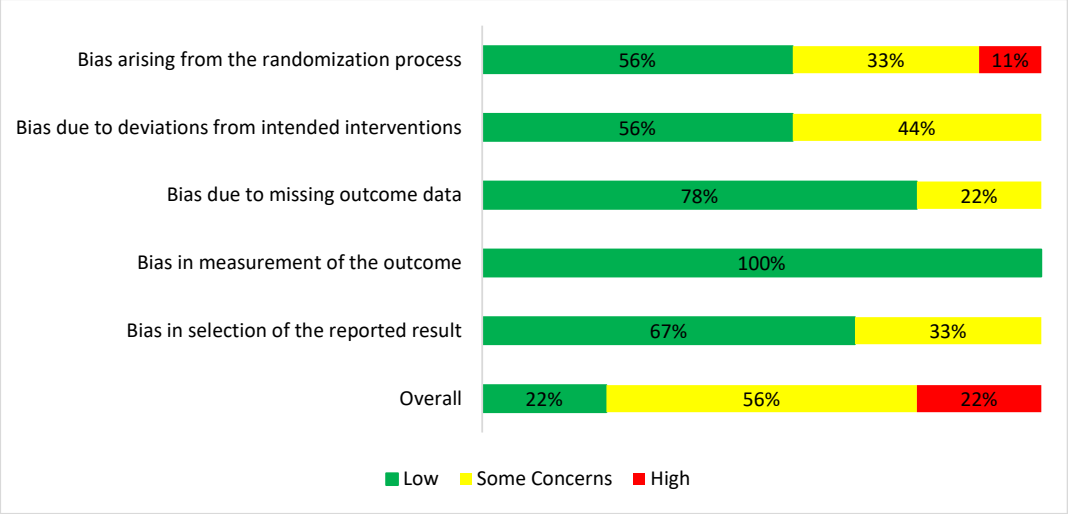
Author, Year	Setting	Tx	Vaccine Type	Platform	Dosage of HA/ strain	Adjuvant	Administration	Frequency
		Tx2	IIV3-Adj (2015/2016, 2016/2017)	Egg-based	Year 1+2: 15 µg/ strain	Year 1: MF59; Year 2: MF59	NR	Single dose
		Tx3	IIV3-SD (2015/2016) + IIV3-HD (2016/2017)	Egg-based	Year 1:15 µg/ strain; Year 2: 60 µg/ strain	NA	NR	Single dose
		Tx4	IIV3-SD (2015/2016) + IIV3-Adj (2016/2017)	Egg-based	Year 1+2: 15 µg/ strain	Year 1: NA; Year 2: MF59	NR	Single dose
Trial registry, 2021[46]	Community	Tx1	IIV4-HD	Egg-based	60 µg/ strain	NA	Intramuscular	Single dose
		Tx2	IIV4-SD	Egg-based	15 µg/strain	NA	Subcutaneous	Single dose

Note: **The** term "-Other" in the vaccine name indicates that there are varying dosages available for different strains**.** As such, it is not categorized as standard dose nor high dose as per guidelines.
Abbreviations- NR: Not reported; N: Northern hemisphere; S: Southern hemisphere; IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; CC: Cell-cultured; RIV: Recombinant influenza vaccine; LAIV: Live attenuated influenza vaccine; USA: United States of America; UK: United Kingdom; RCT: Randomized controlled trial; ARI: Acute respiratory infection; LC-ARI: Laboratory-confirmed acute respiratory infection; ER: Emergency room; LCI: Laboratory-confirmed influenza; ILI: Influenza-like illness; AE: Adverse event; µg: micrograms; NA: Not applicable; Tx: treatment arm

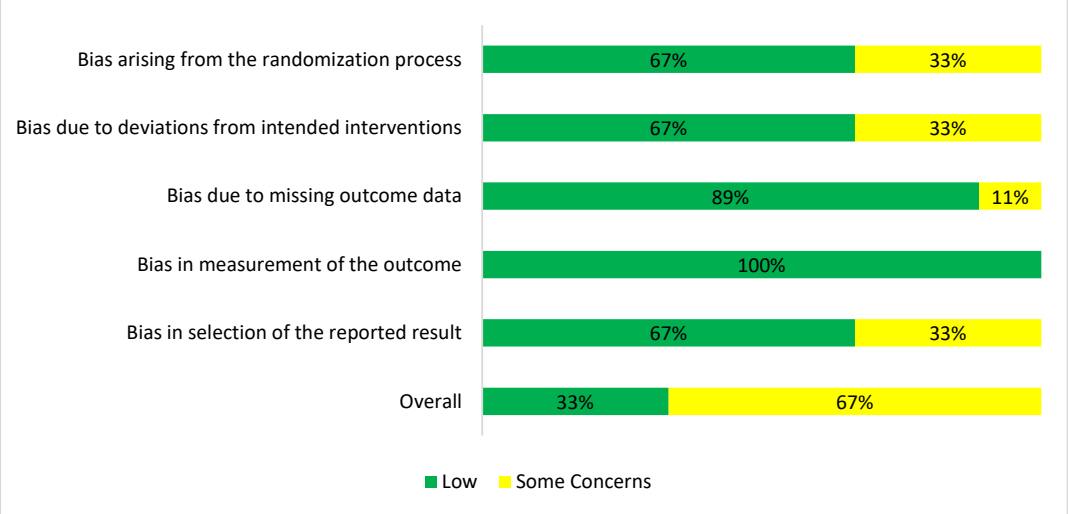
Appendix 14: Aggregate Cochrane Risk-of-bias appraisal results (N=26)

Primary Outcomes

Laboratory-confirmed influenza (LCI) (n=9)

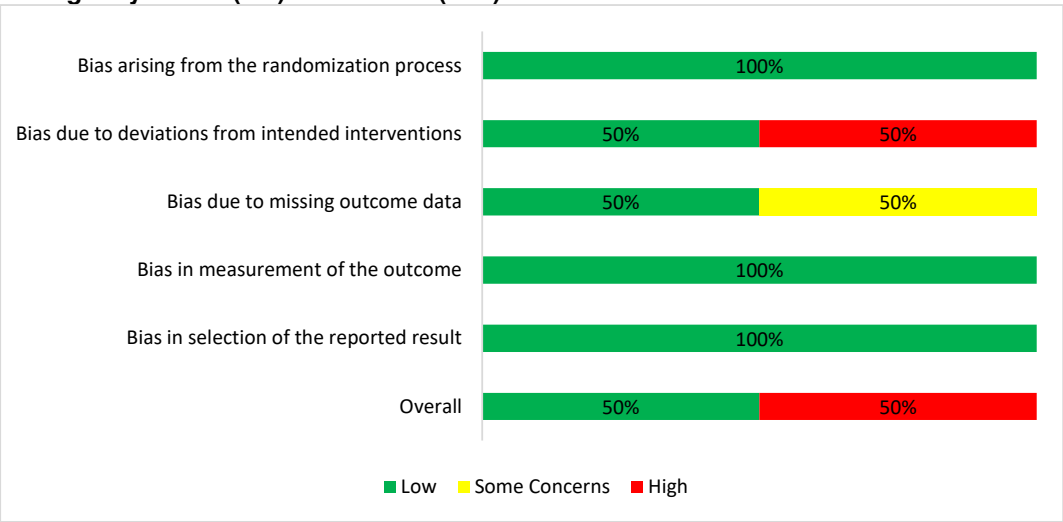


Influenza-like illness (ILI) (n=9)

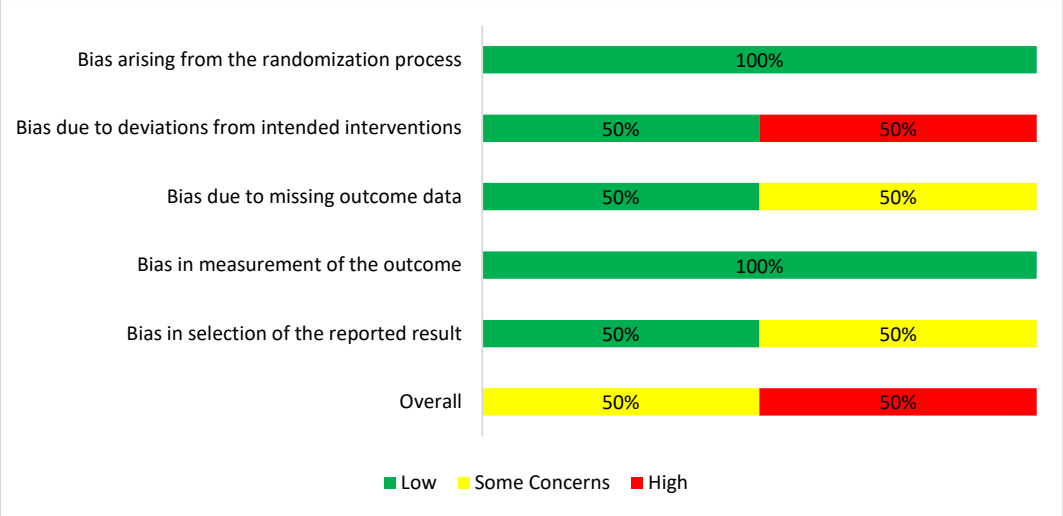


Secondary Outcomes

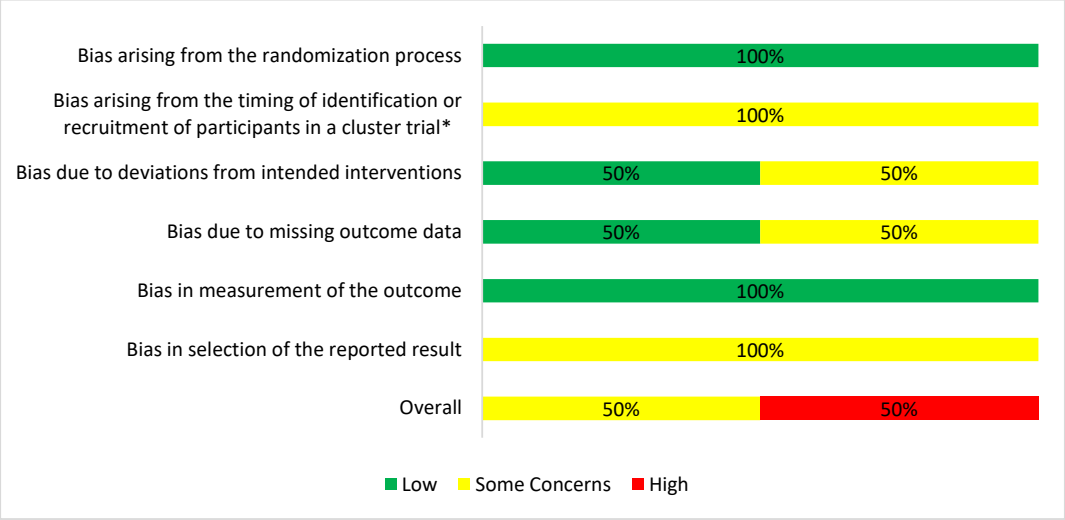
Emergency Room (ER) Visit for ILI (n=2)



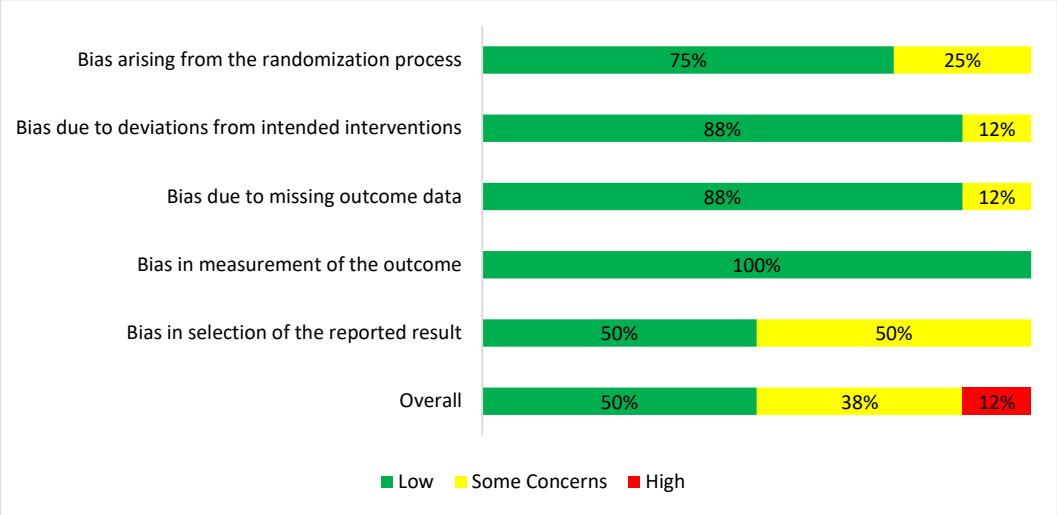
Hospitalization for ILI (n=2)



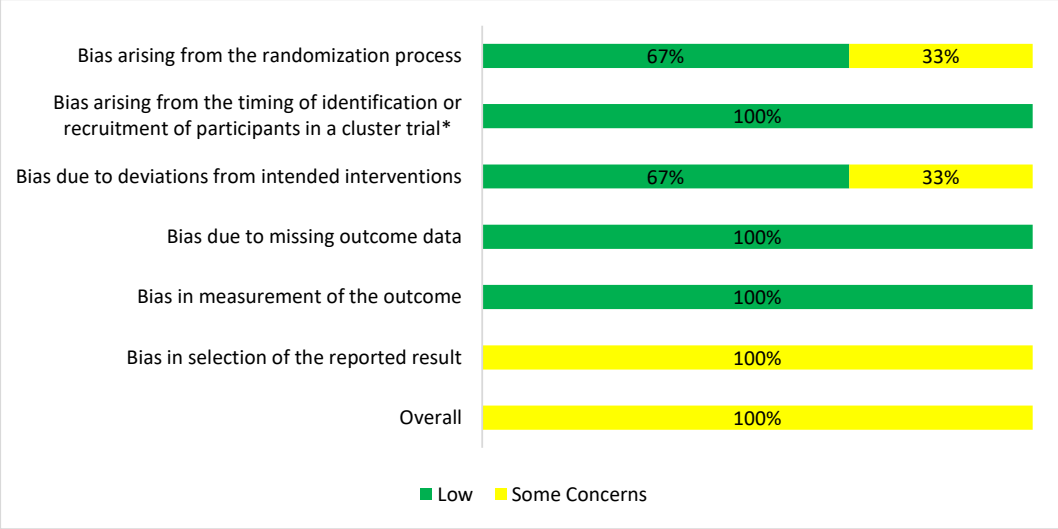
Hospitalization for ARI (n=2)



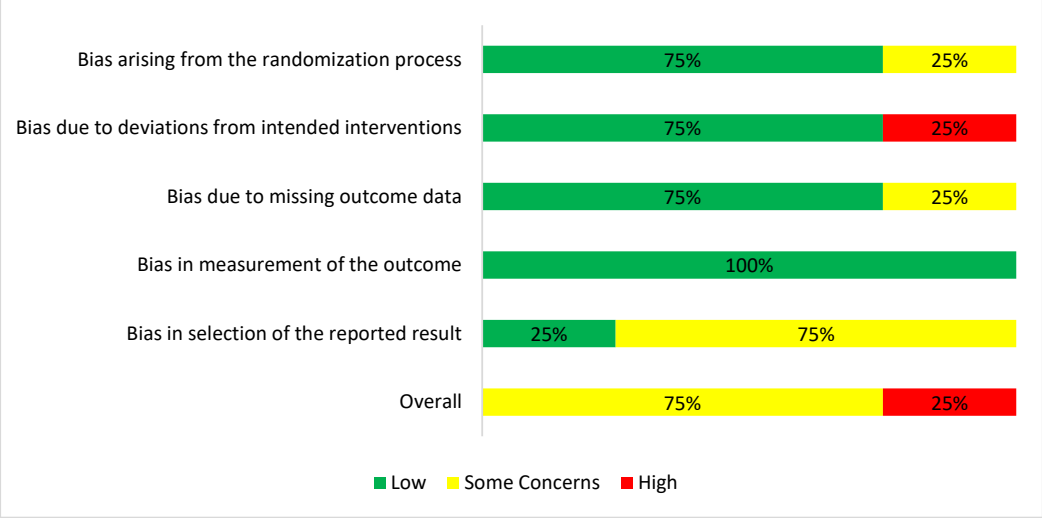
Number of vascular adverse events (n=8)



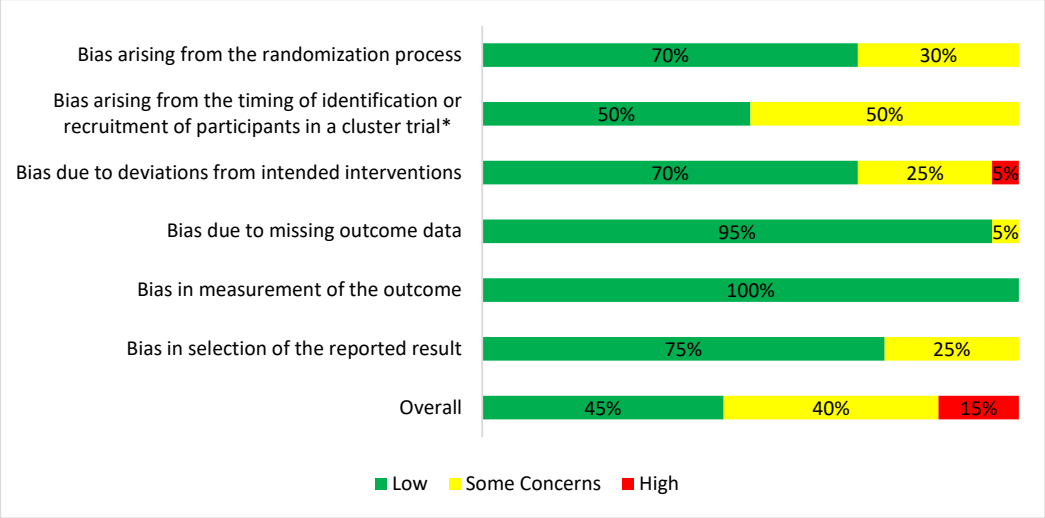
Inpatient hospitalization (any cause) (n=3)



Outpatient visits (n=4)



All-cause mortality (n=20)



Appendix 15: Cochrane Risk-of-bias appraisal results (N=26)

LCI						
Study (Author, Year)	**Bias arising from the randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
DiazGranados, 2013[11]	Low	Some Concerns (Blinding unclear and imbalances present)	Some Concerns (Non-trivial number of missing patients)	Low	Low	Some Concerns
DiazGranados, 2014[16]	Low	Low	Low	Low	Low	Low
Dunkle, 2017[20]	Low	Some Concerns (Not analyzed as ITT)	Low	Low	Low	Some Concerns
Keitel, 2010[10]	Some Concerns (Insufficient details to conduct a proper assessment)	Low	Low	Low	Low	Some Concerns
Wongsurakiat, 2004[7]	Some Concerns (Lacking information relating to the randomization process)	Low	Low	Low	Some Concerns (Trial was not registered)	Some Concerns
Rudenko, 2001[6]	Some Concerns (Insufficient details about randomization or baseline balance)	Some Concerns (Insufficient information about who was blinded and how)	Low	Low	Some Concerns (Trial was not registered)	High
Teh, 2021[30]	Low	Low	Low	Low	Low	Low
Loeb, 2020[24]	Low	Low	Some Concerns (Non-trivial number of missing data and insufficient action to mitigate bias)	Low	Some Concerns (Insufficient information for a proper assessment)	Some Concerns

Belongia, 2020[25]	High (Insufficient details about randomization or baseline balance)	Some Concerns (Lack of blinding in personnel)	Low	Low	Low	High
Abbreviations: LCI: Laboratory-confirmed Influenza						

ILI						
Study (Author, Year)	**Bias arising from the randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
DiazGranados, 2013[11]	Low	Some Concerns (Blinding unclear and imbalances present)	Some Concerns (Non-trivial number of missing patients)	Low	Low	Some Concerns
DiazGranados, 2014[16]	Low	Low	Low	Low	Low	Low
Frey, 2014[15]	Some Concerns (Insufficient details to conduct a proper assessment)	Some Concerns (Only single blinded)	Low	Low	Some Concerns (Outcome not pre-specified)	Some Concerns
Beran, 2021[28]	Low	Low	Low	Low	Low	Low
Dunkle, 2017[20]	Low	Some Concerns (Not analyzed as ITT)	Low	Low	Low	Some Concerns
Allsup, 2004[8]	Low	Low	Low	Low	Some Concerns (No protocol identified)	Some Concerns
Teh, 2021[30]	Low	Low	Low	Low	Low	Low
Keitel, 2010[10]	Some Concerns (Insufficient details to conduct a proper assessment)	Low	Low	Low	Low	Some Concerns
Wongsurakiat, 2004[7]	Some Concerns (Lacking information relating to the randomization process)	Low	Low	Low	Some Concerns (Trial was not registered)	Some Concerns

Abbreviations: ILI: Influenza-like Illness

ER Visit for ILI						
Study (Author, Year)	**Bias arising from the randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
DiazGranados, 2014[16]	Low	Low	Low	Low	Low	Low
DiazGranados, 2013[11]	Low	High (Blinding unclear and per-protocol analysis was inappropriate for ITT effect)	Some Concerns (Non-trivial number of missing patients)	Low	Low	High
Abbreviations: ER: Emergency room						

Hospitalization for ILI						
Study (Author, Year)	**Bias arising from the randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
DiazGranados, 2014[16]	Low	Low	Low	Low	Some Concerns (Multiple outcome definitions)	Some Concerns
DiazGranados, 2013[11]	Low	High (Blinding unclear and per-protocol analysis was inappropriate for ITT effect)	Some Concerns (Non-trivial number of missing patients)	Low	Low	High

Hospitalization for ARI							
Study (Author, Year)	Bias arising from the randomization process	Bias arising from the timing of identification or recruitment	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall

		of participants in a cluster trial*					
DiazGranados, 2014[16]	Low	NA	Low	Low	Low	Some Concerns (Multiple outcome definitions)	Some Concerns
Gravenstein, 2017[19]	Low	Some Concerns (Participants were identified after leaders of facilities agreed to participate)	Some Concerns (Lacking information to conduct a proper assessment)	Some Concerns (Non-trivial amount of missing data)	Low	Some Concerns (Insufficient information regarding definition of outcome in trial registration)	High
*Only applicable to Cluster-RCTs **Abbreviations:** ARI: Acute Respiratory Infection							

Number of vascular adverse events						
Study (Author, Year)	**Bias arising from the randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
Essink, 2020[27]	Low	Low	Low	Low	Low	Low
Chang, 2019[23]	Low	Low	Low	Low	Low	Low
Tsang, 2014[14]	Low	Low	Low	Low	Some Concerns (Not pre-specified)	Some Concerns
Loeb, 2020[24]	Low	Low	Low	Low	Low	Low
Falsey, 2009[9]	Some Concerns (Insufficient details to conduct a proper assessment)	Low	Low	Low	Some Concerns (Not pre-specified)	Some Concerns

DiazGranados, 2013[11]	Low	Low	Some Concerns (Non-trivial number of missing patients)	Low	Some Concerns (Trial was terminated early)	Some Concerns
DiazGranados, 2014[16]	Low	Low	Low	Low	Low	Low
Frey, 2014[15]	Some Concerns (Insufficient details to conduct a proper assessment)	Some Concerns (Only single blinded)	Low	Low	Some Concerns (Outcome not prespecified)	High

Inpatient hospitalization (any cause)							
Study	**Bias arising from the randomization process**	**Bias arising from the timing of identification or recruitment of participants in a cluster trial***	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
Falsey, 2009[9]	Some Concerns (Insufficient details about the randomization process)	NA	Low	Low	Low	Some Concerns (Reported outcome was not pre-registered)	Some Concerns
DiazGranados, 2014[16]	Low	NA	Low	Low	Low	Some Concerns (Multiple outcome definitions)	Some Concerns
Gravenstein, 2018[22]	Low	Low	Some Concerns (No blinding)	Low	Low	Some Concerns (Reporting of outcome not specified in the protocol)	Some Concerns
*Only applicable to Cluster-RCTs							

Outpatient visits						
Study (Author, Year)	**Bias arising from the randomization process**	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
DiazGranados, 2014[16]	Low	Low	Low	Low	Some Concerns (Multiple outcome definitions)	Some Concerns
DiazGranados, 2013[11]	Low	High (Blinding unclear and per-protocol analysis was inappropriate for ITT effect)	Some Concerns (Non-trivial number of missing patients)	Low	Low	High
Allsup, 2004[8]	Low	Low	Low	Low	Some Concerns (No protocol identified)	Some Concerns
Wongsurakiat, 2004[7]	Some Concerns (Lacking information relating to the randomization process)	Low	Low	Low	Some Concerns (Trial was not registered)	Some Concerns

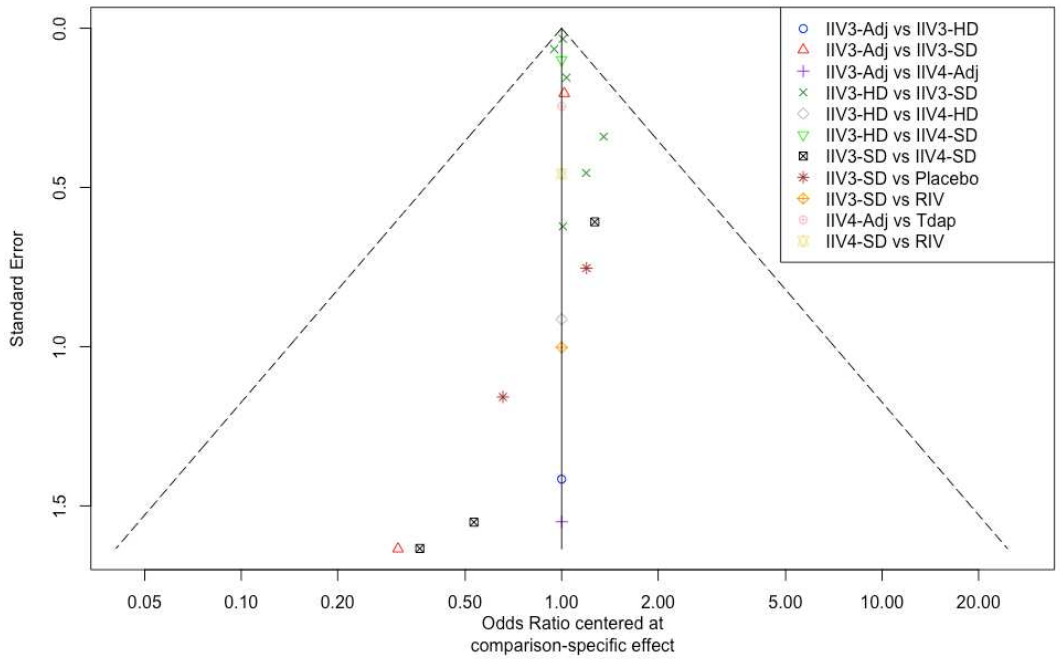
All-cause death							
Study (Author, Year)	**Bias arising from the randomization process**	**Bias arising from the timing of identification or recruitment of participants in a cluster trial***	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall**
Allsup, 2004[8]	Low	NA	Low	Low	Low	Some Concerns (No protocol identified)	Some Concerns
Nace, 2014[17]	Some Concerns (Some imbalances)	NA	Some Concerns (Insufficient	Low	Low	Some Concerns	High

			Information about the analysis)			(Not pre-specified)	
Beran, 2021[28]	Low	NA	Low	Low	Low	Low	Low
Schmader, 2021[29]	Low	NA	Low	Low	Low	Low	Low
Vardeny, 2021[31]	Low	NA	Low	Low	Low	Low	Low
Essink, 2020[27]	Low	NA	Low	Low	Low	Low	Low
Chang, 2019[23]	Low	NA	Low	Low	Low	Low	Low
Dunkle, 2017[20]	Low	NA	Some Concerns (Not analyzed as ITT)	Low	Low	Low	Some Concerns
Treanor, 2017[21]	Low	NA	Low	Low	Low	Low	Low
Pepin, 2013[13]	Some Concerns (Some imbalances)	NA	Low	Low	Low	Low	Some Concerns
Scheifele, 2013[12]	Low	NA	Low	Low	Low	Low	Low
Keitel, 2010[10]	Some Concerns (Insufficient details to conduct a proper assessment)	NA	Low	Low	Low	Low	Some Concerns
Falsey, 2009[9]	Some Concerns (Insufficient details to conduct a proper assessment)	NA	Low	Low	Low	Low	Some Concerns
Wongsurakiat, 2004[7]	Some Concerns (Lacking information relating to the	NA	Low	Low	Low	Some Concerns Trial was not registered)	High

	randomization process)						
DiazGranados, 2013[11]	Low	NA	High (Blinding unclear and imbalances present)	Some Concerns (Non-trivial number of missing patients)	Low	Some Concerns (Trial was terminated early)	High
DiazGranados, 2014[16]	Low	NA	Low	Low	Low	Low	Low
Frey, 2014[15]	Some Concerns (Insufficient details to conduct a proper assessment)	NA	Some Concerns (Only single blinded)	Low	Low	Low	Some Concerns
Bart, 2016[18]	Low	NA	Low	Low	Low	Low	Low
Gravenstein, 2017[19]	Low	Some Concerns (Insufficient details to conduct a proper assessment)	Some Concerns (Insufficient details to conduct a proper assessment)	Low	Low	Low	Some Concerns
Gravenstein, 2018[22]	Low	Low	Some Concerns (No blinding)	Low	Low	Some Concerns (Reporting of outcome not specified in the protocol)	Some Concerns
*Only applicable to Cluster-RCTs							

Appendix 16: Small-study effects and publication bias assessment

Figure 1. Comparison-adjusted funnel plot for the assessment of small-study effects and publication bias for all-cause mortality.



*Hierarchy of interventions based on clinical expertise as follows: 1) RIV4, 2) RIV3, 3) IIV4-HD, 4) IIV4-Adj, 5) IIV4-SD, 6) IIV3-HD, 7) IIV3-Adj, 8) IIV3-SD, 9) Tdap, 10) Placebo

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Appendix 17: Network Meta-Analyses

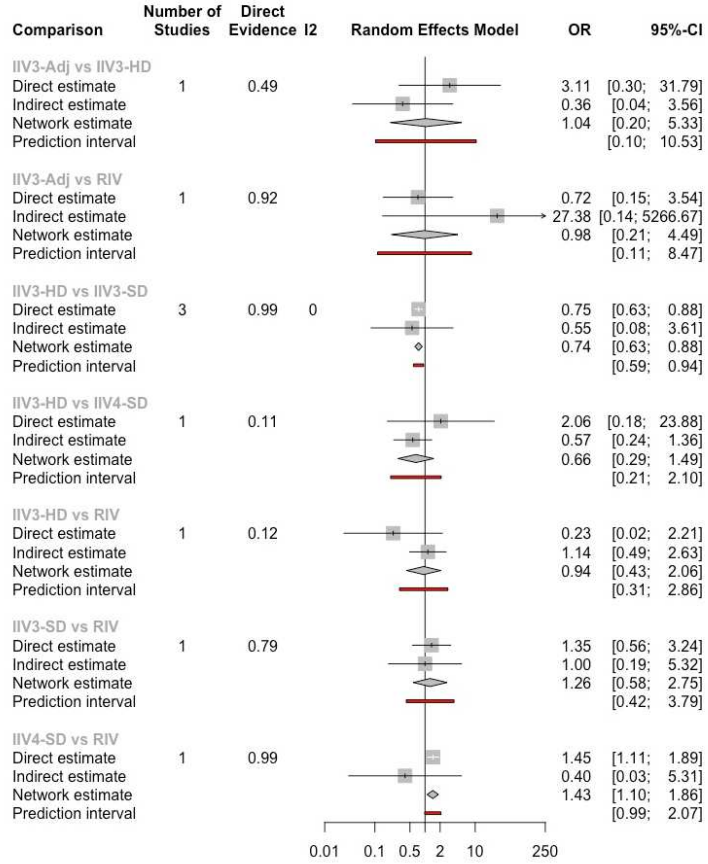
Appendix 17A: Consistency

Table 1. Summary of design-by-treatment interaction model test for global consistency across the four outcomes on which an NMA was conducted: laboratory-confirmed influenza (LCI), all-cause mortality, outpatient visits, and number of vascular adverse events.

Design-by-treatment interaction model test for global consistency				
Outcome	**Chi-square-test**	**Degrees of Freedom**	**P-value**	**Heterogeneity SD**
LCI	2.35	2	0.31	0.00
All-cause mortality	0.23	3	0.98	0.00
Inpatient visits	Inconsistency cannot be assessed because there are no closed loops			
Number of vascular adverse events	Inconsistency cannot be assessed because there are no closed loops			
Abbreviations- LCI: Laboratory-confirmed influenza; SD: Standard deviation				

*P-value > 0.05 indicates no evidence of statistically significant global inconsistency

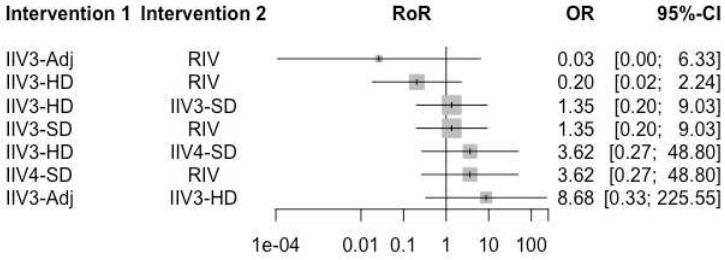
Figure 1. Forest plot for direct, indirect, and network estimates, along with 95% prediction interval where applicable for laboratory confirmed influenza.



*Direct Evidence (%) column in forest plot indicates percentage contribution of direct evidence to network meta-analysis

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval

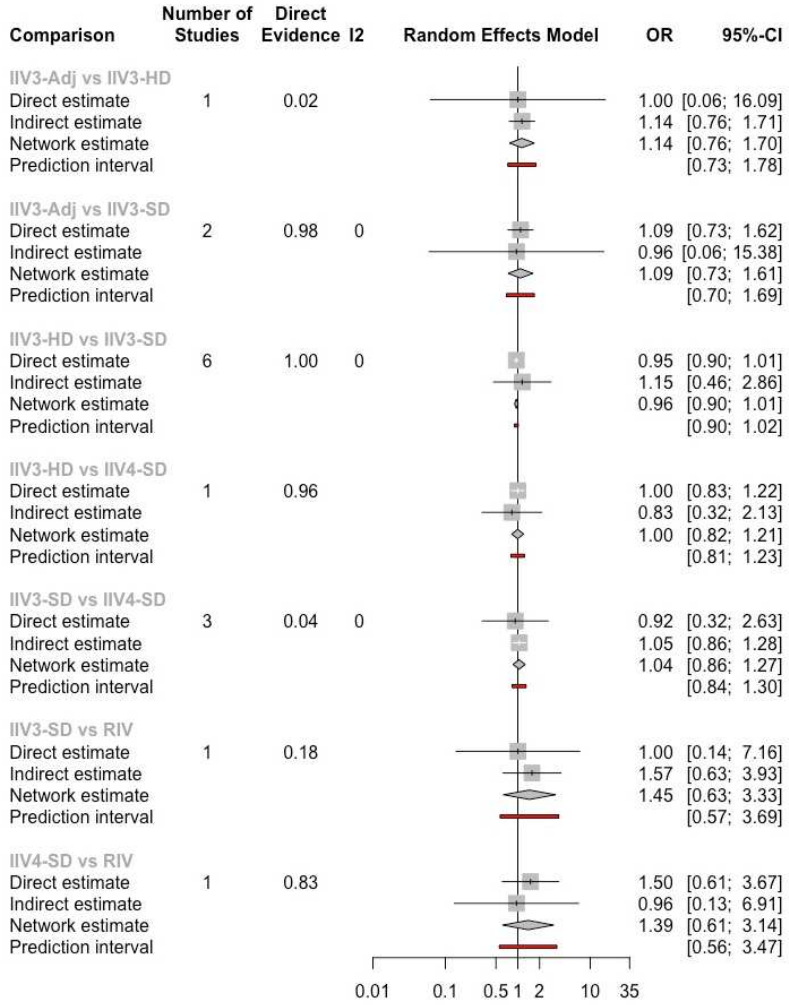
Figure 2. Forest plot illustrating the ratio of odds ratios between direct and indirect estimates as estimated using the node-splitting approach for laboratory-confirmed influenza.



*If the confidence interval for RoR does not include the value 1, it suggests there is evidence of statistically significant inconsistency

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; RoR; Ratio of odds ratio; OR: Odds ratio; CI: Confidence interval

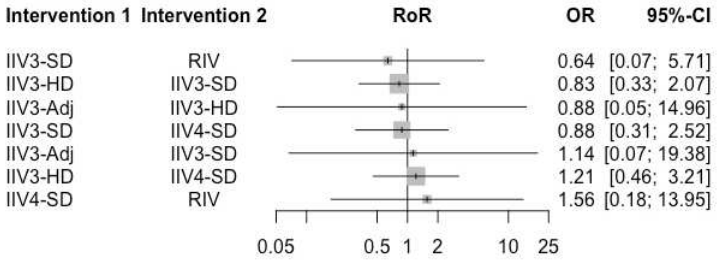
Figure 3. Forest plot for direct, indirect, and network estimates, along with 95% prediction interval where applicable for all-cause mortality



*Direct Evidence (%) column in forest plot indicates percentage contribution of direct evidence to network meta-analysis

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; OR: Odds ratio; CI: Confidence interval

Figure 4. Forest plot illustrating the ratio of odds ratios between direct and indirect estimates as estimated using the node-splitting approach for all-cause mortality



*If the confidence interval for RoR does not include the value 1, it suggests there is evidence of statistically significant inconsistency

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RoR; Ratio of odds ratio; OR: Odds ratio; CI: Confidence interval

Appendix 17B: Transitivity Tables

Table 1. Transitivity table for laboratory-confirmed influenza across age, sex, and overall risk of bias.

Transitivity for laboratory-confirmed influenza								
Comparison	**Number of Studies**	**Age – mean**	**Sex (F%) – mean**	**Low RoB – n (%)**	**Some Concern RoB – n (%)**	**High RoB – n (%)**	**Mode RoB (n)**	**Year of Publication – mean**
IIV3-Adj vs. IIV3-HD	1	70.00	56.20 %	.	.	1 (100%)	High (1)	2020
IIV3-Adj vs. RIV	1	70.00	56.20 %	.	.	1 (100%)	High (1)	2020
IIV3-HD vs. IIV3-SD	3	74.37	59.08 %	1 (33.33%)	2 (66.67%)	.	Some Concern (2)	2015.67
IIV3-HD vs. IIV4-SD	1	60.00	32.00 %	1 (100%)	.	.	Low (1)	2021
IIV3-HD vs. RIV	1	70.00	56.20 %	.	.	1 (100%)	High (1)	2020
IIV3-SD vs. Placebo	2	70.45	37.47 %	.	1 (50%)	1 (50%)	Some concerns/high (1)	2002.5
IIV3-SD vs. RIV	1	72.90	53.20 %	.	1 (100%)	.	Some Concern (1)	2010
RIV4 vs. IIV4-SD	1	64.10	58.50 %	.	.	1 (100%)	High (1)	2017

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; RoB: Risk of bias

Table 2. Transitivity table for number of vascular adverse events across age, sex, and overall risk of bias.

Transitivity for number of vascular adverse events								
Comparison	**Number of Studies**	**Age – mean**	**Sex (F%) – mean**	**Low RoB – n (%)**	**Some Concern RoB – n (%)**	**High RoB – n (%)**	**Mode RoB (n)**	**Year of Publication – mean**
IIV3-Adj vs. IIV4-SD	2	72.85	62.07 %	1 (50%)	.	1 (50%)	Low/High (1)	2013.5
IIV3-Adj vs. IIV4-Adj	1	72.50	56.60 %	1 (100%)	.	.	Low (1)	2020
IIV3-HD vs. IIV3-SD	4	73.03	54.66 %	1 (25%)	3 (75%)	.	Some Concern (3)	2012.5
IIV3-HD vs. IIV4-HD	1	73.00	54.90 %	1 (100%)	.	.	Low (1)	2019

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RoB: Risk of bias

Table 3. Transitivity table for outpatient visits across age, sex, and overall risk of bias.

Transitivity for outpatient visits								
Comparison	**Number of Studies**	**Age – mean**	**Sex (F%) – mean**	**Low RoB – n (%)**	**Some Concern RoB – n (%)**	**High RoB – n (%)**	**Mode RoB (n)**	**Year of Publication – mean**
IIV3-HD vs. IIV3-SD	2	73.05	55.12 %	.	2 (50%)	1 (50%)	Some Concern/High (1)	2013.5
IIV3-SD vs. Placebo	2	68.67	26.20 %	.	2 (100%)	.	Some Concern (2)	2004
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; RoB: Risk of bias								

Table 4. Transitivity table for all-cause mortality across age, sex, and overall risk of bias.

Transitivity for all-cause mortality								
Comparison	**Number of Studies**	**Age – median**	**Sex (F%) – median**	**Low RoB – n (%)**	**Some Concern RoB – n (%)**	**High RoB – n (%)**	**Mode RoB (n)**	**Year of Publication – mean**
IIV3-Adj vs. IIV3-HD	1	76.50	55.50 %	1 (100%)	.	.	Low (1)	2021
IIV3-Adj vs. IIV3-SD	2	72.85	62.07 %	1 (50%)	1 (50%)	.	Low/Some Concern (1)	2013.5
IIV3-Adj vs. IIV4-Adj	1	72.50	56.60 %	1 (100%)		.	Low (1)	2020
IIV3-HD vs. IIV3-SD	6	78.95	62.91 %	1 (16.7%)	3 (50%)	2 (33.33%)	Some Concern (3)	2014.17
IIV3-HD vs. IIV4-HD	1	73.00	54.90 %	1 (100%)	.	.	Low (1)	2019
IIV3-HD vs. IIV4-HD	1	65.50	28.30 %	1 (100%)	.	.	Low (1)	2021
IIV3-SD vs. IIV4-SD	3	NR	54.00 %	2 (66.67%)	1 (33.33%)	.	Low (2)	2015.33
IIV3-SD vs. Placebo	2	68.67	26.20 %	.	2 (100%)	.	Some Concern (2)	2004
IIV3-SD vs. RIV	1	79.20	53.20 %	.	1 (100%)	.	Some Concern (1)	2010
IIV4-Adj vs. Tdap	1	71.90	61.80 %	1 (100%)	.	.	Low (1)	2021
IIV4-SD vs. RIV	1	64.10	58.50 %	.	1 (100%)	.	Some Concern (1)	2017
*__Note:__ Enrollment in one of the studies in this intervention comparison (Pepin, 2013) was stratified by age at each site into adults 18–60 and >60 years of age. However, only data from the >60 age group was used in the analysis. The remaining two studies did not report the median/mean age. **Abbreviations-** IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; RoB: Risk of bias								

Appendix 17C: Network Meta-Analysis Results

Laboratory-confirmed influenza

Table 1. Summary of network meta-analysis results for laboratory-confirmed influenza with original coding of interventions.

Network Meta-analysis Results; 9 studies, 52,202 participants, 7 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj-IIV3-HD	1.04	2.30	0.20	5.33	0.05	0.96	0.10	10.53
IIV3-Adj:IIV3-SD	0.77	2.30	0.15	3.96	-0.31	0.76	0.08	7.81
IIV3-Adj:IIV4-SD	0.69	2.20	0.15	3.21	-0.48	0.63	0.08	6.11
IIV3-Adj:Placebo	0.24	2.50	0.04	1.47	-1.54	0.12	0.02	3.10
IIV3-Adj:RIV	0.98	2.17	0.21	4.49	-0.03	0.98	0.08	8.47
IIV3-HD:IIV3-SD	0.74	1.09	0.63	0.88	-3.51	0.00	0.59	0.94
IIV3-HD: IIV4-SD	0.66	1.52	0.29	1.49	-1.00	0.32	0.21	2.10
IIV3-HD: Placebo	0.23	1.48	0.11	0.51	-3.69	0.00	0.08	0.70
IIV3-HD: RIV	0.94	1.49	0.43	2.06	-0.15	0.88	0.31	2.86
IIV3-SD: IIV4-SD	0.88	1.51	0.39	1.99	-0.30	0.77	0.28	2.79
IIV3-SD: Placebo	0.31	1.47	0.15	0.67	-3.01	0.00	0.11	0.92
IIV3-SD: RIV	1.26	1.49	0.58	2.75	0.59	0.55	0.42	3.79
IIV4-SD: Placebo	0.35	1.76	0.12	1.07	-1.83	0.07	0.07	1.70
IIV4-SD: RIV	1.43	1.14	1.10	1.86	2.67	0.01	0.99	2.07
RIV: Placebo	0.25	1.74	0.08	0.73	-2.52	0.01	0.05	1.15
Common within-network between-study SD (tau)	<0.0001							
I-square	0%							

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 1. Treatment ranking of interventions using P-score for laboratory-confirmed influenza with original coding of interventions.

Treatment Ranking	
Treatment	***P-score***
IIV3-HD	0.78
RIV	0.73
IIV3-Adj	0.65
IIV3-SD	0.45
IIV4-SD	0.37
Placebo	0.02

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine.

Table 2. Vaccine efficacy from network meta-analysis results for laboratory-confirmed influenza with original coding of interventions

Comparison	***OR***	***RR***	***VE***
IIV3-Adj-IIV3-HD	1.04 (0.2,5.33)	1.03 (0.24,2.87)	-3.18 (-186.6,76.22)
IIV3-Adj:IIV3-SD	0.77 (0.15,3.96)	0.81 (0.18,2.49)	19.32 (-149.41,81.95)
IIV3-Adj:IIV4-SD	0.69 (0.15, 3.21)	0.74 (0.18,2.23)	26.47 (-123.1,81.95)
IIV3-Adj:Placebo	0.24 (0.04, 1.47)	0.28 (0.05,1.34)	71.73 (-34.45,95.06)
IIV3-Adj:RIV	0.98 (0.21,4.49)	0.98 (0.25,2.65)	1.61 (-165.22,75.09)
IIV3-HD:IIV3-SD	0.74 (0.63,0.88)	0.78 (0.68,0.90)	21.97 (9.85,32)
IIV3-HD: IIV4-SD	0.66 (0.29,1.49)	0.71 (0.34,1.36)	28.22 (-35.79,66.24)
IIV3-HD: Placebo	0.23 (0.11,0.51)	0.27 (0.13,0.56)	72.85 (43.5,86.64)
IIV3-HD: RIV	0.94 (0.43,2.06)	0.95 (0.48,1.70)	4.67 (-70.18,51.51)
IIV3-SD: IIV4-SD	0.88 (0.39,1.99)	0.90 (0.44,1.66)	9.85 (-66.31,55.63)
IIV3-SD: Placebo	0.31 (0.15,0.67)	0.36 (0.18,0.72)	64.08 (28.3,81.95)
IIV3-SD: RIV	1.26 (0.58,2.75)	1.20 (0.63,2.04)	-19.81 (-104.09,36.72)
IIV4-SD: Placebo	0.35 (0.12,1.07)	0.40 (0.15,1.06)	59.81 (-5.53,85.46)
IIV4-SD: RIV	1.43 (1.1,1.85)	1.32 (1.08,1.59)	-31.75 (-58.87,-7.86)
RIV:Placebo	0.25 (0.08,0.73)	0.29 (0.10,0.77)	70.63 (22.86,90,21)

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: odds ratio; RR: relative risk; VE: vaccine efficacy

Number of Vascular Adverse Events

Table 3. Summary of network meta-analysis results for number of vascular adverse events with original coding of interventions.

Network Meta-analysis results; 8 studies, 57,677 patients, 5 treatments								
Comparison	***IRR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj: IIV3-HD	1.31	1.37	0.71	2.43	0.85	0.39	0.30	5.71
IIV3-Adj: IIV3-SD	0.90	1.30	0.54	1.50	-0.41	0.69	0.23	3.50
IIV3-Adj: IIV4-Adj	5.00	1.44	2.46	10.18	4.44	0.00	1.03	24.22
IIV3-Adj: IIV4-HD	1.96	1.61	0.77	4.99	1.42	0.16	0.31	12.57
IIV3-HD: IIV3-SD	0.69	1.19	0.48	0.97	-2.11	0.03	0.20	2.32
IIV3-HD: IIV4-Adj	3.82	1.62	1.49	9.80	2.79	0.01	0.59	24.79
IIV3-HD: IIV4-HD	1.50	1.43	0.75	3.01	1.14	0.25	0.31	7.14
IIV4-Adj: IIV3-SD	0.18	1.56	0.07	0.43	-3.84	0.00	0.03	1.07
IIV4-HD: IIV3-SD	0.46	1.49	0.21	1.00	-1.96	0.05	0.09	2.41
IIV4-Adj: IIV4-HD	0.39	1.82	0.12	1.27	-1.56	0.12	0.04	3.50
Common within-network between-study SD	0.34							
I-square	97.00%							

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; IRR: Incidence rate ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 2. Treatment ranking of interventions using P-score for number of vascular adverse events with original coding of interventions.

Treatment Ranking	
Treatment	***P-score***
IIV4-Adj	0.98
IIV4-HD	0.71
IIV3-HD	0.48
IIV3-Adj	0.23
IIV3-SD	0.10

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage

Outpatient Visits

Table 4. Summary of network meta-analysis results for outpatient visits with original coding of interventions.

Network Meta-analysis results; 4 studies, 41,995 patients, 3 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-HD: IIV3-SD	1.01	1.09	0.85	1.21	0.16	0.87	0.17	6.09
IIV3-HD: Placebo	0.65	1.36	0.35	1.19	-1.40	0.16	0.01	41.95
IIV3-SD: Placebo	0.64	1.34	0.36	1.14	-1.51	0.13	0.01	35.50
Common within-network between-study SD	0.11							
I-square	60.70%							

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 3. Treatment ranking of interventions using P-score for outpatient visits with original coding of interventions.

Treatment Ranking	
Treatment	***P-score***
IIV3-SD	0.75
IIV3-HD	0.68
Placebo	0.07

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage;

All-cause Mortality

Table 5. Summary of network meta-analysis results for all-cause mortality with original coding of interventions.

Network Meta-analysis results; 20 studies, 140,577 patients, 9 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj: IIV3-HD	1.14	1.23	0.76	1.70	0.64	0.52	0.73	1.78
IIV3-Adj: IIV3-SD	1.09	1.22	0.73	1.61	0.42	0.67	0.70	1.69
IIV3-Adj: IIV4-Adj	0.20	4.71	0.01	4.16	-1.04	0.30	0.01	6.05
IIV3-Adj: IIV4-HD	1.52	2.55	0.24	9.51	0.45	0.66	0.19	11.92
IIV3-Adj: IIV4-SD	1.14	1.25	0.73	1.77	0.57	0.57	0.69	1.86
IIV3-Adj: Placebo	1.60	1.94	0.44	5.85	0.71	0.48	0.37	6.87
IIV3-Adj:RIV	1.58	1.60	0.63	3.96	0.97	0.33	0.56	4.43
IIV3-Adj:Tdap	0.19	4.80	0.01	4.20	-1.05	0.30	0.01	6.13
IIV3-HD: IIV3-SD	0.96	1.03	0.90	1.01	-1.57	0.12	0.90	1.02
IIV3-HD: IIV4-Adj	0.18	4.77	0.01	3.75	-1.11	0.27	0.01	5.47
IIV3-HD: IIV4-HD	1.33	2.49	0.22	7.99	0.31	0.75	0.18	9.96
IIV3-HD: IIV4-SD	1.00	1.10	0.82	1.21	-0.03	0.98	0.81	1.23
IIV3-HD: Placebo	1.40	1.88	0.41	4.84	0.53	0.59	0.35	5.63
IIV3-HD:RIV	1.38	1.53	0.60	3.18	0.77	0.44	0.55	3.52
IIV3-HD:Tdap	0.17	4.87	0.01	3.78	-1.12	0.26	0.01	5.54
IIV3-SD: IIV4-Adj	0.18	4.77	0.01	3.92	-1.09	0.28	0.01	5.72
IIV3-SD: IIV4-HD	1.40	2.49	0.23	8.38	0.36	0.72	0.19	10.44
IIV3-SD: IIV4-SD	1.04	1.11	0.86	1.27	0.42	0.67	0.84	1.30
IIV3-SD: Placebo	1.47	1.88	0.43	5.06	0.61	0.54	0.37	5.89
IIV3-SD:RIV	1.45	1.53	0.63	3.33	0.88	0.38	0.57	3.69
IIV3-SD:Tdap	0.18	4.87	0.01	3.96	-1.09	0.28	0.01	5.79
IIV4-Adj: IIV4-HD	7.61	6.11	0.22	264.64	1.12	0.26	0.14	409.44
IIV4-Adj: IIV4-SD	5.69	4.79	0.26	122.55	1.11	0.27	0.18	178.75
IIV4-Adj: Placebo	8.00	5.40	0.29	217.74	1.23	0.22	0.20	326.88
IIV4-Adj:RIV	7.90	5.05	0.33	188.95	1.28	0.20	0.22	279.17
IIV4-Adj:Tdap	0.97	1.28	0.60	1.57	-0.12	0.91	0.57	1.67
IIV4-HD: IIV4-SD	0.75	2.51	0.12	4.53	-0.32	0.75	0.10	5.65

IIV4-HD: Placebo	1.05	3.04	0.12	9.28	0.04	0.96	0.09	12.13
IIV4-HD:RIV	1.04	2.74	0.14	7.48	0.04	0.97	0.11	9.53
IIV4-HD:Tdap	0.13	6.22	0.00	4.58	-1.13	0.26	0.00	7.12
IIV4-SD: Placebo	1.41	1.90	0.40	4.92	0.53	0.59	0.34	5.74
IIV4-SD:RIV	1.39	1.52	0.61	3.14	0.79	0.43	0.56	3.47
IIV4-SD:Tdap	0.17	4.88	0.01	3.82	-1.12	0.26	0.01	5.59
RIV:Placebo	1.01	2.14	0.23	4.49	0.02	0.99	0.19	5.40
Tdap:Placebo	8.24	5.49	0.29	232.17	1.24	0.22	0.19	350.03
RIV:Tdap	0.12	5.14	0.00	3.05	-1.28	0.20	0.00	4.52
Common within-network between-study SD	<0.0001							
I-square	0.00%							

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 4. Treatment ranking of interventions using P-score for all-cause mortality with original coding of interventions.

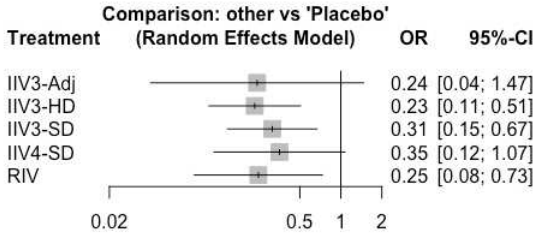
Treatment Ranking	
Treatment	***P-score***
RIV	0.75
Placebo	0.71
IIV4-HD	0.66
IIV3-HD	0.60
IIV4-SD	0.56
IIV3-SD	0.45
IIV3-Adj	0.42
IIV4-Adj	0.18
Tdap	0.17

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Forest Plots

Laboratory-confirmed influenza

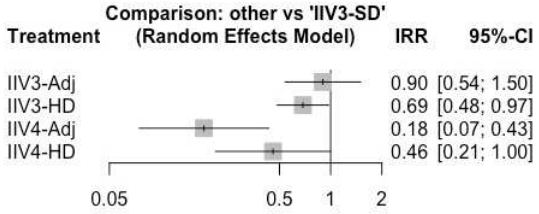
Figure 5. Forest Plots of network estimates relative to placebo for laboratory-confirmed influenza with original coding of interventions



*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval

Number of Vascular Adverse Events

Figure 7. Forest Plots of network estimates relative to IIV3-SD for number of vascular adverse events with original coding of interventions

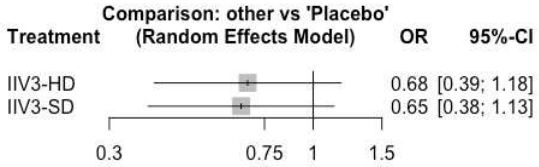


*IRR>1 favours IIV3-SD; IRR<1 favours intervention

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; IRR: Incidence rate ratio; CI: Confidence interval

Outpatient Visits

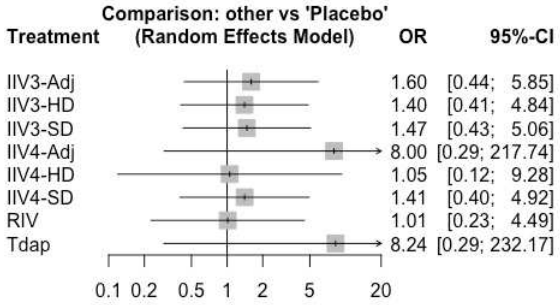
Figure 8. Forest Plots of network estimates relative to placebo for outpatient visits with original coding of interventions



*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; OR: Odds ratio; CI: Confidence interval

All-cause mortality

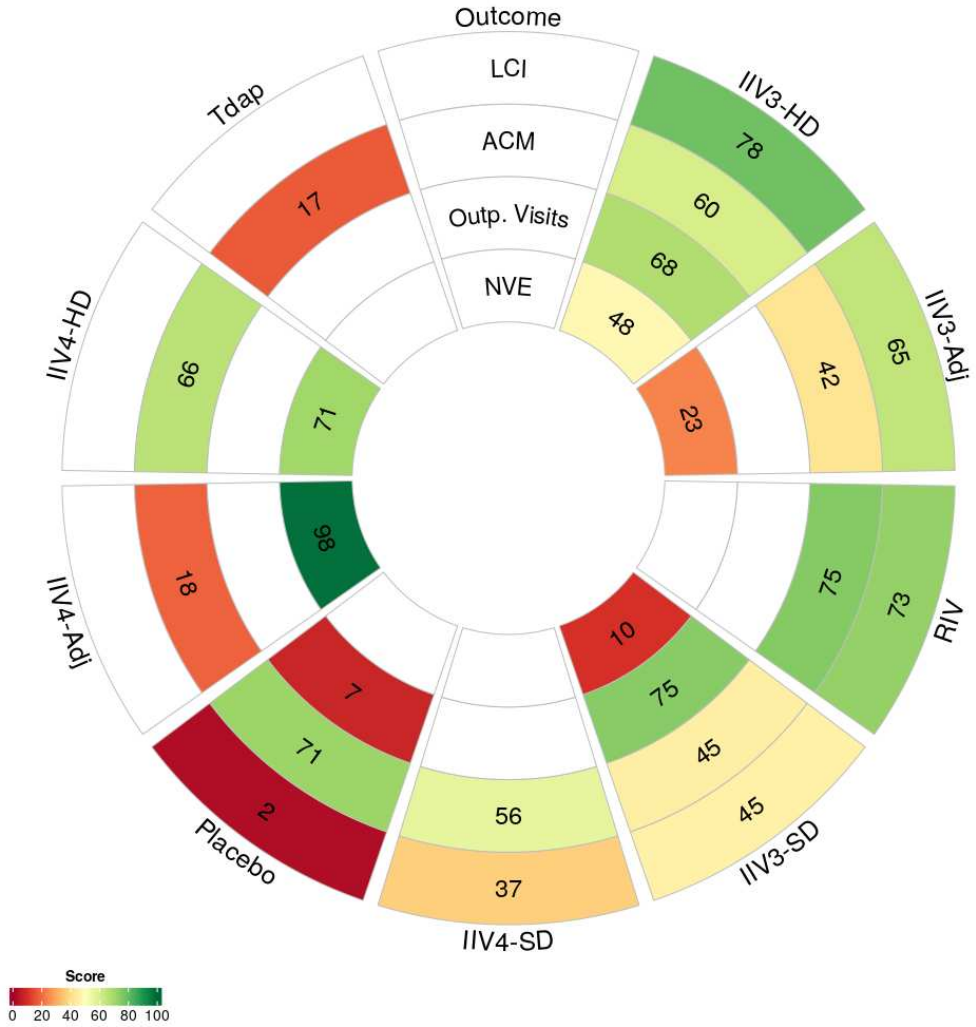
Figure 9. Forest Plots of network estimates relative to placebo for all-cause mortality with original coding of interventions



*OR>1 favours placebo; OR<1 favours intervention

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interval

Figure 10. Rank heat plot across 4 outcomes analyzed in network meta-analysis



Abbreviations – IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; LCI: Laboratory confirmed influenza; ACM: All-cause mortality; Outp. Visit: Outpatient Visit; NVE: Number of Vascular Adverse Events

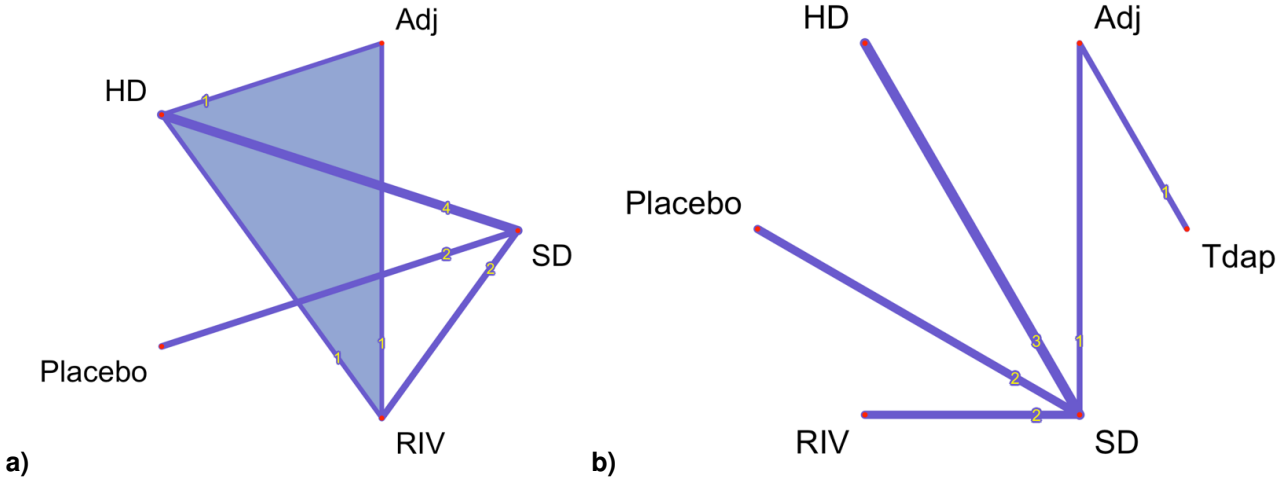
Appendix 18: Results on Secondary outcomes and additional analyses

Appendix 18A: Results on Secondary outcomes analyzed in a pairwise meta-analysis only

Pairwise meta-analysis suggested that IIV3-HD was comparable to IIV3-SD (2 RCTs[11, 16], 41,141 participants; OR 0.94, 95%CI [0.74 to 1.19], I^2=0%, τ=0.00; moderate certainty of evidence) for the prevention of ER visits for ILI. IIV3-HD was superior to IIV3-SD for preventing hospitalizations for ILI (2 RCTs[11, 16], 41,141 participants; OR 0.72, 95%CI [0.57 to 0.92], I^2=0%, τ=0.00; high certainty of evidence) and hospitalizations for ARI (2 RCTs[16, 19], 84,991 participants; OR 0.87, 95%CI [0.79 to 0.95], I^2=0%, τ=0.00; moderate certainty of evidence). For IIV3-HD versus IIV3-SD, inconclusive results were identified for the prevention of inpatient hospitalizations (3 RCTs[9, 16, 19, 46], 38,816 participants; OR 0.76, 95%CI [0.40 to 1.42], I^2=86%, τ=0.26; low certainty of evidence), which were in agreement when the analysis was restricted to low ROB studies (2 RCTs[16, 22, 46], 34,940 participants; OR 0.76, 95%CI [0.52 to 1.13], I^2=93%, τ=0.28; moderate certainty of evidence). Precision increased for IIV3-HD versus IIV3-SD when restricting to studies with participants over 80 years of age (2 RCTs[16, 22], 35,859 participants; OR 0.92, 95%CI [0.86 to 0.99], I^2=0%, τ=0.00; moderate certainty of evidence; Table 5).

Appendix 18B: Additional Analyses

Figure 1. Network plots for the network meta-analyses with combined coding of interventions of a) laboratory-confirmed influenza, b) influenza-like illness.



Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Appendix 18C: Sensitivity Analyses

Laboratory-confirmed influenza

Table 1. Sensitivity Analysis: Summary of network meta-analysis results for laboratory-confirmed influenza with original coding of interventions, restricted to studies in which the proportion of females was at least 50%.

Network Meta-analysis results; 7 studies, 52,009 patients, 6 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj: IIV3-HD	1.15	2.32	0.22	5.98	0.17	0.86	0.03	42.79
IIV3-Adj: IIV3-SD	0.85	2.31	0.17	4.41	-0.19	0.85	0.02	31.46
IIV3-Adj: IIV4-SD	0.66	2.20	0.14	3.08	-0.53	0.59	0.02	19.59
IIV3-Adj: Placebo	0.39	2.67	0.06	2.70	-0.95	0.34	0.01	26.88
IIV3-Adj: RIV	0.95	2.18	0.21	4.37	-0.06	0.95	0.03	27.01
IIV3-HD: IIV3-SD	0.74	1.09	0.63	0.87	-3.56	0.00	0.51	1.07
IIV3-HD: IIV4-SD	0.57	1.56	0.24	1.36	-1.27	0.20	0.08	3.84
IIV3-HD: Placebo	0.34	1.68	0.12	0.94	-2.08	0.04	0.04	3.16
IIV3-HD: RIV	0.83	1.53	0.36	1.89	-0.46	0.65	0.13	5.08
IIV3-SD: IIV4-SD	0.77	1.55	0.33	1.81	-0.60	0.55	0.12	5.05
IIV3-SD: Placebo	0.46	1.66	0.17	1.26	-1.51	0.13	0.05	4.14
IIV3-SD: RIV	1.11	1.52	0.49	2.52	0.26	0.79	0.19	6.68
IIV4-SD: Placebo	0.60	1.96	0.16	2.24	-0.76	0.45	0.03	10.81
IIV4-SD: RIV	1.45	1.14	1.11	1.89	2.76	0.01	0.81	2.59
RIV: Placebo	0.41	1.93	0.11	1.51	-1.34	0.18	0.02	7.04
Common within-network between-study SD (tau)	<0.0001							
I-square	0%							

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 1. Treatment ranking of interventions using P-score for laboratory-confirmed influenza with original coding of interventions, restricted to studies in which the proportion of females was at least 50%.

Treatment Ranking	
Treatment	***P-score***
IIV3-HD	0.82
RIV	0.66
IIV3-Adj	0.61
IIV3-SD	0.50
IIV4-SD	0.29
Placebo	0.11

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

Table 2. Sensitivity Analysis: Summary of network meta-analysis results for laboratory-confirmed influenza with combined coding of interventions.

Network Meta-analysis results; 9 studies, 52,202 patients, 5 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
Adj: HD	0.96	2.18	0.21	4.42	-0.06	0.95	0.13	7.12
Adj: Placebo	0.22	2.38	0.04	1.22	-1.73	0.08	0.02	2.08
Adj: RIV	1.00	2.17	0.22	4.56	0.00	1.00	0.14	7.31
Adj: SD	0.71	2.18	0.15	3.27	-0.44	0.66	0.10	5.25
HD: Placebo	0.23	1.48	0.11	0.50	-3.69	0.00	0.08	0.64
HD: RIV	1.05	1.17	0.78	1.42	0.32	0.75	0.71	1.55
HD: SD	0.74	1.09	0.63	0.88	-3.53	0.00	0.60	0.92
RIV: Placebo	0.22	1.50	0.10	0.49	-3.70	0.00	0.08	0.63
SD: Placebo	0.31	1.47	0.15	0.67	-3.01	0.00	0.12	0.85
RIV: SD	0.71	1.14	0.55	0.91	-2.70	0.01	0.51	0.98
Common within-network between-study SD (tau)	<0.0001							
I-square	0%							

Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 2. Treatment ranking of interventions using P-score for laboratory-confirmed influenza with combined coding of interventions..

Treatment Ranking	
Treatment	***P-score***
RIV	0.78
HD	0.71
Adj	0.66
SD	0.33
Placebo	0.01

Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

Table 3. Sensitivity Analysis: Summary of network meta-analysis results for laboratory-confirmed influenza with original coding of interventions, restricted to matched studies

Network Meta-analysis results; 7 studies, 52,009 patients, 6 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj:IIV3-HD	1.23	2.37	0.23	6.72	0.24	0.81	0.03	54.51
IIV3-Adj:IIV3-SD	0.85	2.36	0.16	4.60	-0.18	0.85	0.02	36.84
IIV3-Adj:IIV4-SD	2.54	4.61	0.13	50.89	0.61	0.54	0.00	1899.21
IIV3-Adj:Placebo	0.27	2.58	0.04	1.71	-1.39	0.16	0.00	16.81
IIV3-Adj: RIV	0.94	2.21	0.20	4.46	-0.07	0.94	0.03	30.79
IIV3-HD: IIV3-SD	0.69	1.19	0.50	0.97	-2.17	0.03	0.25	1.92
IIV3-HD: IIV4-SD	2.06	3.53	0.17	24.40	0.57	0.57	0.01	489.55
IIV3-HD: Placebo	0.22	1.55	0.09	0.51	-3.50	0.00	0.03	1.61
IIV3-HD: RIV	0.76	1.59	0.31	1.90	-0.58	0.56	0.09	6.36
IIV3-SD: IIV4-SD	0.34	3.57	0.03	4.06	-0.86	0.39	0.00	83.59
IIV3-SD: Placebo	3.21	1.50	1.45	7.06	2.89	0.00	0.49	20.89
IIV3-SD: RIV	0.90	1.55	0.38	2.15	-0.23	0.82	0.12	6.86
IIV4-SD: Placebo	0.10	3.80	0.01	1.43	-1.69	0.09	0.00	34.04
IIV4-SD: RIV	0.37	3.83	0.03	5.15	-0.74	0.46	0.00	125.18
RIV:Placebo	3.54	1.82	1.10	11.42	2.12	0.03	0.25	51.00
Common within-network between-study SD (tau)	0.17							
I-square	16.8%							

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Note: This analysis incorporates DiazGranados' 2014 study categorized as matched [16].

Figure 3. Treatment ranking of interventions using P-score for laboratory-confirmed influenza with original coding of interventions, restricted to matched studies

Treatment Ranking	
Treatment	***P-score***
IIV4-SD	0.80
IIV3-HD	0.72
IIV3-Adj	0.54
RIV	0.51
IIV3-SD	0.41
Placebo	0.03

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

Note: This analysis incorporates DiazGranados' 2014 study categorized as matched [16].

Table 4. Sensitivity Analysis: Summary of network meta-analysis results for laboratory-confirmed influenza with original coding of interventions, restricted to matched studies

Network Meta-analysis results; 7 studies, 52,009 patients, 6 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj:IIV3-HD	1.63	2.49	0.27	9.75	0.24	0.81	0.00	233156.46
IIV3-Adj:IIV3-SD	0.75	2.41	0.13	4.20	-0.18	0.85	0.00	72688.61
IIV3-Adj:IIV4-SD	3.37	4.76	0.16	71.72	0.61	0.54	0.00	1626520650.37
IIV3-Adj:Placebo	0.23	2.64	0.03	1.57	-1.39	0.16	0.00	70720.59
IIV3-Adj: RIV	0.87	2.24	0.18	4.23	-0.07	0.94	0.00	33527.26
IIV3-HD: IIV3-SD	0.46	1.52	0.20	1.05	-2.17	0.03	0.00	176.28
IIV3-HD: IIV4-SD	2.06	3.55	0.17	24.68	0.57	0.57	0.00	24787969.68
IIV3-HD: Placebo	0.14	1.80	0.04	0.45	-3.50	0.00	0.00	397.02
IIV3-HD: RIV	0.53	1.78	0.17	1.65	-0.58	0.56	0.00	1283.40
IIV3-SD: IIV4-SD	0.22	3.80	0.02	3.04	-0.86	0.39	0.00	6280021.74
IIV3-SD: Placebo	3.21	1.51	1.43	7.21	2.89	0.00	0.01	1123.64
IIV3-SD: RIV	0.86	1.58	0.35	2.10	-0.23	0.82	0.00	502.06
IIV4-SD: Placebo	0.07	4.04	0.00	1.07	-1.69	0.09	0.00	4275629.92
IIV4-SD: RIV	0.26	4.02	0.02	3.96	-0.74	0.46	0.00	15005749.72
RIV:Placebo	3.74	1.85	1.12	12.52	2.12	0.03	0.00	14333.37
Common within-network between-study SD (tau)	0.21							
I-square	3.7%							

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Note: This analysis incorporates DiazGranados' 2014 study categorized as mismatched.[16]

Figure 4. Treatment ranking of interventions using P-score for laboratory-confirmed influenza with original coding of interventions, restricted to matched studies

Treatment Ranking	
Treatment	***P-score***
IIV4-SD	0.83
IIV3-HD	0.76
IIV3-Adj	0.53
RIV	0.47
IIV3-SD	0.38
Placebo	0.02

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

Note: This analysis incorporates DiazGranados' 2014 study categorized as mismatched.[16]

Influenza-like Illness

Note: NMA of original coding of interventions was not conducted because the number of studies was smaller than the number of nodes.

Table 5. Sensitivity Analysis: Summary of network meta-analysis results for influenza-like illness with combined coding of interventions.

Network Meta-analysis results; 9 studies, 65,658 participants, 6 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
Adj: HD	1.05	1.09	0.89	1.25	0.60	0.55	0.80	1.39
Adj: Placebo	0.40	1.60	0.16	0.99	-1.97	0.05	0.09	1.77
Adj: RIV	1.04	1.10	0.86	1.26	0.44	0.66	0.76	1.42
Adj: SD	1.03	1.09	0.87	1.21	0.34	0.73	0.79	1.34
Adj: Tdap	0.98	1.06	0.87	1.10	-0.36	0.72	0.82	1.17
HD: Placebo	0.38	1.59	0.15	0.93	-2.12	0.03	0.09	1.63
HD: RIV	0.99	1.06	0.89	1.11	-0.17	0.87	0.83	1.19
HD: SD	0.98	1.02	0.93	1.02	-0.99	0.32	0.90	1.05
HD: Tdap	0.93	1.11	0.76	1.14	-0.70	0.49	0.67	1.30
Placebo: RIV	0.38	1.59	0.15	0.94	-2.09	0.04	0.60	11.59
Placebo: SD	0.38	1.59	0.16	0.95	-2.07	0.04	0.60	11.25
Placebo: Tdap	0.40	1.60	0.16	1.02	-1.92	0.06	0.55	11.13
RIV: SD	0.99	1.05	0.89	1.09	-0.27	0.78	0.84	1.16
RIV: Tdap	0.94	1.12	0.75	1.17	-0.56	0.58	0.66	1.35
SD: Tdap	0.95	1.11	0.78	1.16	-0.49	0.63	0.69	1.31
Common within-network between-study SD (tau)	<0.0001							
I-square	0.00%							

Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 5. Treatment ranking of interventions using P-score for influenza-like illness with combined coding of interventions.

Treatment Ranking	
Treatment	***P-score***
Adj	0.52
HD	0.77
Placebo	0.02
RIV	0.68
SD	0.57
Tdap	0.44

Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Number of vascular adverse events

Table 6. Summary of network meta-analysis results for number of vascular adverse events with original coding of interventions, restricted to studies in which the overall risk of bias was low.

Network Meta-analysis results; 4 studies, 37,043 patients, 5 treatments								
Comparison	***IRR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj: IIV3-HD	1.16	4.15	0.07	18.94	0.11	0.91	.	.
IIV3-Adj: IIV3-SD	1.01	4.12	0.06	16.27	0.01	0.99	.	.
IIV3-Adj: IIV4-Adj	5.01	4.71	0.24	104.53	1.04	0.30	.	.
IIV3-Adj: IIV4-HD	1.75	4.58	0.09	34.60	0.37	0.71	.	.
IIV3-HD: IIV3-SD	0.87	1.15	0.67	1.14	-1.02	0.31	.	.
IIV3-HD: IIV4-Adj	4.30	8.20	0.07	265.99	0.69	0.49	.	.
IIV3-HD: IIV4-HD	1.50	1.72	0.52	4.34	0.75	0.45	.	.
IIV3-SD: IIV4-Adj	0.20	8.16	0.00	12.39	-0.76	0.45	.	.
IIV3-SD: IIV4-HD	0.58	1.75	0.19	1.73	-0.98	0.33	.	.
IIV4-Adj: IIV4-HD	0.35	8.78	0.00	24.69	-0.48	0.63	.	.
Common within-network between-study SD	0							
I-square	0.00%							

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; IRR: Incidence rate ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

Figure 6. Treatment ranking of interventions using P-score for number of vascular adverse events with original coding of interventions, restricted to studies in which the overall risk of bias was low.

Treatment Ranking	
Treatment	***P-score***
IIV4-Adj	0.77
IIV4-HD	0.64
IIV3-HD	0.46
IIV3-Adj	0.36
IIV3-SD	0.26

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage

All-cause mortality

Table 7. Summary of network meta-analysis results for all-cause mortality with original coding of interventions, restricted to studies in which the overall risk of bias was low.

Network Meta-analysis results; 9 studies, 52,902 patients, 7 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj:IIV3-HD	0.63	2.92	0.08	5.17	-0.43	0.67	0.01	63.79
IIV3-Adj:IIV3-SD	0.62	2.93	0.08	5.10	-0.44	0.66	0.01	63.17
IIV3-Adj:IIV4-Adj	0.20	4.71	0.01	4.16	-1.04	0.30	0.00	157.13
IIV3-Adj:IIV4-HD	0.84	4.09	0.05	13.34	-0.12	0.90	0.00	361.86
IIV3-Adj:IIV4-SD	0.64	2.93	0.08	5.24	-0.42	0.67	0.01	65.23
IIV3-Adj:Tdap	0.19	4.80	0.01	4.20	-1.05	0.30	0.00	165.84
IIV3-HD:IIV3-SD	0.98	1.16	0.73	1.32	-0.11	0.91	0.52	1.87
IIV3-HD:IIV4-Adj	0.32	6.58	0.01	12.69	-0.61	0.54	0.00	1049.28
IIV3-HD:IIV4-HD	1.33	2.49	0.22	7.99	0.31	0.75	0.03	67.99
IIV3-HD:IIV4-SD	1.00	1.10	0.83	1.22	0.05	0.96	0.66	1.53
IIV3-HD:Tdap	0.31	6.69	0.01	12.71	-0.62	0.53	0.00	1091.33
IIV3-SD:IIV4-Adj	3.12	6.59	0.08	125.57	0.60	0.55	0.00	10406.29
IIV3-SD:IIV4-HD	0.74	2.52	0.12	4.53	-0.33	0.74	0.01	39.65
IIV3-SD:IIV4-SD	0.98	1.19	0.70	1.38	-0.12	0.91	0.46	2.08
IIV3-SD:Tdap	3.21	6.70	0.08	133.40	0.61	0.54	0.00	11475.22
IIV4-Adj:IIV4-HD	4.23	8.12	0.07	256.30	0.69	0.49	0.00	34656.14
IIV4-Adj:IIV4-SD	3.18	6.60	0.08	128.57	0.61	0.54	0.00	10692.71
IIV4-Adj:Tdap	0.97	1.28	0.60	1.57	-0.12	0.91	0.34	2.79
IIV4-HD:IIV4-SD	0.75	2.51	0.12	4.56	-0.31	0.76	0.01	39.29
IIV4-HD:Tdap	0.23	8.24	0.00	14.34	-0.70	0.49	0.00	2005.28
IIV4-SD:Tdap	0.31	6.71	0.01	12.71	-0.62	0.53	0.00	1097.64
Common within-network between-study SD				<0.0001				
I-square				0.00%				

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval ; se: Standard error

Figure 7. Treatment ranking of interventions using P-score for outpatient visits with original coding of interventions, restricted to studies in which the overall risk of bias was low.

Treatment Ranking	
Treatment	***P-score***
IIV3-Adj	0.71
IIV4-HD	0.64
IIV4-SD	0.54
IIV3-HD	0.53
IIV3-SD	0.51
IIV4-Adj	0.29
Tdap	0.27

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; Tdap: Tetanus, diphtheria, pertussis

Table 8. Sensitivity Analysis**:** Summary of network meta-analysis results for all-cause mortality with original coding of interventions, restricted to studies in which the proportion of females was at least 50%.

Network Meta-analysis results; 16 studies, 102,519 patients, 6 treatments								
Comparison	***OR***	***seOR***	***Lower CI***	***Upper CI***	***Statistic***	***p-value***	***Lower PI***	***Upper PI***
IIV3-Adj:IIV3-HD	1.12	1.23	0.75	1.68	0.58	0.56	0.70	1.80
IIV3-Adj:IIV3-SD	1.09	1.22	0.73	1.61	0.42	0.67	0.68	1.73
IIV3-Adj:IIV4-HD	1.50	2.55	0.24	9.40	0.43	0.67	0.17	12.99
IIV3-Adj:IIV4-SD	1.12	1.25	0.72	1.74	0.50	0.62	0.66	1.88
IIV3-Adj:Placebo	1.60	1.94	0.44	5.85	0.71	0.48	0.35	7.36
IIV3-Adj:RIV	1.56	1.60	0.62	3.91	0.94	0.35	0.53	4.60
IIV3-HD:IIV3-SD	0.97	1.03	0.91	1.03	-0.99	0.32	0.90	1.04
IIV3-HD:IIV4-HD	1.33	2.49	0.22	7.99	0.31	0.75	0.16	10.97
IIV3-HD:IIV4-SD	0.99	1.10	0.82	1.21	-0.06	0.95	0.79	1.25
IIV3-HD:Placebo	1.42	1.88	0.41	4.90	0.55	0.58	0.33	6.10
IIV3-HD:RIV	1.38	1.53	0.60	3.18	0.77	0.44	0.52	3.68
IIV3-SD:IIV4-HD	1.38	2.50	0.23	8.27	0.35	0.73	0.17	11.35
IIV3-SD:IIV4-SD	1.03	1.11	0.84	1.26	0.26	0.79	0.81	1.31
IIV3-SD:Placebo	1.47	1.88	0.43	5.06	0.61	0.54	0.34	6.29
IIV3-SD:RIV	1.43	1.53	0.62	3.29	0.84	0.40	0.54	3.81
IIV4-HD:IIV4-SD	0.75	2.51	0.12	4.52	-0.32	0.75	0.09	6.21
IIV4-HD:Placebo	1.06	3.04	0.12	9.40	0.06	0.96	0.08	13.81
IIV4-HD:RIV	1.04	2.74	0.14	7.48	0.04	0.97	0.10	10.60
IIV4-SD:Placebo	1.43	1.90	0.41	5.00	0.56	0.58	0.33	6.24
IIV4-SD vs. RIV	1.39	1.52	0.62	3.15	0.80	0.43	0.53	3.64
RIV vs. Placebo	1.03	2.14	0.23	4.55	0.03	0.97	0.18	5.93
Common within-network between-study SD		<0.0001						
I-square		0.00%						

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; se: Standard error

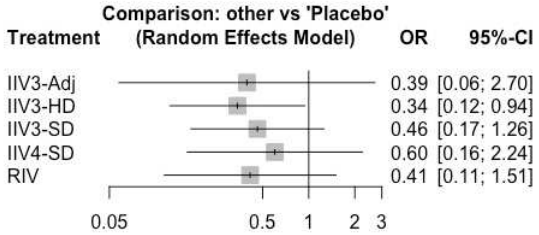
Figure 8. Treatment ranking of interventions using P-score for all-cause mortality with original coding of interventions, restricted to studies in which the proportion of females was at least 50%.

Treatment Ranking	
Treatment	***P-score***
IIV3-HD	0.82
RIV	0.66
IIV3-Adj	0.61
IIV3-SD	0.50
IIV4-SD	0.29
Placebo	0.11

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

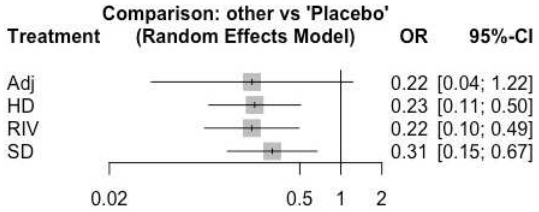
Laboratory-confirmed influenza

Figure 9. Sensitivity Analysis: Forest Plots of network estimates relative to placebo for laboratory-confirmed influenza with original coding of interventions, restricted to studies in which the proportion of females was at least 50%.



*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval

Figure 10. Sensitivity Analysis: Forest Plots of network estimates relative to placebo for laboratory-confirmed influenza with combined coding of interventions.

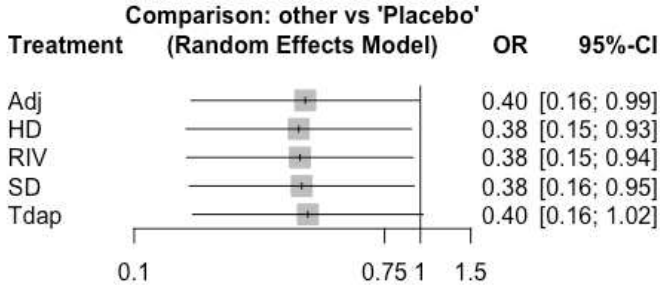


*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; OR: Odds ratio; CI: Confidence interval

Influenza-like illness

Note: NMA of original coding of interventions was not conducted because the number of studies was smaller than the number of nodes.

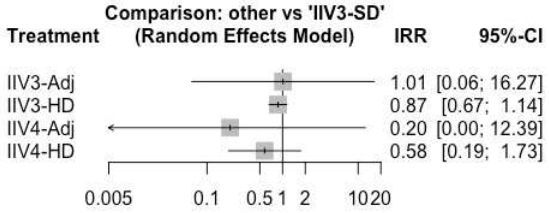
Figure 11. Sensitivity Analysis: Forest Plots of network estimates relative to placebo for influenza-like illness with combined coding of interventions.



*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interval

Number of vascular adverse events

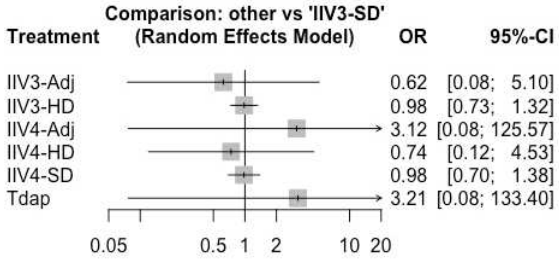
Figure 12. Forest Plot of network estimates relative to IIV3-SD for number of vascular adverse events with original coding of interventions, restricted to studies in which the overall risk of bias was low.



*IRR>1 favours IIV3-SD; IRR<1 favours intervention
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; HD: High dosage; IRR: incidence rate ratio; CI: Confidence interval

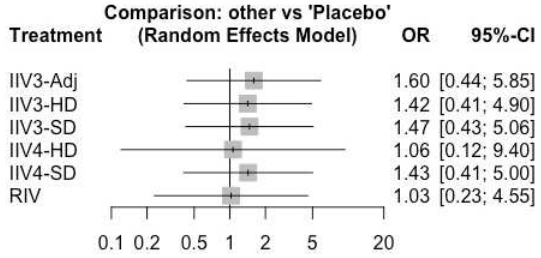
All-cause mortality

Figure 13. Sensitivity Analysis: Forest Plots of network estimates relative to IIV3-SD for all-cause mortality with original coding of interventions, restricted to studies in which the overall risk of bias was low.



*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interval

Figure 14. Sensitivity Analysis: Forest Plots of network estimates relative to placebo for all-cause mortality with original coding of interventions, restricted to studies in which the proportion of females was at least 50%.



*OR>1 favours placebo; OR<1 favours intervention
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis; OR: Odds ratio; CI: Confidence interva

Appendix 18D: Confidence in Network Meta-Analysis (CINeMA) Assessments Under NACI-Recommended Minimally Important Differences.

Laboratory-confirmed influenza

Table 1. CINeMA assessment providing credibility for each treatment comparison for laboratory-confirmed influenza under NACI-recommended minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-Adj:IIV3-HD	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:RIV	1	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:IIV3-SD	3	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High	Not applicable
IIV3-HD:IIV4-SD	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low	["Within-study bias","Imprecision","Heterogeneity"]
IIV3-HD:RIV	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-SD:Placebo	2	Major concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low	["Within-study bias","Indirectness"]
IIV3-SD:RIV	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-SD:RIV	1	Major concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low	["Within-study bias","Heterogeneity"]
Indirect Evidence									
IIV3-Adj:IIV3-SD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:IIV4-SD	0	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:Placebo	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low	["Within-study bias","Imprecision","Heterogeneity"]
IIV3-HD:Placebo	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low	["Within-study bias","Indirectness"]
IIV3-SD:IIV4-SD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

IIV4-SD:Placebo	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Very low	["Within-study bias","Imprecision","Heterogeneity"]
Placebo:RIV	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low	["Within-study bias","Heterogeneity"]

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

Number of vascular adverse events

Table 2. CINeMA assessment providing credibility for each treatment comparison for number of vascular adverse events under NACI-recommended minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-Adj:IIV3-SD	2	Major concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-Adj:IIV4-Adj	1	No concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Moderate	["Incoherence"]
IIV3-HD:IIV3-SD	4	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low	["Heterogeneity","Incoherence"]
IIV3-HD:IIV4-HD	1	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low	["Heterogeneity","Incoherence"]
Indirect Evidence									
IIV3-Adj:IIV3-HD	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-Adj:IIV4-HD	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-HD:IIV4-Adj	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]

IIV3-SD:IIV4-Adj	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-SD:IIV4-HD	0	No concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Low	["Heterogeneity","Incoherence"]
IIV4-Adj:IIV4-HD	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage									

Outpatient visits

Table 3. CINeMA assessment providing credibility for each treatment comparison for outpatient visits under recommended minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-HD:IIV3-SD	2	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-SD:Placebo	2	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Very low	["Within-study bias","Imprecision","Heterogeneity","Incoherence"]
Indirect Evidence									
IIV3-HD:Placebo	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Very low	["Within-study bias","Imprecision","Heterogeneity","Incoherence"]
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage									

All-cause mortality

Table 4. CINeMA assessment providing credibility for each treatment comparison for all-cause mortality under recommended minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-Adj:IIV3-HD	1	Some concerns	No concerns	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
IIV3-Adj:IIV3-SD	2	Some concerns	No concerns	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
IIV3-Adj:IIV4-Adj	1	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-HD:IIV3-SD	6	Some concerns	No concerns	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
IIV3-HD:IIV4-HD	1	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-HD:IIV4-SD	1	No concerns	No concerns	Some concerns	No concerns	No concerns	No concerns	Moderate	["Indirectness"]
IIV3-SD:IIV4-SD	3	No concerns	No concerns	No concerns	No concerns	No concerns	No concerns	High	Not applicable
IIV3-SD:Placebo	2	Some concerns	No concerns	Some concerns	Some concerns	No concerns	No concerns	Very low	["Within-study bias","Indirectness","Imprecision"]
IIV3-SD:RIV	1	Some concerns	No concerns	No concerns	Some concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-Adj:Tdap	1	No concerns	No concerns	No concerns	No concerns	No concerns	No concerns	High	Not applicable
IIV4-SD:RIV	1	Some concerns	No concerns	No concerns	Some concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
Indirect Evidence									
IIV3-Adj:IIV4-HD	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:IIV4-SD	0	Some concerns	No concerns	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
IIV3-Adj:Placebo	0	Some concerns	No concerns	No concerns	Some concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:RIV	0	Some concerns	No concerns	No concerns	Some concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

IIV3-HD:IIV4-Adj	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:Placebo	0	Some concerns	No concerns	No concerns	Some concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:RIV	0	Some concerns	No concerns	No concerns	Some concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-SD:IIV4-Adj	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-SD:IIV4-HD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-SD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-Adj:IIV4-HD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-Adj:IIV4-SD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-Adj:Placebo	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-Adj:RIV	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-HD:IIV4-SD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-HD:Placebo	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-HD:RIV	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-HD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-SD:Placebo	0	Some concerns	No concerns	Some concerns	Some concerns	No concerns	No concerns	Very low	["Within-study bias","Indirectness","Imprecision"]
IIV4-SD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
Placebo:RIV	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
Placebo:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
RIV:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Appendix 18E: Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Assessments of Subgroup Analysis

Comparison 1: High Dose Trivalent Vaccine compared to Standard Dose Trivalent Vaccine for preventing influenza.

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Dose Trivalent Vaccine	Standard Dose Trivalent Vaccine	Relative (95% CI)	Absolute (95% CI)		
Inpatient hospitalization (any cause)- SUBGROUP: Low RoB												
RCTs	Not serious	Not serious[i]	Not serious	Serious[j]	None	1727/17456 (9.9%)	1944/17489 (11.1%)	**OR 0.70** (0.52 to 1.13)	**31 fewer per 1,000** (from 50 fewer to 13 more)	⨁⨁⨁◯ Moderate	RCTs	
Inpatient hospitalization (any cause)- SUBGROUP >80y												
RCTs	Serious[h]	Not serious	Not serious	Not serious	None	1531/18578 (8.2%)	1644/17281 (9.5%)	**OR 0.92** (0.86 to 0.99)	**7 fewer per 1,000** (from 12 fewer to 1 fewer)	⨁⨁⨁◯ Moderate		

Abbreviations – RCTs: Randomized controlled trials; CI: Confidence interval; OR**:** Odds ratio

Explanations

a. Study that carried large weight for the overall effect estimated rated as some concerns due to bias arising from the randomization process and bias in selection of the reported result. Another study that carried small weight for the overall effect estimated rated as high risk of bias due to missing outcome data

b. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm, including only 27 events in total.

c. Study that carried large weight for the overall effect estimated rated as high risk of bias due to some concerns in the timing of identification or recruitment of participants in a cluster trial, bias due to deviations from intended interventions and bias due to missing outcome data.

d. Study that carried large weight for the overall effect estimated was rated as low risk of bias, and the other study, that carried small weight for the overall effect estimated, was rated as high risk of bias due to deviations from intended interventions.

e. I^2 value is 87%, suggesting some heterogeneity; We could not find the reasons for this high heterogeneity

f. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm, including only 287 events in total

g. Study that carried large weight for the overall effect estimated rated as some concerns due to bias in selection of the reported result. No rating down due to RoB

h. Study that carried large weight for the overall effect estimated rated as high risk of bias due to missing outcome data

i. I^2=87%, suggesting substantial heterogeneity, but of questionable clinical importance, because the two studies with more weight in the meta-analysis show a significant effect. We did not rate down due to inconsistency

j. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm.

Appendix 18F: Pairwise Subgroup Meta-Analyses

Table 1. Pairwise meta-analysis results for each outcome in which a subgroup analysis was conducted

Primary Outcomes															
Outcome	***Comparison***	***Number of studies***	***Number of participants***	***OR***	***lower CI***	***upper CI***	***lower PI***	***upper PI***	***tau***	***tau² lower CI***	***tau² upper CI***	***Q***	***Q df***	***Q P-value***	***I²***
LCI – Matched strains (DiazGranados 2014 defined as Match)	IIV3-HD : IIV3-SD	2	330	0.74	0.63	0.88	.	.	0	.	.	0.86	1	0.35	0
LCI – Mismatched strains (DiazGranados 2014 defined as Match)	IIV3-HD : IIV3-SD	1	9158	0.87	0.56	1.36	.	.	.	.	.	.	.	.	.
LCI – Matched strains (DiazGranados 2014 defined as Mismatch)	IIV3-HD : IIV3-SD	1	612	0.52	0.35	0.77	.	.	.	.	.	.	.	.	.
LCI – Mismatched strains (DiazGranados 2014 defined as Mismatch)	IIV3-HD : IIV3-SD	2	31,141	0.76	0.64	0.90	.	.	0	.	.	0.11	1	0.75	0
Secondary Outcomes															
Outcome	***Comparison***	***Number of studies***	***Number of participants***	***OR***	***lower CI***	***upper CI***	***lower PI***	***upper PI***	***tau***	***tau² lower CI***	***tau² upper CI***	***Q***	***Q df***	***Q P-value***	***I²***
Inpatient Hospitalization (any cause) – Low RoB subgroup	IIV3-HD : IIV3-SD	2	34940	0.76	0.52	1.13	.	.	0.27	.	.	14.00	1	0.00	93%
Inpatient Hospitalization (any cause) – Over 80 y.o. subgroup	IIV3-HD : IIV3-SD	2	35859	0.92	0.86	0.99	.	.	0.00	.	.	0.20	1	0.66	0%

Laboratory confirmed influenza

Figure 1. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control), restricted to matched studies.

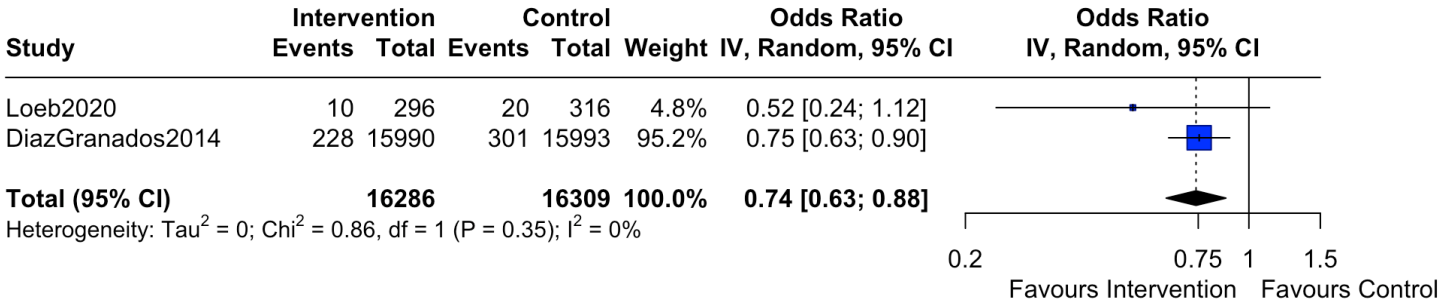
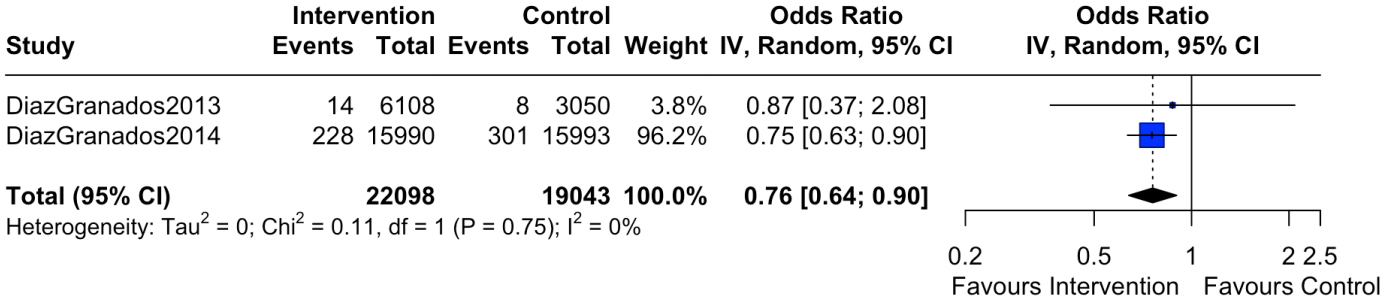


Figure 2. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control), restricted to mismatched studies



Appendix 19: Methods for lab-confirmed influenza diagnoses

Author, Year	Source of Diagnosis	Influenza Diagnosis
DiazGranados, 2013[11]	Determined by Investigator	"If a participant met the criteria for ILI, the study site was to arrange for a nasopharyngeal (NP) swab to be taken within 5 days of ILI episode onset. NP samples underwent tissue culture and molecular testing (Polymerase-Chain-Reaction [PCR]-based assays) for laboratory confirmation of influenza."
DiazGranados, 2014[16]	Determined by Investigator	"If a participant met the criteria for any respiratory illness, staff members at the study site were to collect a nasopharyngeal swab within 5 days after onset of the illness. Laboratory confirmation of influenza in nasopharyngeal swabs was accomplished by a positive result on culture, a polymerase-chain-reaction (PCR) assay, or both."
Beran, 2021[28]	Determined by Investigator	"By two commercial lab tests: RT-PCR; viral expansion in Madin Darby Canine Kidney cell culture. Viral strain antigenic typing was determined by means of HA inhibition or microneutralization assays."
Belongia, 2020[25]	Determined by Investigator	"Nasal and oropharyngeal swabs were combined and tested for influenza type and subtype using real time reverse transcription polymerase chain reaction (RT-PCR) at the Marshfield Clinic Research Institute using CDC primers and probes."
Dunkle, 2017[20]	NR	NR
Keitel, 2010[10]	Determined by Investigator	"By cell culture and then treatment with virus A and virus B strain specific fluorescent antibodies." "Virus isolation was carried out using standard cell culture methods in primary rhesus monkey kidney (PRhMK) cells. Briefly, clinical samples were absorbed onto PRhMK monolayers for approximately 60 min, and then monitored daily for cytopathic effect up to 14 days. If a cytopathic effect score of 2+ was reached, the presence (or absence) of either influenza A or B was determined by fluorescent antibody testing with monoclonal antibodies."
Wongsurakiat, 2004[7]	Determined by Investigator	"A fourfold HI titer increase in convalescent serum compared to acute serum with a titer of 40 and/or demonstration of influenza antigen with or without positive culture finding was considered as meeting the criteria for influenza virus infection."
Rudenko, 2001[6]	Determined by Investigator	"The presence of influenza-like illness in association with isolation of influenza virus, or a >= 4 fold rise in serum HI antibody between acute- and convalescent- phase serum samples, or both."
Teh, 2021[30]	Determined by Investigator	"Patients who reported ILI were asked to present to their general practitioner or study center for medical review and multiplex polymerase chain reaction (PCR) testing for respiratory viruses including influenza."
Loeb, 2020[24]	Determined by Investigator	"Influenza illness was documented by PCR detection of influenza during an ARI or seroconversion (4-fold rise in antibody titers) in association with an ARI."
McLean, 2021[45]	Determined by Investigator	"Respiratory samples were tested for influenza using reverse transcription polymerase chain reaction (RT-PCR) with primers and probes provided by CDC at MCRI."

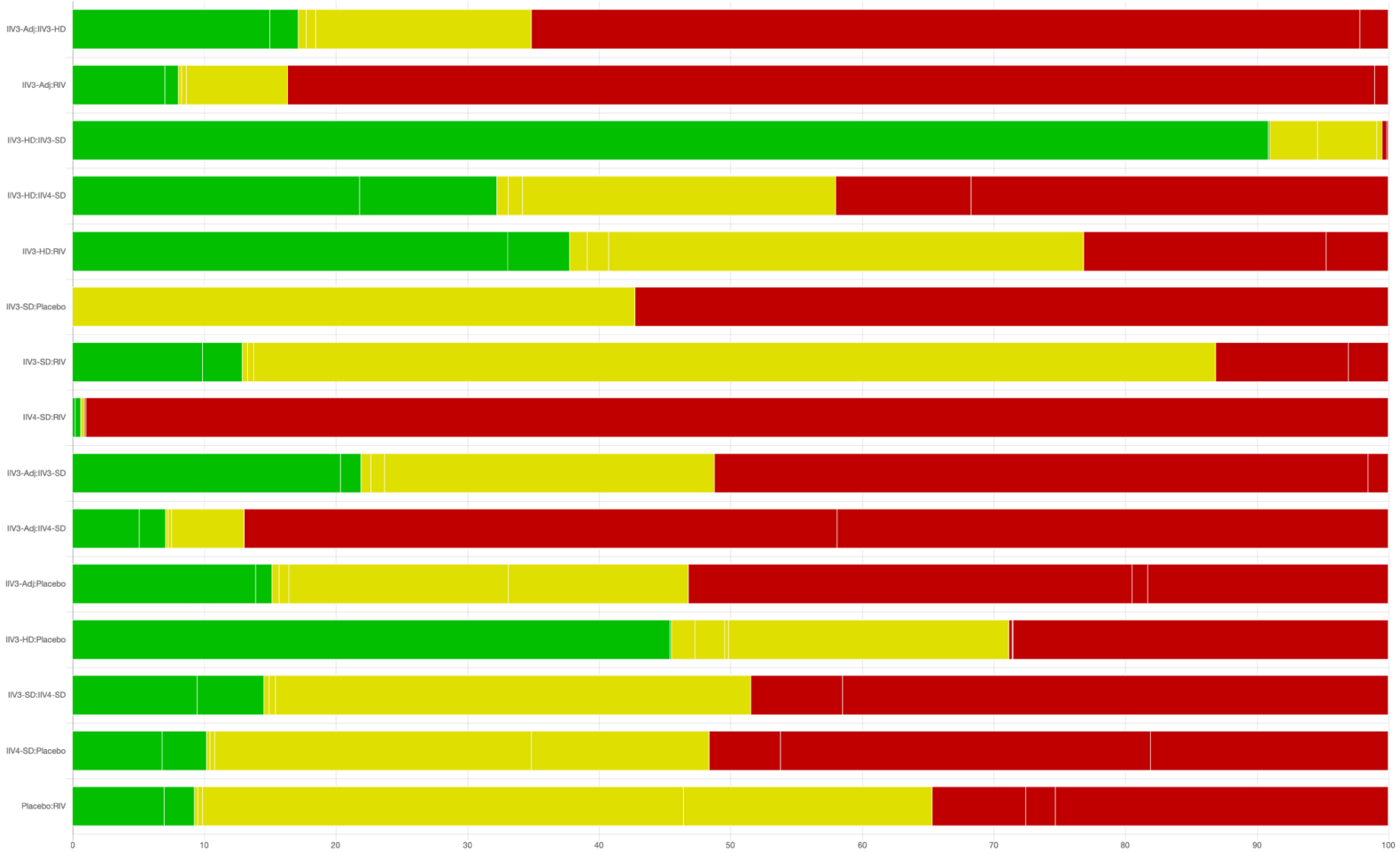
Abbreviations: ARI = Acute respiratory infection; CDC = Centers for Disease Control and Prevention ; HA = hemagglutinin; ILI = Influenza-Like Illness; MCRI = Marshfield Clinic Research Institute; RT-PCR = real time reverse transcription polymerase chain reaction; NR = not reported.

Appendix 20: Confidence in Network Meta-Analysis (CINeMA) Assessments

CINeMA assessments were conducted using the CINeMA tool.[2] Using the tool, all comparisons are graded across six domains (i.e., within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence). Within study bias is obtained from the overall risk of bias assessments where were conducted using the Cochrane RoB2 tool or the RoB2-CRT for cluster trials. Reporting bias was informed by funnel plots where possible, and otherwise was set to “some concern”. An overall confidence rating for each comparison is provided. The rating starts off at “High” and may be downgraded if there are concerns in any of the domains. For our purposes, to be conservative, we treated “some concerns” and “serious concerns” equally. That is, the overall confidence rating was downgraded by one level for each domain (except within-study bias since there was limited information) that had “some concern” or “serious concern”, up to an overall confidence rating of very low. CINeMA assessments are provided for two different minimally important differences, namely, a null effect, and a literature/expert informed important effect. Both results are presented, with minor differences in the overall assessments.

Laboratory-confirmed Influenza

Figure 1. Contribution Matrix plot illustrating the risk of bias for each treatment comparison for laboratory-confirmed influenza



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

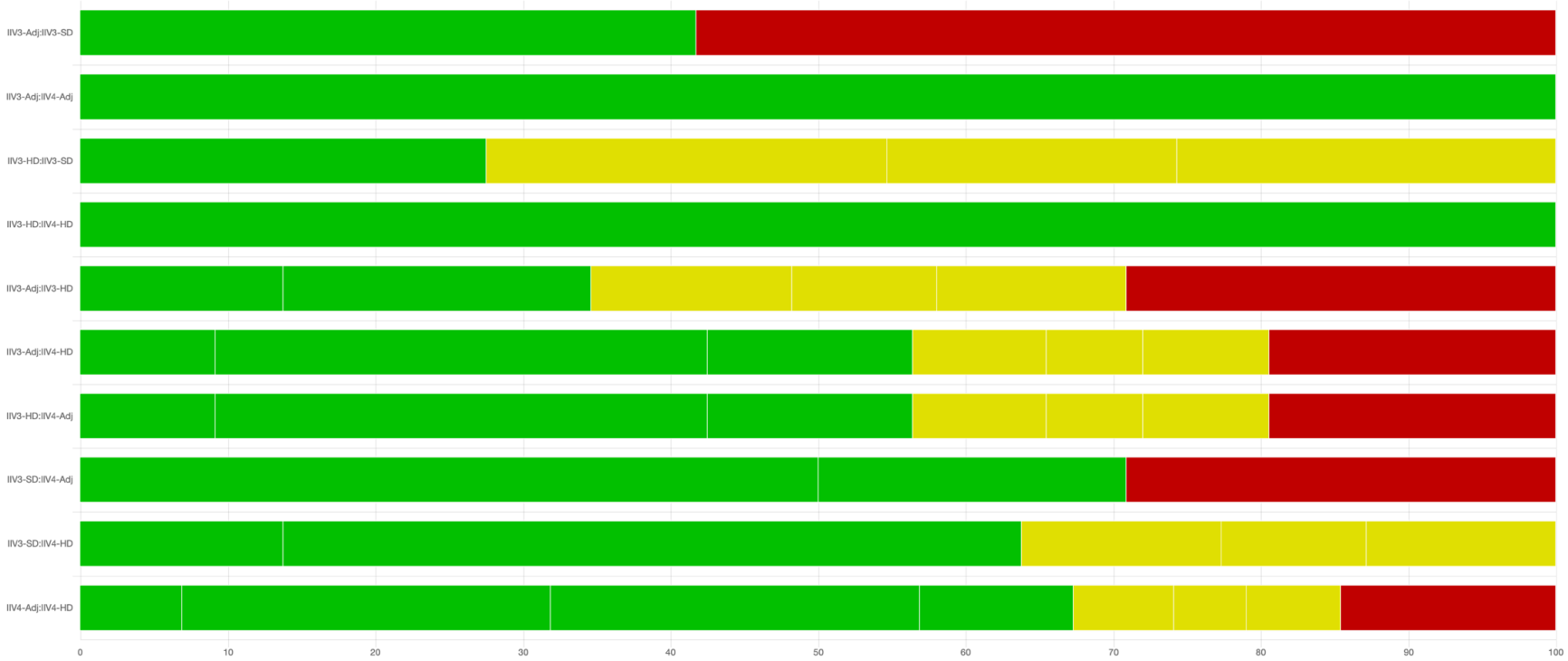
Table 1. CINeMA assessment providing credibility for each treatment comparison for laboratory-confirmed influenza under null minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-Adj:IIV3-HD	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:RIV	1	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:IIV3-SD	3	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High	Not applicable
IIV3-HD:IIV4-SD	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:RIV	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-SD:Placebo	2	Major concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low	["Within-study bias","Indirectness"]
IIV3-SD:RIV	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-SD:RIV	1	Major concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low	["Within-study bias","Heterogeneity"]
Indirect Evidence									
IIV3-Adj:IIV3-SD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:IIV4-SD	0	Major concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:Placebo	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:Placebo	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low	["Within-study bias","Indirectness"]
IIV3-SD:IIV4-SD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-SD:Placebo	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
Placebo:RIV	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low	["Within-study bias","Heterogeneity"]

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine

Number of Vascular Adverse Events

Figure 2. Contribution Matrix plot illustrating the risk of bias for each treatment comparison for number of vascular adverse events



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage

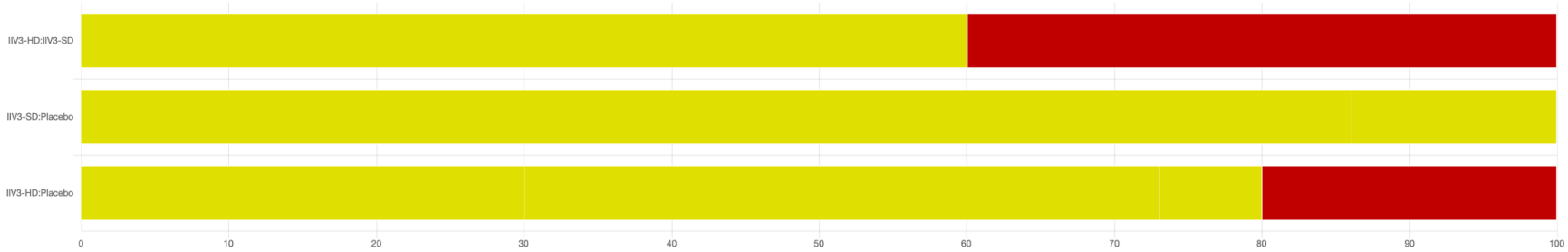
Table 2. CINeMA assessment providing credibility for each treatment comparison for number of vascular adverse events under null minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-Adj:IIV3-SD	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low	["Within-study bias","Imprecision","Incoherence"]
IIV3-Adj:IIV4-Adj	1	No concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Moderate	["Incoherence"]
IIV3-HD:IIV3-SD	4	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-HD:IIV4-HD	1	No concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision","Incoherence"]
Indirect Evidence									
IIV3-Adj:IIV3-HD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low	["Within-study bias","Imprecision","Incoherence"]
IIV3-Adj:IIV4-HD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low	["Within-study bias","Imprecision","Incoherence"]
IIV3-HD:IIV4-Adj	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-SD:IIV4-Adj	0	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias","Heterogeneity","Incoherence"]
IIV3-SD:IIV4-HD	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision","Incoherence"]
IIV4-Adj:IIV4-HD	0	No concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision","Incoherence"]

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage

Outpatient Visits

Figure 3. Contribution Matrix plot illustrating the risk of bias for each treatment comparison for outpatient visits



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage

Table 3. CINeMA assessment providing credibility for each treatment comparison for outpatient visits under null minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-HD:IIV3-SD	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low	["Within-study bias","Imprecision","Incoherence"]
IIV3-SD:Placebo	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low	["Within-study bias","Imprecision","Incoherence"]
Indirect Evidence									
IIV3-HD:Placebo	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low	["Within-study bias","Imprecision","Incoherence"]
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage									

All-cause mortality

Figure 4. Contribution Matrix plot illustrating the risk of bias for each treatment comparison for all-cause mortality

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Table 4. CINeMA assessment providing credibility for each treatment comparison for all-cause mortality under null minimally important differences.

Treatment Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Direct Evidence									
IIV3-Adj:IIV3-HD	1	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:IIV3-SD	2	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:IIV4-Adj	1	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-HD:IIV3-SD	6	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:IIV4-HD	1	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-HD:IIV4-SD	1	No concerns	No concerns	Some concerns	Major concerns	No concerns	No concerns	Low	["Indirectness","Imprecision"]
IIV3-SD:IIV4-SD	3	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-SD:Placebo	2	Some concerns	No concerns	Some concerns	Major concerns	No concerns	No concerns	Very low	["Within-study bias","Indirectness","Imprecision"]
IIV3-SD:RIV	1	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-Adj:Tdap	1	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-SD:RIV	1	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
Indirect Evidence									
IIV3-Adj:IIV4-HD	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:IIV4-SD	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:Placebo	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:RIV	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-Adj:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-HD:IIV4-Adj	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:Placebo	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:RIV	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV3-HD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

IIV3-SD:IIV4-Adj	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-SD:IIV4-HD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV3-SD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-Adj:IIV4-HD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-Adj:IIV4-SD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-Adj:Placebo	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-Adj:RIV	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-HD:IIV4-SD	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-HD:Placebo	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IIV4-HD:RIV	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-HD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IIV4-SD:Placebo	0	Some concerns	No concerns	Some concerns	Major concerns	No concerns	No concerns	Very low	["Within-study bias","Indirectness","Imprecision"]
IIV4-SD:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
Placebo:RIV	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
Placebo:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Imprecision"]
RIV:Tdap	0	No concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	["Imprecision"]

Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; RIV: Recombinant influenza vaccine; Tdap: Tetanus, diphtheria, pertussis

Appendix 21: Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Assessments

Comparison 1: High Dose Trivalent Vaccine compared to Standard Dose Trivalent Vaccine for preventing influenza.

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Dose Trivalent Vaccine	Standard Dose Trivalent Vaccine	Relative (95% CI)	Absolute (95% CI)		
Influenza-like illness (ILI) cases												
2	RCTs	Not serious	Not serious	Not serious	Not serious	None	5065/22098 (22.9%)	4489/19043 (23.6%)	**OR 0.98** (0.93 to 1.02)	**4 fewer per 1,000** (from 13 fewer to 4 more)	⊕⊕⊕⊕ High	
Hospitalization due to acute respiratory infection (ARI)												
2	RCTs	Serious[a]	Not serious	Not serious	Not serious	None	890/42629 (2.1%)	1013/42362 (2.4%)	**OR 0.87** (0.79 to 0.95)	**3 fewer per 1,000** (from 5 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	
ER Visit due to Influenza-like illness (ILI)												
2	RCTs	Not serious[b]	not serious[c]	Not serious	Serious[d]	None	149/22098 (0.7%)	138/19043 (0.7%)	**OR 0.94** (0.74 to 1.19)	**0 fewer per 1,000** (from 2 fewer to 1 more)	⊕⊕⊕◯ Moderate	
Hospitalization due to Influenza-like illness (ILI)												
2	RCTs	Not serious[e]	Not serious	Not serious	Not serious	None	127/22098 (0.6%)	155/19043 (0.8%)	**OR 0.72** (0.57 to 0.92)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⊕⊕⊕⊕ High	
Inpatient Hospitalization (any cause)												
3	RCTs	Serious[f]	Not serious[g]	Not serious	Serious[h]	None	1728/20039 (8.6%)	1945/18777 (10.4%)	**OR 0.76** (0.40 to 1.42)	**23 fewer per 1,000** (from 59 fewer to 37 more)	⊕⊕◯◯ Low	

Abbreviations – RCTs: Randomized controlled trials; CI: Confidence interval; OR**:** Odds ratio

Explanations

a. Study that carried large weight for the overall effect estimated rated as high risk of bias due to some concerns in the timing of identification or recruitment of participants in a cluster trial, bias due to deviations from intended interventions and bias due to missing outcome data.
b. Study that carried large weight for the overall effect estimated was rated as low risk of bias, and the other study, that carried small weight for the overall effect estimated, was rated as high risk of bias due to deviations from intended interventions.
c. I^2 value is 87%, suggesting some heterogeneity; We could not find the reasons for this high heterogeneity
d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm, including only 287 events in total
e. Study that carried large weight for the overall effect estimated rated as some concerns due to bias in selection of the reported result. No rating down due to RoB
f. Study that carried large weight for the overall effect estimated rated as high risk of bias due to missing outcome data
g. I^2=87%, suggesting substantial heterogeneity, but of questionable clinical importance, because the two studies with more weight in the meta-analysis show a significant effect. We did not rate down due to inconsistency
h. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm.

Comparison 2: Standard Dose Trivalent vaccine compared to Placebo for preventing influenza.

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Standard Dose Trivalent vaccine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Influenza-like illness cases												
2	RCTs	Serious[a]	Not serious	Not serious	Serious[b]	None	10/614 (1.6%)	17/240 (7.1%)	**OR 0.39** (0.15 to 1.02)	**42 fewer per 1,000** (from 60 fewer to 1 more)	⨁⨁◯◯ Low	

Abbreviations – RCTs: Randomized controlled trials; CI: Confidence interval; OR**:** Odds ratio

Explanations

a. Study that carried large weight for the overall effect estimated rated as some concerns due to bias arising from the randomization process and bias in selection of the reported result. Another study that carried small weight for the overall effect estimated rated as high risk of bias due to missing outcome data
b. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm, including only 27 events in total.

Appendix 22: Pairwise Meta-Analyses

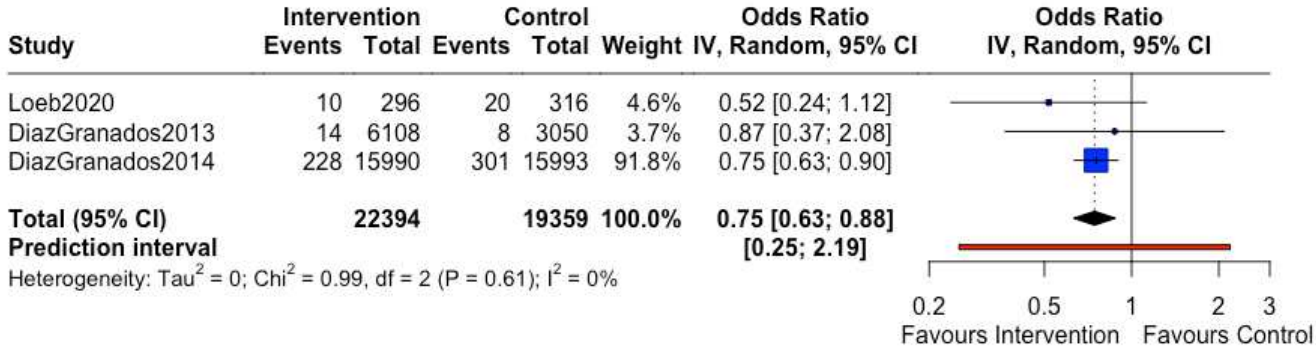
Table 1. Pairwise meta-analysis results for each outcome

Primary Outcomes															
Outcome	***Comparison***	***Number of studies***	***Number of participants***	***OR***	***lower CI***	***upper CI***	***lower PI***	***upper PI***	***tau***	***tau² lower CI***	***tau² upper CI***	***Q***	***Q df***	***Q P-value***	***I²***
LCI	IIV3-HD : IIV3-SD	3	41753	0.75	0.63	0.88	0.25	2.19	0.00	0.00	2.72	1.00	2	0.61	0%
	IIV3-SD : Placebo	2	330	0.31	0.13	0.75	.	.	0.33	.	.	1.4	1	0.25	26 %
ILI	IIV3-HD : IIV3-SD	2	41141	0.98	0.93	1.02	.	.	0.00	.	.	0.14	1	0.71	0%
	IIV3-SD : Placebo	2	854	0.39	0.15	1.02	.	.	0.21	.	.	1.08	1	0.3	7.6 %
Secondary Outcomes															
Outcome	***Comparison***	***Number of studies***	***Number of participants***	***OR***	***lower CI***	***upper CI***	***lower PI***	***upper PI***	***tau²***	***tau² lower CI***	***tau2 upper CI***	***Q***	***Q df***	***Q P-value***	***I²***
ER Visit for ILI	IIV3-HD : IIV3-SD	2	41141	0.94	0.74	1.19	.	.	0.00	.	.	0.20	1	0.66	0%
Hospitalization for ILI	IIV3-HD : IIV3-SD	2	41141	0.72	0.57	0.92	.	.	0.00	.	.	0.40	1	0.52	0%
Hospitalization for ARI	IIV3-HD : IIV3-SD	2	84991	0.87	0.79	0.95	.	.	0.00	.	.	0.00	1	0.98	0%
Number of Vascular Events	IIV3-Adj : IIV3-SD	2	7577	0.83	0.54	1.27	.	.	0.00	.	.	0.00	1	0.89	0%
	IIV3-HD : IIV3-SD	4	45656	0.74	0.43	1.29	0.21	2.58	0.23	0.00	2.20	4.90	3	0.18	39 %
Inpatient Hospitalization (any cause)	IIV3-HD : IIV3-SD	3	38816	0.76	0.40	1.42	0.01	50.27	0.27	0.01	3.22	14.00	2	0.00	86 %
Outpatient Visit	IIV3-HD : IIV3-SD	2	41141	1.04	0.99	1.09	.	.	0	.	.	0.80	1	0.38	0%
	IIV3-SD : Placebo	2	814	0.40	0.07	2.14	.	.	1.09	.	.	4.30	1	0.04	77 %
All-cause Death	IIV3-Adj : IIV3-SD	2	7577	1.09	0.73	1.62	.	.	0.00	.	.	0.50	1	0.47	0%
	IIV3-HD : IIV3-SD	6	101187	0.97	0.92	1.02	0.90	1.04	0.00	0.00	0.02	1.20	5	0.95	0%
	IIV4-SD : IIV3-SD	3	3864	1.08	0.38	3.09	0.00	970.40	0.00	0.00	15.12	0.70	2	0.70	0%
	IIV3-SD : Placebo	2	854	1.47	0.43	5.06	.	.	0.00	.	.	0.20	1	0.66	0%
Influenza-related death	IIV3-Adj:IIV3-SD	1	6961	0.75	0.17	3.36									
	IIV4-SD:IIV3-SD	1	1741	3.01	0.12	73.19									

Abbreviations- IIV3: Trivalent inactivated influenza vaccine; IIV4: Quadrivalent inactivated influenza vaccine; Adj: Adjuvanted; SD: Standard dosage; HD: High dosage; ARI: Acute respiratory infection; LC-ARI: Laboratory-confirmed acute respiratory infection; ER: Emergency room; LCI: Laboratory-confirmed influenza; ILI: Influenza-like illness; OR: Odds ratio; CI: Confidence interval; PI: Prediction interval; df: Degrees of freedom

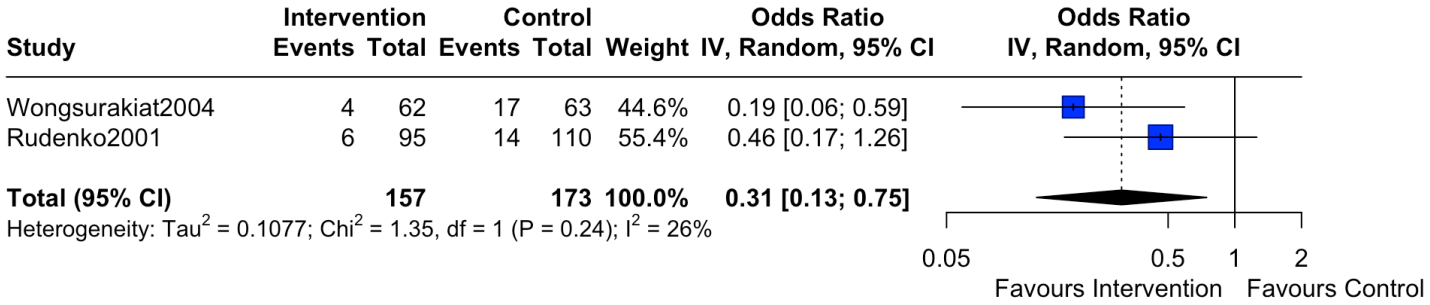
Laboratory-confirmed Influenza (LCI)

Figure 1. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

Figure 2. Forest plot of pairwise meta-analysis comparing IIV3-SD (intervention) vs. Placebo (control)



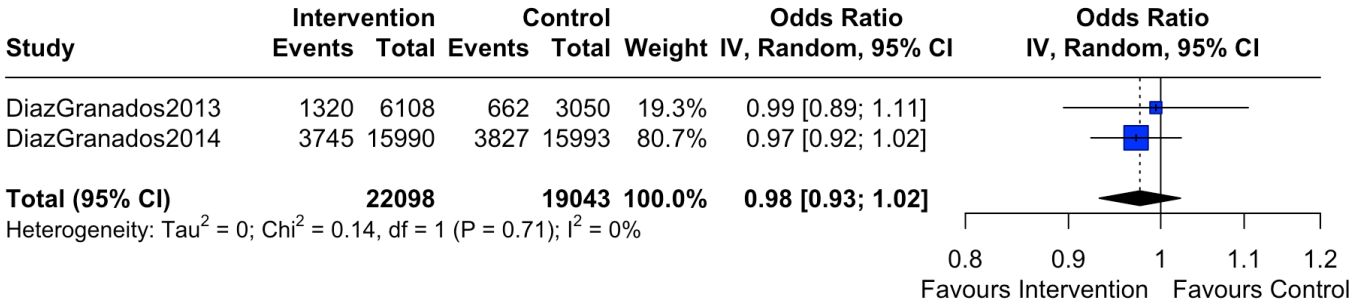
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; CI: Confidence interva

Table 2. Vaccine efficacy from pairwise meta-analysis results for laboratory-confirmed influenza with original coding of interventions

Comparison	*OR*	*RR*	*VE*
IIV3-HD : IIV3-SD	0.75 (0.63,0.88)	0.79 (0.68,0.90)	21.08 (9.65,32.00)
IIV3-SD : Placebo	0.31 (0.13,0.75)	0.36 (0.16,0.79)	64.08 (21.08,84.29)
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; OR: odds ratio; RR: relative risk ; VE: vaccine efficacy			

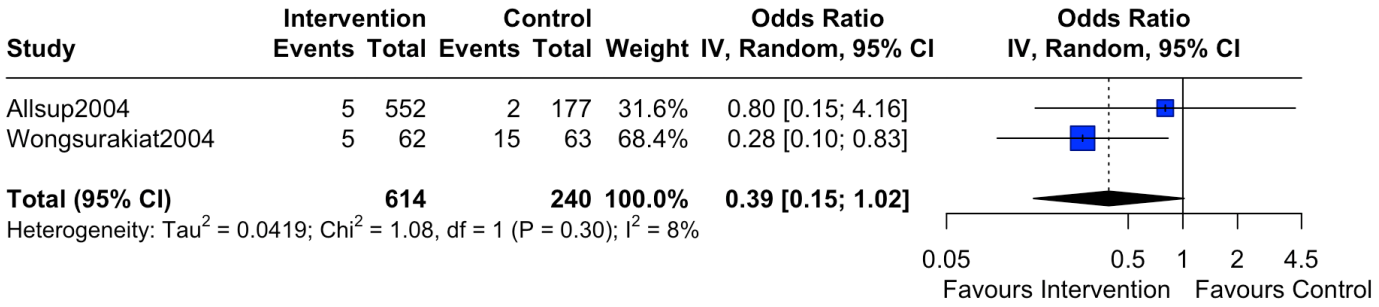
Influenza-like illness (ILI)

Figure 3. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

Figure 4. Forest plot of pairwise meta-analysis comparing IIV3-SD (intervention) vs. Placebo (control)



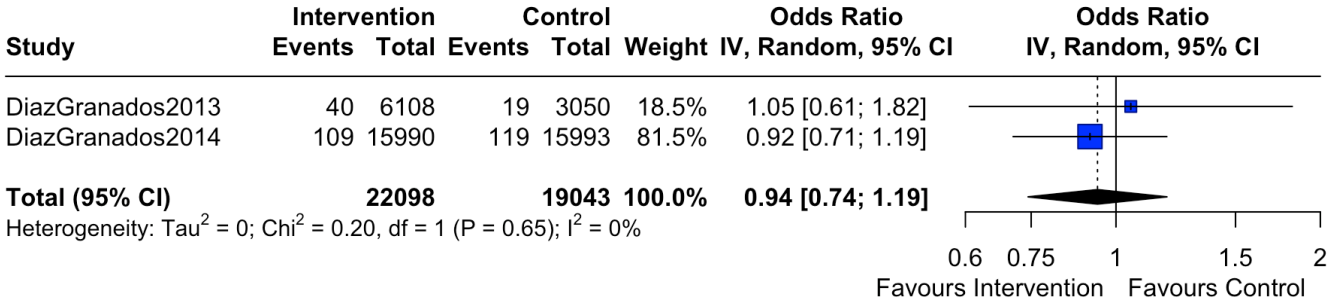
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; CI: Confidence interval

Table 3. Vaccine efficacy from pairwise meta-analysis results for influenza-like illness with original coding of interventions

Comparison	***OR***	***RR***	***VE***
IIV3-HD : IIV3-SD	0.98 (0.93,1.02)	0.98 (0.93,1.02)	1.76 (-1.75,6.18)
IIV3-SD : Placebo	0.39 (0.15,1.02)	0.42 (0.17,1.02)	57.79 (-1.75,83.22)
Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; OR: odds ratio; RR: relative risk ; VE: vaccine efficacy			

ER Visit for ILI

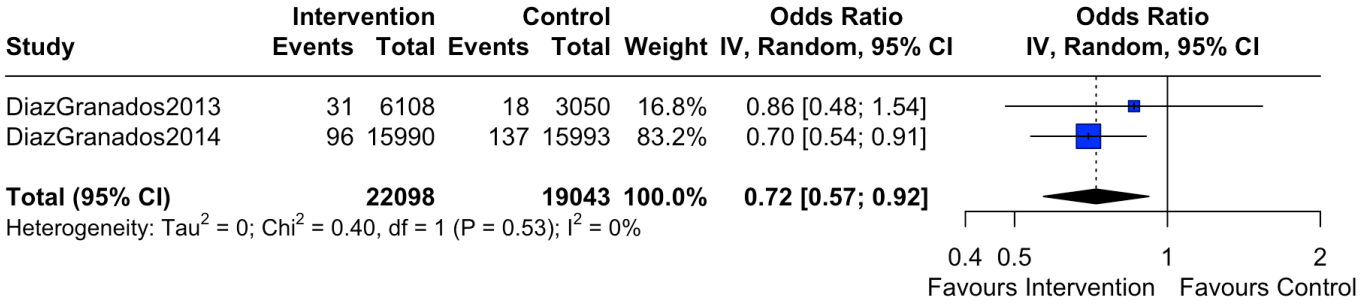
Figure 5. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

Hospitalization for ILI

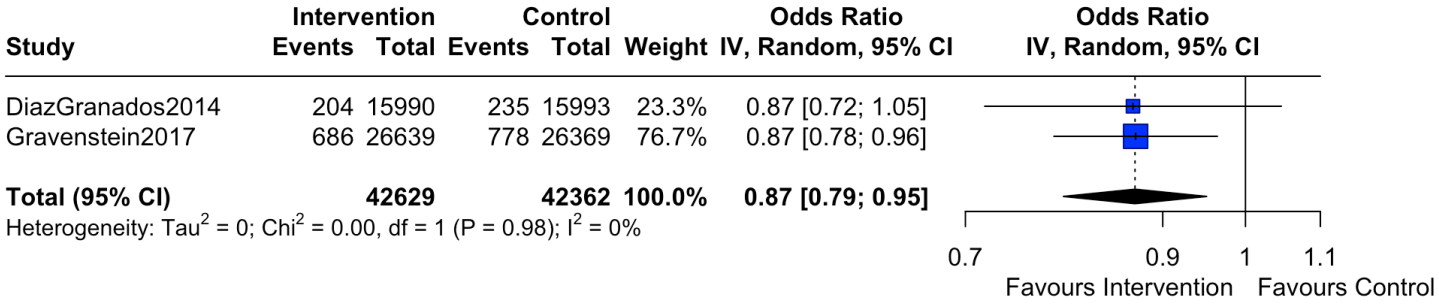
Figure 6. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

Hospitalization for acute respiratory infection (ARI)

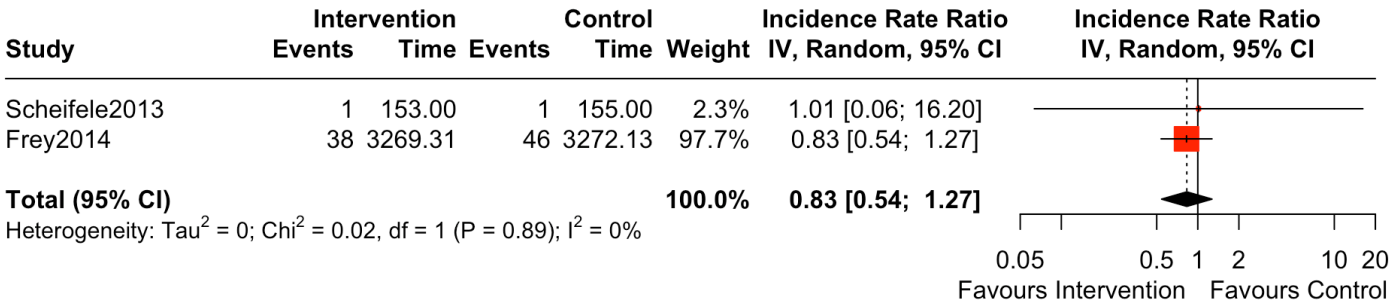
Figure 7. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

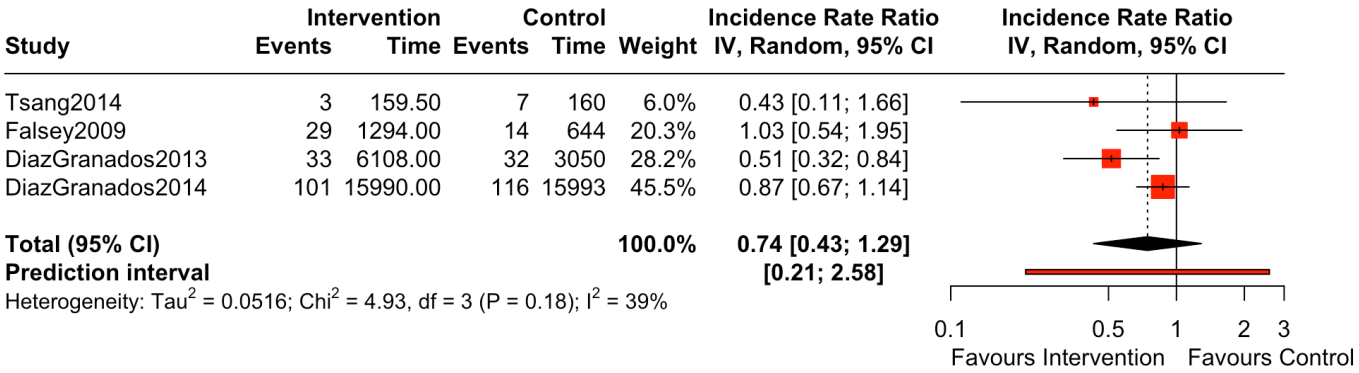
Number of vascular adverse events

Figure 8. Forest plot of pairwise meta-analysis comparing IIV3-Adj (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; Adj: Adjuvanted; CI: Confidence interval

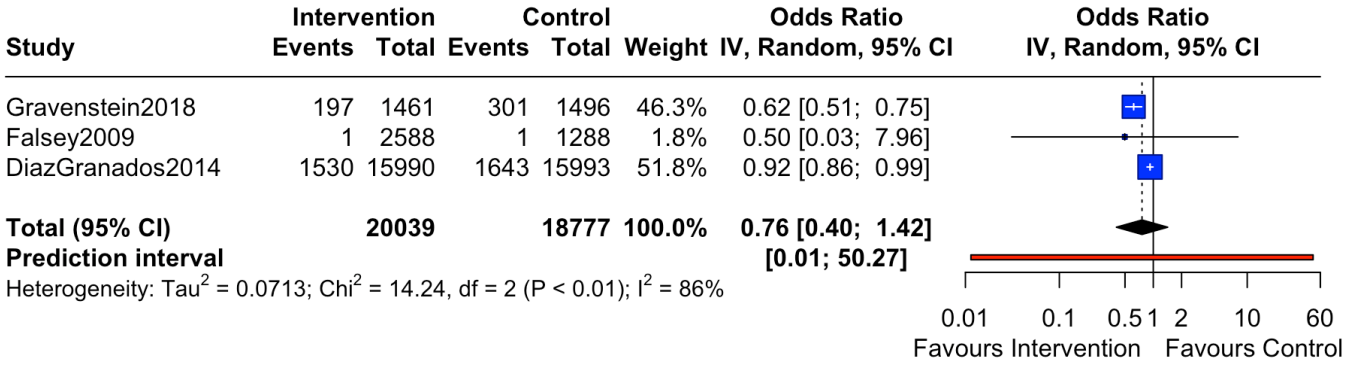
Figure 9. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

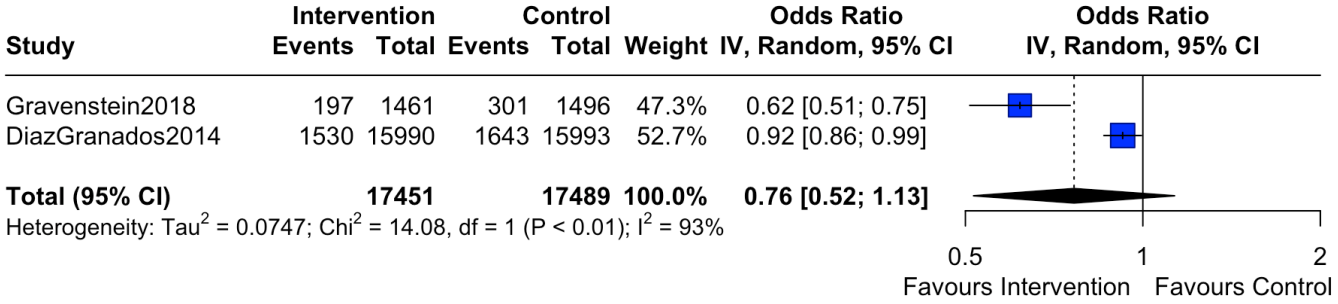
Inpatient Hospitalization

Figure 10. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



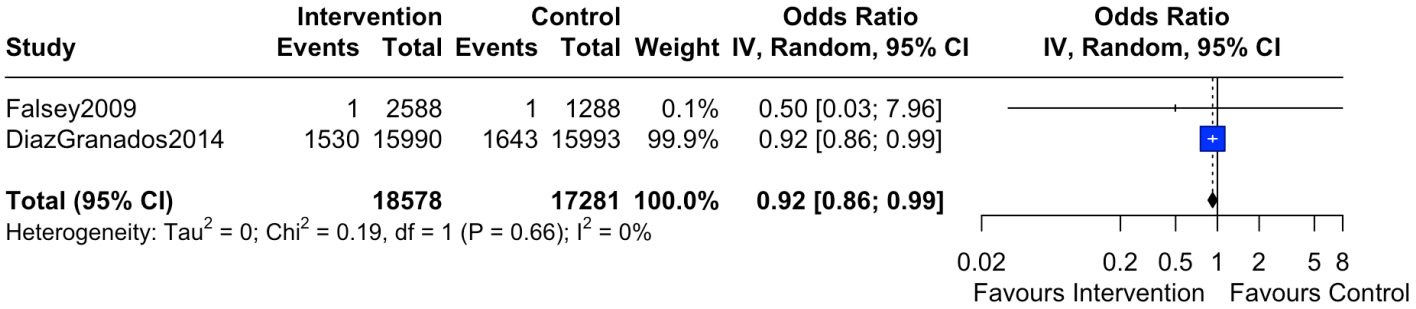
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

Figure 11. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control) restricted to studies with a low overall risk of bias



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

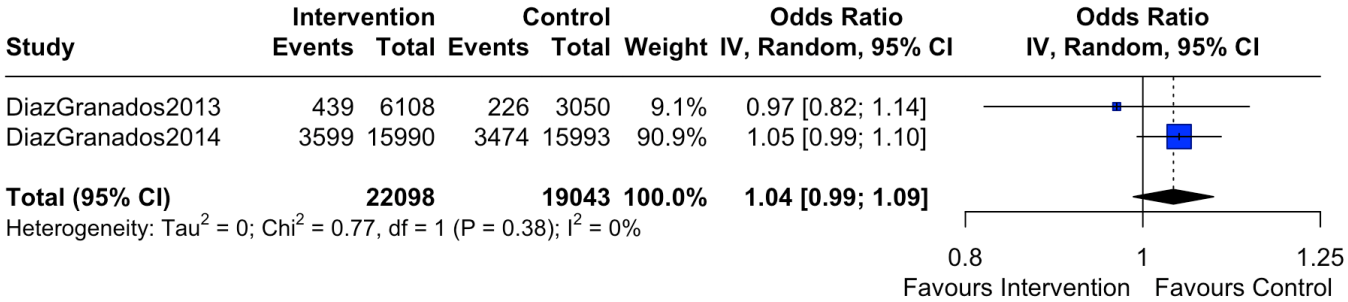
Figure 12. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control) restricted to studies whose mean age is over 80 years of age.



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

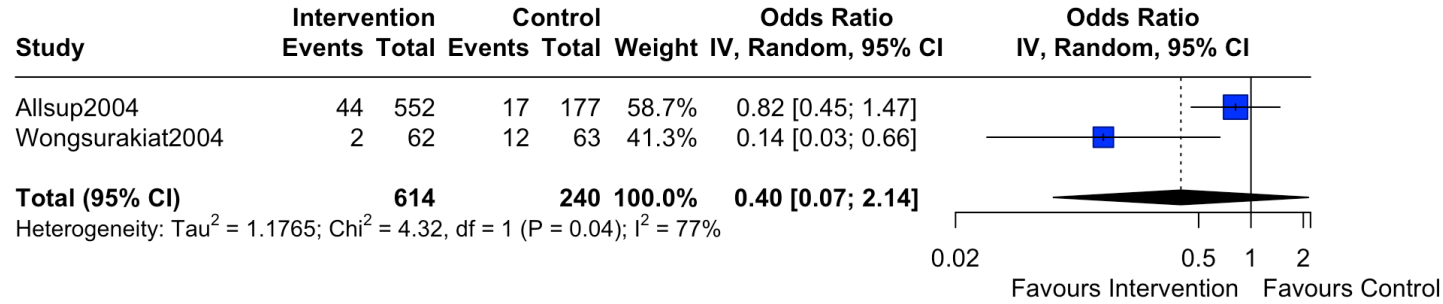
Outpatient visit

Figure 13. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD; High dosage; CI: Confidence interval

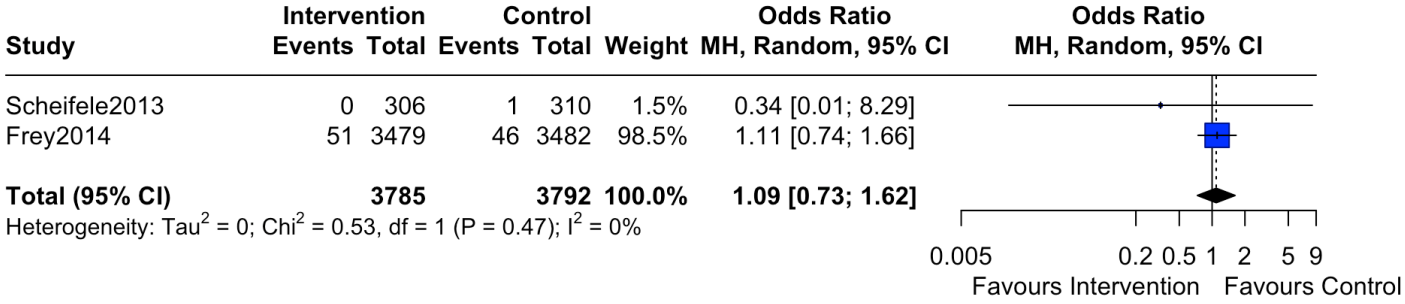
Figure 14. Forest plot of pairwise meta-analysis comparing IIV3-SD (intervention) vs. Placebo (control)



Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; CI: Confidence interval

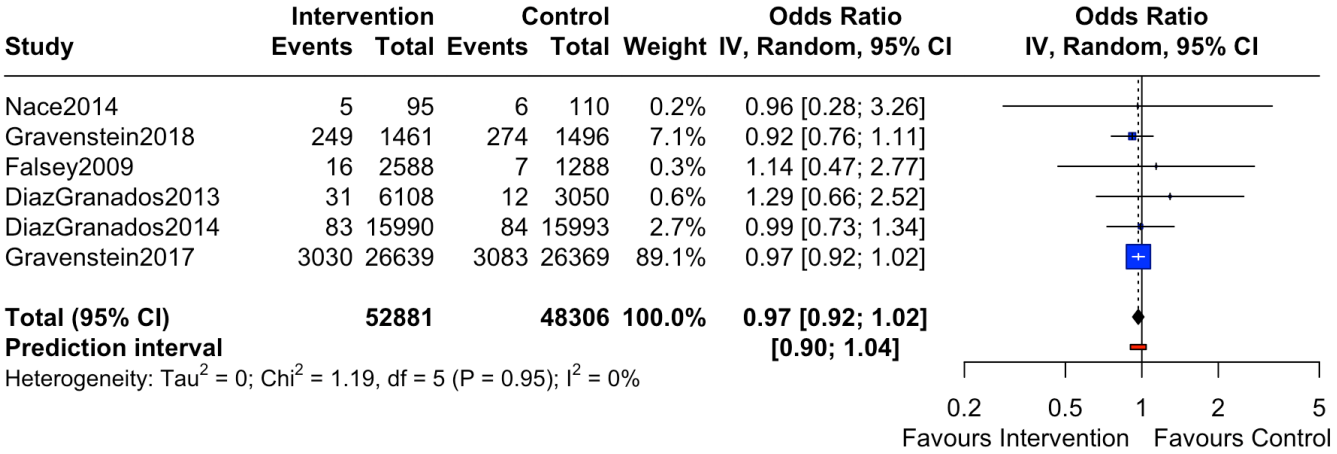
All-cause mortality

Figure 15. Forest plot of pairwise meta-analysis comparing IIV3-Adj (intervention) vs. IIV3-SD (control)



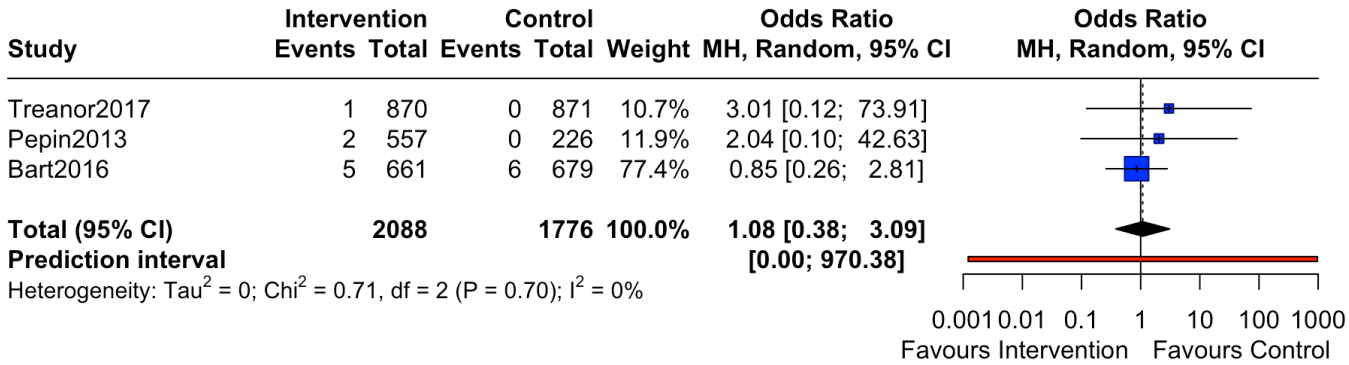
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; Adj: Adjuvanted; CI: Confidence interval

Figure 16. Forest plot of pairwise meta-analysis comparing IIV3-HD (intervention) vs. IIV3-SD (control)



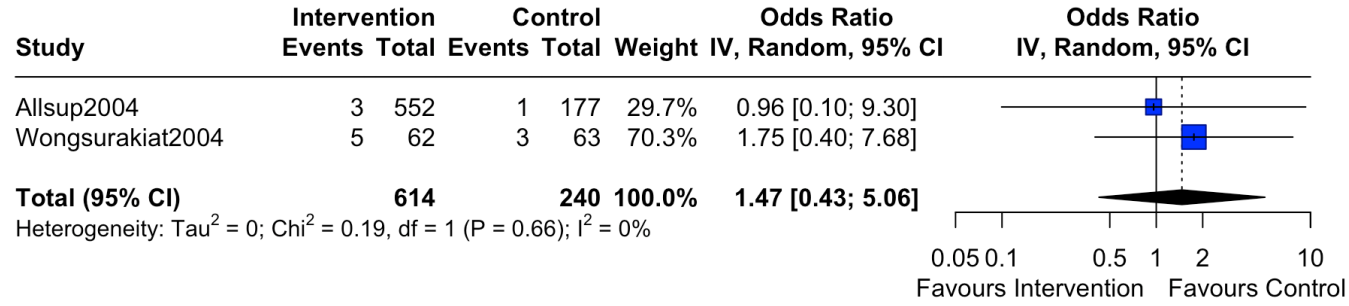
Abbreviations- IIV3: Trivalent inactivated influenza vaccine; SD: Standard dosage; HD: High dosage; CI: Confidence interval

Figure 17. Forest plot of pairwise meta-analysis comparing IIV4-SD (intervention) vs. IIV3-SD (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; IIV4: Quadrivalent **i**nactivated influenza vaccine; SD: Standard dosage; CI: Confidence interval

Figure 18. Forest plot of pairwise meta-analysis comparing IIV3-SD (intervention) vs. Placebo (control)



Abbreviations- IIV3: Trivalent **i**nactivated influenza vaccine; SD: Standard dosage; CI: Confidence interval

Appendix 23: Definitions of influenza-like illness (ILI)

Author, Year	Source of Definition	Definition
DiazGranados, 2013[11]	Determined by Investigator	"A new onset (or exacerbation of a pre-existing condition) of at least one of the following systemic symptoms: temperature >37.2 ◦C (>99.0 ◦F), feverishness (feeling of warmth), chills, tiredness, headaches or myalgia; and at least one of the following respiratory symptoms: nasal congestion or rhinorhea, sore throat, cough, sputum production, wheezing, chest tightness, shortness of breath, or chest pain with breathing."
DiazGados, 2014[16]	Determined by Investigator	"A respiratory illness with sore throat, cough, sputum production, wheezing, or difficulty breathing, concurrent with one or more of the following: temperature above 37.2°C, chills, tiredness, headaches, or myalgia."
Frey, 2014[15]	Determined by Investigator	"Temperature of ≥37.2◦C or feverishness and at least two of the following symptoms: headache, myalgia, cough, or sore throat."
Beran, 2021[28]	Determined by Investigator	"At least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature >37·2°C, chills, tiredness, headache, or myalgia)."
Dunkle, 2017[20]	Determined by Investigator	"At least one symptom in both the respiratory and systemic illness categories, regardless of severity."
Keitel, 2010[10]	Determined by Investigator	"An influenza symptoms score of 2 or greater on the Flu Symptoms Card (based on presence of fever, cough, sore throat, and runny nose/stuffy nose, muscle or joint aches, headache, chills/sweats, and tiredness/malaise), or if they sought medical care for their acute illness."
Wongsurakiat, 2004[7]	Determined by Investigator	"Patients had symptoms of generalized aches, fever, and headache with or without upper respiratory tract symptoms."
Rudenko, 2001[6]	Determined by Investigator	"A temperature of ≥37.28C, and at least one respiratory symptom: cough, coryza, or sore throat."
Teh, 2021[30]	Determined by Investigator	"Presence of fever (≥38°C) and at least 1 respiratory symptom."
Allsup, 2004[8]	Determined by Investigator	"An illness of sudden onset with features of cough, feverishness, prostration, myalgia and widespread aches and pains."

Abbreviations: None.

Appendix 24: Definitions of vascular adverse events

Author, Year	Source of Definition	Definition
DiazGranados, 2013[11]	Results from trial registry	"Acute myocardial infarction, myocardial infarction, cardiac arrest, cardiac failure, cardiac failure acute, cardiac failure congestive, cardiac failure chronic, cerebral ischaemia, haemorrhagic stroke, ischaemic stroke."
DiazGranados, 2014[16]	Results from trial registry	"Acute myocardial infarction, cardiac arrest, myocardial infarction, myocardial ischaemia, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cerebral infarction, cerebral ischaemia, ischaemic stroke, vascular infarction, vascular ischaemia, haemorrhagic stroke."
Frey, 2014[15]	Results from trial registry	"Acute myocardial infarction, myocardial infarction, myocardial ischemia, cardiac arrest, cardiac failure, cardiac failure congestive, cerebral infraction, cerebral ischaemia, ishaemic stroke."
Beran, 2021[28]	Results from trial registry	"Acute myocardial infarction, myocardial infarction, cardiac arrest, cardiac failure, cardiac failure acute, cardiac failure congestive, cardiac failure chronic, cerebral infarction, ischaemic stroke, haemorrhagic stroke."
Dunkle, 2017[28]	Results from trial registry	"Myocardial infarction, cardiac arrest, cardiac failure, acute myocardial infarction, embolic stroke, hemorrhagic stroke."
Essink, 2020[27]	Results from trial registry	"Myocardial infarction, Ischaemic cerebral infarction."
Chang, 2019[23]	Results from trial registry	"Acute Myocardial Infarction, cardiac failure congestive, myocardial infarction, cerebrovascular accident, ischaemic cerebral infarction."
Falsey, 2009[9]	Results from trial registry	"Acute coronary syndrome, Acute myocardial infarction, Cardiac arrest, Cardiac Failure, Cardiac failure congestive, Cardio-respiratory arrest, Myocardial infarction, Cerebrovascular accident, Transient ischaemic attack."
Novartis Vaccines and Diagnostics, 2016[40]	Results from trial registry	"Myocardial Infarction, Cerebral Vascular Accident."
Schmader, 2021[29]	Results from trial registry	"Congestive heart failure, Transient ischemic attack."
Pepin, 2013[13]	Results from trial registry	"Cardiac arrest, myocardial infarction."
Szymczakiewicz-Multanowska, 2009[34]	Results from trial registry	"Acute myocardial infraction and cerebral infraction, Transient ischaemic attack."
Szymczakiewicz-Multanowska, 2012[a][35]	Results from trial registry	"Acute myocardial infraction and cerebral infraction, Transient ischaemic attack."
Szymczakiewicz-Multanowska, 2012[b][36]	Results from trial registry	"Acute myocardial infraction, cardiac arrest, cardiac failure, myocardial infraction, myocardial ischaemia, ischaemic stroke, cerebrovascular accident."
Tsang, 2014[14]	Results from trial registry	"Acute myocardial infarction, cardiac arrest, cardiac failure, cardiac failure congestive & thrombotic stroke; death reported in text as: "no treatment-related serious adverse events or treatment-related deaths occurred during the study."
Scheifele, 2013[12]	SAE determined by investigator	"Vascular".

Abbreviations: SAE: Serious Adverse Event.

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