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TECHNICAL REPORT

Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over

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A working group under the EU/EEA National Immunisation Technical Advisory Group (NITAG) collaboration formed in June 2019 on newer and enhanced inactivated seasonal influenza vaccines consisted of the following members:

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Contents

Figures

Tables

Abbreviations

aIIV3	Adjuvanted trivalent inactivated influenza vaccine
aIIV4	Adjuvanted quadrivalent inactivated influenza vaccine
ccIIV3	Cell-based trivalent inactivated influenza vaccine
ccIIV4	Cell-based quadrivalent inactivated influenza vaccine
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DALY	Disease-adjusted life year
FEM	Fixed-effect model
GRADE	Grading of recommendations assessment, development and evaluation
HA	Haemagglutinin
HD-IIV3	High-dose trivalent inactivated influenza vaccine
HD-IIV4	High-dose quadrivalent inactivated influenza vaccine
HIQA	Health Information and Quality Authority
ICD	International classification of diseases
ILI	Influenza-like illness
LAIV	Live attenuated influenza vaccine
NITAG	National immunisation technical advisory group
NRSI	Non-randomised studies of intervention
PICO	Participants, intervention, comparison, outcomes
PRISMA	Preferred reporting items for systematic reviews and meta analyses
RCT	Randomised controlled trial
REM	Random-effects model
RIV3	Recombinant trivalent inactivated influenza vaccine
RIV4	Recombinant quadrivalent inactivated influenza vaccine
ROBINS-I	Risk of bias in non-randomised studies of interventions
RT-PCR	Reverse transcription-polymerase chain reaction
RR	Risk ratio
SAE	Serious adverse event
SD-IIV3	Standard-dose trivalent inactivated influenza vaccine
SD-IIV4	Standard-dose quadrivalent inactivated influenza vaccine
VE	Vaccine effectiveness
WHO	World Health Organization

Abstract

Background

Seasonal influenza is an infectious respiratory disease which circulates annually and is associated with a considerable health and economic burden globally. The most effective means of preventing seasonal influenza is through strain-specific vaccination. For many decades, only trivalent influenza vaccines (that include two influenza A strains and one influenza B strain) have been available. In recent years, quadrivalent (two influenza A strains and two influenza B strains) have been authorised and are increasingly available. Traditional influenza vaccines have limitations in terms of immune response and the substrate used in their manufacturing which can reduce overall effectiveness. Newer and enhanced influenza vaccines have been developed, both in trivalent and quadrivalent forms, in an attempt to counteract these limitations.

Objective

The objective of this systematic review is to assess and synthesise the literature on the efficacy, effectiveness and safety of newer and enhanced inactivated seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years or older, namely: MF59® adjuvanted, cell-based, high-dose, and recombinant haemagglutinin (HA) influenza vaccines.

Methods

A systematic literature search was conducted in electronic databases (MEDLINE, Embase, CINAHL and The Cochrane Library) and grey literature sources up to 7 February 2020. No restrictions were placed on date or language. Randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs) were eligible for inclusion. Returned records were screened for relevance and the full-text of potentially relevant articles assessed, applying predefined eligibility criteria.

Two reviewers independently extracted data, and pooling was considered where two or more studies reported an outcome. Study results were pooled using both fixed and random effects meta-analysis.

Two reviewers independently assessed the risk of bias of included studies using standardised tools. Certainty of evidence for key outcomes was assessed using the GRADE methodology.

Main results

The collective search returned 28 846 records. Removal of duplicates and screening resulted in 868 full-texts being assessed for relevance with 110 studies being included. Of these 110 studies, 48 possessed results relevant to adjuvanted influenza vaccines, 36 to high-dose influenza vaccines, 19 to cell-based influenza vaccines, and 10 to recombinant HA influenza vaccines. The primary outcomes of interest to this review are presented below, with consideration towards the hierarchy of evidence whereby only the highest available level is presented. No studies were identified which compared any, or all, of these newer and enhanced vaccines to each other.

No efficacy data were identified for adjuvanted influenza vaccines for any comparator (another vaccine, placebo or 'no vaccination'). In terms of relative vaccine effectiveness, there was no significant difference in vaccine effectiveness reported by included studies that compared adjuvanted trivalent vaccine with either non-adjuvanted trivalent or quadrivalent vaccines in adult or older adult (aged ≥65 years) populations. Adjuvanted trivalent influenza vaccines displayed a significant effect in preventing laboratory-confirmed influenza in older adults (aged ≥65 years) when compared with no vaccination for any influenza subtype (vaccine effectiveness (VE) = 45%, 95% CI 23 to 61, five NRSIs across three influenza seasons, random effects model (REM), I^2=63%, low-certainty evidence), influenza A(H1N1) (VE=61%, 95% CI 44 to 73, four NRSIs across two influenza seasons, REM, I^2=14.5%, low-certainty evidence) and influenza B (VE=29%, 95% CI 5 to 46, five NRSIs across three influenza seasons, REM, I^2=0%, low-certainty evidence), but not for influenza A(H3N2) (VE=11%, 95% CI -25 to 36, 8 NRSIs across five influenza seasons, REM, I^2=49%, very-low certainty evidence).

Pooled analyses of effectiveness data comparing adjuvanted with non-adjuvanted vaccines was restricted by limited study numbers and statistical and clinical heterogeneity. Compared with traditional trivalent influenza vaccines, adjuvanted trivalent influenza vaccines were associated with a greater number of combined local adverse events (risk ratio (RR)= 1.90, 95% CI 1.50 to 2.39, four RCTs, REM, I^2=0%, moderate-certainty evidence), pain at injection site (RR=2.02, 95% CI 1.53 to 2.67, 12 RCTs, REM, I^2=75%, moderate-certainty evidence), combined systemic reactions (RR=1.18, 95% CI 1.02 to 1.38, five RCTs, REM, I^2=8%, moderate-certainty evidence), myalgia (RR=1.71, 95% CI 1.09 to 2.69, 10 RCTs, REM, I^2=31%, moderate-certainty evidence), fever (RR=1.97, 95% CI 1.07 to 3.61, nine RCTs, REM, I^2=31%, low-certainty evidence) and chills (RR=1.70, 95% CI 1.20 to 2.40, seven RCTs, REM, I^2=0%, moderate-certainty evidence).

High-dose trivalent influenza vaccination was shown to have higher relative vaccine efficacy in preventing influenza compared with standard-dose trivalent influenza vaccines in older adults aged 65 years and over (VE=24%, 95% CI 10 to 37, one RCT, moderate-certainty evidence). One NRSI demonstrated significant effect for high-dose trivalent vaccine against influenza B (VE=89%, 95% CI 47 to 100), but not for influenza A(H3N2) (VE=22%, 95% CI -82 to 66) when compared with no vaccination in older adults (aged ≥65 years). Based on pooled estimates, high dose trivalent and quadrivalent vaccines were associated with significantly higher rates of a range of local and systemic adverse events compared with their standard dose trivalent and quadrivalent equivalents. Specifically, they were associated with significantly higher rates of combined local reactions (RR=1.40, 95% CI 1.20 to 1.64, three RCTs, FEM, I^2=25%, low-certainty evidence), pain at injection site (RR=1.56, 95% CI 1.26 to 1.93, seven RCTs, REM, I^2=57%, moderate-certainty evidence), swelling (RR=2.20, 95% CI 1.12 to 4.32, I^2=46%, six RCTs, low-certainty evidence), induration (RR=1.63 95% CI 1.10 to 2.39, FEM, I^2=68%, two RCTS, low-certainty evidence), headache (RR=1.35, 95% CI 1.02 to 1.77, REM, I^2=0%, seven RCTs, moderate-certainty evidence), chills (RR=1.73, 95% CI 1.07 to 2.81, REM, I^2=0%, four RCTs, low-certainty evidence), and malaise (RR=1.28, 95% CI 1.08 to 1.51, REM, I^2=0%, seven RCTs, moderate-certainty evidence).

No relative efficacy data were identified for the direct comparison of cell-based vaccines compared with traditional vaccines. Efficacy data were available comparing cell-based trivalent influenza vaccines with placebo in adults (aged 18-49 years), against any influenza (VE=70%, 95% CI 61% to 77%, two RCTS, fixed effects model (FEM), I^2=0%, moderate-certainty evidence), influenza A(H1N1) (VE=82%, 95% CI 71% to 89%, two RCTs, FEM, I^2=62%, moderate-certainty evidence), influenza A(H3N2) (VE=72%, 95% CI 39% to 87%, two RCTs, FEM, I^2= 0%, moderate-certainty evidence) and influenza B (VE=52%, 95% CI 30% to 68%, two RCTs, FEM I^2=0%, moderate-certainty evidence). Limited and heterogeneous data were presented for effectiveness when compared with no vaccination. One NRSI compared cell-based trivalent and quadrivalent vaccination with traditional trivalent and quadrivalent influenza vaccines which highlighted no significant difference in effect for any influenza or specific strains in older adults. The safety profile of cell-based trivalent vaccines was comparable to traditional trivalent influenza vaccines with higher rates of ecchymosis in cell-based vaccine recipients being the only significant difference (RR=1.27, 95% CI 1.03 to 1.56, three RCTs, FEM, I^2=47%, low-certainty evidence).

One study found that the quadrivalent recombinant HA influenza vaccine had higher relative vaccine efficacy in preventing influenza compared with traditional quadrivalent influenza vaccination in adults aged ≥50 years (VE=30%, 95% CI 10 to 47, one RCT, moderate-certainty evidence). Another study found that the trivalent recombinant HA vaccine had higher efficacy compared with placebo (VE=45%, 95% CI 19 to 63, one RCT) in adults aged 18-55 years. No effectiveness data were identified for comparison with no vaccination or traditional influenza vaccines. Pooled estimates indicate that, with the exception of a higher rate of chills (RR=1.33, 95% CI 1.03 to 1.72, three RCTs, FEM, I^2=46%, low-certainty evidence), the safety profile of the recombinant HA trivalent and quadrivalent influenza vaccines was comparable to that of their traditional trivalent and quadrivalent vaccine equivalents.

Conclusions

The evidence base for the efficacy and effectiveness of newer and enhanced influenza vaccines is limited at present. Based on reviewed evidence, it is probable that these vaccines provide greater protection than no vaccination. Evidence regarding the comparability of these vaccines with traditional seasonal influenza vaccines is uncertain due to a dearth of available literature, clinical and statistical heterogeneity. A large body of evidence was presented for the safety of these influenza vaccines, with the safety profiles found to be largely in keeping with that expected when considering their individual compositions. Reporting within individual studies limited the data coverage of this review. Recommendations are provided to enhance research conduct and reporting regarding these newer and enhanced influenza vaccines which are anticipated to improve data coverage overall. A large number of potentially relevant studies were identified as ongoing, highlighting a need for this review to be updated in the near future.

Summary of findings

Summary of findings - MF59® adjuvanted influenza vaccines

Effectiveness of adjuvanted trivalent inactivated influenza vaccine (aIIV3) compared with no vaccination for prevention of laboratory-confirmed influenza

Patient or population: Older adults (aged ≥65 years)
Setting: Any setting
Intervention: aIIV3
Comparison: No vaccination

Outcomes	Vaccine effectiveness* (95% CI)	Number of studies	Certainty of the evidence (GRADE)
Influenza (any)	**VE 44.9%** (22.7 to 60.8)	5 observational studies (across 3 seasons: 2011-12; 2017-18; 2018-19)	⊕⊕◯◯ LOW [a,c]
Influenza A(H1N1)	**VE 61.2%** (43.7 to 73.3)	4 observational studies (across 2 seasons: 2017-18; 2018-19)	⊕⊕◯◯ LOW [a,c]
Influenza A(H3N2)	**VE 10.6%** (-24.5 to 35.7)	8 observational studies (across 5 seasons: 2014-15; 2015-16; 2016-17; 2017-18; 2018-19)	⊕◯◯◯ VERY LOW [a,b,c]
Influenza B	**VE 28.5%** (5.4 to 46.0)	5 observational studies (across 3 seasons: 2014-15; 2015-16; 2017-18)	⊕⊕◯◯ LOW [a,c]

aIIV3: adjuvanted trivalent inactivated influenza vaccine; **CI:** Confidence interval
VE: Vaccine effectiveness [(1 – Odds Ratio)*100%]
*Given the outcome of interest typically incorporating adjustments results are not presented as raw rates. Total participant numbers for vaccine of interest were not presented by all included studies.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level for risk of bias (see Table 3.3 for additional details)
b. Downgraded one level due to inconsistency in results
c. Downgraded one level due to imprecision

Safety of aIIV3 compared with trivalent inactivated influenza vaccine IIV3

Patient or population: Adults (aged ≥18 years)
Setting: Safety in any setting
Intervention: aIIV3
Comparison: IIV3

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with IIV3	Risk with aIIV3			
Combined local events	172 per 1 000	327 per 1 000 (258 to 411)	**RR 1.90** (1.50 to 2.39)	8 043 (4 RCTs)	⊕⊕⊕◯ MODERATE [a]
Pain	135 per 1 000	274 per 1 000 (207 to 362)	**RR 2.02** (1.53 to 2.67)	11 298 (12 RCTs)	⊕⊕⊕◯ MODERATE [a]
Combined systemic events	67 per 1 000	80 per 1 000 (69 to 93)	**RR 1.18** (1.02 to 1.38)	8 651 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]
Fever	30 per 1 000	58 per 1 000 (32 to 107)	**RR 1.97** (1.07 to 3.61)	10 236 (9 RCTs)	⊕⊕◯◯ LOW [a,b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
aIIV3: adjuvanted trivalent inactivated influenza vaccine; **CI:** Confidence interval; **IIV3:** trivalent inactivated influenza vaccine; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to serious risk of bias (see Figures 3.22 and 3.23 for additional details) b. Downgraded one level due to imprecision

Summary of findings - High-dose influenza vaccines

Efficacy and safety of high-dose inactivated influenza vaccine (HD-IIV) compared with standard-dose inactivated influenza vaccine (SD-IIV) for the prevention of laboratory-confirmed influenza

Patient or population: Adults (efficacy ≥ 65 years; safety aged ≥18 years)
Setting: Any setting
Intervention: HD-IIV (Efficacy HD-IIV3; Safety HD-IIV3 or HD-IIV4)
Comparison: SD-IIV (Efficacy SD-IIV3; Safety SD-IIV3 or SD-IIV4)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with SD-IIV	Risk with HD-IIV			
Influenza (any)^	19 per 1 000	14 per 1 000	**VE 24.2%** (9.7 to 36.5)	31 983 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Combined local events	376 per 1 000	527 per 1 000 (452 to 617)	RR 1.40 (1.20 to 1.64)	779 (3 RCTs)	⊕⊕◯◯ LOW [a,b]
Pain	268 per 1 000	418 per 1 000 (337 to 518)	RR 1.56 (1.26 to 1.93)	5 625 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]
Combined systemic events	302 per 1 000	353 per 1 000 (257 to 486)	RR 1.17 (0.85 to 1.61)	4 911 (5 RCTs)	⊕⊕◯◯ LOW [a,c]
Fever	18 per 1 000	37 per 1 000 (15 to 92)	RR 2.06 (0.84 to 5.06)	5 620 (7 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HD-IIV:** high-dose inactivated influenza vaccine; **RR:** Risk ratio; **SD-IIV:** standard-dose inactivated influenza vaccine; **VE:** Vaccine efficacy
^Disaggregated analysis by influenza subtype limited by low case numbers

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to risk of bias (see Figures 3.42 and Figure 3.43 for additional details)
b. Downgraded one level due to imprecision c. Downgraded one level due to inconsistency in results

Summary of findings-cell-based influenza vaccines

Efficacy of cell-based trivalent inactivated influenza vaccine (ccIIV3) compared with placebo for laboratory-confirmed influenza

Patient or population: Adults (18-49 years)
Setting: Any setting
Intervention: ccIIV3
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with ccIIV3			
Influenza (any)	29 per 1 000	9 per 1 000 (7 to 12)	**VE 70%** (61% to 77%)	14 855 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Influenza A(H1N1)	15 per 1 000	3 per 1 000 (2 to 4)	**VE 82%** (71% to 89%)	14 825 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Influenza A(H3N2)	4 per 1 000	1 per 1 000 (1 to 2)	**VE 72%** (39% to 87%)	14 855 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Influenza B	11 per 1 000	5 per 1 000 (3 to 8)	**VE 52%** (30% to 68%)	14 855 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ccIIV3: cell-based trivalent inactivated influenza vaccine; **CI:** Confidence interval; **VE:** Vaccine efficacy

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Safety of ccIIV3 compared with IIV3					
Patient or population: Aged (≥18 years) **Setting:** Any setting **Intervention:** ccIIV3 **Comparison:** IIV3					
Outcomes	**Anticipated absolute effects*** (95% CI)		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with IIV3	**Risk with ccIIV3**			
Combined local events	397 per 1 000	432 per 1 000 (353 to 536)	**RR 1.09** (0.89 to 1.35)	5 328 (4 RCTs)	⨁⨁◯◯ LOW [a,b]
Pain	210 per 1 000	250 per 1 000 (206 to 303)	**RR 1.19** (0.98 to 1.44)	14 665 (5 RCTs)	⨁⨁◯◯ LOW [a,b]
Combined systemic events	409 per 1 000	433 per 1 000 (380 to 495)	**RR 1.06** (0.93 to 1.21)	2 120 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]
Fever	9 per 1 000	9 per 1 000 (5 to 18)	**RR 1.01** (0.51 to 2.00)	15 396 (6 RCTs)	⨁⨁⨁◯ MODERATE [a]
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **ccIIV3:** cell-based trivalent inactivated influenza vaccine; **CI:** Confidence interval; **IIV3:** trivalent inactivated influenza vaccine; **RR:** Risk ratio					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Explanations
a. Downgraded one level due to risk of bias (see Figures 3.64 and 3.65 for additional details)
b. Downgraded one level due to imprecision

Summary of findings - recombinant HA influenza vaccines

Efficacy and safety of recombinant inactivated influenza vaccine (RIV) compared with inactivated influenza vaccine (IIV) for the prevention of laboratory-confirmed influenza					
Patient or population: Adults (Efficacy ≥ 50 years; safety ≥ 15 years) **Setting**: Any setting **Intervention**: RIV (Efficacy RIV4; Safety RIV3 or RIV4) **Comparison**: IIV (Efficacy IIV4; Safety IIV3 or IIV4)					
Outcomes¥	**Anticipated absolute effects*** (95% CI)		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with IIV	**Risk with RIV**			
Influenza (any)^	32 per 1 000	22 per 1 000	**VE 30%** (10 to 47)	8 604 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
Combined local events	420 per 1 000	395 per 1 000 (378 to 412)	**RR 0.94** (0.90 to 0.98)	10 556 (3 RCTs)	⨁⨁◯◯ LOW [a,b]
Pain	231 per 1 000	217 per 1 000 (169 to 280)	**RR 0.94** (0.73 to 1.21)	15 094 (7 RCTs)	⨁⨁⨁◯ MODERATE [a]
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **IIV:** inactivated influenza vaccine; **RIV:** recombinant inactivated influenza vaccine; **RR:** Risk ratio; **VE:** Vaccine efficacy ¥ No data presented for combined systemic or fever outcomes ^Disaggregated analysis by influenza subtype limited by lack of reporting of raw event counts					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Explanations
a. Downgraded one level due to risk of bias (see Figures 3.76 and 3.77 for additional details)
b. Downgraded one level due to inconsistency in results

1. Introduction

Seasonal influenza is an infectious respiratory disease which circulates in annual epidemics worldwide, with the period of circulation typically occurring from November to April in the Northern hemisphere and from June to October in the Southern hemisphere [1]. Seasonal influenza is largely transmitted between humans through droplet transmission, indirect contact and aerosol transmission [2].

Influenza viruses are from the Orthomyxoviridae family of ribonucleic acid viruses and are classified as four specific types: A, B, C and D. Influenza A, B and C are known to cause human infection, with D predominantly found in cattle [3,4]. Influenza C is responsible for very few human infections and hence influenza A and influenza B provide the primary focus when discussing seasonal influenza [1,3]. Influenza A is further categorised into subtypes based on the presence of specific haemagglutinin (HA) and neuraminidase proteins on the surface of the virus, with A(H1N1) and A(H3N2) commonly circulating [3]. Influenza B comprises two specific lineages, Victoria and Yamagata. Relative to influenza A, it typically exhibits a much lower mutation rate and generally results in a lower severity of infection [1,3]. In adults, influenza A(H1N1), influenza A(H3N2) and influenza B generally co-circulate each year in varying proportions depending on the season [1]. The highest burden of influenza in adults has tended to be in seasons with a predominance of influenza A(H3N2) circulation [5].

Annual estimates of influenza infection are inconsistent due to variation in the circulating virus strains. However, one study from England provides estimates across five influenza seasons with 18% of all unvaccinated individuals being infected based on serological findings, and the majority of these cases being asymptomatic [6]. The clinical presentation of symptomatic infection with seasonal influenza is characterised by pyrexia, myalgia, malaise, cough and other respiratory symptoms [5]. The severity of such symptoms can range from mild to severe, with otherwise healthy individuals typically recovering in relatively short timeframes, whereas higher morbidity and mortality is predominantly seen in those deemed to be higher risk groups, such as those with chronic diseases, immunosuppressive conditions, and the elderly [7].

The scale of the effect of seasonal influenza is dependent on a number of factors including the predominantly circulating strains, vaccination coverage and the mutation of the virus relative to previous seasons [5]. Collectively, the World Health Organization (WHO) estimates that annual seasonal influenza epidemics result in three to five million severe cases and 290 000 to 650 000 respiratory deaths worldwide [7]. All-cause influenza-attributable mortality was estimated to be 25.4 (95% CI 25.0 to 25.8) per 100 000 population and 118.2 (95%CI 116.4 to 119.9) per 100 000 for adults aged 65 in the 2017-2018 influenza season in Europe [8]. Influenza is reported to have the highest burden of all infectious diseases in Europe in terms of disease-adjusted life years (DALYs), with 81.1 DALYs per 100 000 population (95% UI 76.9 to 86.5) representing 30% of the total burden of all included diseases [9]. The economic burden of seasonal influenza is substantial with regard to both direct healthcare costs and indirect societal costs, stemming largely from the associated morbidity and mortality in more severe cases combined with estimated productivity losses for less severe infections [1].

The most effective means to prevent influenza infection is through strain-specific vaccination [7]. To facilitate strain-specific vaccination, WHO issues recommendations to vaccine manufacturers regarding vaccine strain inclusion. These recommendations are based on predictions of the likely circulating strains, which have been informed by analysis and interpretation of global surveillance data [7, 10]. Recommendations are issued for the composition of both trivalent (two A strains and one B strain) and quadrivalent (two A strains and two B strains) vaccines and include specific viral subtyping for influenza A [7, 11]. However, due to antigenic drift, whereby genetic changes arise from ongoing evolution of the virus, antigenic mismatch between the virus strains contained in the vaccine and those in circulation in the seasonal epidemic can occur. Accurate predictive matching of vaccine strains to those that circulate is a key determinant of vaccine effectiveness [7, 10, 11]. Seasons in which a mismatch occur are typically associated with higher overall morbidity and mortality, such as the 2014-2015 influenza season [10, 12].

Beyond strain-specific matching, additional considerations for vaccine effectiveness are:

- the generation of a sufficient immune response
- the substrate used during vaccine production.

The immune response to traditional influenza vaccines can be suboptimal [11]. Newer and enhanced influenza vaccines have been developed in an attempt to improve vaccine effectiveness, particularly in the elderly for whom there is evidence of immunosenescence. Strategies to enhance the immune response include the use of adjuvants and higher doses of HA per vaccine strain. The addition of an adjuvant, such as the oil-in-water emulsion MF59®, aims to increase immunogenicity, resulting in comparatively higher levels of HA inhibition antibodies and an enhanced immunological response [11]. High-dose influenza vaccines contain a fourfold increase of HA per strain, that is, 60µg of HA per strain instead of 15µg of HA typically included in standard dose vaccines [13]. As with the MF59® adjuvant, the increase in HA dose is intended to induce a larger overall immune response, thereby improving vaccine effectiveness [14].

In terms of the substrate utilised for influenza vaccine production, traditional injectable influenza vaccines are typically manufactured through egg-derived processes, with virus propagation in embryonated hen eggs and subsequent recovery and inactivation in whole, split or subunit forms [10, 11]. Mutations to HA proteins during vaccine production can occur with the use of egg substrates which can reduce overall vaccine effectiveness [10]. Vaccines manufactured through new substrates have been created and include the use of mammalian cell-culture and recombinant HA proteins produced in insect cells using baculovirus-expression [5, 10]. These new processes remove the possibility of strain mutation associated with egg-based propagation [5, 10]. Such substrates may offer further benefits, such as higher production speed for greater overall yield [10], and negate the potential risk to those individuals with severe ovalbumin allergies [15, 16].

There is a need to assess the clinical efficacy, effectiveness and safety of such newer and enhanced seasonal influenza vaccines, to inform decision-making regarding future vaccination strategies.

1.1 Objective

The objective of this report is to review, assess and synthesise the literature on newer and enhanced inactivated seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years or older.

2. Methodology

The proposed methodology for this systematic review was agreed upon with the EU/EEA National Immunisation Technical Advisory Group (NITAG) collaboration working group and subsequently registered on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020156800). This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [17].

2.1 Research questions

This systematic review aimed to answer the following research questions:

- What is the efficacy, effectiveness and safety of trivalent (aIIV3) and quadrivalent (aIIV4) egg-based MF59® adjuvanted seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent (HD-IIV3) and quadrivalent (HD-IIV4) egg-based high-dose seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent (ccIIV3) and quadrivalent (ccIIV4) cell-based seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent (RIV3) and quadrivalent (RIV4) recombinant HA seasonal influenza vaccine by influenza type, subtype (clade if available), age and risk group?
- What is the relative efficacy/effectiveness between respective newer and enhanced seasonal influenza vaccines when compared to standard seasonal influenza vaccines?
- What is the duration of protection within-season of the four newer and enhanced seasonal influenza vaccines against any type of influenza and by subtype (clade if available)?

2.2 Eligibility criteria

The population, intervention, comparison, outcomes and study design (PICOS) criteria for inclusion of studies in this systematic review are provided in Table 2.1. No restrictions were placed on language or date of publication.

Table 2.1 PICOS criteria for review questions

Population	Subjects aged ≥18 years irrespective of health status or setting
Intervention	One of the following newer and enhanced seasonal influenza vaccines: • MF59® aIIV3 or MF59® aIIV4 • HD-IIV3 or HD-IIV4 • ccIIV3 or ccIIV4 • RIV3 or RIV4
Comparator	One of the following comparators^: • Any seasonal influenza vaccine • Placebo • No vaccination • Other type of vaccine
Outcomes	**Efficacy or effectiveness – main outcomes** • Laboratory-confirmed influenza** • Influenza-related mortality* • Influenza-related hospitalisation* • Influenza-associated cardiovascular disease* • Influenza-associated pneumonia or lower respiratory tract disease* **Efficacy or effectiveness – additional outcomes** • Influenza-like illness (symptoms of influenza only) by international case definitions • Any International Statistical Classification of Diseases and Related Health Problems (ICD)- 9 or -10 coded respiratory disease or cardiovascular mortality • Exacerbation of primary disease where there was pre-existing respiratory or cardiovascular disease **Safety – main outcomes** • Systemic adverse events • Local adverse events **Safety – additional outcomes in pregnant women** • Spontaneous abortion, foetal death, stillbirth, preterm birth (less than 37 weeks), pre-eclampsia and eclampsia • Congenital malformations (minor and major), neonatal death.

Study design	The following study designs were deemed relevant^: • Randomised controlled trials • Non-randomised controlled trials • Quasi-experimental studies • Prospective and retrospective cohort studies • Case control studies • Analytical cross sectional studies

^study designs which did not include comparators were included for safety outcomes
**laboratory-confirmed by PCR, virus culture or antigen detection*
***symptoms of influenza with a positive laboratory diagnosis by PCR, virus culture or antigen detection.*

2.2.1 Exclusion criteria

The following study and vaccine types were excluded:

- Animal studies
- Case studies
- Immunogenicity studies
- Studies conducted during pandemic periods
- Pandemic vaccines
- Pre-pandemic vaccines
- Zoonotic vaccines.

High-dose intradermal influenza vaccines were excluded, unless they were compared with an intramuscular enhanced influenza vaccine of interest to this review. This decision reflects the position that no high-dose intradermal seasonal influenza vaccine is licensed and available for use for the 2019/2020 season in the EU/EEA. However, such vaccines may be relevant in future iterations of this review should they be authorised and available for use [15].

2.3 Search strategy

Electronic searches were conducted in Embase, MEDLINE (via PubMed), Cumulative Index to Nursing and Allied Health (CINAHL) and The Cochrane Library. The search terms and detailed search strategy for each database are provided in Appendix 1. Searches were originally conducted on the 26 September 2019, with the searches updated on the 7 February 2020 prior to analyses. The reference lists of included studies were further examined and a forward searching methodology used to identify any other potentially relevant studies.

A search of grey literature sources (Appendix 2) was conducted in an attempt to source any unpublished or ongoing studies which may be relevant to future iterations of this systematic review.

2.4 Data collection and analysis

2.4.1 Selection of eligible studies

All citations identified from the collective searches were exported to EndNote® (Version X8) for reference management, where duplicates were identified and removed. Using Covidence®, three reviewers independently reviewed the titles and available summaries of the remaining citations to identify those which warranted full-text review. The full texts were obtained and independently evaluated by two reviewers applying the defined eligibility criteria outlined in Table 2.1. Where disagreements occurred, discussions were held to reach consensus and where necessary, a third reviewer was involved. Citations excluded during the full-text review stage were documented, alongside the reasoning for their exclusion and included in a study flow diagram.

2.4.2 Data extraction and management

Data extraction was conducted in Microsoft Excel. A data extraction form was developed and piloted by the reviewers, with necessary modifications made. Two reviewers then independently extracted data using the agreed data extraction form which was compared upon completion. Where disagreements occurred, discussions were held to reach consensus and where necessary, a third reviewer was involved. Extracted information included the following:

- Author, year, country, location and setting
- Participants' characteristics (age, sex, co-morbid conditions)
- Type of vaccine
- Type of comparator
- Method of vaccination status establishment

- Diagnostic or confirmatory method for outcomes of interest
- Influenza season and circulating influenza virus strains (and clades where available)
- The degree of matching of circulating influenza strains to vaccine-strains
- Reported outcomes and results.

Where additional data were required, authors were contacted by email to request this information. For safety outcomes, data relating to the influenza season, vaccine strains and circulating strains were not deemed to be relevant and therefore were not extracted.

2.4.3 Assessment of risk of bias in included studies

Two reviewers independently assessed the included studies for risk of bias, using validated critical appraisal tools. Where disagreements occurred, discussions were held to reach consensus and where necessary, a third reviewer was involved.

For the assessment of risk of bias in randomised controlled trials (RCTs), the Cochrane Risk of Bias tool was used [18]. Certain domains within the risk of bias tool were designated as key domains to enable a summary assessment of risk of bias within and between studies [19]. For efficacy studies, the designated key domains were; funding sources (other bias), random sequence generation, and incomplete outcome data. For safety studies, the designated key domains were; funding sources (other bias), blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data. Risk of bias graphs were generated using the Cochrane Review Manager software (Version 5.3).

Non-randomised studies of interventions were assessed for risk of bias using the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool [20]. The tool was piloted by the reviewers for each study type included within this review with specifications and alterations made as required. Results were presented in tabular form, with the agreed consensus of risk of bias for each of the seven included domains and the overall risk of bias for each study denoted by the highest risk of bias score in any singular domain, as per the ROBINS-I methodology [20]. Where adjusted and unadjusted estimates were extracted from a study the risk of bias was assessed for each outcome.

Studies which did not possess a comparator were not assessed for risk of bias as no suitable tool was identified.

2.4.4 Measures of treatment effect

For test-negative design [case-control] studies, the outcome was defined as vaccine effectiveness which was uniformly defined as (1 – Odds Ratio)*100%, where a value of 100% indicates prevention of all cases of influenza and 0% indicates prevention of no cases of influenza. The odds ratio was the odds of being vaccinated among cases (laboratory-confirmed influenza) divided by the odds of being vaccinated among controls.

For cohort studies, the outcome was also defined as vaccine effectiveness. However, rather than using an odds ratio, the studies used either the risk ratio, incidence risk ratio, or hazard ratio.

For both test-negative design case-control and cohort studies, the vaccine effectiveness was, in almost all cases, adjusted for a number of patient characteristics. The choice of covariates was not uniform across studies, although age and sex were almost uniformly included. Some studies only included covariates that demonstrated some level of association with outcomes in a univariate analysis. Where studies reported both unadjusted and adjusted vaccine effectiveness, the adjusted figure was used in the results as it was considered the less biased estimate of treatment effect.

For safety studies, numbers of events were extracted and the risk ratio was used as the preferred measure of treatment effect.

2.4.5 Data synthesis

Where two or more studies reported an outcome, pooling was considered. Study results were pooled using both fixed and random effects meta-analysis. Fixed effect meta-analysis was conducted using the Mantel-Haenszel method. Random effects meta-analysis was conducted using the Sidik-Jonkman estimator combined with the Hartung and Knapp adjustment [21, 22]. Given the differences in studies, the preference was to use a random effects analysis. However, the estimate of between study variance is considered to be unreliable when there are few studies available for pooling [23, 24]. As such, the fixed effect estimate is used when only two or three studies are available for pooling.

For vaccine effectiveness, pooling was only carried out for studies with matching intervention and comparator groups. For example, studies of adjuvanted vaccines with a comparator of IIV3 were not combined with studies where the comparator was a mix of IIV3 and IIV4. The specific lineage of influenza B was not consistently and clearly reported across studies. Therefore, consistent with similar reviews [25, 26], data were pooled across lineage to provide a summary estimate of effect.

As outcomes for the test-negative design and cohort studies were generally reported as adjusted vaccine effectiveness, it was not possible to use the two by two table for pooling. As such, pooling was on the basis of the log odds ratio and variance, with the exponential of the pooled result re-expressed as vaccine effectiveness.

2.4.6 Dealing with missing data

Where issues with missing data were encountered, the study authors were contacted. No imputation of missing data was used.

2.4.7 Assessment of heterogeneity

Heterogeneity across studies could arise for a variety of reasons, most typically because of clinical diversity, differences in study design and risk of bias. Consideration was given to study characteristics such as patient population and influenza season when investigating potential clinical heterogeneity.

In this review, potential statistical heterogeneity was assessed on the basis of the I^2 statistic, with an I^2 of between 30% and 60% interpreted as moderate heterogeneity, 50% to 90% as substantial heterogeneity, and 75% to 100% as considerable heterogeneity, in line with the Cochrane methodology [19]. The I^2 value was interpreted based on the magnitude and direction of effects, and on the strength of evidence for heterogeneity based on the chi-squared statistic.

2.4.8 Subgroup analysis and investigation of heterogeneity

Where multiple studies were available for a given outcome and there was evidence of heterogeneity, consideration was given to subgroup analysis and meta-regression to identify potential sources of heterogeneity. Given the small numbers of studies available for most comparisons, there was limited power to explore sources of heterogeneity and a risk of identifying spurious associations.

Subgroup analysis was considered where studies could be meaningfully grouped based on consistently provided data. Meta-regression was only considered if there were ten or more studies available reporting a given outcome.

2.5 GRADE and 'summary of findings' table

The certainty of evidence for each outcome of interest within this review was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [27]. Primary outcomes are presented separately for each of the newer and enhanced influenza vaccines within this review (see main summary of findings tables). For each vaccine type of interest, the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) were interpreted by two reviewers to assess the quality of the body of evidence for each outcome. New guidance regarding the assessment of non-randomised studies of interventions (NRSIs) was incorporated, whereby these types of studies are not penalised for their design and begin the assessment as a high certainty of evidence like their RCT counterparts [28]. Given the nature of the uniform variable of vaccine effectiveness for influenza and influenza-related outcomes within NRSIs, results are presented without raw counts. As a broad range of safety outcomes were assessed by the included studies, a number were chosen which were thought to best reflect this outcome as a whole and which were relatively consistent across the vaccines of interest within this review: combined local reactions, pain, combined systemic reactions, and fever. For completeness, where sufficient data were presented for additional outcomes the certainty of evidence was assessed and presented as supplementary material within the appendices of this report (Appendix 9.1 to 9.4). Summary of findings tables were generated using the GRADEpro® software.

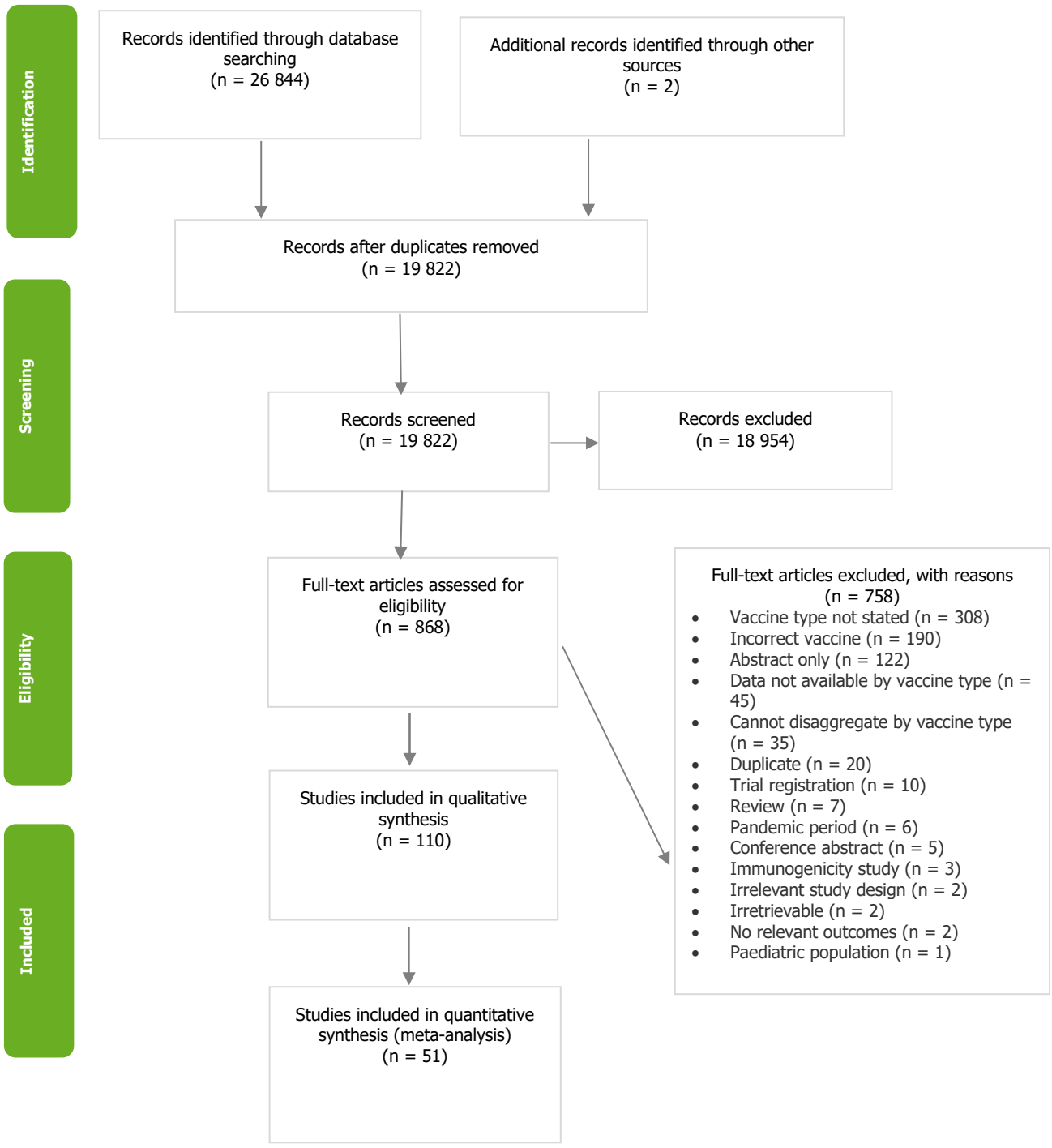
3. Results

As shown in the PRISMA flow diagram in Figure 3.1, the collective searches up until 7 February 2020 returned 26 844 records, with two further records being identified from additional sources. The removal of duplicates resulted in 19 822 records being screened for relevance, with 868 meriting full-text review. Of these records, 758 were subsequently excluded, based on the predefined eligibility criteria. A list of excluded studies and detailed overview of the reasons for exclusion is provided in Appendix 3. This resulted in 110 studies being included in this systematic review [29-139].

Of these 110 studies, 48 possessed results relevant to adjuvanted influenza vaccines, 19 to cell-based influenza vaccines, 36 to high-dose influenza vaccines, and 10 to recombinant HA influenza vaccines. For the primary outcome of laboratory-confirmed influenza, five efficacy RCTs and 15 test-negative case-control designs were included. In terms of additional influenza-related outcomes which were not laboratory-confirmed, data were presented by four case-control studies and 14 cohort studies. Sixty-one RCTs presented results relating to the safety of the vaccines of interest to this review, with further data from five cohort studies and ten single-arm studies. These results are presented in terms of the efficacy, effectiveness and safety of each of the four influenza vaccine types of interest to this review. Efficacy/effectiveness data by influenza clade were not identified.

Twenty studies were identified which were classified as ongoing or completed without published results. The titles, status and identifiers for these studies are provided in Appendix 4.

Figure 3.1 PRISMA flow diagram



3.1 Unadjusted and adjusted vaccine effectiveness

Vaccine effectiveness was reported as both unadjusted and adjusted in a number of the test-negative case-control and cohort studies. A minority of studies reported only unadjusted effectiveness. The difference between adjusted and unadjusted estimates can be substantial (Figure 3.2), and is not clearly influenced by the sample size of the study (Figure 3.3). While unadjusted effectiveness was used where adjusted was not reported, there is clearly a risk of bias associated with the unadjusted estimate.

Figure 3.2 Adjusted versus unadjusted vaccine effectiveness

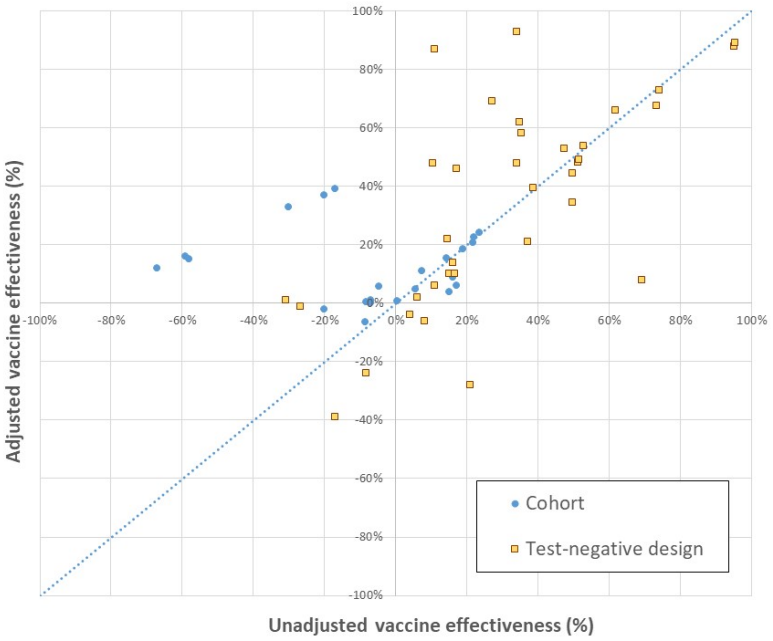
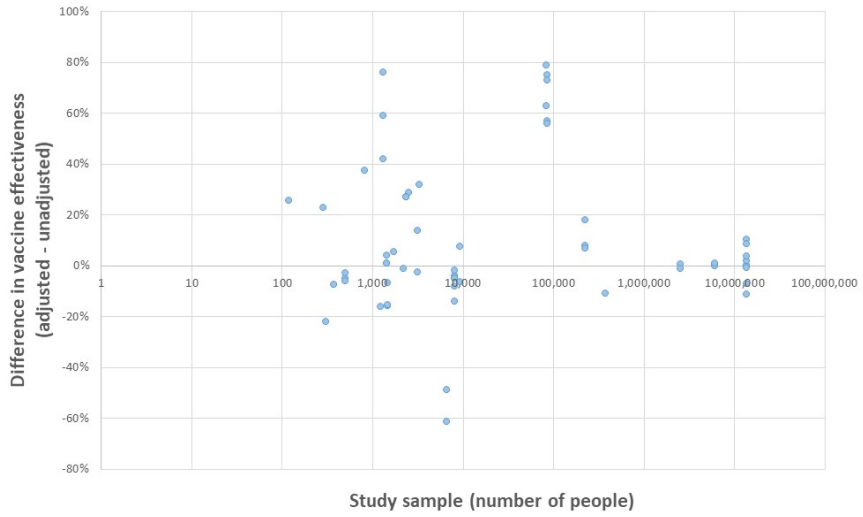


Figure 3.3 Difference between adjusted and unadjusted vaccine effectiveness by study sample size



3.2 MF59® adjuvanted influenza vaccines

Forty-eight studies in this review provided results concerning MF59® adjuvanted influenza vaccines [30, 34-36, 48-50, 59, 62, 64, 66-70, 76, 78, 85-89, 93, 94, 96, 97, 99, 102-105, 107-110, 112-115, 118, 119, 121, 123, 130, 132-135]. Of these studies, 22 related to vaccine effectiveness [34-36, 68, 70, 76, 78, 85, 86, 94, 97, 104, 105, 108-110, 112-114, 123, 132, 133] and 26 related to vaccine safety [30, 48-50, 59, 62, 64, 66, 67, 69, 87-89, 93, 96, 99, 102, 103, 107, 115, 118, 119, 121, 130, 134, 135]. The characteristics of studies relating to the effectiveness of adjuvanted influenza vaccines are provided in Appendix 5.1. The vaccine and circulating strain characteristics associated with these studies are provided Appendix 6.1. The characteristics of studies relating to the safety of adjuvanted influenza vaccines are provided in Appendix 7.1.

3.2.1 Efficacy - adjuvanted influenza vaccines

No published RCTs investigating the efficacy of MF59® adjuvanted influenza vaccines were identified that met the eligibility criteria for this review.

3.2.2 Effectiveness - adjuvanted influenza vaccines

Twenty-two studies contained results relevant to the effectiveness of MF59® adjuvanted influenza vaccines [34-36, 68, 70, 76, 78, 85, 86, 94, 97, 104, 105, 108-110, 112-114, 123, 132, 133]. Seventeen were case-control studies [34, 35, 68, 70, 85, 86, 97, 104, 105, 108, 109, 112-114, 123, 132, 133] comprising 15 unique datasets, and five were cohort studies [36, 76, 78, 94, 110].

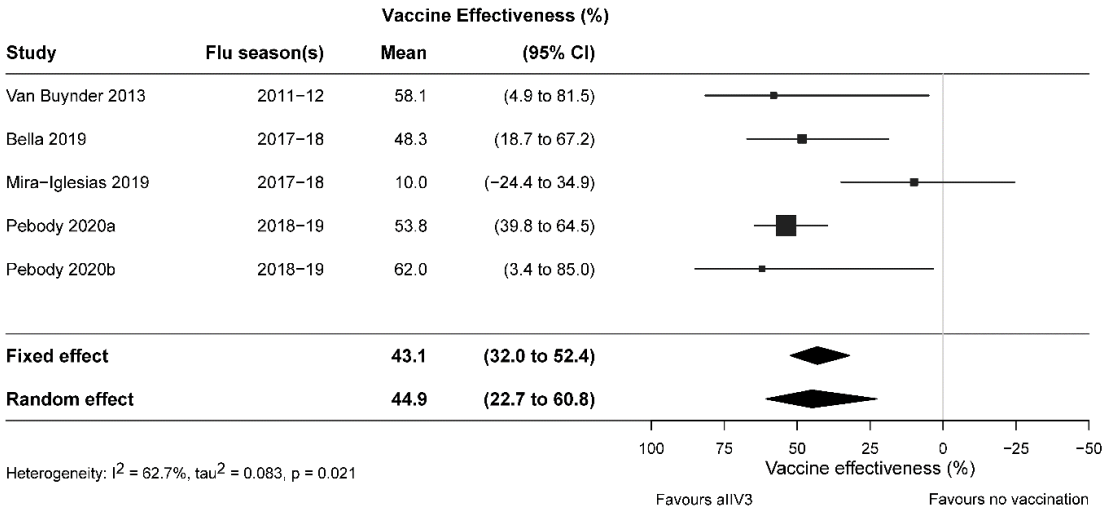
3.2.2.1 Effectiveness against laboratory-confirmed influenza

Eleven studies provided data relevant to the primary outcome of laboratory-confirmed influenza [34, 35, 70, 85, 97, 104, 105, 113, 114, 132, 133]. All were related to aIIV3 vaccines and were of test-negative case-control design in older adult populations (aged ≥65 years), with the exception of one study which also presented data for adults over the age of 18 years [105]. Table 3.1 outlines for each relevant comparison, the type of influenza, comparator, vaccine effectiveness, and degree of matching to circulating strains, as interpreted from the narrative within each individual study, subcategorised by the influenza season.

3.2.2.1.1 Effectiveness against any influenza type/subtype

Six studies presented data regarding the effectiveness of aIIV3 vaccines against any influenza type [34, 35, 97, 104, 105, 133]. In older adults (aged ≥65 years) across all influenza seasons, aIIV3 was significantly more effective than no vaccination (VE=44.9%, 95% CI 22.7 to 60.8, REM, I^2=62.7%, low-certainty evidence) (Figure 3.4). Crude estimates from a single study which presented data for an adult population (aged ≥18 years) did not show a significant difference between aIIV3 and no vaccination [105]. As summarised in Table 3.1, there was no significant difference in vaccine effectiveness reported by included studies which compared aIIV3 with IIV3 or IIV4 in adult or older adult populations.

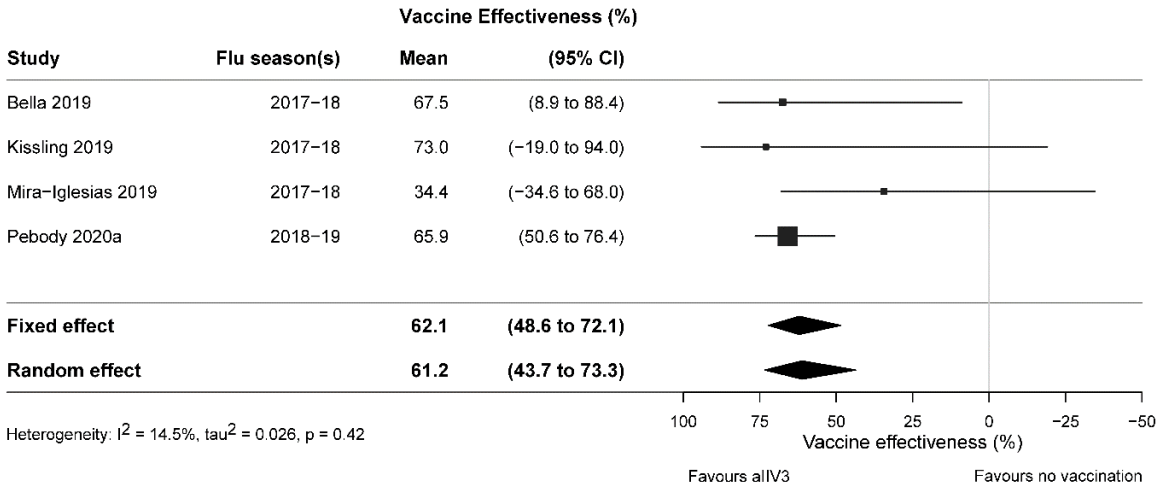
Figure 3.4 Vaccine effectiveness of aIIV3 versus no vaccination against any influenza, adults aged 65 years and older



3.2.2.1.2 Effectiveness against Influenza A(H1N1)

Four studies presented data regarding the effectiveness of aIIV3 against influenza A(H1N1) [34, 85, 97, 104]. As shown in Figure 3.5, aIIV3 was significantly more effective than no vaccination in preventing influenza A(H1N1) (VE=61.2%, 95% CI 43.7 to 73.3, REM, I^2=14.5%, low-certainty evidence). As summarised in Table 3.1, there was no significant difference reported by included studies which compared aIIV3 with IIV3 or IIV4 in terms of vaccine effectiveness against influenza A(H1N1).

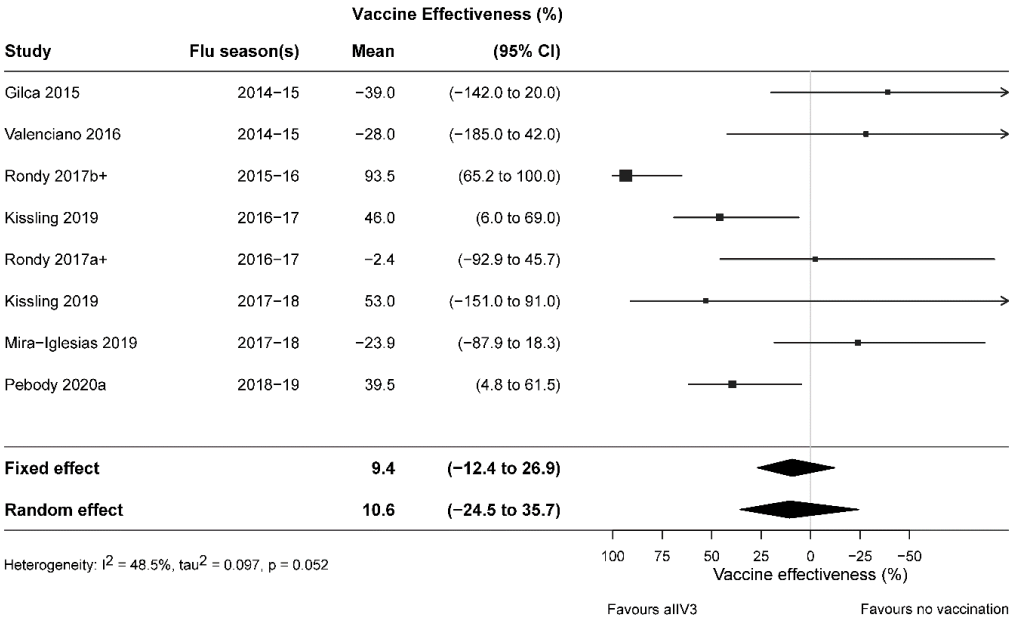
Figure 3.5 Vaccine effectiveness of aIIV3 versus no vaccination against Influenza A(H1N1), adults aged 65 years and older



3.2.2.1.3 Effectiveness against Influenza A(H3N2)

Seven studies presented data regarding the effectiveness of aIIV3 against influenza A(H3N2) [70, 85, 97, 104, 113, 114, 132]. As shown in Figure 3.6, there was no significant difference found between aIIV3 and no vaccination (VE=10.6%, 95% CI -24.5 to 35.7, REM, I^2=48.5%, very low-certainty evidence) across all influenza seasons. However, as highlighted in Table 3.1, there was considerable heterogeneity in terms of the matching of vaccine strains to circulating strains across the influenza seasons included in the analyses. As presented in Table 3.1, four studies compared aIIV3 with IIV3 or IIV4, with three showing no significant difference between these comparisons for effectiveness against influenza A(H3N2).

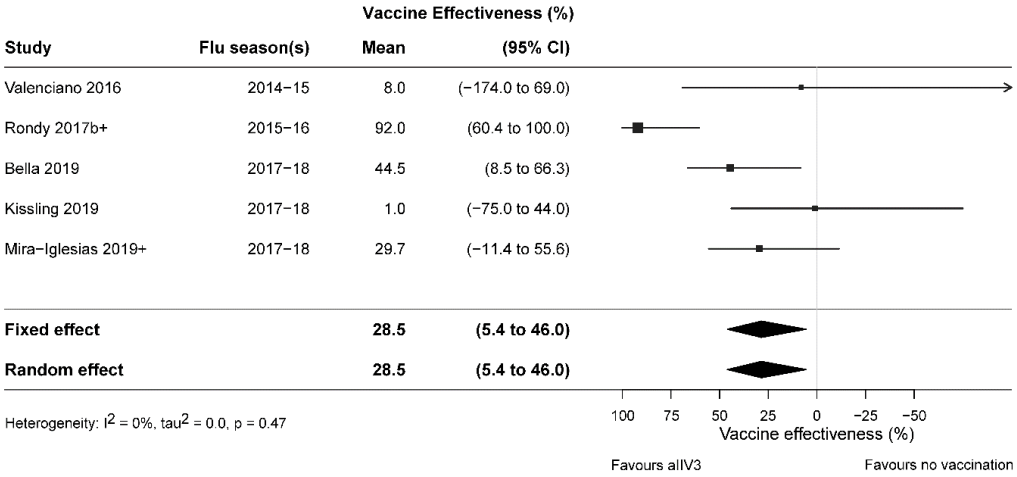
Figure 3.6 Vaccine effectiveness of aIIV3 versus no vaccination against Influenza A(H3N2), adults aged 65 years and older



3.2.2.1.4 Effectiveness against Influenza B

Five studies investigated the effectiveness of aIIV3 against influenza B [34, 85, 97, 114, 132]. As shown in Figure 3.7, across all influenza seasons there was significant effect in favour of aIIV3 compared with no vaccination (VE=28.5%, 95% CI 5.4 to 46.0, REM, I^2=0%, low-certainty evidence). Two studies compared aIIV3 to IIV3 with conflicting results shown and both studies providing crude estimates (Table 3.1).

Figure 3.7 Vaccine effectiveness of aIIV3 versus no vaccination against Influenza B, adults aged 65 years and older



3.2.3 Additional outcomes

As presented in Table 3.2, nine studies presented data related to additional outcomes relevant to this review; influenza-related hospitalisation, pneumonia –related hospitalisation, influenza- or pneumonia- related hospitalisation, influenza-related hospital encounters, influenza-like illness and influenza-related office visits [36, 68, 76, 78, 94, 108-110, 123]. Of these, four were case-control studies, [68, 108, 109, 123] five were cohort studies, [36, 68, 76, 78, 110] and all investigated aIIV3 in older (aged ≥65 years) adult populations.

3.2.3.1 Influenza-related hospitalisation

Three studies presented data related to the effectiveness of aIIV3 in preventing influenza-related hospitalisations [36, 78, 110]. One study found aIIV3 to be significantly more effective than no vaccination across three influenza seasons (Table 3.2) [36]. Two studies compared the effectiveness of aIIV3 to IIV3 for this outcome with no significant difference shown [78, 110].

3.2.3.2 Influenza- or pneumonia-related hospitalisations

Three studies presented data related to the effectiveness of aIIV3 in preventing influenza- or pneumonia- related hospitalisations compared with no vaccination (one study) or IIV3 (two studies) [68, 94, 123]. Regardless of the comparator, all included studies displayed a significant effect in favour of aIIV3 (Table 3.2) [68, 94, 108, 109, 123].

3.2.3.3 Pneumonia-related hospitalisations

Two studies presented data specifically concerning the effectiveness of aIIV3 in preventing pneumonia-related hospitalisations compared with no vaccination. As shown in Table 3.2 a significant effect in favour of aIIV3 was shown for both studies [108, 109].

3.2.3.4 Influenza-related hospital encounters or office visits

As shown in Table 3.2, one study presented data relating to the effectiveness of aIIV3 compared with IIV3 for the prevention of influenza-related hospital encounters or office visits with a small, but statistically significant difference highlighted for hospital encounters in favour of aIIV3 and no significant difference shown for office visits [78].

3.2.3.5 Influenza-like illness

As shown in Table 3.2, one study presented data that related to the effectiveness of aIIV3 for the prevention of influenza-like illness compared with no vaccination and with IIV3 for long-term care facility residents [76]. The results show a significant effect in favour of aIIV3 for both comparisons. However, these results should be interpreted with caution as they are crude estimates and the unvaccinated population represent a small portion of residents who refused vaccination.

Table 3.1 Effectiveness of MF59® adjuvanted influenza vaccines against laboratory-confirmed influenza

Author	Comparator	Vaccine effectiveness (1-odds ratio)	95%CI (lower)	95%CI (upper)	Strain mismatch^
All influenza strains					
2011-2012 season					
Van Buynder 2013 [133]	Unvaccinated	0.58	0.05	0.82	Not reported
Van Buynder 2013 [133]	IIV3	0.42*	-0.08	0.69	Not reported
2017-2018 season					
Bella 2019 [34]	Unvaccinated	0.48	0.19	0.67	B
Mira-Iglesias 2019 [97]	Unvaccinated	0.10	-0.24	0.35	B and H3N2
Mira-Iglesias 2019 [97]	IIV3	0.19*	-0.10	0.41	B and H3N2
2018-2019 season					
Pebody 2020a [104]	IIV3/IIV4	0.30	-0.83	0.73	Well-matched
Pebody 2020b** [105]	Unvaccinated	0.51*	-0.54	0.84	Well-matched
Pebody 2020a [104]	Unvaccinated	0.54	0.40	0.65	Well-matched
Pebody 2020b [105]	Unvaccinated	0.62	0.03	0.85	Well-matched
Pebody 2020b** [105]	IIV4	0.16*	-1.76	0.75	Well-matched
Bellino 2019a [35]	IIV4	-0.01	-1.22	0.58	Probable mismatch B
Influenza A(H1N1)					
2017-2018 season					
Bella 2019 [34]	Unvaccinated	0.68	0.09	0.88	Not reported
Kissling 2019 [85]	Unvaccinated	0.73	-0.19	0.94	Mismatch
Mira-Iglesias 2019 [97]	Unvaccinated	0.34	-0.35	0.68	Not reported
Mira-Iglesias 2019 [97]	IIV3	-0.03*	-1.26	0.53	Not reported
2018-2019 season					
Pebody 2020a [104]	IIV3/ IIV4	0.03	-3.58	0.79	Well-matched
Pebody 2020a [104]	Unvaccinated	0.66	0.51	0.76	Well-matched
Influenza A(H3N2)					
2014-2015 season					
Gilca 2015 [70]	Unvaccinated	-0.39	-1.42	0.20	Not reported
Valenciano 2016 [132]	Unvaccinated	-0.28	-1.85	0.42	Mismatch
2015-2016 season					
Rondy 2017b [114]	IIV3	0.88*	0.51	1.00	Not reported
Rondy 2017b [114]	Unvaccinated	0.94*	0.65	1.00	Not reported
2016-2017 season					
Rondy 2017a [113]	IIV3	-0.30*	-1.46	0.31	Well-matched
Rondy 2017a [113]	Unvaccinated	-0.02*	-0.93	0.46	Well-matched
Kissling 2019 [86]	Unvaccinated	0.46	0.06	0.69	Mismatch
2017-2018 season					
Kissling 2019 [85]	Unvaccinated	0.53	-1.51	0.91	Mismatch
Mira-Iglesias 2019 [97]	Unvaccinated	-0.24	-0.88	0.18	Mismatch
Mira-Iglesias 2019 [97]	IIV3	0.20*	-0.17	0.46	Mismatch
2018-2019 season					
Pebody 2020a [104]	IIV3/ IIV4	0.43	-1.34	0.86	Well-matched
Pebody 2020a [105]	Unvaccinated	0.40	0.05	0.62	Well-matched
Influenza B					
2014-2015 season					
Valenciano 2016 [132]	Unvaccinated	0.08	-1.74	0.69	Not reported
2015-2016 season					
Rondy 2017b [114]	IIV3	0.87*	0.30	1.00	Mismatch
Rondy 2017b [114]	Unvaccinated	0.92*	0.60	1.00	Mismatch
2017-2018 season					
Bella 2019 [34]	Unvaccinated	0.45	0.09	0.66	Mismatch
Kissling 2019 [85]	Unvaccinated	0.01	-0.75	0.44	Mismatch
Mira-Iglesias 2019 [97]	Unvaccinated	0.30*	-0.11	0.56	Mismatch
Mira-Iglesias 2019 [97]	IIV3	0.06*	-0.58	0.44	Mismatch

**Denotes unadjusted estimate of vaccine effectiveness, ** Denotes adult (≥18 years) population*
^Interpreted from narrative provided by included studies

Table 3.2 Effectiveness of MF59® adjuvanted influenza vaccines for additional outcomes

Author	Season	Comparator	Vaccine effectiveness (1- risk ratio)	95%CI lower	95%CI higher	Strain mismatch^
Influenza-related hospitalisation						
Bellino2019b [35]	2014-2015	Unvaccinated	0.12	0.03	0.20	Not reported
Bellino 2019b [35]	2015-2016	Unvaccinated	0.16	0.07	0.24	B
Bellino 2019 [35]b	2016-2017	Unvaccinated	0.15	0.06	0.23	Not reported
Puig-Barbera 2013 [110]	2010-2011	IIV3	0.06	-1.38	0.63	Well-matched
Izurieta 2019 [78]	2017-2018	IIV3	0.03	-0.01	0.06	Not reported
Influenza- or pneumonia-related hospitalisation						
Mannino 2012 [94]	2006-2009	IIV3	0.25	0.02	0.43	Mismatch
Gasparini 2013 [68]	2010-2011	Unvaccinated	0.88	0.00	0.99	Well-matched
Spadea 2014 [123]	2010-2011	IIV3	0.48	0.29	0.62	Well-matched
Spadea 2014 [123]	2011-2012	IIV3	0.49	0.30	0.60	Mismatch
Pneumonia-related hospitalisation						
Puig-Barbera 2004 [108]	2002-2003	Unvaccinated	0.48	0.20	0.66	Not reported
Puig-Barbera 2007 [109]	2004-2005	Unvaccinated	0.69	0.29	0.86	Not reported
Influenza-related hospital encounters						
Iziureta 2019 [78]	2017-2018	IIV3	0.04	0.01	0.06	Not reported
Influenza-related office visits						
Iziureta 2019 [78]	2017-2018	IIV3	-0.07	-0.10	-0.04	Not reported
Influenza-like illness						
Iob 2005 [76]	1998-1999	Unvaccinated	0.20*	0.14	0.31	Well-matched
Iob 2005 [76]	1998-1999	IIV3	0.76*	0.59	0.97	Well-matched

**Denotes unadjusted estimate of vaccine effectiveness*
^Interpreted from narrative provided by included studies

3.2.4 Safety- MF59® adjuvanted influenza vaccines

Twenty-six studies concerned the safety of adjuvanted influenza vaccines [30, 48-50, 59, 62, 64, 66, 67, 69, 87-89, 93, 96, 99, 102, 103, 107, 115, 118, 119, 121, 130, 134, 135]. Of these, 21 were RCTs [30, 48-50, 59, 62, 64, 66, 67, 69, 87, 88, 93, 96, 99, 107, 115, 118, 119, 121, 134] and five possessed results from non-randomised studies. [89, 102, 103, 130, 135].

3.2.4.1 Serious adverse events

Three RCTs [66, 88, 134] and two non-randomised studies [130, 135] reported vaccine-related serious adverse events (SAEs), with all comparing aIIV3 with IIV3. Frey et al [66]. reported four SAEs; one in the aIIV3 group (bronchitis) and three in the IIV3 group (asthmatic crisis, chronic obstructive pulmonary disease (unspecified issue) and Guillain–Barré syndrome). One death attributable to respiratory depression secondary to Guillain–Barré syndrome in the aIIV3 group was considered possibly vaccine-related. Li et al [88]. reported a SAE of high fever in a recipient of an aIIV3. A third study reported a case of facial herpes zoster that was deemed by the investigator to be possibly vaccine-related [134]. Tsai et al. [130] reported no cases of narcolepsy in either vaccine group, and further found no increase in adverse sleep-related events in the aIIV3 recipients. Villa et al. [135] highlight no difference in the rate of hospitalisation for adverse events related to vaccination between aIIV3 and IIV3 groups.

3.2.4.2 Local reactions

Twelve studies possessed sufficient data to enable a quantitative synthesis of local reactions, all of which compared aIIV3 with IIV3 in adult populations [48, 49, 59, 64, 66, 69, 88, 96, 115, 118, 119, 121]. Sub-group analyses are presented in Appendix 8.1. Pooled estimates for combined local reactions, pain, redness, swelling, and induration are presented in Figures 3.8 to 3.12. As shown, aIIV3 was associated with a greater number of combined local reactions (RR=1.90, 95% CI 1.50 to 2.39, four RCTs, REM, I^2=0%, moderate-certainty evidence), with pain in particular being more frequently reported in recipients of aIIV3 vaccines (RR=2.02, 95% CI 1.53 to 2.67, 12 RCTs, REM, I^2=75%, moderate-certainty evidence). No significant difference between aIIV3 and IIV3 was noted for redness, swelling or induration based on the remaining pooled analyses (low-moderate certainty of evidence, see Appendix 9.1). As shown in Appendix 8.1, similar results were displayed for older adults within sub-group analyses.

In terms of studies that were excluded from pooled analyses, in agreement with the results of the pooled analyses, local injection site reactions were typically more frequent with adjuvanted compared with non-adjuvanted vaccines in older adults [48, 50, 89, 119, 134]. One study set out to assess if the inclusion of an additional B- strain in an aIIV4 influenced the safety profile of the vaccine compared with an aIIV3. Overall, no clinically relevant difference in the frequencies of individual local solicited adverse events was identified. Rates of local events were reported to be in line with expected for aIIV3 vaccination in a single-arm study by Otten et al. [102] report and a surveillance study conducted by Panatto et al. [103].

Figure 3.8 Relative risk of combined local adverse events, adjuvanted versus non-adjuvanted vaccines

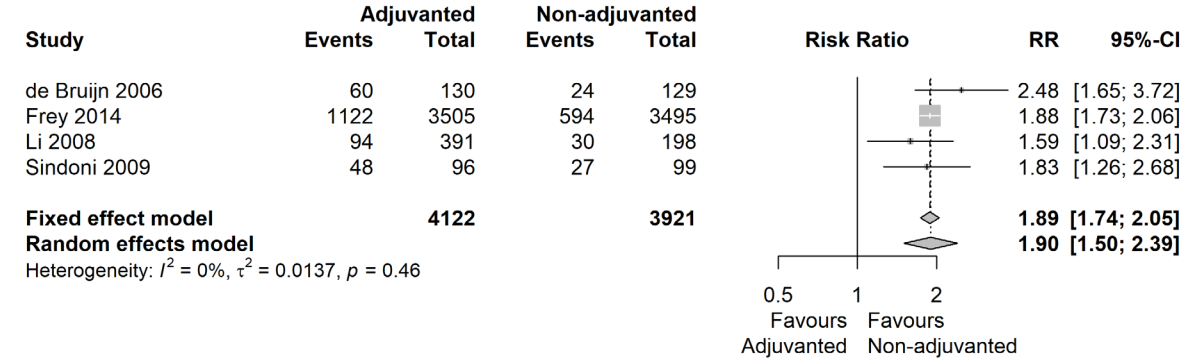


Figure 3.9 Relative risk of local pain, adjuvanted versus non-adjuvanted vaccines

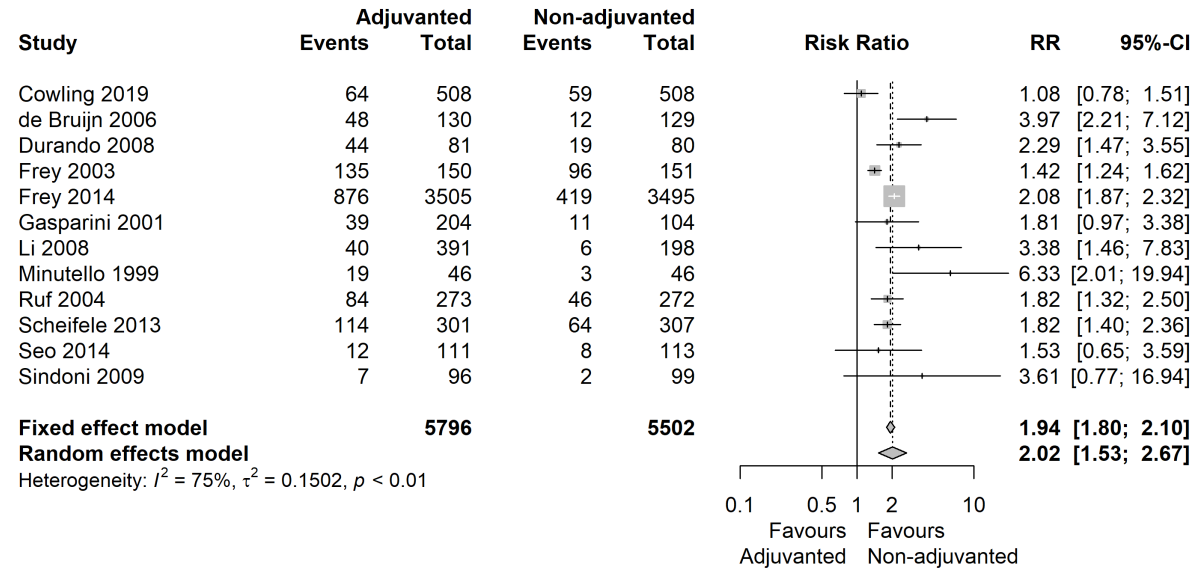


Figure 3.10 Relative risk of redness-erythema, adjuvanted versus non-adjuvanted vaccines

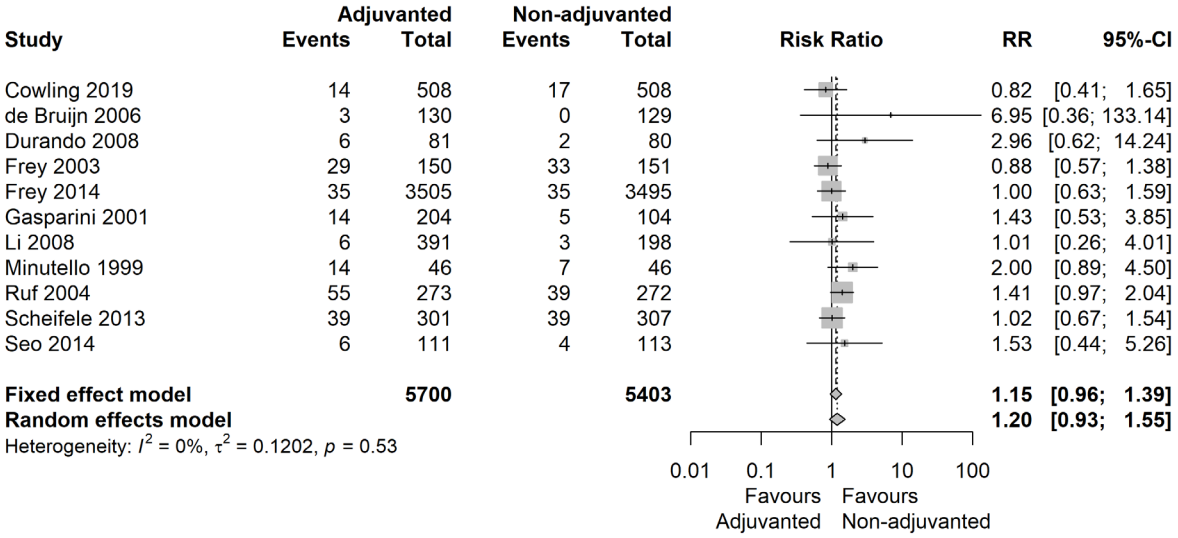


Figure 3.11 Relative risk of swelling, adjuvanted versus non-adjuvanted vaccines

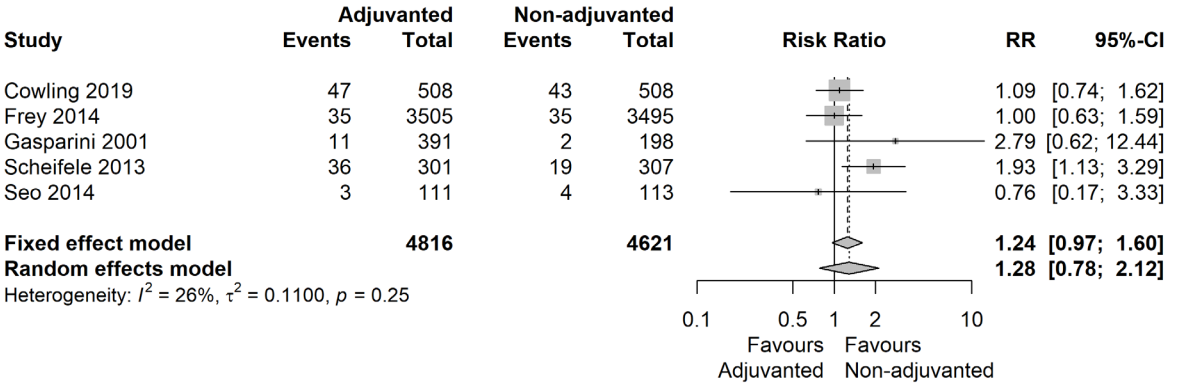
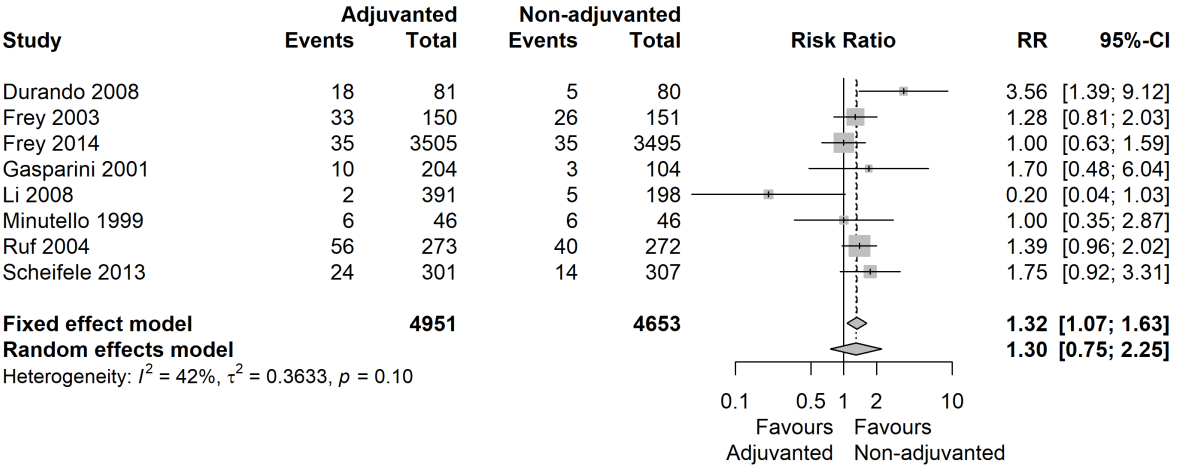


Figure 3.12 Relative risk of induration, adjuvanted versus non-adjuvanted vaccines



3.2.4.3 Systemic reactions

Twelve studies reported sufficient data to enable quantitative synthesis of systemic reactions with all comparing aIIV3 with IIV3 in adult populations [48, 49, 59, 64, 66, 69, 88, 96, 115, 118, 121]. Pooled estimates for the reported outcomes (combined systemic reactions, myalgia, fever, headache, shivers and chills, arthralgia, malaise, nausea and fatigue) are presented in Figures 3.13 to 3.21. The relative risk of combined systemic reactions (RR=1.18, 95% CI 1.02 to 1.38, five RCTs, REM, I^2=8%, moderate-certainty evidence), myalgia (RR=1.71, 95% CI 1.09 to 2.69, 10 RCTs REM, I^2=31%, moderate-certainty evidence), fever (RR=1.97, 95% CI 1.07 to 3.61, nine RCTs, REM, I^2=31%, low-certainty evidence) and chills (RR=1.70, 95% CI 1.20 to 2.40, seven RCTs, REM, I^2=0%, moderate-certainty evidence (Appendix 9.1)) were significantly higher compared with aIIV3, however no significant difference were noted for arthralgia, malaise, headache, nausea or fatigue (low-moderate certainty evidence, see Appendix 9.1). As shown in Appendix 8.1, similar results were displayed for older adults within sub-group analyses.

In terms of studies which were excluded from the pooled analyses, in general, the frequency of systemic adverse events was similar for recipients of adjuvanted and non-adjuvanted vaccines [48, 50, 89, 119, 134]. Essink et al. [62] reported no clinically relevant difference in the frequency of systemic adverse events between aIIV4 and aIIV3 groups. Panatto et al. [103] highlighted chills and fatigue as most frequently experienced systemic adverse events in a surveillance study of aIIV3 vaccine recipients.

3.2.4.4 Safety of adjuvanted influenza vaccines in at-risk populations

Six studies included in this review were deemed to include at-risk populations including: a diagnosis of HIV, [59. 67] transplant recipients [93, 99], institutionalised older adults [107], and those receiving regular medical care [30].

For local reactions, only one study reports a significant difference between adjuvanted and non-adjuvanted influenza vaccines; in individuals who receive regular medical care, local reactions were more common in those receiving adjuvanted compared with non-adjuvanted vaccines [30].

For systemic reactions, there was no significant difference in rates between adjuvanted and non-adjuvanted vaccines for individuals who receive regular medical care [30], institutionalised older adults [107] or haematopoietic stem cell transplantation recipients [99]. Shivers and fever were more commonly reported among HIV-seropositive patients vaccinated with aIIV3 compared with IIV3 [59, 67]. Among heart-transplant recipients, there was no difference in the frequency of acute myocardial rejection or early side effects for recipients of adjuvanted vaccines compared with non-adjuvanted [93].

Figure 3.13 Relative risk of combined systemic adverse events, adjuvanted versus non-adjuvanted vaccines

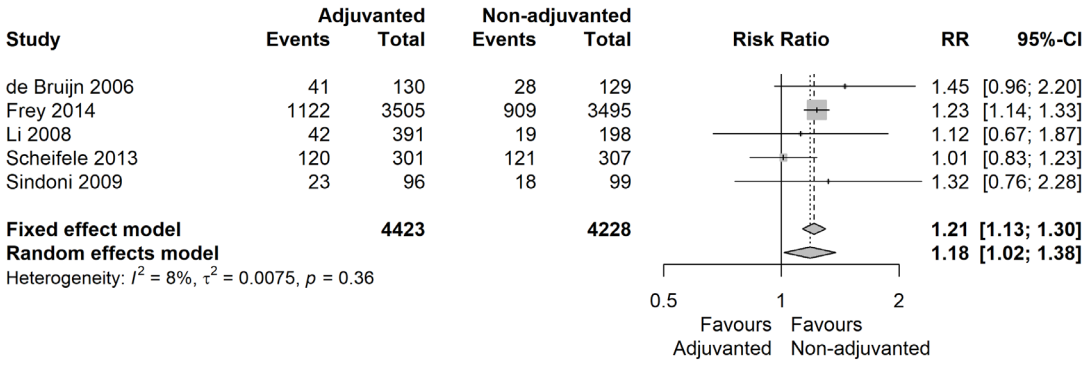


Figure 3.14 Relative risk of myalgia, adjuvanted versus non-adjuvanted vaccines

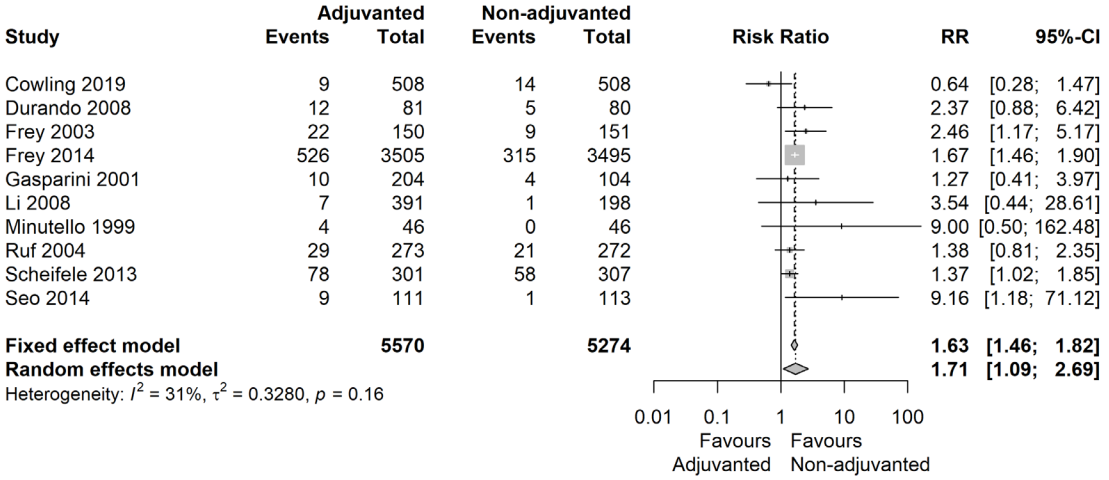


Figure 3.15 Relative risk of fever, adjuvanted versus non-adjuvanted vaccines

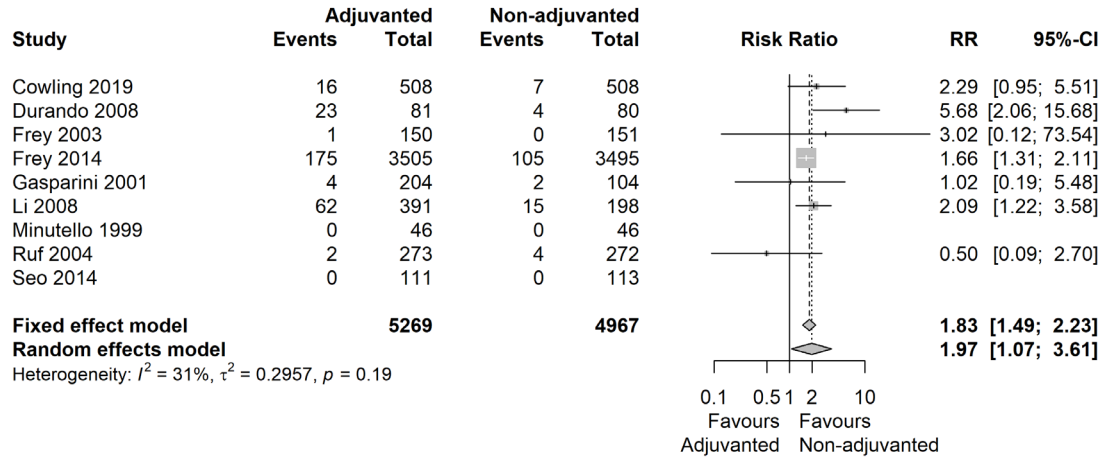


Figure 3.16 Relative risk of headache, adjuvanted versus non-adjuvanted vaccines

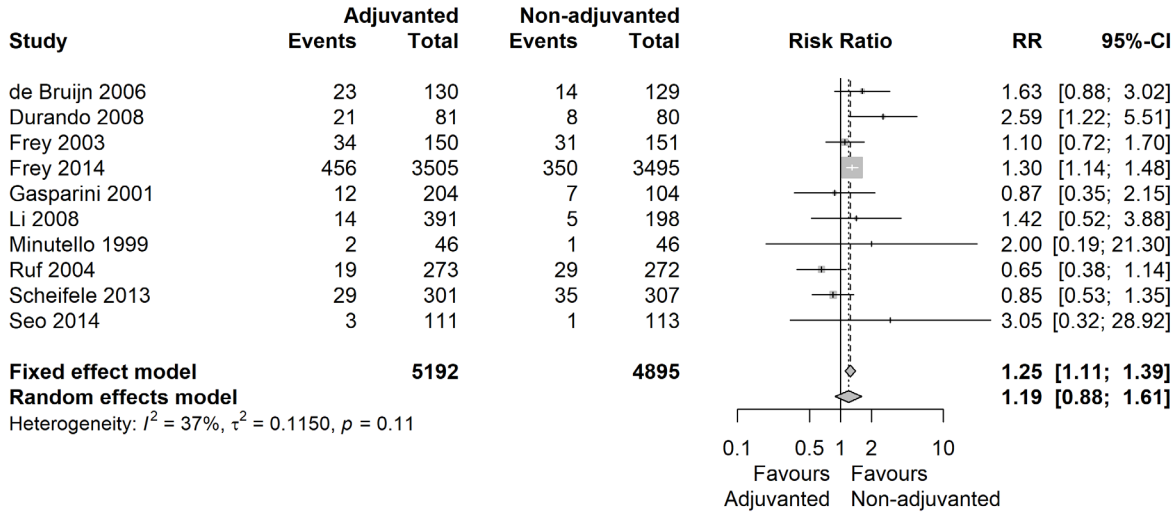


Figure 3.17 Relative risk of shiver and chills, adjuvanted versus non-adjuvanted vaccines

Study	Adjuvanted Events	Adjuvanted Total	Non-adjuvanted Events	Non-adjuvanted Total	RR	95%-CI
Durando 2008	16	81	7	80	2.26	[0.98; 5.19]
Frey 2003	7	150	1	151	7.05	[0.88; 56.58]
Frey 2014	245	3505	175	3495	1.40	[1.16; 1.69]
Gasparini 2001	8	204	3	104	1.36	[0.37; 5.02]
Minutello 1999	3	46	1	46	3.00	[0.32; 27.79]
Ruf 2004	21	273	13	272	1.61	[0.82; 3.15]
Seo 2014	3	111	2	113	1.53	[0.26; 8.96]
Fixed effect model		**4370**		**4261**	**1.48**	**[1.24; 1.75]**
Random effects model					**1.70**	**[1.20; 2.40]**

Heterogeneity: I^2 = 0%, τ^2 = 0.0977, p = 0.68

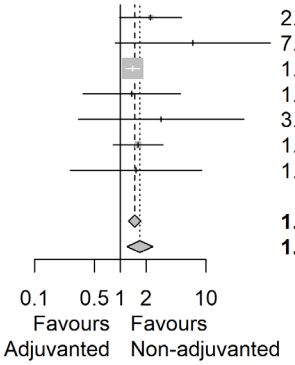


Figure 3.18 Relative risk of arthralgia, adjuvanted versus non-adjuvanted vaccines

Study	Adjuvanted Events	Adjuvanted Total	Non-adjuvanted Events	Non-adjuvanted Total	RR	95%-CI
de Bruijn 2006	1	130	2	129	0.50	[0.05; 5.40]
Durando 2008	10	81	6	80	1.65	[0.63; 4.32]
Frey 2003	4	150	0	151	9.06	[0.49; 166.81]
Frey 2014	280	3505	245	3495	1.14	[0.97; 1.34]
Gasparini 2001	10	204	4	104	1.27	[0.41; 3.97]
Minutello 1999	0	46	0	46		
Ruf 2004	9	273	16	272	0.56	[0.25; 1.25]
Scheifele 2013	38	301	34	307	1.14	[0.74; 1.76]
Seo 2014	6	111	1	113	6.11	[0.75; 49.92]
Fixed effect model		**4801**		**4697**	**1.15**	**[0.99; 1.33]**
Random effects model					**1.25**	**[0.68; 2.31]**

Heterogeneity: I^2 = 18%, τ^2 = 0.4640, p = 0.29

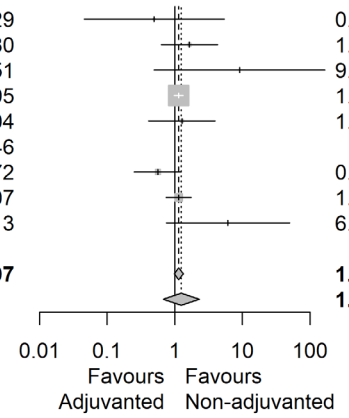


Figure 3.19 Relative risk of malaise, adjuvanted versus non-adjuvanted vaccines

Study	Adjuvanted Events	Adjuvanted Total	Non-adjuvanted Events	Non-adjuvanted Total	RR	95%-CI
Durando 2008	27	81	13	80	2.05	[1.14; 3.68]
Frey 2003	14	150	12	151	1.17	[0.56; 2.45]
Gasparini 2001	12	204	9	104	0.68	[0.30; 1.56]
Minutello 1999	7	46	0	46	15.00	[0.88; 255.13]
Scheifele 2013	33	301	35	307	0.96	[0.61; 1.51]
Seo 2014	6	111	0	113	13.23	[0.75; 232.12]
Fixed effect model		**893**		**801**	**1.33**	**[1.00; 1.76]**
Random effects model					**1.65**	**[0.54; 5.09]**

Heterogeneity: I^2 = 57%, τ^2 = 0.9952, p = 0.04

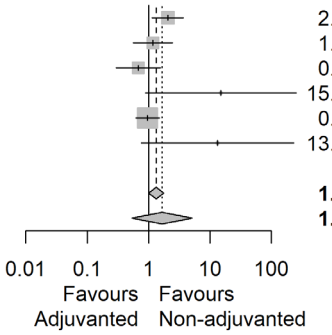


Figure 3.20 Relative risk of nausea, adjuvanted versus non-adjuvanted vaccines

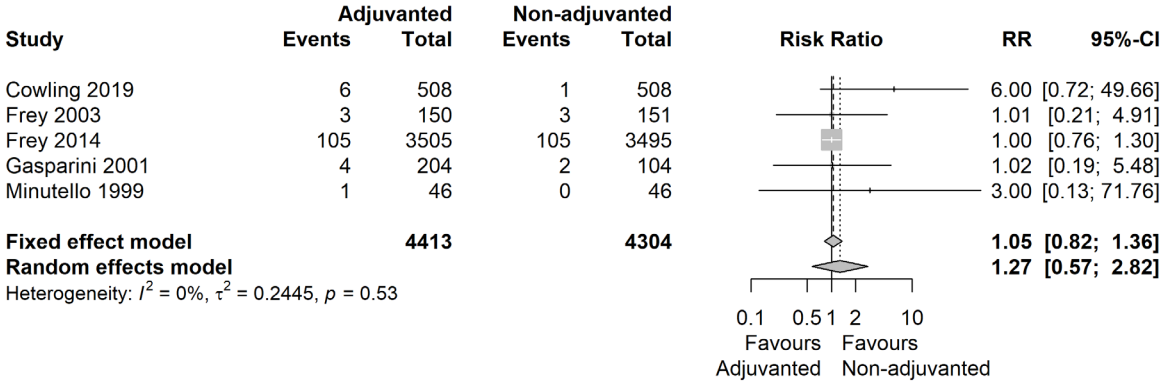
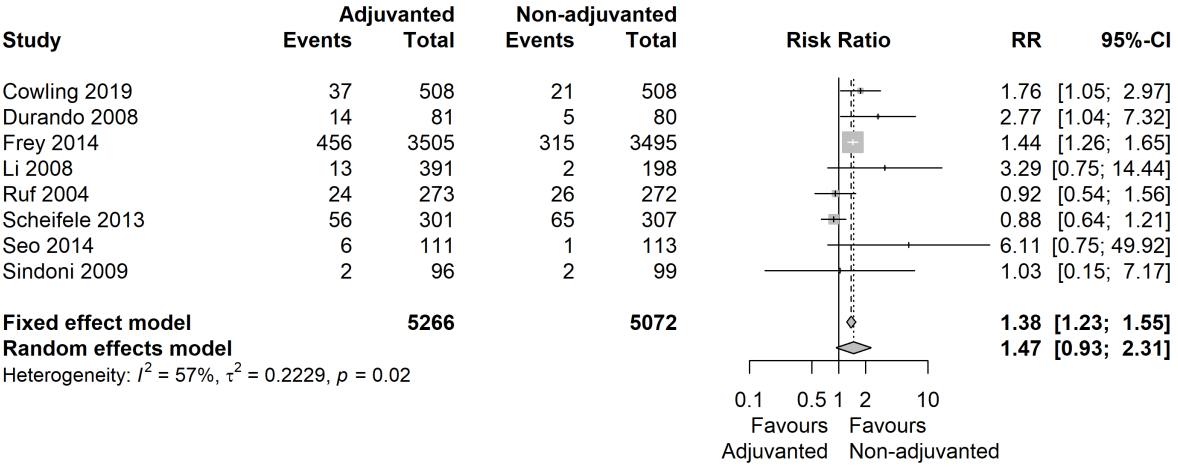


Figure 3.21 Relative risk of fatigue, adjuvanted versus non-adjuvanted vaccines



3.2.5 Risk of bias-adjuvanted influenza vaccines

The risk of bias of RCTs investigating the safety of MF59® adjuvanted influenza vaccines is summarised in Figures 3.22 and 3.23. Fifteen (71.4%) of the included RCTs were deemed to be at an unclear risk of bias due to lack of clarity in one or more of the key domains assessed, with the remaining six (28.6%) studies deemed to be at a high risk of bias due to a high risk of bias in one or more of the key domains. Of note, the influence of industry funding, as captured under the domain of other bias, resulted in the majority of studies being deemed to be at an unclear risk of bias overall.

The risk of bias of NRSIs providing data on the effectiveness and safety of MF59® adjuvanted influenza vaccines is summarised in Table 3.3. Of 14 test-negative design case-control studies investigating the prevention of influenza, four (28.6%) were assessed to be at a low risk of bias, four (28.6%) at moderate risk and six (42.8%) at a high risk of bias. As shown, areas of poor reporting included adequate control of confounding variables and selection bias. Of note, a number of studies provided adjusted and unadjusted outcomes depending on the comparator investigated and have been assessed separately in these instances. Four (44.4%) NRSIs investigating additional outcomes were deemed to be at a low risk of bias, one (11.1%) at a moderate risk, three (33.3%) at a serious risk and, one (11.1%) at a critical risk of bias. Areas of poor reporting included confounding variables, selection bias and missing data. Two studies presented data relating to safety with both deemed to be at a serious risk of bias.

Figure 3.22 Risk of bias summary: review authors' judgment of each risk of bias item, presented as percentages across all included studies

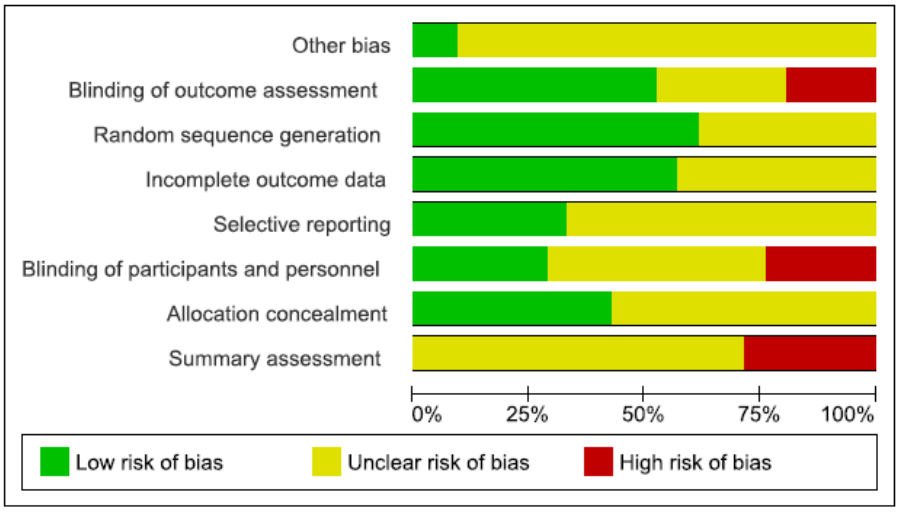


Figure 3.23 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

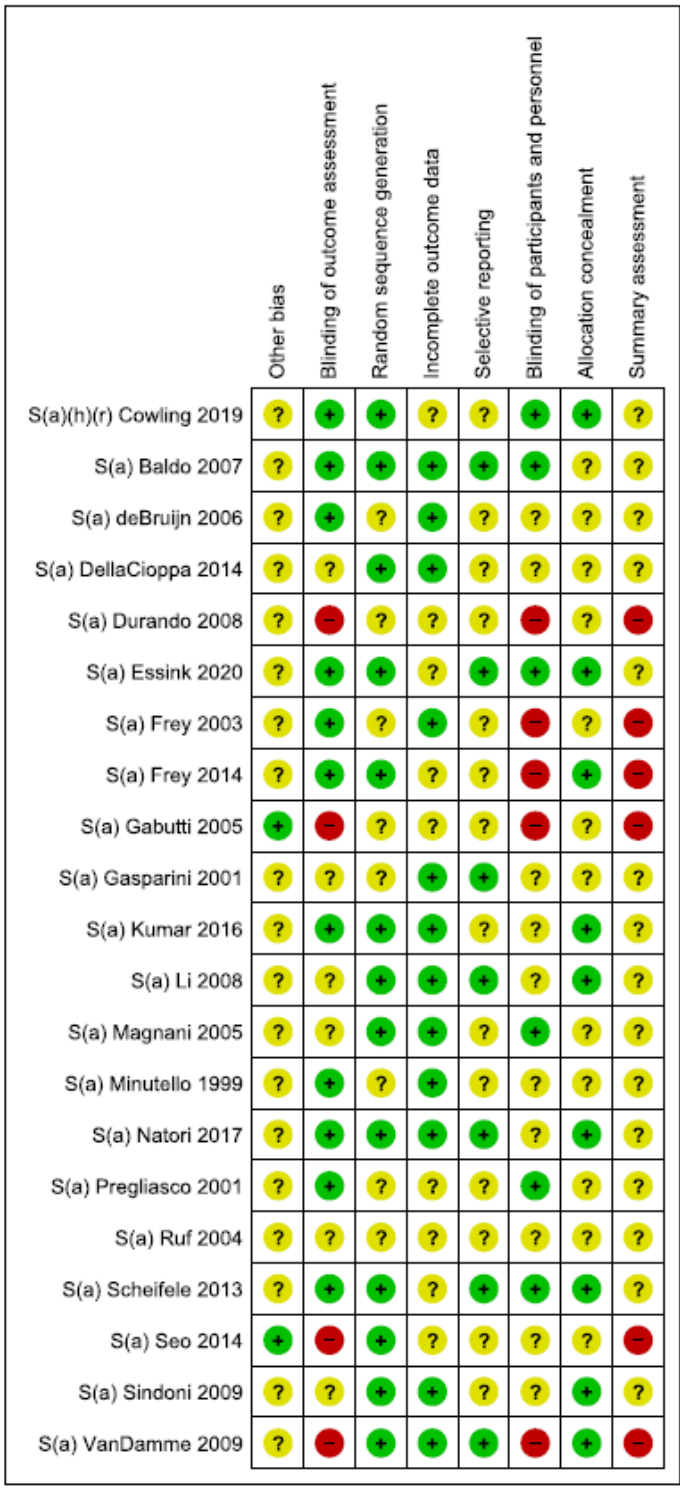


Table 3.3 ROBINS-I assessment of risk of bias of non-randomised studies of interventions

Author year	Confounding	Selection	Classification	Deviation from intervention	Missing data	Outcome measurement	Reported results	Overall bias
Effectiveness (primary outcome)- test-negative design case-control studies								
Bella 2019 [34]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Bellino 2019a [35]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Gilca 2015 [70]	Low	Moderate	Moderate	Low	Serious	Low	Moderate	Serious
Kissling 2019 [85]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Mira-Iglesias 2019 [97]	Low	Low	Low	Low	Low	Low	Low	Low
Mira-Iglesias 2019 [97]*	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Pebody 2020a [104]	Low	Low	Low	Low	Low	Low	Low	Low
Pebody 2020b [105]	Low	Low	Low	Low	Low	Low	Low	Low
Pebody 2020b [105]*	Serious	Low	Low	Low	Low	Low	Low	Serious
Rondy 2017a [113]*	Serious	Moderate	Low	Low	No information	Low	Low	Serious
Rondy 2017b [114]*	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Valenciano 2016 [132]	Low	Low	Low	Low	Low	Low	Low	Low
Van Buynder 2013 [133]	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate
Van Buynder 2013 [133]*	Serious	Low	Moderate	Low	Moderate	Low	Low	Serious
Effectiveness (additional outcomes)- case control and cohort studies								
Bellino 2019b [36]	Low	Moderate	Moderate	Low	Low	Low	Low	Moderate
Gasparini 2013 [68]	Serious	Low	Low	Low	No information	Low	Low	Serious
Iob 2005 [76]	Critical	Serious	Low	Low	Moderate	Moderate	Moderate	Critical
Iziureta 2019 [78]	Low	Low	Low	Low	Low	Low	Low	Low
Mannino 2012 [94]	Serious	Moderate	Low	Low	No information	Low	Moderate	Serious
Puig-Barbera 2004 [108]	Low	Low	Low	Low	Low	Low	Low	Low
Puig-Barbera 2007 [109]	Low	Low	Low	Low	Low	Low	Low	Low
Puig-Barbera 2013 [110]	Low	Low	Low	Low	Low	Low	Low	Low
Spadea 2014 [123]	Serious	Moderate	Low	Low	No information	Low	Low	Serious
Tsai 2011 [130]	Serious	Serious	Low	Low	No information	Low	Low	Serious
Villa 2013 [135]	Serious	Serious	Low	Low	Low	Low	Low	Serious

**denotes assessment of unadjusted outcomes*

3.3 High-dose influenza vaccines

Thirty-six studies within this review presented results concerning high-dose influenza vaccines [29, 38, 41, 43, 45-48, 52-56, 63, 71, 73, 78-83, 92, 95, 98, 100, 101, 106, 111, 117, 120, 124, 131, 137-139]. Of these studies, two related to efficacy [53, 71] (with two additional analysis papers of DiazGranados et al. contributing to overall results) [52, 55], nine related to effectiveness [41, 78, 79, 92, 111, 120, 137-140] and 23 related to safety (with additional safety data from the efficacy study by DiazGranados et al.) [29, 38, 43, 45-48, 53, 54, 56, 63, 73, 80-83, 95, 98, 100, 101, 106, 117, 124, 131]. The characteristics of studies relating to efficacy or effectiveness of high-dose influenza vaccines are provided in Appendix 5.2. The vaccine and circulating strains' characteristics associated with these studies are provided in Appendix 6.2. The characteristics of studies relating to the safety of high-dose influenza vaccines are provided in Appendix 7.2.

3.3.1 Efficacy - high-dose influenza vaccines

One study met the eligibility criteria for this systematic review which investigated the efficacy of high-dose influenza vaccines [53], examining the relative efficacy of HD-IIV3 compared with SD-IIV3 in older adults (aged ≥65 years) for laboratory-confirmed influenza, culture-confirmed influenza, and respiratory illness across protocol-defined influenza-like illness and modified CDC-defined influenza-like illness for all strains and vaccine specific strains. This paper was associated with two additional analyses papers [52, 55]. The authors reported vaccine efficacy against influenza-like illness and respiratory illness based on both laboratory- and culture-confirmed diagnosis. The high-dose vaccine had higher efficacy relative to standard-dose vaccine for laboratory-confirmed protocol-defined influenza-like illness (VE=24.2%, 95% CI 9.7 to 36.5, moderate-certainty evidence), but not for a modified CDC-defined influenza-like illness (VE=20.6%, 95% CI -4.6 to 39.9). The high-dose vaccine had higher efficacy against respiratory illness (VE=18.3%, 95% CI 5.0 to 29.8). There was limited evidence regarding efficacy in relation to influenza subtypes due to the small number of cases other than influenza A(H3N2). High-dose vaccination was further associated with reduced all-cause hospitalisation (VE=6.9%, 95% CI 0.5 to 12.8), serious cardio-respiratory events (VE=17.7%, 95% CI 6.6 to 27.4), and pneumonia events (VE=39.8%, 95% CI 19.3 to 55.1). There was no statistically significant effect on asthma/ chronic obstructive pulmonary disease (COPD)/bronchial events, influenza events, or other respiratory events.

The second study identified reported data for an additional outcome (not laboratory-confirmed) [71]. The study investigated the relative efficacy of HD-IIV3 compared with SD-IIV3 in older adults (aged ≥65 years) for the prevention of respiratory-related hospital admissions. The primary outcome was hospital admissions related to pulmonary and influenza-like conditions on the basis of ICD-9 coded Medicare claims. The authors reported higher vaccine efficacy for HD-IIV3 compared with SD-IIV3 against respiratory-related hospital admissions (VE=12.7%, 95% CI 1.8 to 22.4%) and pneumonia-related hospital admissions (VE=20.9%, 95% CI 4.7 to 73.3%), based on a sample of 38 225 nursing home residents who had 'fee-for-service' Medicare data available. In intention-to-treat analyses (that included nursing home residents without 'fee-for-service' data), a reduction in all-cause hospitalisations was reported (VE=6.7%, 95% CI 1.5 to 11.6%).

3.3.2 Effectiveness - high-dose influenza vaccines

Nine studies contained results relevant to the effectiveness of high-dose influenza vaccines [41, 78, 79, 92, 111, 120, 137-139]. Of these, one was a test-negative case-control study [139] and eight were cohort studies [41, 78, 79, 92, 111, 120, 137, 138].

Only one study presented data relevant to the prevention of laboratory-confirmed influenza for high-dose influenza vaccines [139]. This study compared HD-IIV3 with no vaccination in older adults for the 2014-2015 season and reported a vaccine effectiveness of 0.22 (95% CI -0.82 to 0.66) and 0.89 (95% CI 0.47 to 1.00) for influenza A(H3N2) and influenza B, respectively. The authors note a probable mismatch with the influenza A(H3N2) strain in circulation.

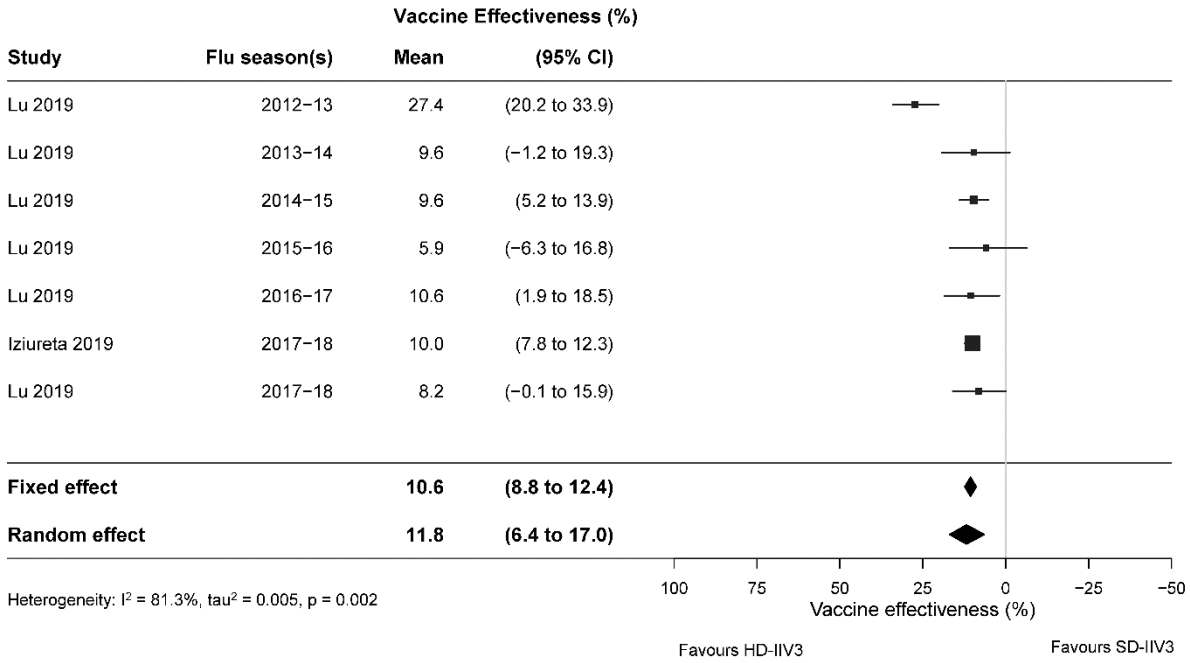
3.3.3 Additional outcomes

Eight studies presented data related to additional outcomes relevant to this review; influenza-related hospitalisation, influenza- or pneumonia-related hospitalisation, influenza hospital encounters, influenza office visits and influenza-like illness (Table 3.4) [41, 77, 78, 92, 111, 120, 137, 138]. All of these studies were cohort design and compared HD-IIV3 with SD-IIV3 in older adult populations.

3.3.3.1 Influenza-related hospitalisations

Two studies presented data for the prevention of influenza-related hospitalisations across six influenza seasons [78, 92]. As shown in Figure 3.24, there was a significant difference in effect in favour of HD-IIV3 for this outcome across all influenza seasons (VE=11.8%, 95% CI 6.4 to 17.0, REM, I^2=81.3%, low-certainty evidence (Appendix 9.2)).

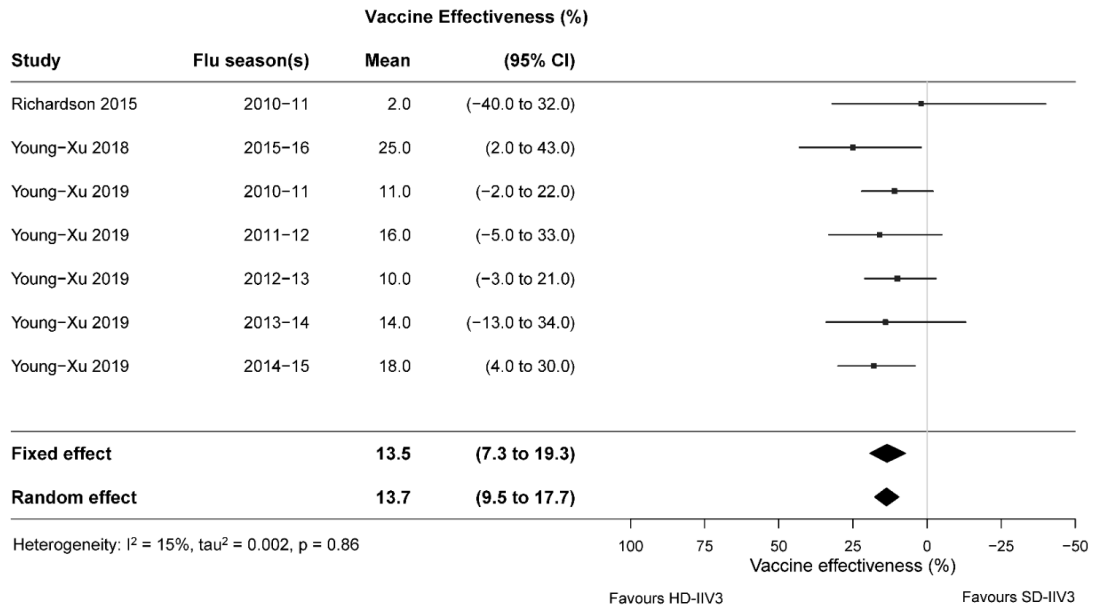
Figure 3.24 Vaccine effectiveness of HD-IIV3 versus SD-IIV3 against any influenza-related hospitalisation



3.3.3.2 Influenza- or pneumonia-related hospitalisations

Four studies presented data regarding influenza- or pneumonia- related hospitalisations across six influenza seasons [41, 111, 137, 138], three of which were included in pooled analyses. As shown in Figure 3.25, relative to SD-IIV3, there was a significant difference in effect in favour of HD-IIV3 across all influenza seasons (VE=13.7%, 95% CI 9.5 to 17.7, REM, I^2=15.0%, low-certainty evidence (Appendix 9.2)). One study was excluded from pooled analyses as it was conducted in older adults undergoing maintenance haemodialysis, the authors noted no significant difference between the vaccines [41].

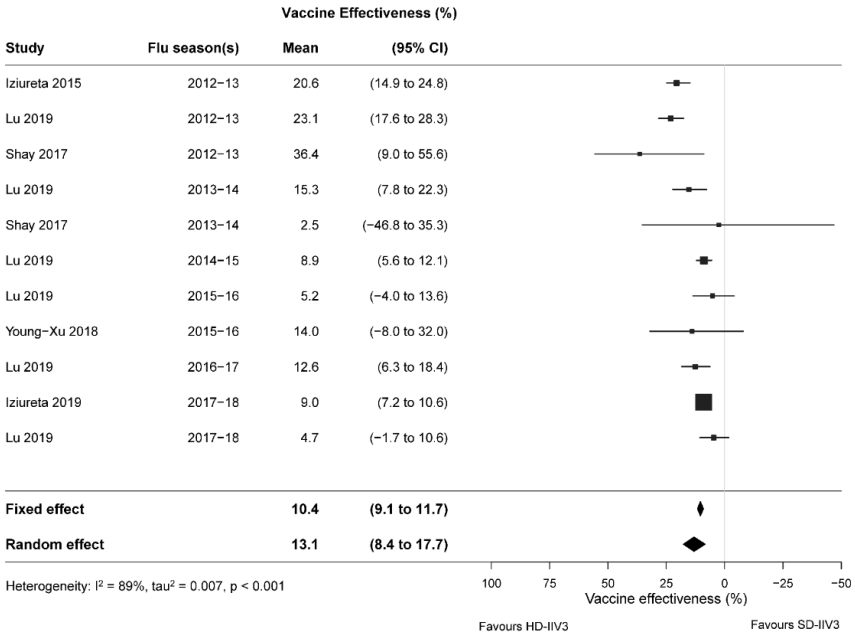
Figure 3.25 Vaccine effectiveness of HD-IIV3 versus SD-IIV3 against any influenza- or pneumonia-related hospitalisation



3.3.3.3 Influenza-related hospital encounters

Five studies presented data regarding influenza-related hospital encounters across six influenza seasons [77, 78, 92, 120, 137]. As shown in Figure 3.26, relative to SD-IIV3 there was a significant difference in effect in favour of HD-IIV3 across all influenza seasons (VE=13.1%, 95% CI 8.4 to 17.7, REM, I^2=89%, low-certainty evidence (Appendix 9.2)).

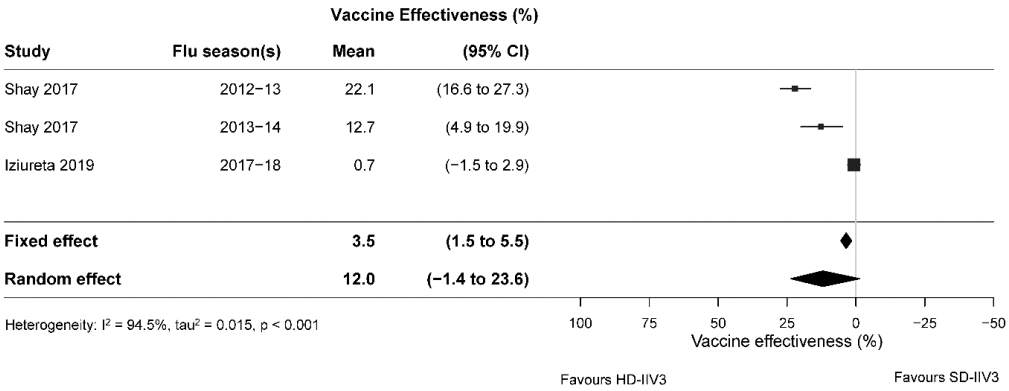
Figure 3.26 Vaccine effectiveness of HD-IIV3 versus SD-IIV3 against any influenza-related hospital encounters



3.3.3.4 Influenza-related office visits

Two studies possessed data relating to influenza-related office visits across three influenza seasons [78, 120]. As shown in Figure 3.27, there was a significant difference in favour of HD-IIV3 for this outcome (VE=3.5%, 95% CI 1.5 to 5.5, FEM, I^2=94.5%, low-certainty evidence (Appendix 9.2)).

Figure 3.27 Vaccine effectiveness of HD-IIV3 versus SD-IIV3 against any influenza-related hospital encounters



3.3.3.5 Influenza-like illness

As shown in Table 3.4, one study presented data regarding influenza-like illness with a pooled estimate of vaccine effectiveness across five influenza seasons for older adults undergoing maintenance haemodialysis [41]. The authors note no significant difference in vaccine effectiveness between HD-IIV3 and SD-IIV3 for influenza-like illness.

Table 3.4 Effectiveness of high-dose influenza vaccines for additional outcomes

Author	Season	Comparator	Vaccine effectiveness (1-risk ratio)	95%CI (lower)	95%CI (upper)	Strain mismatch
Influenza-related hospitalisation						
Lu 2019 [92]	2012-2013	SD-IIV3	0.27	0.20	0.34	Well-matched
Lu 2019 [92]	2013-2014	SD-IIV3	0.10	-0.01	0.19	Well-matched
Lu 2019 [92]	2014-2015	SD-IIV3	0.10	0.05	0.14	Mismatch
Lu 2019 [92]	2015-2016	SD-IIV3	0.06	-0.06	0.17	Well-matched
Lu 2019 [92]	2016-2017	SD-IIV3	0.11	0.02	0.19	Well-matched
Izurieta 2019 [78]	2017-2018	SD-IIV3	0.10	0.08	0.12	Not reported
Lu 2019 [92]	2017-2018	SD-IIV3	0.08	0.00	0.16	Well-matched
Influenza- or pneumonia-related hospitalisation						
Butler 2019* [41]	2010-2015	SD-IIV3	-0.02	-0.10	0.08	Variable
Richardson 2015 [111]	2010-2011	SD-IIV3	0.02	-0.40	0.32	Well-matched
Young-Xu 2019 [138]	2010-2011	SD-IIV3	0.11	-0.02	0.22	Not reported
Young-Xu 2019 [138]	2011-2012	SD-IIV3	0.16	-0.05	0.33	Not reported
Young-Xu 2019 [138]	2012-2013	SD-IIV3	0.10	-0.03	0.21	Not reported
Young-Xu 2019 [138]	2013-2014	SD-IIV3	0.14	-0.13	0.34	Not reported
Young-Xu 2019 [138]	2014-2015	SD-IIV3	0.18	0.04	0.30	Not reported
Young-Xu 2018 [137]	2015-2016	SD-IIV3	0.25	0.02	0.43	Well-matched
Influenza-related hospital encounters						
Izurieta 2015 [79]	2012-2013	SD-IIV3	0.21	0.15	0.25	Not reported
Lu 2019 [92]	2012-2013	SD-IIV3	0.23	0.18	0.28	Well-matched
Shay 2017 [120]	2012-2013	SD-IIV3	0.36	0.09	0.56	Well- matched
Lu 2019 [92]	2013-2014	SD-IIV3	0.15	0.08	0.22	Well-matched
Shay 2017 [120]	2013-2014	SD-IIV3	0.03	-0.47	0.35	Mismatch
Lu 2019 [92]	2014-2015	SD-IIV3	0.09	0.06	0.12	Mismatch
Lu 2019 [92]	2015-2016	SD-IIV3	0.05	-0.04	0.14	Well-matched
Young-Xu 2018	2015-2016	SD-IIV3	0.14	-0.08	0.32	Well-matched
Lu 2019 [92]	2016-2017	SD-IIV3	0.13	0.06	0.18	Well-matched
Izurieta 2019 [78]	2017-2018	SD-IIV3	0.09	0.07	0.11	Not reported
Lu 2019 [92]	2017-2018	SD-IIV3	0.05	-0.02	0.11	Well-matched
Influenza-related office visits						
Shay 2017 [120]	2012-2013	SD-IIV3	0.22	0.17	0.27	Well-matched
Shay 2017 [120]	2013-2014	SD-IIV3	0.13	0.05	0.20	Mismatch
Izurieta 2019 [78]	2017-2018	SD-IIV3	0.01	-0.02	0.03	Not reported
Influenza-like illness						
Butler 2019* [41]	2009-2015	SD-IIV3	0.00	-0.04	0.05	Variable

^Interpreted from narrative provided by included studies
**Older adult population undergoing maintenance haemodialysis*

3.3.4 Safety - high-dose influenza vaccines

Twenty-four studies included in this systematic review concerned the safety of high-dose influenza vaccines [29, 38, 43, 45-48, 53, 54, 56, 63, 73, 80-83, 95, 98, 100, 101, 106, 117, 124, 131]. Of these, 19 were RCTs [43, 46-48, 53, 54, 56, 63, 73, 80, 82, 83, 95, 98, 100, 101, 106, 117, 131] and five were non-randomised studies [29, 38, 45, 81, 124].

3.3.4.1 Serious adverse events

Four studies reported SAEs which were deemed to be potentially related to receipt of a high-dose influenza vaccine [43, 56, 63]. Chang et al. [43] reported small-fibre neuropathy in a subject 42 days after vaccination with HD-IIV3. DiazGranados et al. [56] reported one case of cranial-nerve VI palsy, one case of hypovolemic shock associated with diarrhoea and one case of acute disseminated encephalomyelitis. During the six-month follow-up period in the study conducted by Falsey et al.[63] one diagnosis of Crohn's disease and one of myasthenia gravis were noted. An active surveillance study for Guillain-Barré syndrome conducted by Arya et al. [29] noted no excess risk after high-dose vaccination in the primary analysis. However, an elevated risk of Guillain-Barré syndrome in the secondary analysis timeframe (8–21 days) was reported.

3.3.4.2 Local reactions

Seven studies possessed sufficiently comparable data to enable quantitative synthesis regarding local reactions for high-dose influenza vaccines [47, 56, 63, 83, 101, 106, 131]. All compared HD-IIV3 with SD-IIV3 or SD-IIV4 for outcomes including combined local reactions, pain, redness, swelling, induration and ecchymosis. The pooled estimates for these outcomes are shown in Figures 3.28 to Figure 3.33. As shown, HD-IIV were associated with a significantly higher frequency of combined local reactions (RR=1.40, 95% 1.20 to 1.64, three RCTs, FEM, I^2=25%, low-certainty evidence), pain (RR=1.56, 95% CI 1.26 to 1.93, seven RCTs, REM, I^2=57%, moderate-certainty evidence), swelling (RR=2.20, 95% CI 1.12 to 4.32, I^2=46%, six RCTs, low-certainty evidence (appendix 9.2)) and induration (RR=1.63, 95% CI 1.10 to 2.39, FEM, I^2=68%, two RCTS, low-certainty evidence (appendix 9.2)). There was no significant difference between vaccines for the remaining outcomes (low- moderate certainty evidence, see Appendix 9.2). As shown in Appendix 8.2, similar results were displayed for older adults within sub-group analyses.

Among studies which were excluded from pooled analyses, Cowling et al. [48] reported a statistically higher frequency of tenderness and swelling in those who received HD-IIV3 compared with SD-IIV4. Similarly Kaka et al.[81] reported a significantly higher frequency of local reactions in HD-IIV3 versus SD- IIV3, with the difference largely related to injection site pain. Sanchez et al. [117] compared intramuscular HD- IIV4, subcutaneous HD-IIV4 and subcutaneous SD- IIV4; intramuscular administration was associated with lower reactogenicity than subcutaneous administrations. Chang et al. [43] noted comparable rates of adverse reactions when a HD-IIV4 was compared with a HD-IIV3.

Figure 3.28 Relative risk of combined local adverse events, high-dose versus standard-dose

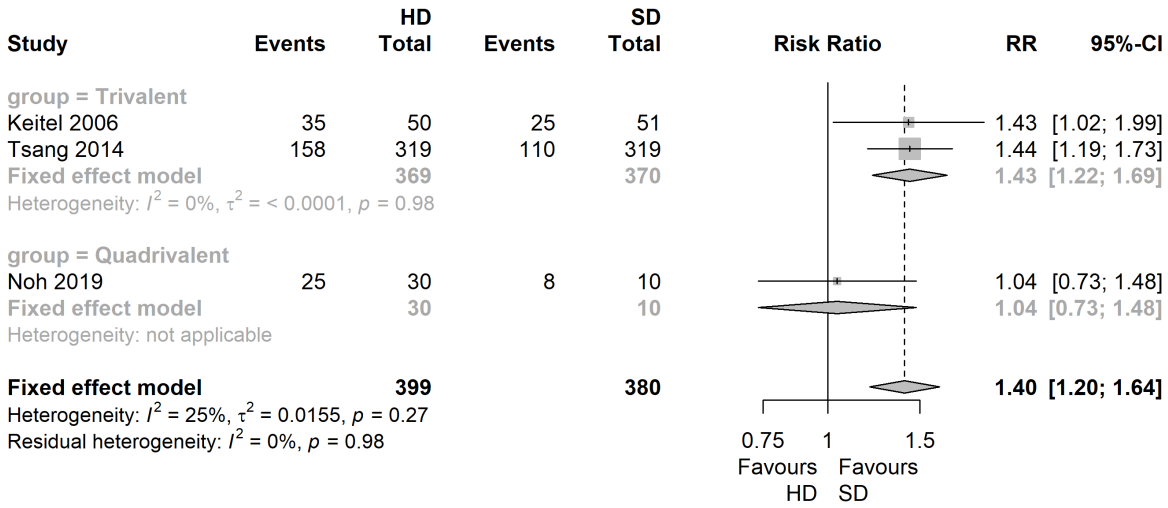


Figure 3.29 Relative risk of ecchymosis, high-dose versus standard-dose

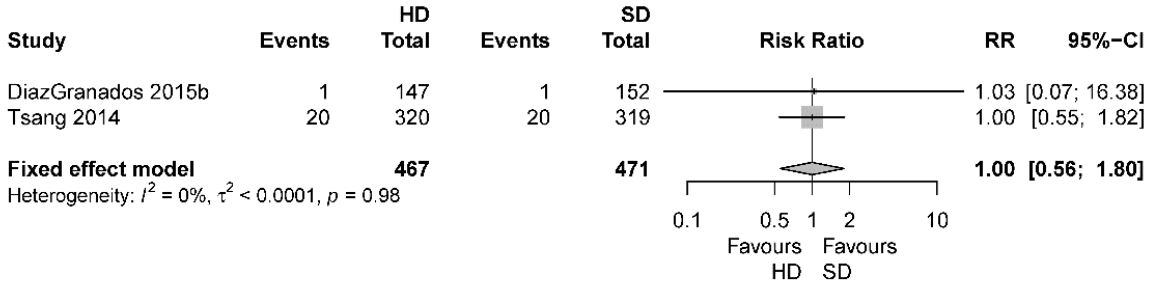


Figure 3.30 Relative risk of induration, high-dose versus standard-dose

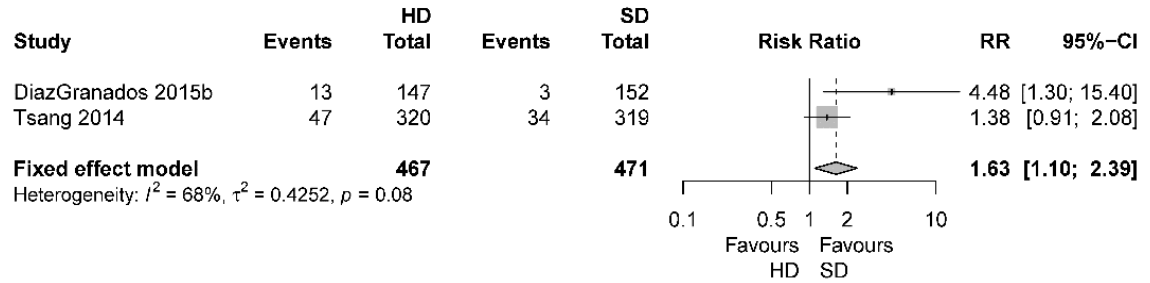


Figure 3.31 Relative risk of pain, high-dose versus standard-dose

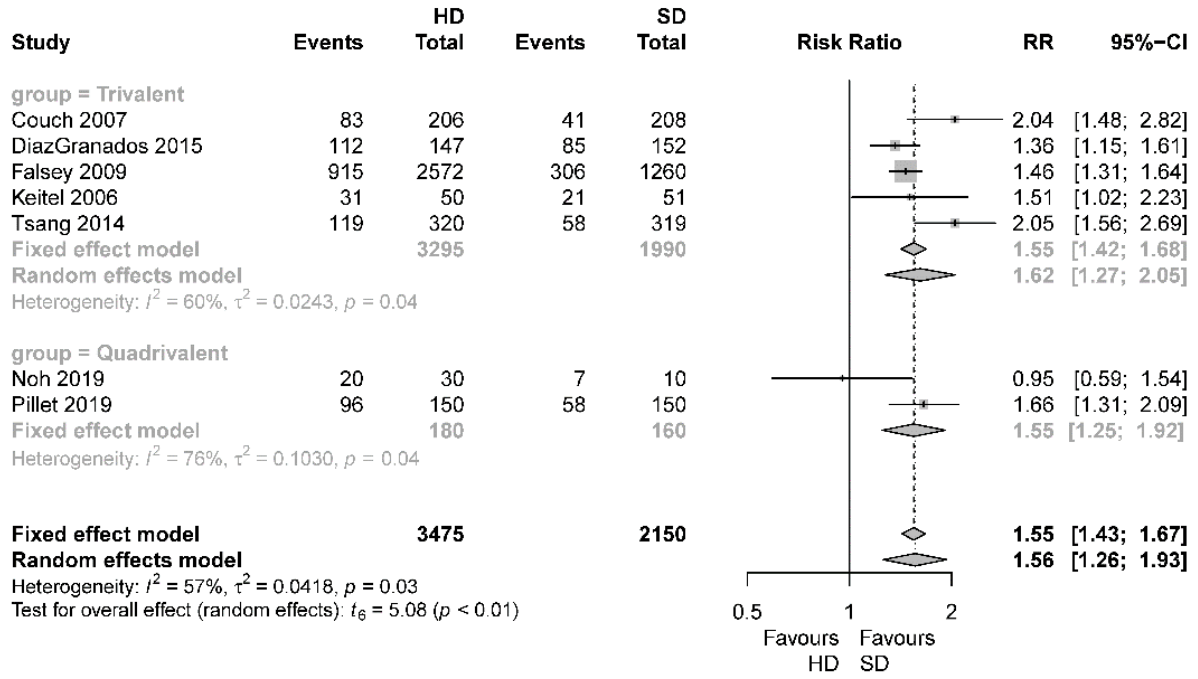


Figure 3.32 Relative risk of redness and erythema, high-dose versus standard-dose

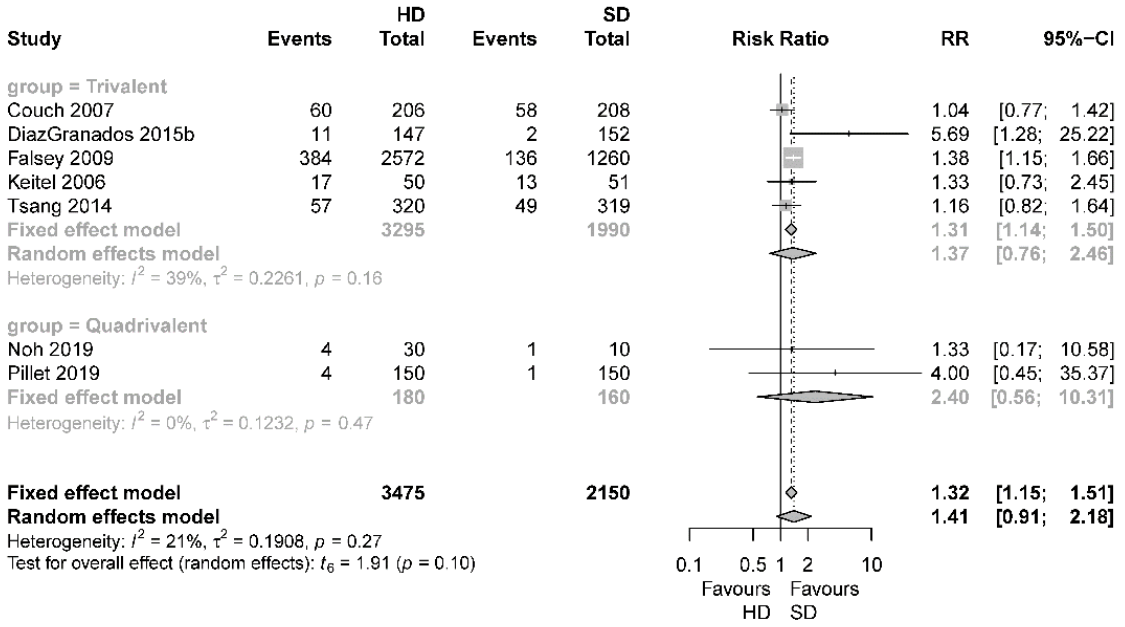
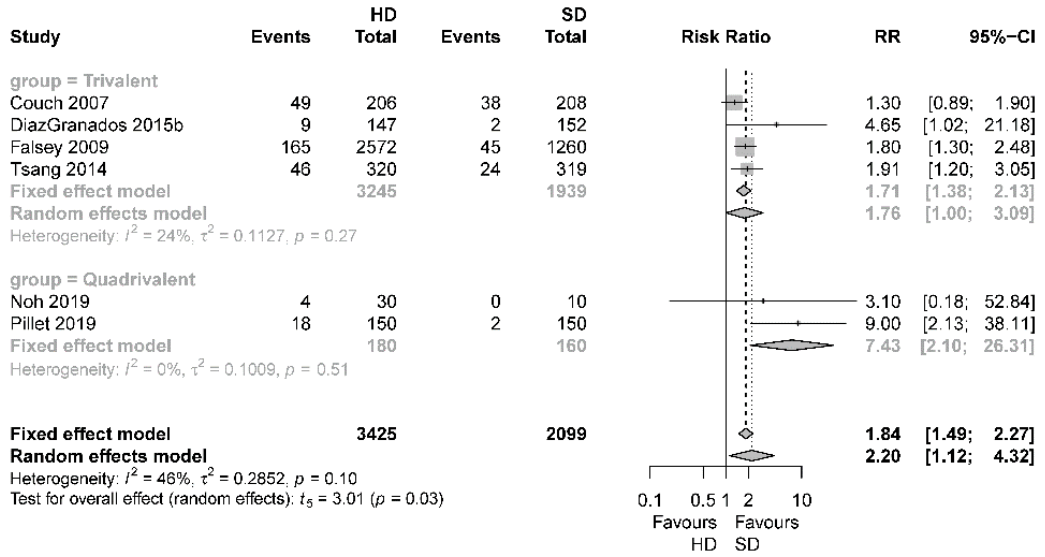


Figure 3.33 Relative risk of swelling, high-dose versus standard-dose



3.3.4.3 Systemic reactions

Seven studies had sufficiently comparable data to enable quantitative synthesis regarding systemic reactions to high-dose influenza vaccines. [47, 56, 63, 83, 101, 106, 131]. All compared HD-IIV3 or HD-IIV4 with SD-IIV3 or SD-IIV4 for the following outcomes: combined systemic reactions, fever, headache, malaise, myalgia, chills, diarrhoea and fatigue. The pooled analyses for these outcomes are presented in Figures 3.34 to Figure 3.41. As shown, HD-IIV were associated with a significantly higher frequency of headache (RR=1.35, 95% CI 1.02 to 1.77, REM, I^2=0%, seven RCTs, moderate-certainty evidence (appendix 9.2)), chills (RR=1.73, 95% CI 1.07 to 2.81, REM, I^2=0%, four RCTs, low-certainty evidence (appendix 9.2)), and malaise (RR=1.28, 95% CI 1.08 to 1.51, REM, I^2=0%, seven RCTs, moderate-certainty evidence (appendix 9.2)). No significant difference between vaccine groups was noted for the remaining outcomes (very-low to moderate certainty evidence, see main summary of findings and appendix 9.2). As shown in Appendix 8.2, similar results were displayed for older adults within sub-group analyses.

Sanchez et al. [117] compared intramuscular HD-IIV4, subcutaneous HD-IIV4 and subcutaneous SD-IIV4; intramuscular administration was associated with a lower overall frequency of systemic reactions. Chang et al. [43] noted comparable rates of adverse reactions when a HD-IIV4 was compared with a HD-IIV3.

Figure 3.34 Relative risk of combined systemic adverse events, high-dose versus standard-dose

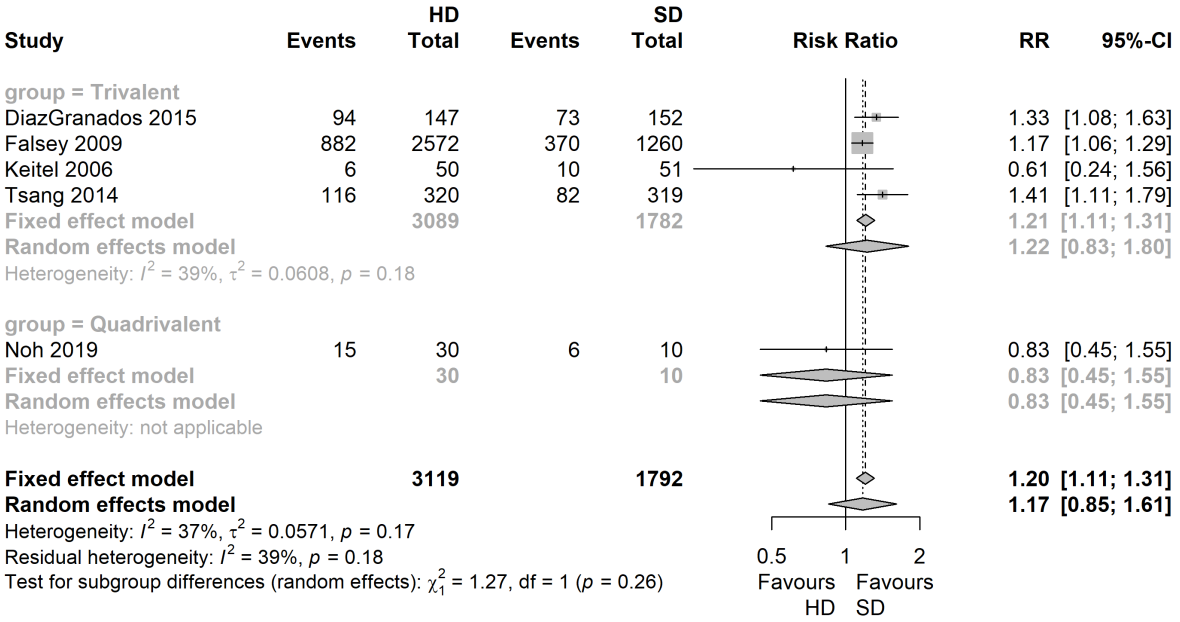


Figure 3.35 Relative risk of fever, high-dose versus standard-dose

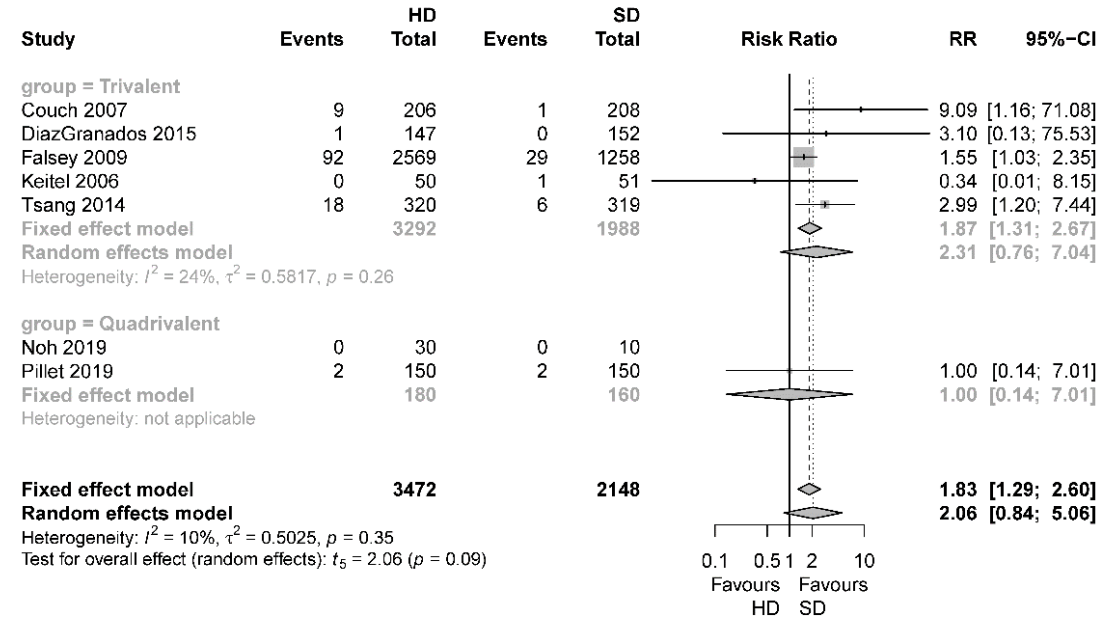


Figure 3.36 Relative risk of headache, high-dose versus standard-dose

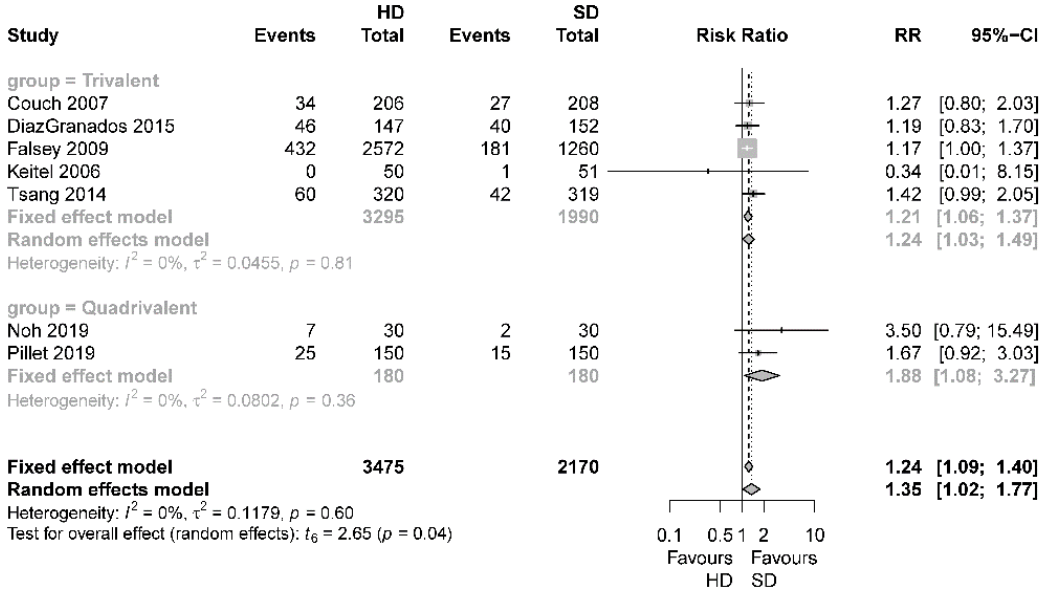


Figure 3.37 Relative risk of malaise, high-dose versus standard-dose

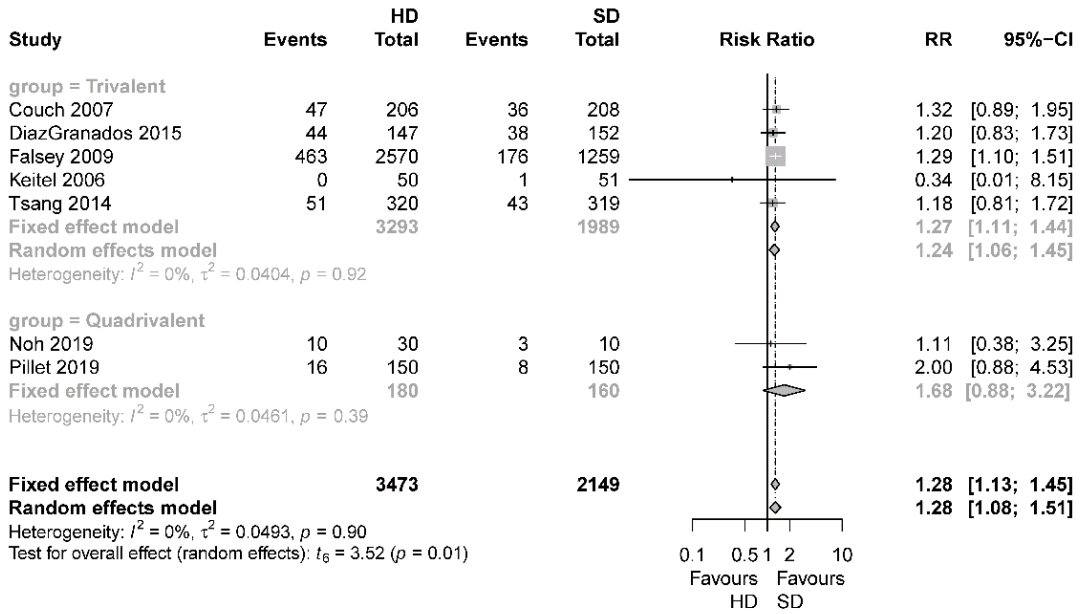


Figure 3.38 Relative risk of myalgia, high-dose versus standard-dose

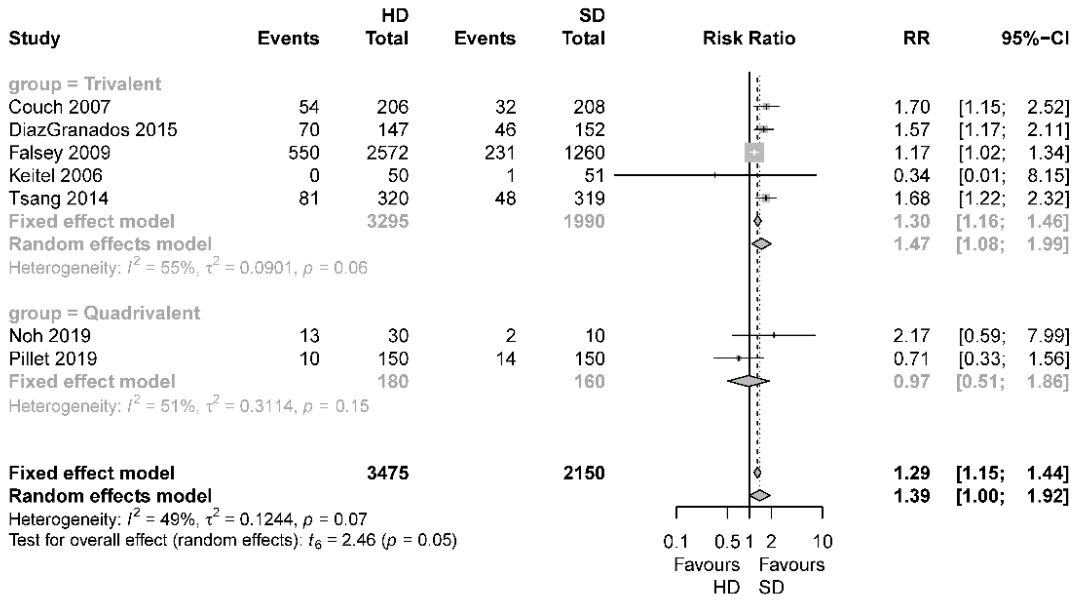


Figure 3.39 Relative risk of shiver and chills, high-dose versus standard-dose

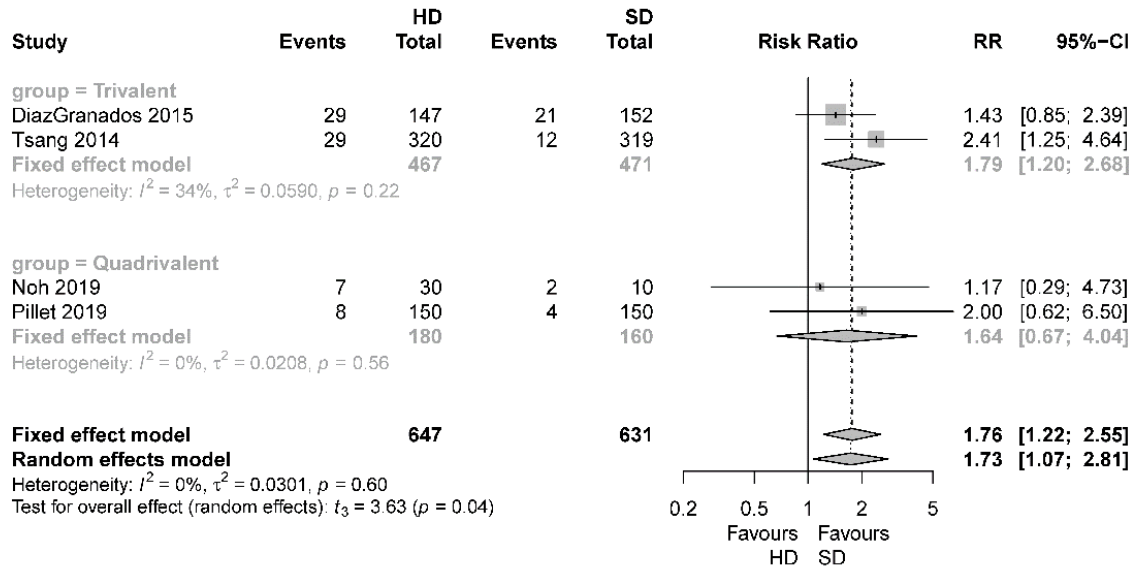


Figure 3.40 Relative risk of diarrhoea, high-dose versus standard- dose

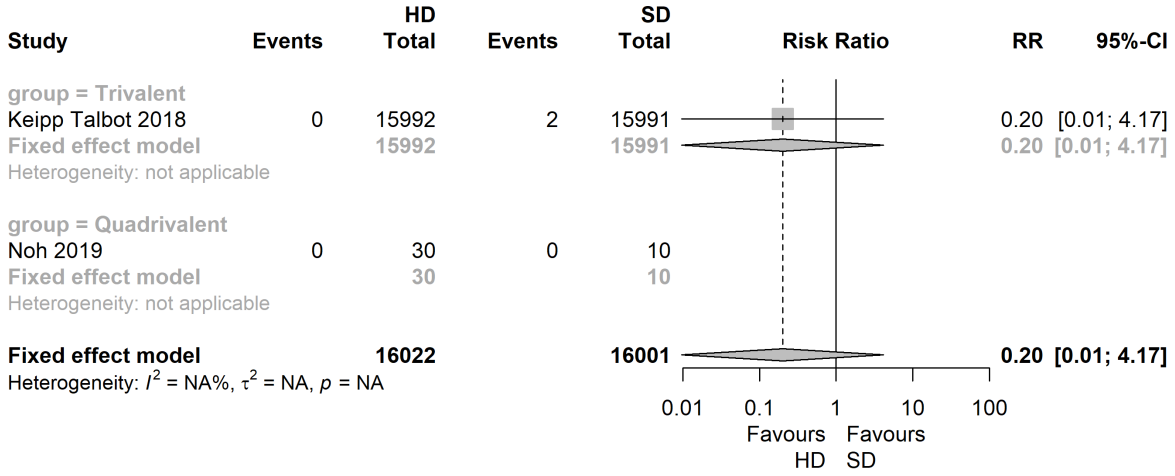
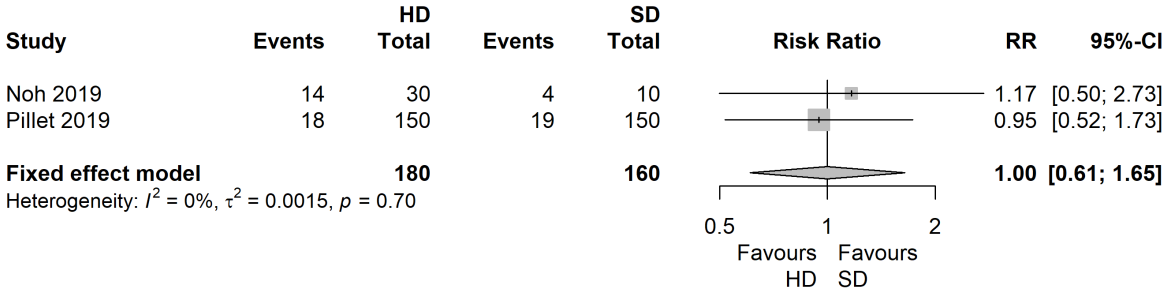


Figure 3.41 Relative risk of fatigue, high-dose versus standard-dose



3.3.4.4 Safety of high-dose influenza vaccines in at-risk populations

Nine studies included within this review were categorised as investigating the safety profile of high-dose influenza vaccines in at-risk groups, namely: individuals with malignancy, [38, 45, 124] rheumatoid arthritis, [46] haematopoietic stem cell transplant recipients, [73] transplant recipients, [100] those undergoing oncological interventions, [80] and individuals diagnosed with HIV [95].

With regards to individuals with malignancy or undergoing oncological treatment, Chong et al. [45] reported no significant difference in the incidence of new onset immune-related adverse events following vaccination with HD-IIV3 compared with SD-IIV3 or SD-IIV4. Strowd et al., [124] and Branagan et al., [38] noted that high-dose vaccination was well-tolerated in their respective single-arm trials, and Jamshed et al. [80] noted that high dose vaccination was generally well-tolerated compared with SD-IIV.

In patients with rheumatoid arthritis who received HD-IIV3 or SD-IIV4, Colmegna et al. [46] reported similar frequencies of local and systemic reactions in both groups. Similarly, no significant differences in local or systemic reactions were noted between HD-IIV3 and SD-IIV3 in solid-organ transplant recipients [100]. In HSCT recipients, Halasa et al. [73] noted a significantly higher frequency of combined local reactions in those receiving HD-IIV3 compared with SD-IIV3, with no difference noted between the groups in terms of systemic reactions. In individuals with HIV, McKittrick et al. [95] noted no significant difference in local or systemic reactions between recipients of HD-IIV3 compared with SD-IIV3.

3.3.5 Risk of bias - high-dose influenza vaccines

The risk of bias for efficacy and safety RCTs investigating high-dose influenza vaccines is summarised in Figures 3.42 and Figure 3.43. The two efficacy RCTs were deemed to be at an unclear risk of bias due to lack of clarity in one key domain. Of the 19 RCTs assessing a safety outcome of high-dose influenza vaccines, one (5%) was judged to be at a low risk of bias, 16 (84%) were deemed to be at an unclear risk of bias and two (11%) were deemed to be at a high risk of bias. Of note, the influence of industry funding as captured under the domain of other bias, resulted in the majority of studies being deemed to be at an unclear risk of bias overall.

The risk of bias of NRSIs providing data on the effectiveness and safety of high-dose influenza vaccines is summarised in Table 3.5. One test-negative design case-control study, which investigated the prevention of influenza, was deemed to be at a low risk of bias. One (12.5%) NRSI investigating additional outcomes was deemed to be at a low risk of bias, four (50.0%) at a moderate risk, and three (37.5%) at a serious risk. Areas of poor reporting included confounding variables, selection bias and missing data. Three studies presented data relating to safety with all deemed to be at a serious risk of bias.

Figure 3.42 Risk of bias summary: Review authors' judgment of each risk of bias item, presented as percentages across all included studies

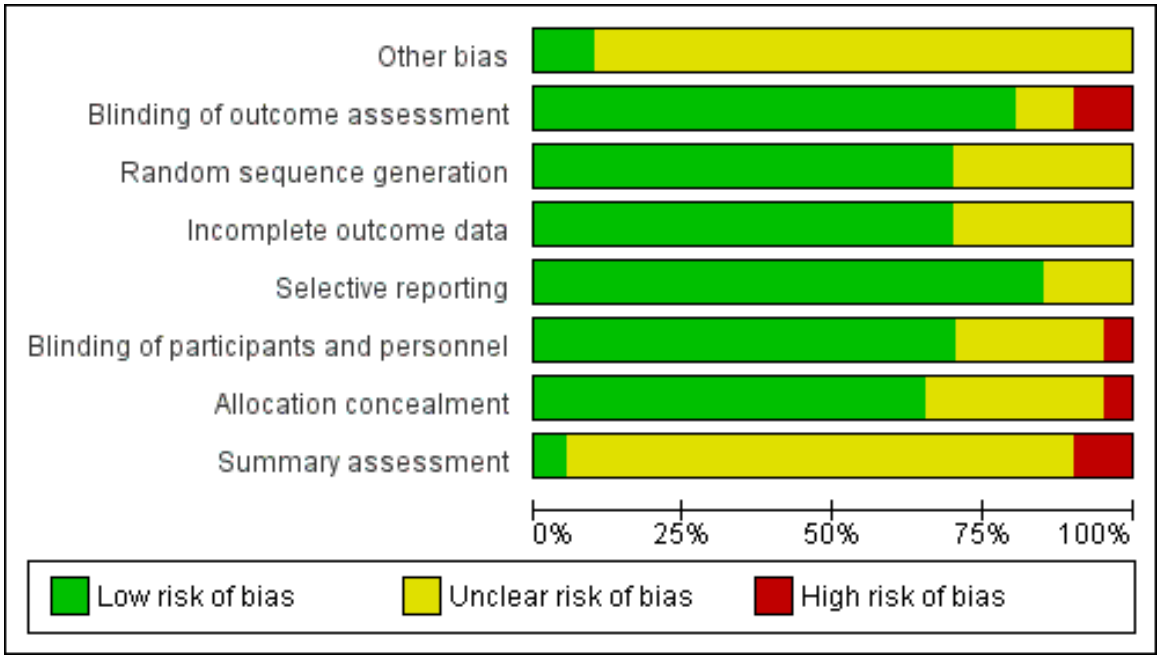


Figure 3.43 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

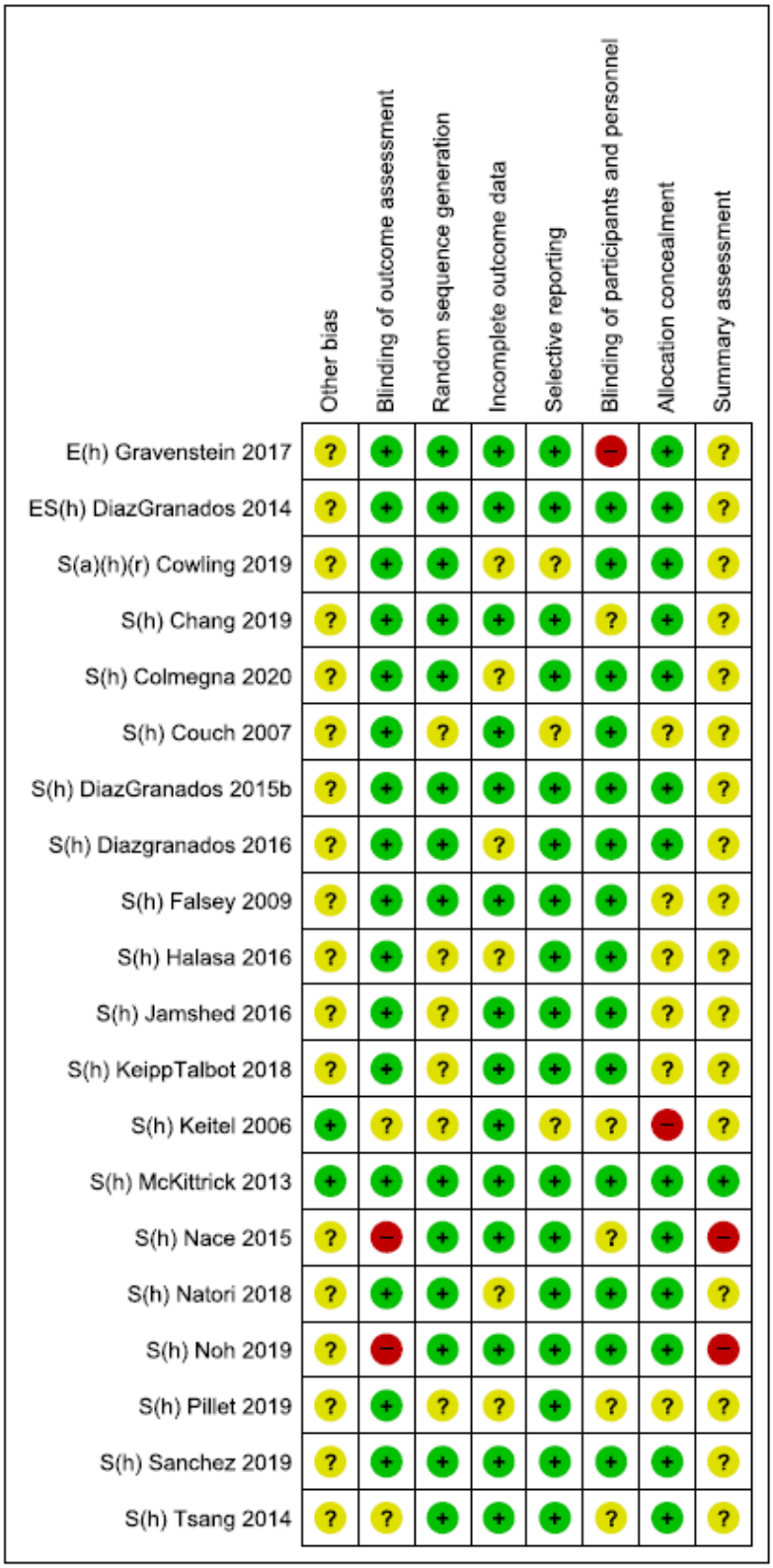


Table 3.5 ROBINS-I assessment of risk of bias of non-randomised studies of interventions

Author Year	Confounding	Selection	Classification	Deviation from intervention	Missing data	Outcome measurement	Reported results	Overall bias
Effectiveness (primary outcome)- Test-negative design case-control studies								
Zimmerman 2016 [139]	Low	Low	Low	Low	Low	Low	Low	Low
Effectiveness (additional outcomes)- Case control and cohort studies								
Butler 2019 [41]	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Izurieta 2015 [79]	Low	Moderate	Low	Low	No information	Low	Low	Moderate
Izurieta 2019 [78]	Low	Low	Low	Low	Low	Low	Low	Low
Lu 2019 [92]	Low	Moderate	Low	Low	No information	Low	Low	Moderate
Richardson 2015 [111]	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Shay 2017 [120]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Young-Xu 2018 [137]	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Young-Xu 2019 [138]	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Safety								
Arya 2019 [29]	Serious	Serious	Low	Low	Low	Low	Serious	Serious
Chong 2020 [45]	Serious	Serious	Low	Low	No information	Low	Low	Serious
Kaka 2017 [81]	Serious	Serious	Low	Low	Low	Moderate	Low	Serious

3.4 Cell-based influenza vaccines

Nineteen studies within this review presented results concerning cell-based influenza vaccines [31, 32, 40, 42, 44, 51, 60, 61, 65, 72, 74, 75, 78, 90, 91, 122, 125, 126, 136]. Of these, two studies related to efficacy, [31, 65] four related to effectiveness [40, 42, 51, 78] and 15 related to safety [31, 32, 44, 60, 61, 65, 72, 74, 75, 90, 91, 122, 125, 126, 136]. The characteristics of studies relating to efficacy or effectiveness of cell-based influenza vaccines are provided in Appendix 5.3. The vaccine and circulating strains' characteristics associated with these studies are provided in Appendix 6.3. The characteristics of studies relating to the safety of cell-based influenza vaccines are provided in Appendix 7.3.

3.4.1 Efficacy - cell-based influenza vaccines

Two studies met the eligibility criteria for this systematic review which investigated the efficacy of ccIIV3 in adult populations (aged 18-49 years) compared with placebo [31, 65]

As shown in Figures 3.44 to Figure 3.47, the pooled estimate for the two studies shows a significant effect in favour of cell-based influenza vaccines for the prevention of any influenza (VE=70%, 95% CI 60% to 77%, two RCTs, FEM, I^2=0%, moderate-certainty evidence), influenza A(H1N1) (VE=82%, 95% CI 71% to 89%, two RCTs, FEM, I^2=62%, moderate-certainty evidence), influenza A(H3N2) (VE=72%, 95% CI 39% to 87%, two RCTs, FEM, I^2=0%, moderate-certainty evidence) and influenza B (VE=52%, 95% CI 30% to 68%, two RCTs, FEM, I^2=0%, moderate-certainty evidence).

Figure 3.44 Vaccine efficacy of ccIIV3 versus placebo against any influenza, adults aged 18 to 49 years

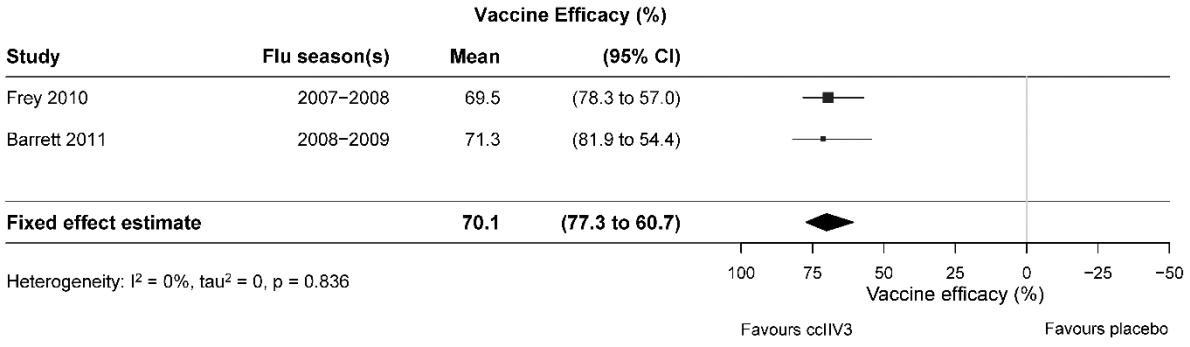


Figure 3.45 Vaccine efficacy of ccIIV3 versus placebo against Influenza A(H1N1), adults aged 18 to 49 years

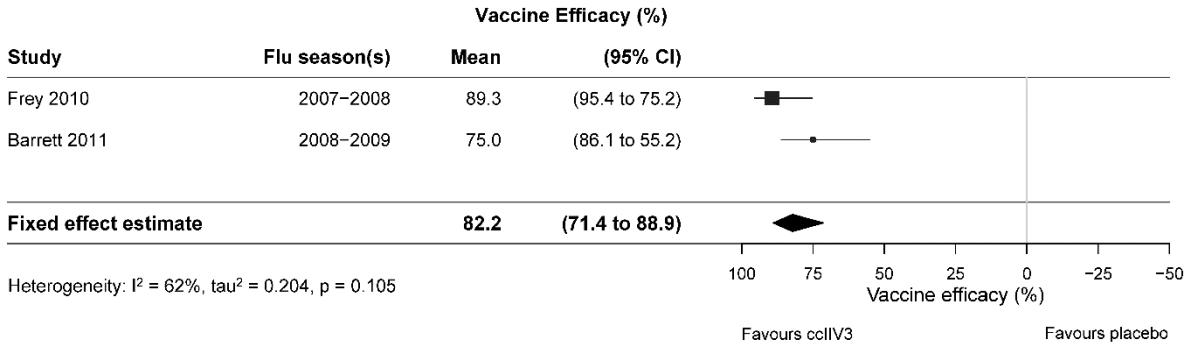


Figure 3.46 Vaccine efficacy of ccIIV3 versus placebo against Influenza A(H3N2), adults aged 18 to 49 years

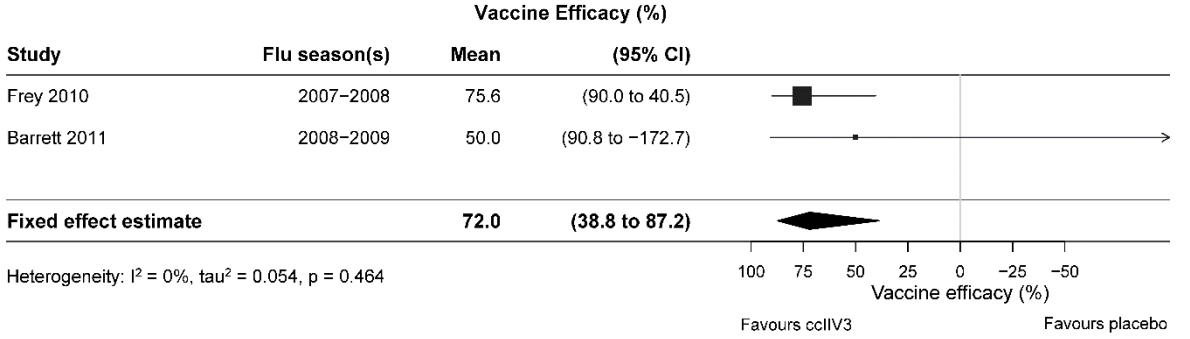
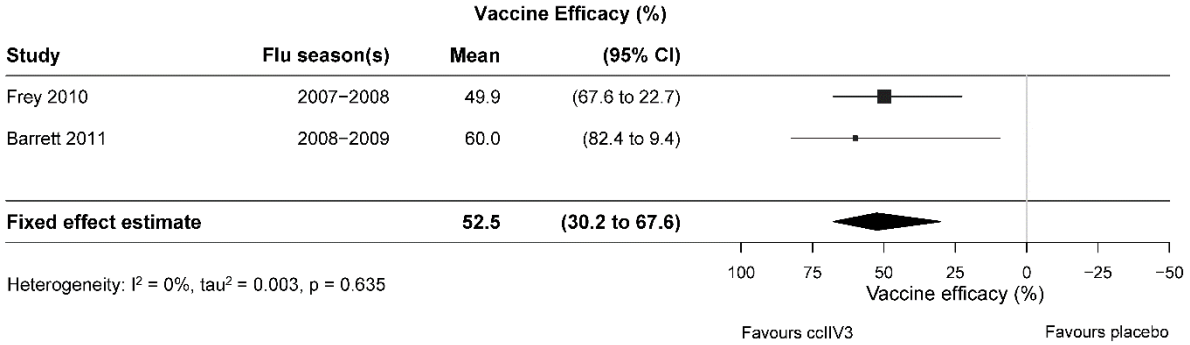


Figure 3.47 Vaccine efficacy of ccIIV3 versus placebo against Influenza B, adults aged 18 to 49 years



3.4.2 Effectiveness - cell-based influenza vaccines

Four studies included in this systematic review contained results relevant to the effectiveness of cell-based influenza vaccines [40, 42, 51, 78]. Of these, three were case-control studies [40, 42, 51] and one was a cohort study [78].

3.4.2.1 Primary outcome – effectiveness against laboratory-confirmed influenza

Three studies provided data relevant to the primary outcome of laboratory-confirmed influenza [40, 42, 51]. All of the studies were of test-negative case-control design with two in adult populations and one specifically in an older adult ≥ 65 years population. The type of influenza, population, comparator, vaccine effectiveness, 95% confidence intervals and degree of matching to circulating strains, as interpreted from each individual study, for each relevant comparison is highlighted in Table 3.4, subcategorised by the influenza season.

3.4.2.2 Effectiveness against any influenza subtype

Three studies presented data regarding the effectiveness of cell-based vaccines against any influenza type/subtype [40, 42, 51]. As presented in Table 3.4, one study reported no significant difference compared with traditional influenza vaccines and with no vaccination for older populations [40]. Two studies, reporting for different influenza seasons, reported conflicting findings for cell-based vaccines compared with no vaccination for adult populations 42, 51].

3.4.2.3 Effectiveness against influenza A(H1N1)

One study presented data for the effectiveness of a cell-based vaccine against influenza A(H1N1) in an adult population, with the comparator being no vaccination. A significant difference was shown in favour of the cell-based vaccine [51].

3.4.2.4 Effectiveness against influenza A(H3N2)

Three studies presented data regarding the effectiveness of cell-based vaccines against influenza A(H3N2) (Table 3.6) [40, 42, 51]. There was no significant difference in comparison to no vaccination or traditional influenza vaccines for older populations based on one study [40]. There were conflicting results based on two studies for cell-based vaccines, compared to no vaccination for adult populations across two influenza seasons [42, 51].

3.4.2.5 Effectiveness against influenza B

Three studies presented data regarding the effectiveness of cell-based vaccines against any influenza type B (Table 3.4) [40, 42, 51]. One study of older adults reported no significant difference compared with no vaccination [40]. Two studies, reporting for different influenza seasons, reported conflicting findings for cell-based vaccines compared with no vaccination for adult populations [42, 51].

3.4.3 Additional outcomes

One study presented data relevant to additional outcomes of interest to this review [78]. The study compared a cell-based vaccine to IIV3 in an older adult population (aged ≥65 years). Results indicated a significant difference in favour of cell-based vaccines for all reported outcomes of interest; influenza-related hospitalisation, influenza-related hospital encounters and influenza-related office visits.

Table 3.6 Effectiveness of cell-based influenza vaccines for the prevention of laboratory-confirmed influenza

Author	Population	Comparator	Vaccine effectiveness (1-odds ratio)	95%CI (lower)	95%CI (upper)	Strain mismatch^
All influenza						
2014-2015 season						
Castilla 2016 [42]	≥18 years	Unvaccinated	0.21	-0.12	0.44	Mismatch
2017-2018 season						
Bruxvoort 2019 [40]	≥65 years	Unvaccinated	0.10	-0.44	0.44	Mismatch
Bruxvoort 2019 [40]	≥65 years	IIV3/IIV4	0.06	-0.46	0.39	Mismatch
DeMarcus 2019 [51]	≥18 years	Unvaccinated	0.52	0.36	0.64	Not reported
Influenza A(H1N1)						
2017-2018 season						
DeMarcus 2019 [51]	≥18 years	Unvaccinated	0.71	0.44	0.85	Not reported
Influenza A(H3N2)						
2014-2015 season						
Castilla 2016 [42]	≥18 years	Unvaccinated	0.02	-0.49	0.36	Mismatch
2017-2018 season						
Bruxvoort 2019 [40]	≥65 years	Unvaccinated	0.02	-0.67	0.42	Mismatch
Bruxvoort 2019 [40]	≥65 years	IIV3/IIV4	-0.04	-0.70	0.37	Mismatch
DeMarcus 2019 [51]	≥18 years	Unvaccinated	0.47	0.25	0.63	Not reported

Author	Population	Comparator	Vaccine effectiveness (1-odds ratio)	95%CI (lower)	95%CI (upper)	Strain mismatch^
Influenza B						
2014-2015 season						
Castilla 2016 [42]	≥18 years	Unvaccinated	0.34	-0.03	0.58	Mismatch
2017-2018 season						
Bruxvoort 2019 [40]	≥65 years	Unvaccinated	-0.06	-1.63	0.57	Mismatch
DeMarcus 2019 [51]	≥18 years	Unvaccinated	0.54	0.31	0.69	Not reported

^Interpreted from narrative provided by included studies
Note – Bruxvoort 2019 also provided data on individuals aged 4 to 64 years. However, disaggregated effectiveness data for adults aged 18-64 years were not presented.

3.4.4 Safety - cell-based influenza vaccines

Fifteen studies included in this systematic review related to the safety of cell-based influenza vaccines [31, 32, 44, 60, 61, 65, 72, 74, 75, 90, 91, 122, 125, 126, 136]. Of these, 11 were RCTs [31, 32, 44, 60, 61, 65, 72, 75, 122, 125, 126] comprising 10 unique datasets, and four were non-randomised studies [74, 90, 91, 136].

3.4.4.1 Serious adverse events

One study included within this review reported a serious adverse event associated with cell-based influenza vaccines, with one serious hypersensitivity reaction noted [60].

3.4.4.2 Local reactions

Six studies possessed sufficiently comparable data to enable quantitative synthesis related to local reactions for cell-based influenza vaccines [60, 65, 72, 75, 122, 125]. All of these studies compared ccIIV3 with IIV3. Pooled estimates for combined local reactions, pain, redness, swelling, induration, and ecchymosis are presented in Figures 3.48 to Figure 3.53. As shown, cell-based vaccines were associated with significantly higher rates of ecchymosis (RR=1.27, 95 %CI 1.03 to 1.56, three RCTs, FEM, I^2=47%, low-certainty evidence (Appendix 9.3)), with no significant differences noted for the remaining outcomes (low-moderate certainty evidence, see main summary of findings table and appendix 9.3). As shown in Appendix 8.3, similar results were displayed for older adults within sub-group analyses.

With regards to studies that were excluded from the pooled analyses, two studies compared ccIIV4 with ccIIV3 [32, 44], with both noting a significantly higher rate of injection site pain or tenderness events in those receiving ccIIV4. Similarly, two studies compared ccIIV3 with placebo with a higher frequency of local reactions noted in the cell-based group, particularly in terms of injection site pain [31, 65]. An extension study of revaccination effect comparing ccIIV3 with IIV3 further noted injection site pain as the most commonly reported local reaction [126]. In line with other results, two non-randomised studies reported a higher frequency of local reactions with cell-based vaccines compared with non-cell-based vaccines, with injection site pain again being the most common event [90, 91]. An uncontrolled study by Vinnemeier et al. [136] noted similar rates of local reactions in those aged 18-61 years compared with those aged over 61 years.

Figure 3.48 Relative risk of combined local adverse events, ccIIV3 versus IIV3

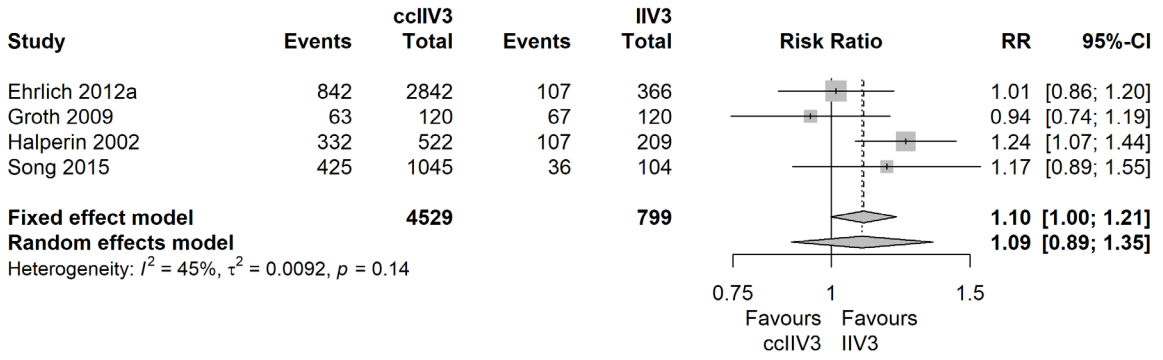


Figure 3.49 Relative risk of pain, ccIIV3 versus IIV3

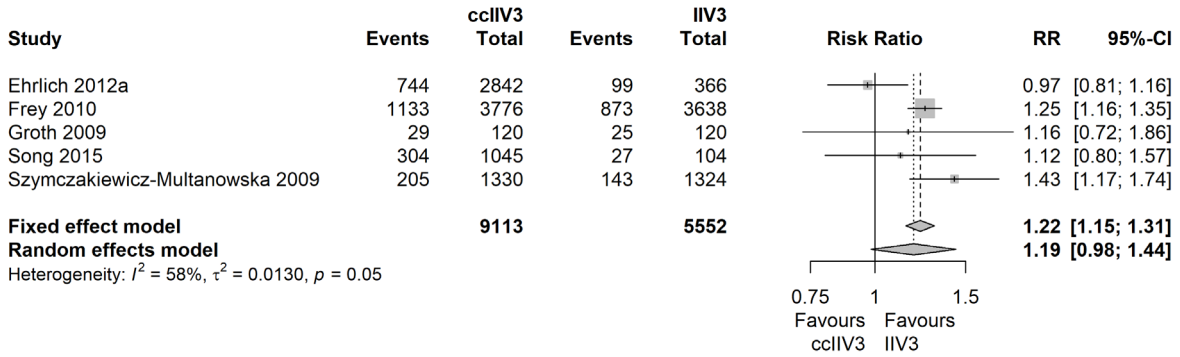


Figure 3.50 Relative risk of redness and erythema, ccIIV3 versus IIV3

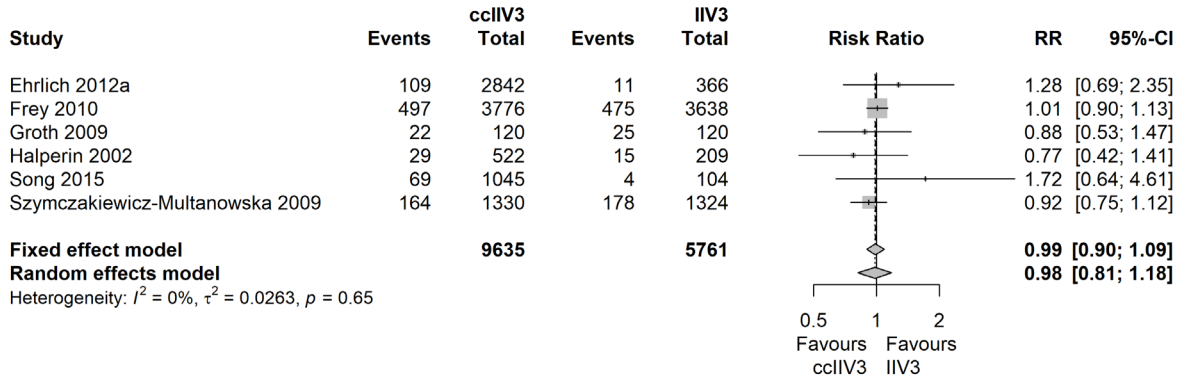


Figure 3.51 Relative risk of swelling, ccIIV3 versus IIV3

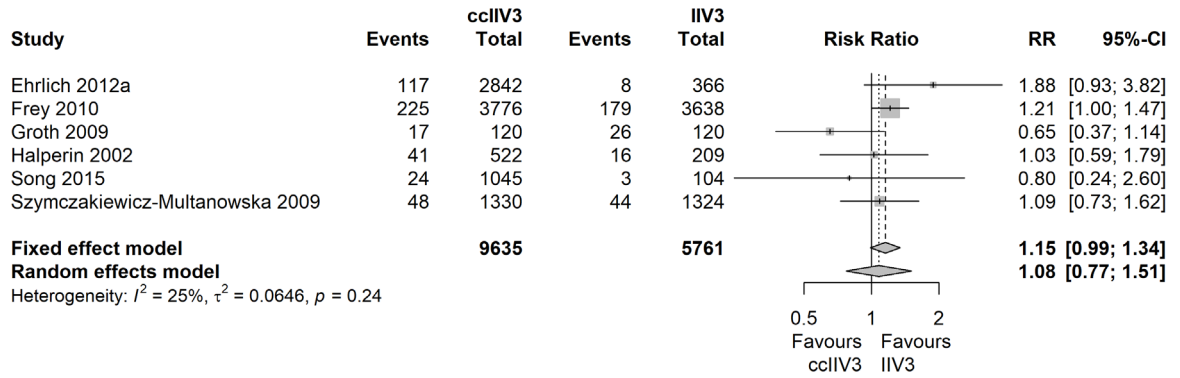


Figure 3.52 Relative risk of induration, ccIIV3 versus IIV3

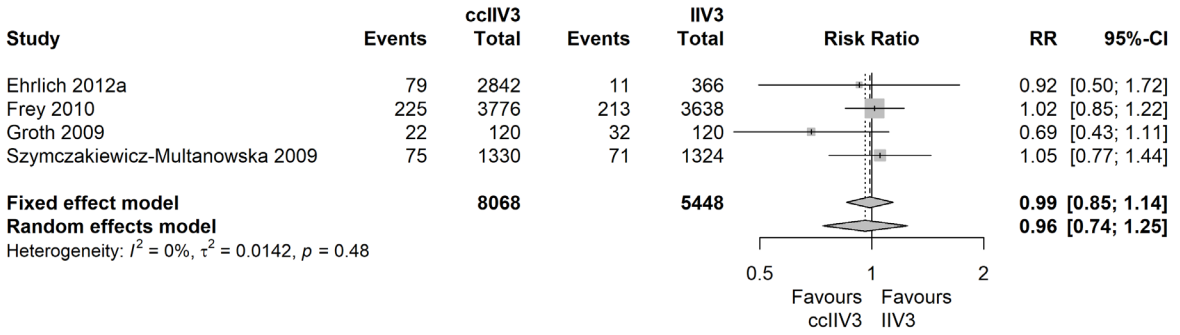
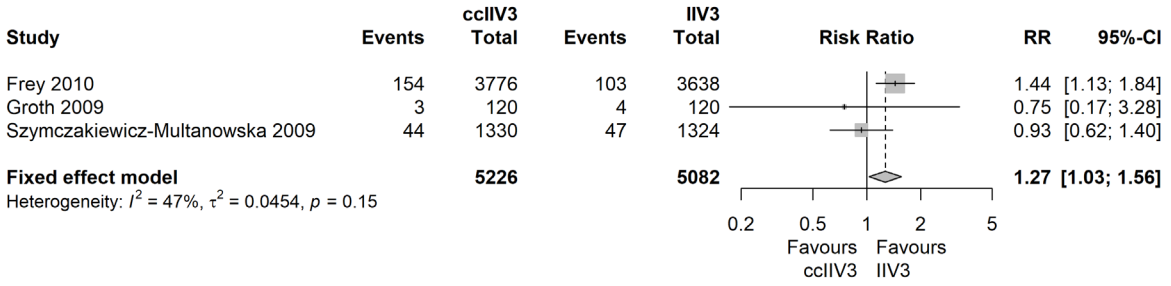


Figure 3.53 Relative risk of ecchymosis, ccIIV3 versus IIV3



3.4.4.3 Systemic reactions

Six studies possessed sufficiently comparable data to enable quantitative synthesis regarding systemic reactions for cell-based influenza vaccines [60, 65, 72, 75, 122, 125]. All of these studies compared ccIIV3 with IIV3 for outcomes including combined systematic reactions, arthralgia, myalgia, malaise, fever, headache, chills, fatigue vomiting and diarrhoea. The pooled estimates for these outcomes are presented in Figures 3.54 to Figure 3.63. As shown, no significant differences were shown between the two vaccines for any outcome (low-moderate certainty evidence, see Appendix 9.3). As shown in Appendix 8.3, similar results were displayed for older adults within sub-group analyses.

With regards to studies that were too heterogeneous to be included in pooled analyses, a similar trend was noted. Two studies comparing ccIIV4 with ccIIV3 note similar rates of systemic reactions in both groups [32, 44], with similar results also shown in a study which compared ccIIV3 with IIV3 [126]. Two studies compared ccIIV3 with placebo, with one [65] noting comparable rates between groups and the other reporting significantly more systemic reactions in those receiving ccIIV3, albeit the majority of which were mild-moderate. An uncontrolled study by Vinnemeier et al. [136] noted similar rates of systemic reactions in those aged 18-61 years compared with those aged over 61 years.

Figure 3.54 Relative risk of combined systemic adverse events, ccIIV3 versus IIV3

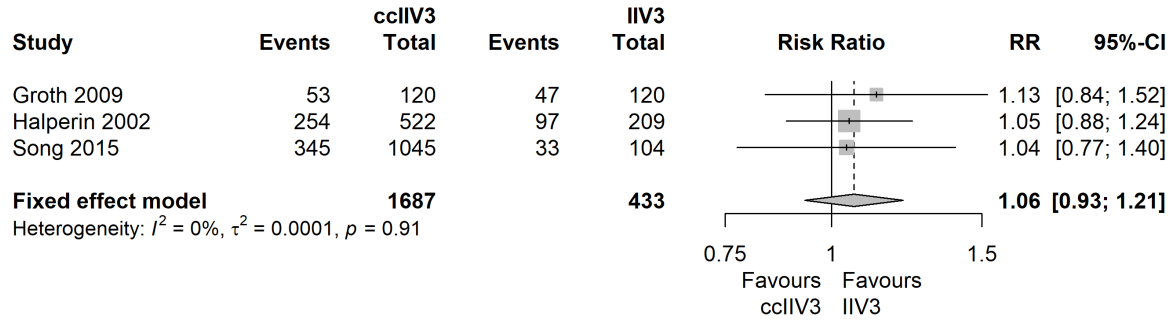


Figure 3.55 Relative risk of chills, ccIIV3 versus IIV3

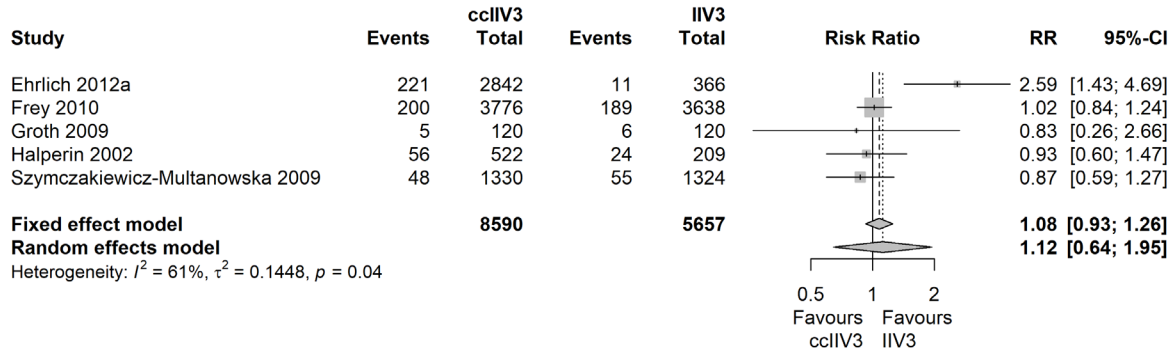


Figure 3.56 Relative risk of arthralgia, ccIIV3 versus IIV3

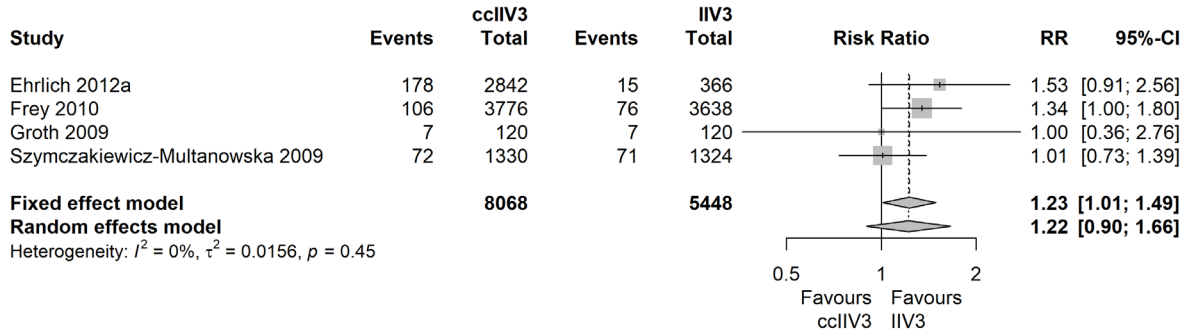


Figure 3.57 Relative risk of myalgia, ccIIV3 versus IIV3

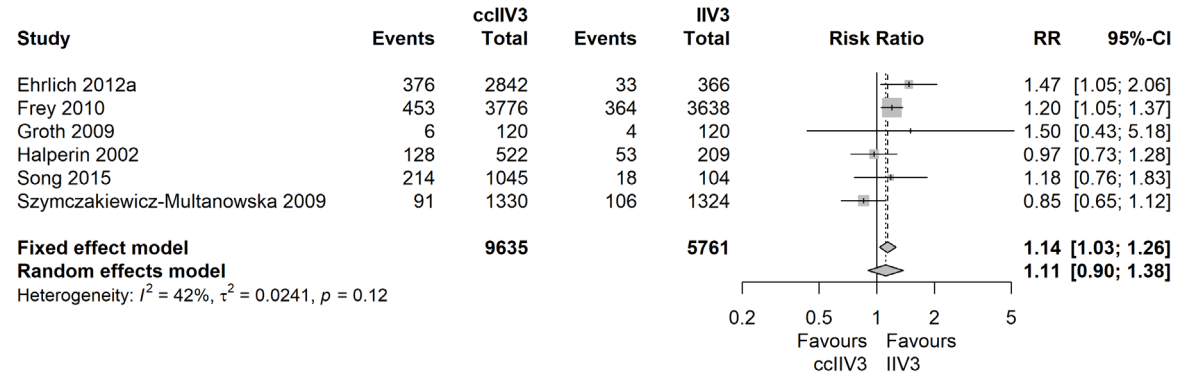


Figure 3.58 Relative risk of malaise, ccIIV3 versus IIV3

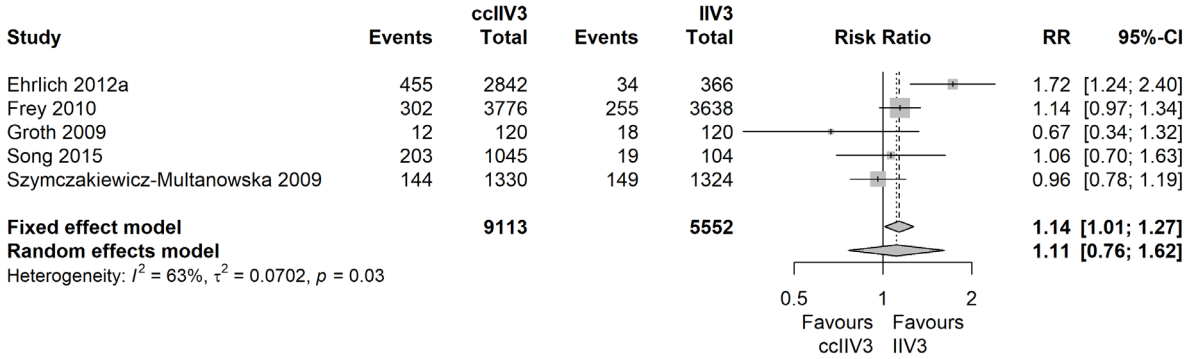


Figure 3.59 Relative risk of headache, ccIIV3 versus IIV3

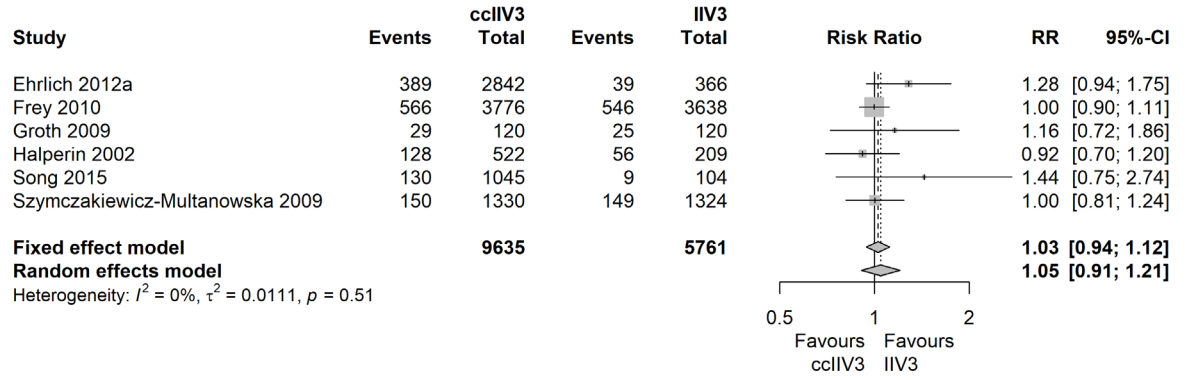


Figure 3.60 Relative risk of fatigue, ccIIV3 versus IIV3

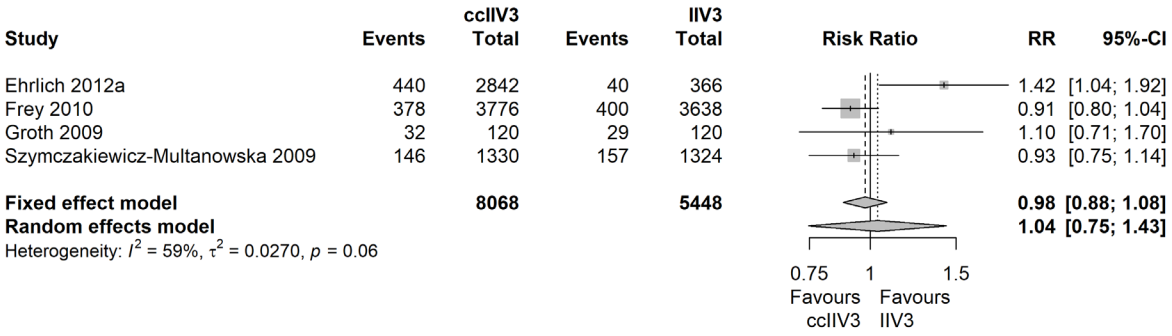


Figure 3.61 Relative risk of fever, ccIIV3 versus IIV3

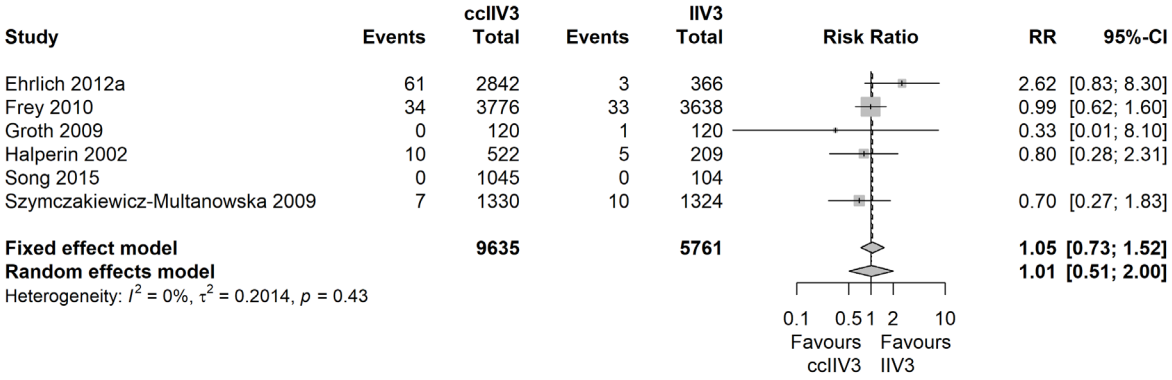


Figure 3.62 Relative risk of vomiting, ccIIV3 versus IIV3

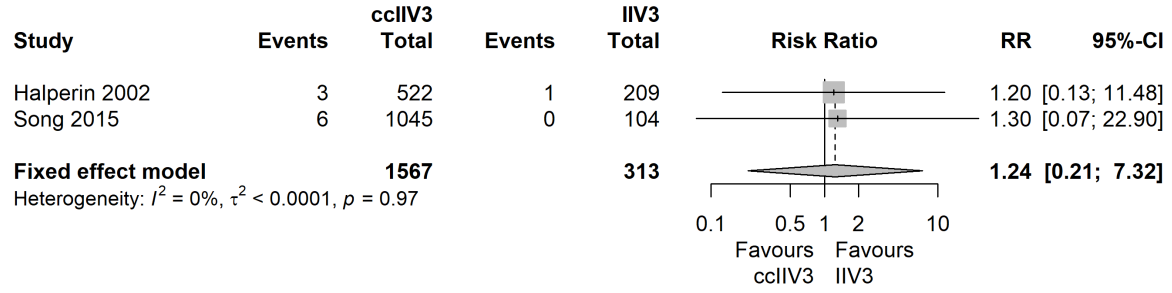
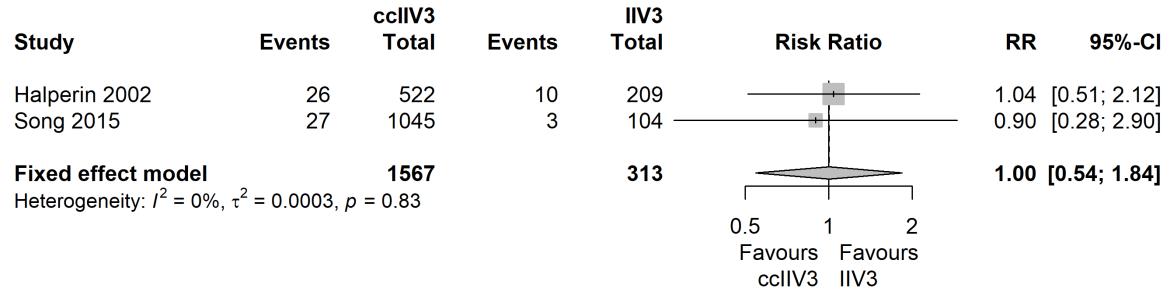


Figure 3.63 Relative risk of diarrhoea, ccIIV3 versus IIV3



3.4.5 Risk of bias - cell-based influenza vaccines

The risk of bias for efficacy and safety RCTs investigating cell-based influenza vaccines is summarised in Figures 3.64 and 3.65. Both efficacy RCTs were deemed to be at an unclear risk of bias, due to lack of clarity in one or more key domains. Of the 10 RCTs assessing a safety outcome of cell-based influenza vaccines, nine (90%) were deemed to be at an unclear risk of bias and one (10%) at a high risk of bias. Of note, the influence of industry funding as captured under the domain of other bias resulted in the majority of studies being deemed to be at an unclear risk of bias overall.

The risk of bias of NRSIs providing data on the effectiveness of cell-based influenza vaccines is summarised in Table 3.7. Of three test-negative design case-control studies which investigated the prevention of influenza, one each were assessed to be at a low risk, moderate risk and serious risk of bias. One study investigating additional outcomes was deemed to be at a low risk of bias.

Figure 3.64 Risk of bias summary: review authors' judgment of each risk of bias item, presented as percentages across all included studies

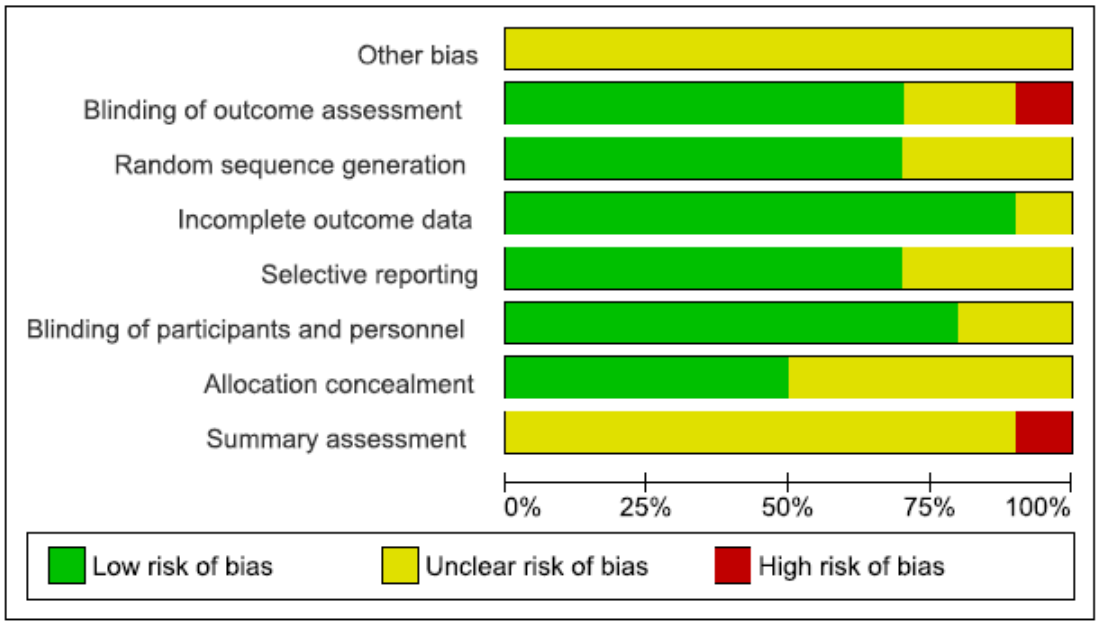


Figure 3.65 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

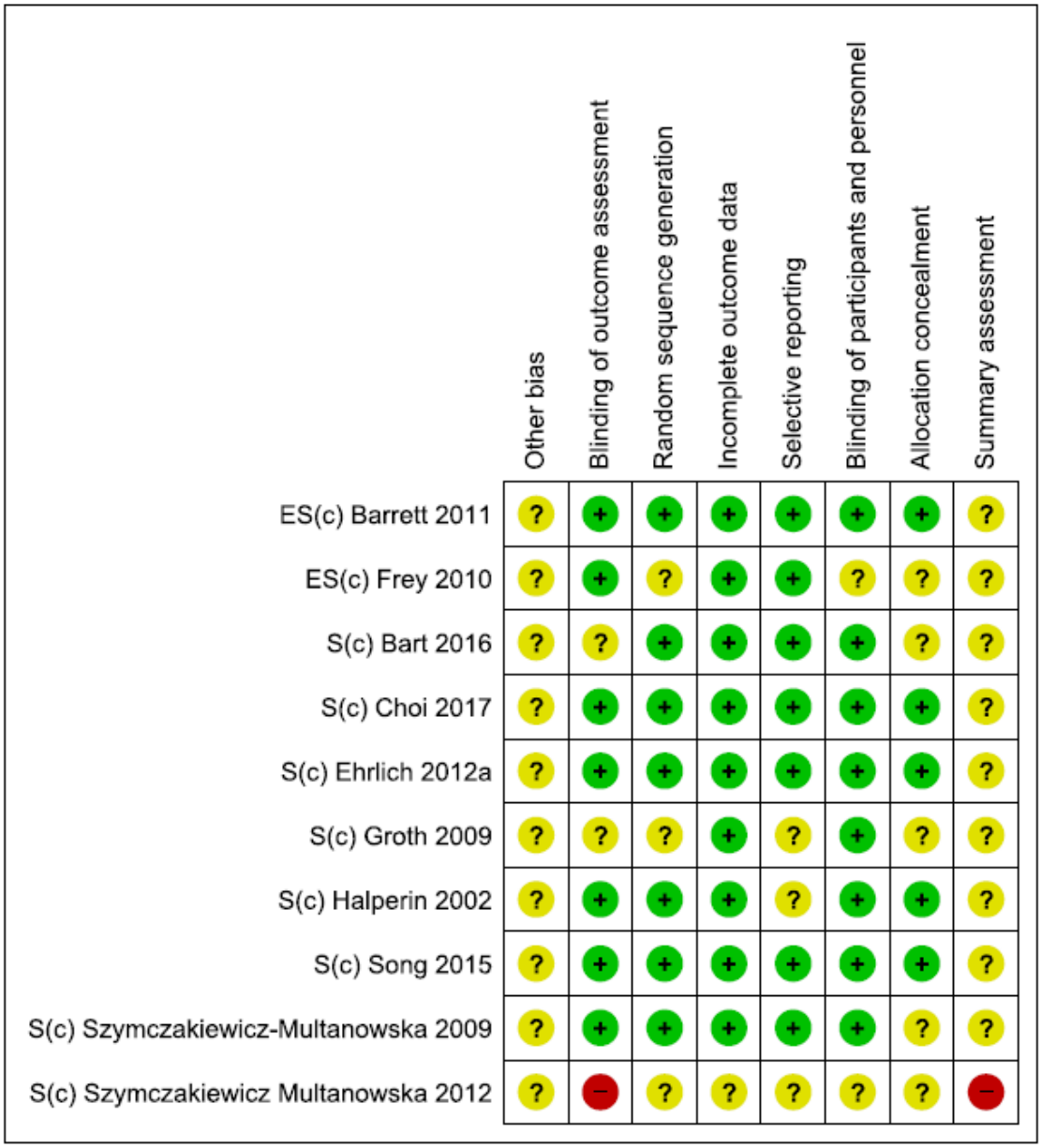


Table 3.7 ROBINS-I assessment of risk of bias of non-randomised studies of intervention

Author Year	Confounding	Selection	Classification	Deviation from intervention	Missing data	Outcome measurement	Reported results	Overall bias
Effectiveness (primary outcome)- Test-negative design case-control studies								
Bruxvoort 2019 [40]	No information	Low	No information	Low	No information	Low	Low	Moderate
Castilla 2016 [42]	Low	Low	Low	Low	Low	Low	Low	Low
DeMarcus 2019 [51]	Serious	Moderate	Low	Low	No information	Low	Low	Serious
Effectiveness (additional outcomes)- Case control and cohort studies								
Izurieta 2019 [78]	Low	Low	Low	Low	Low	Low	Low	Low

3.5 Recombinant HA influenza vaccines

Ten studies within this review presented results concerning recombinant HA influenza vaccines [33, 48, 57, 58, 77, 84, 116, 127-129]. Of these studies, two related to efficacy/safety [57, 127] and 10 related to safety only [33, 48, 57, 58, 77, 84, 116, 127-129]. The characteristics of studies relating to the efficacy of recombinant HA influenza vaccines are provided in Appendix 5.4. The vaccine and circulating strains' characteristics associated with these studies are provided in Appendix 6.4. The characteristics of studies relating to the safety of recombinant HA influenza vaccines are provided in Appendix 7.4.

3.5.1 Efficacy - recombinant HA influenza vaccines

Two studies met the eligibility criteria for this systematic review which investigated the efficacy of recombinant HA influenza vaccines [57, 127].

The first study conducted by Dunkle et al., [57] compared a RIV4 with an IIV4 in adults aged ≥50 years during the 2014-2015 influenza season for laboratory-confirmed and culture-confirmed influenza. The authors noted the RIV4 had higher efficacy for laboratory-confirmed protocol-defined influenza-like illness with a relative vaccine efficacy of 30% (95% CI 10% to 47%, moderate-certainty evidence). In a subgroup analysis by influenza type, RIV had higher efficacy for influenza A with a relative vaccine efficacy of 36% (95% CI 14% to 53%, moderate-certainty evidence), but not for influenza B (VE= 4%, 95% CI -72% to 46%, moderate-certainty evidence). Additional subgroup analysis by age presents a significant effect for those aged 50-64 years with a relative vaccine efficacy of 42% (95% CI 15% to 61%), but not in those aged over 64 years (VE= 17%, 95% CI -20% to 43%). Similar results were presented for culture-confirmed influenza like illness.

Consistent findings are presented in a second study conducted by Treanor et al. [127] comparing a RIV3 with saline in adults aged 18-55 years during the 2007-2008 influenza season. The authors present a significant vaccine efficacy for influenza positive CDC-defined influenza-like illness of 44.6% (95% CI 18.8% to 62.6%) for any influenza and 54.4% (95% CI 26.1% to 72.5%) for influenza A, but not for influenza B (VE=23.1%, 95% CI -49.0% to 60.9%). Similar findings are presented for influenza positive illness.

3.5.2 Effectiveness - recombinant HA influenza vaccines

No studies met the eligibility criteria of this systematic review which investigated the effectiveness of recombinant HA influenza vaccines.

3.5.3 Safety - recombinant HA influenza vaccines

Ten studies included in this systematic review concerned the safety of recombinant HA influenza vaccines, all of which were RCTs [33, 48, 57, 58, 77, 84, 116, 127-129].

3.5.3.1 Serious adverse events

Two trials assessing the safety of recombinant HA influenza vaccines documented SAEs possibly related to vaccination. Baxter et al. [33] reported an incident of vasovagal syncope of moderate severity in a RIV3 recipient, possibly associated with the injection procedure rather than the vaccine composition. Treanor et al. [127] reported a possible association between a case of pericardial effusion and vaccination with a RIV3.

3.5.3.2 Local reactions

Seven studies within this systematic review possessed sufficiently comparable data to enable quantitative synthesis with regards to local reactions to recombinant HA influenza vaccines [33, 48, 57, 58, 77, 84, 128]. All studies compared a recombinant HA influenza vaccine with IIV3 or IIV4 for the following outcomes: combined local reactions, pain, erythema, swelling and tenderness. The pooled estimates for these analyses are presented in Figures 3.66 to Figure 3.70. As shown, for combined local reactions recombinant HA was shown to have significantly fewer local reactions compared with standard influenza vaccines (RR=0.94, 95% CI 0.90 to 0.98, three RCTs, FEM, I^2=0%, low-certainty evidence). There was no significant difference between vaccines for the remaining outcomes (low-moderate certainty evidence, see main summary of findings table and Appendix 9.4).

In terms of studies that could not be quantitatively pooled, two studies compared a recombinant HA influenza vaccine with placebo, with both studies noting significantly more injection site pain in the recombinant HA vaccine recipients [127, 129].

Figure 3.66 Relative risk of combined local adverse events, recombinant HA versus IIV

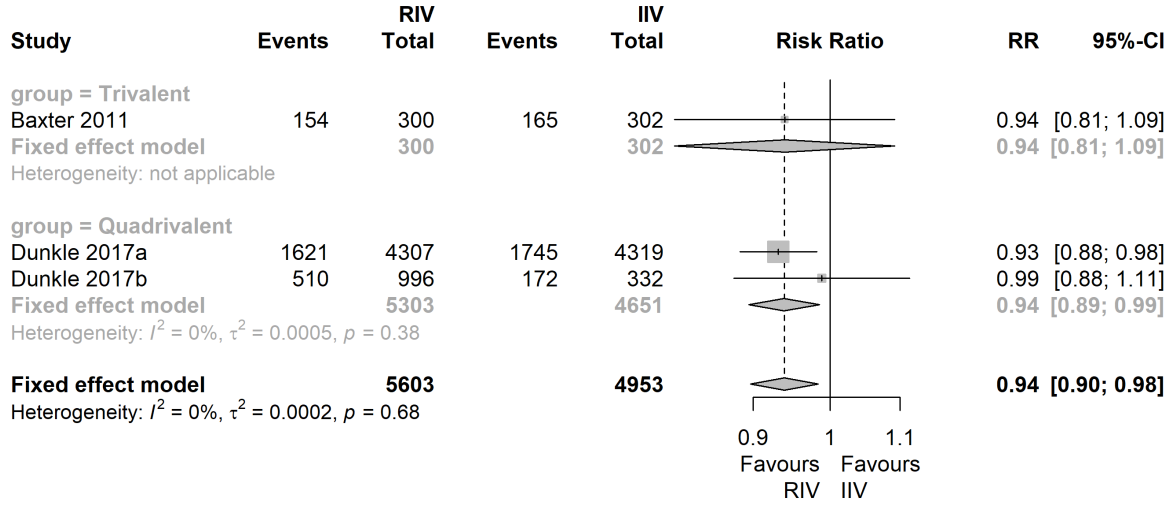


Figure 3.67 Relative risk of pain, recombinant HA versus IIV

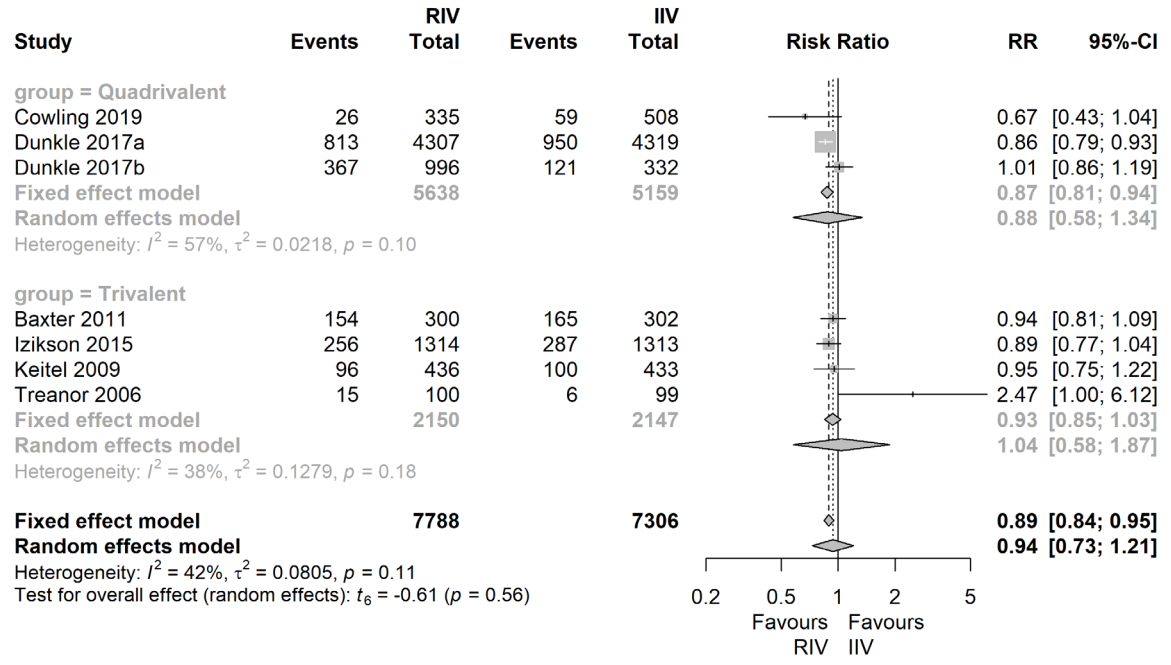


Figure 3.68 Relative risk of redness and erythema, recombinant HA versus IIV

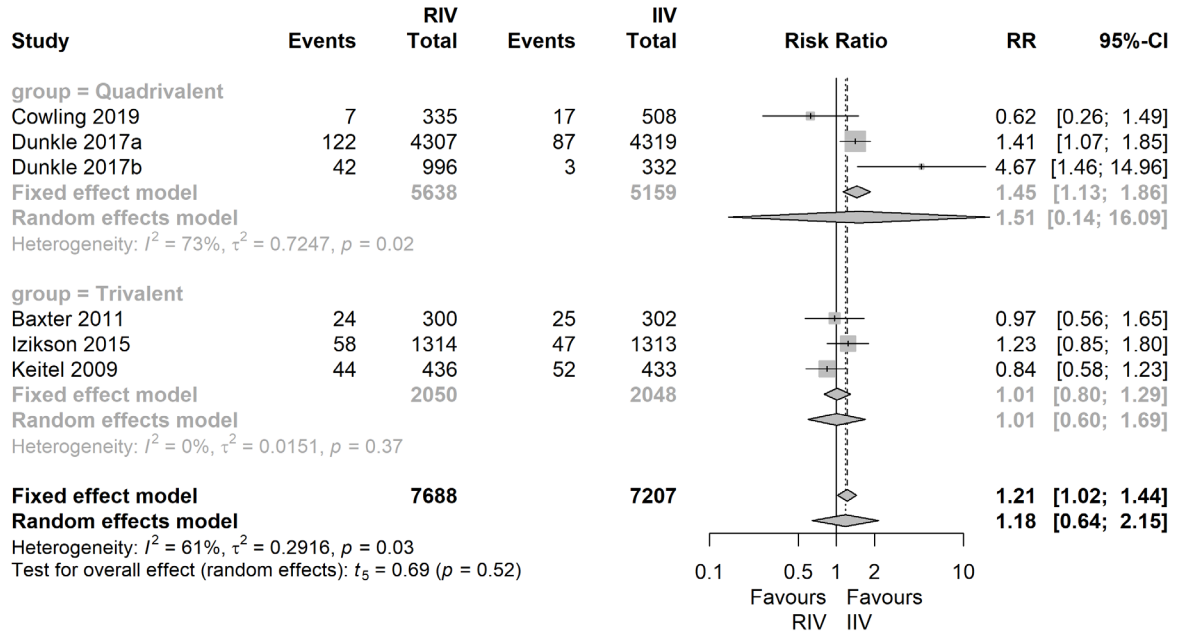


Figure 3.69 Relative risk of swelling, recombinant HA versus IIV

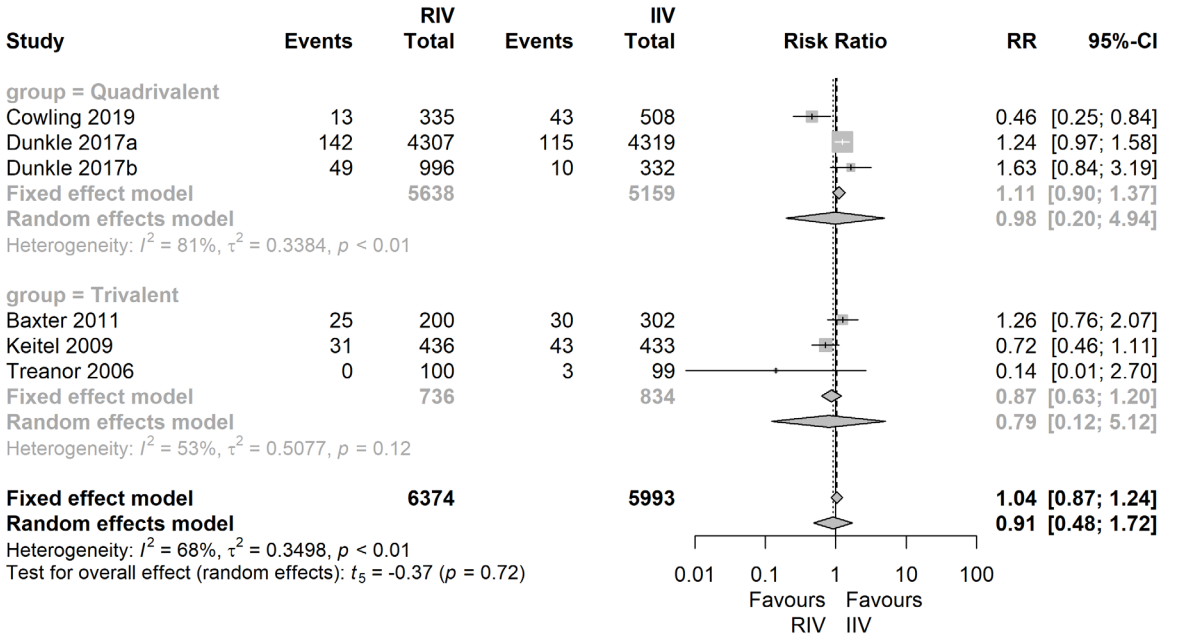
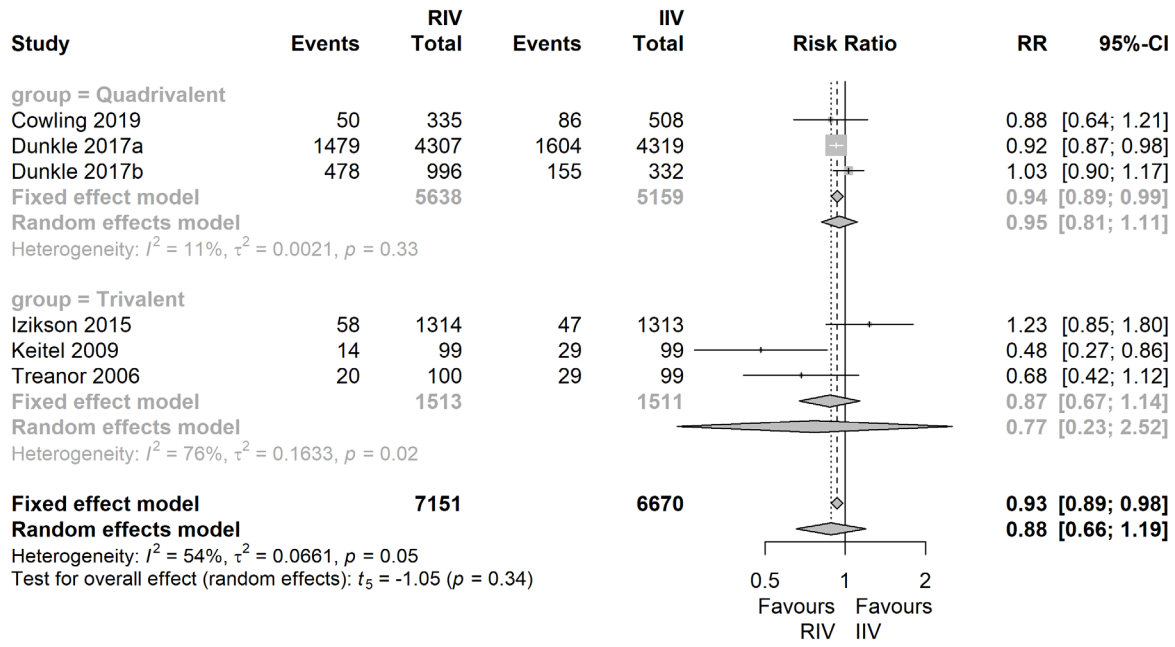


Figure 3.70 Relative risk of tenderness, recombinant HA versus IIV



3.5.3.3 Systemic reactions

Seven studies possessed sufficiently comparable data to enable quantitative synthesis with regards to systemic reactions to recombinant HA influenza vaccines [33, 48, 57, 58, 77, 84, 128]. All studies compared a recombinant HA influenza vaccine with IIV3 or IIV4 for the following outcomes: chills, fatigue, headache, myalgia and nausea. The pooled estimates for these outcomes are presented in Figures 3.71 to Figure 3.75. As shown, recombinant HA vaccines were associated with a significantly higher risk of chills compared with IIV (RR=1.33, 95% CI 1.03 to 1.72, three RCTs, FEM, I^2=14%, low-certainty evidence (Appendix 9.4)), with no significant difference noted for any other outcome (low-moderate certainty evidence, see Appendix 7.4).

Two studies could not be included in the pooled analyses due to clinical heterogeneity, with both comparing recombinant HA vaccines with placebo and no differences noted between the groups in terms of systemic reactions [127, 128].

Figure 3.71 Relative risk of chills, recombinant HA versus IIV

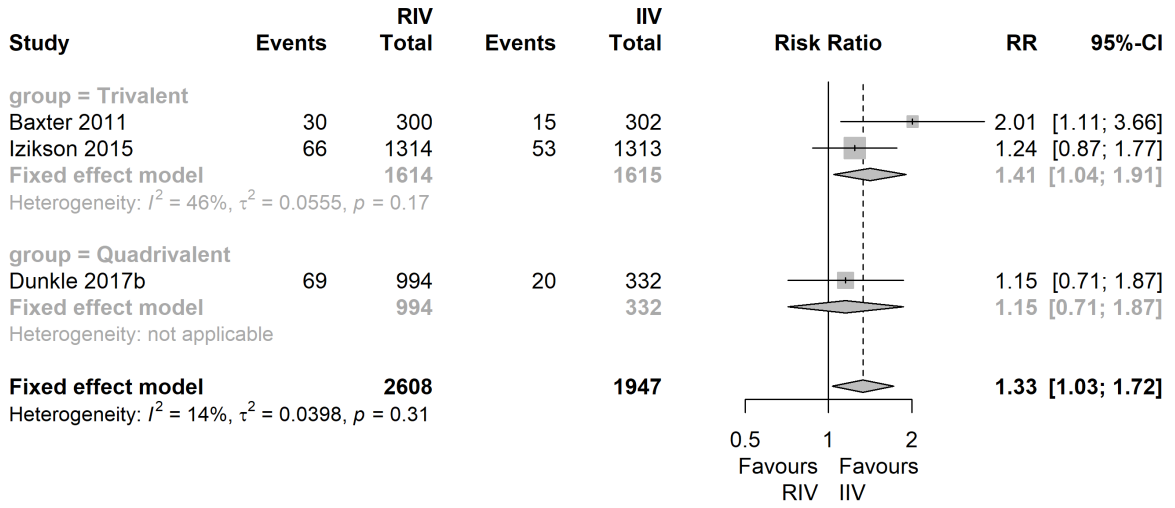


Figure 3.72 Relative risk of fatigue, recombinant HA versus IIV

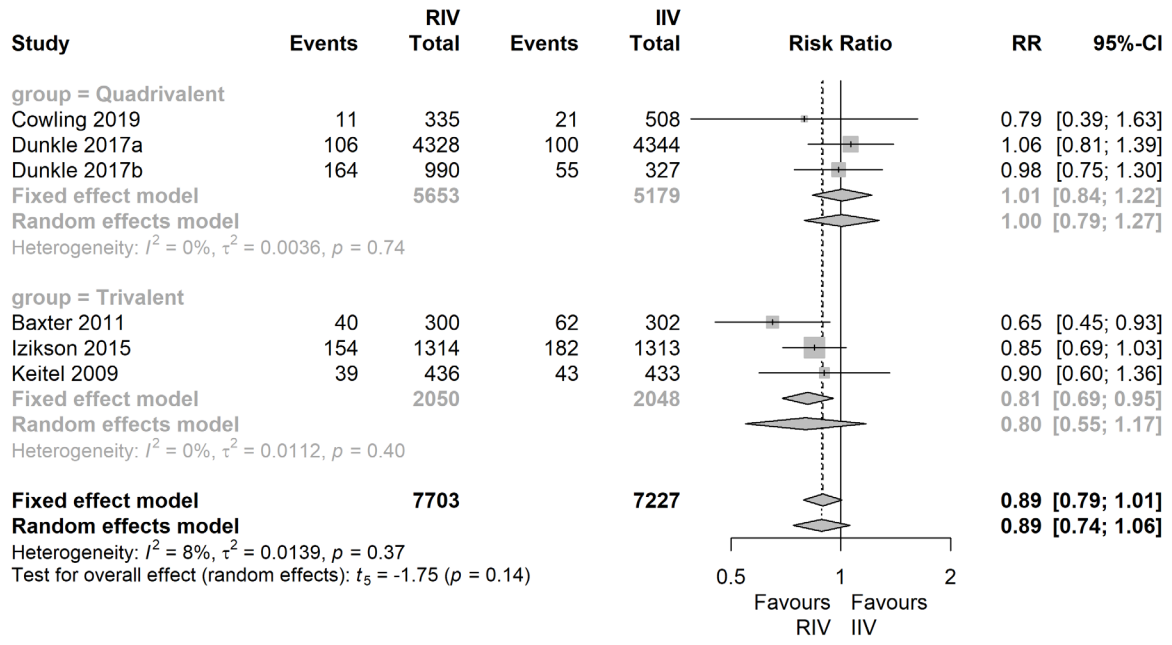


Figure 3.73 Relative risk of headache, recombinant HA versus IIV

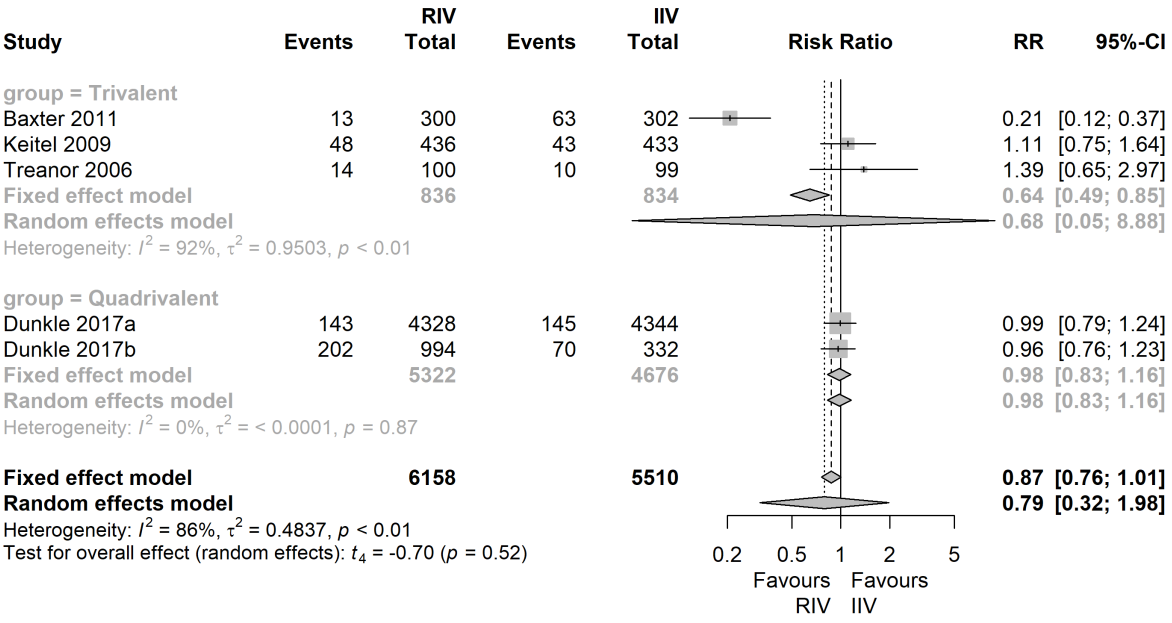


Figure 3.74 Relative risk of myalgia, recombinant HA versus IIV

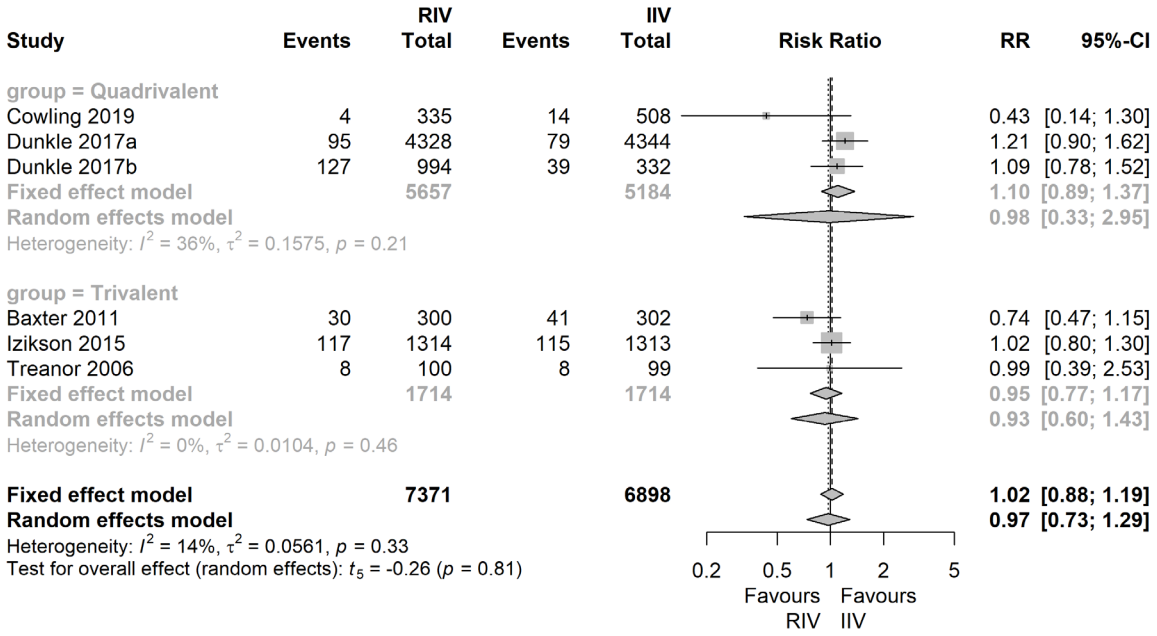
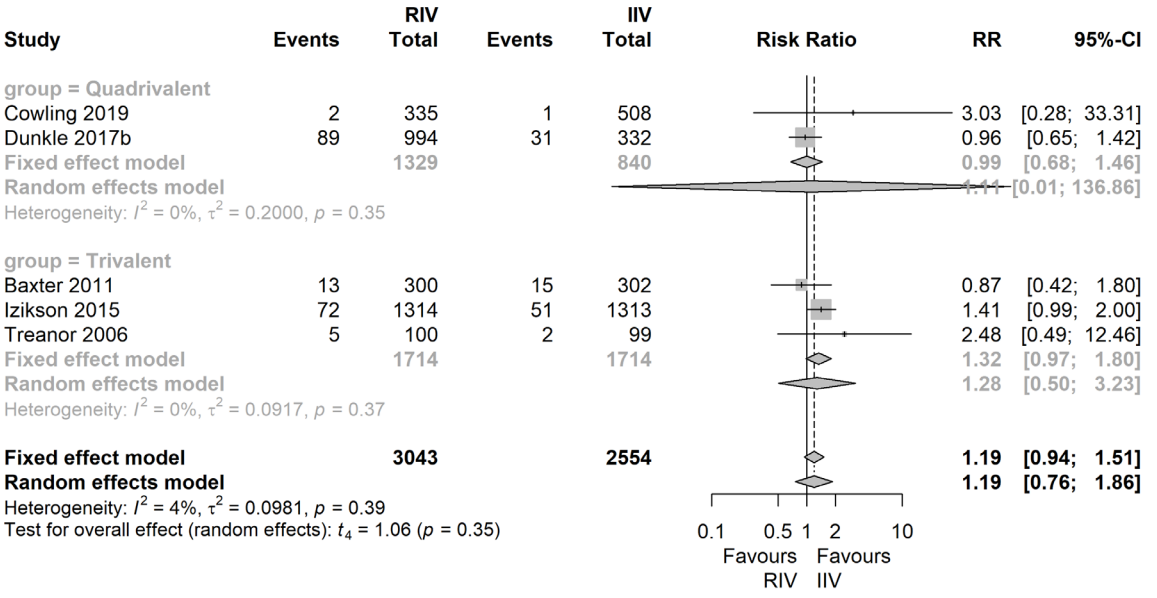


Figure 3.75 Relative risk of nausea, recombinant HA versus IIV



3.5.3.4 Safety of recombinant HA influenza vaccines in at-risk populations

One study assessed the safety of recombinant HA influenza vaccines in an at-risk population [116]. Twenty-seven patients with non-Hodgkin B cell lymphoma were randomised to receive IIV3 or a recombinant HA vaccine. Six patients reported redness, tenderness, malaise, or myalgia after vaccination with the recombinant HA vaccine with two patients reporting moderate malaise and myalgia. Due to the small sample size, it is not possible to comment on the clinical or statistical significance of these results.

3.5.4 Risk of bias - recombinant HA influenza vaccines

The risk of bias for efficacy and safety RCTs investigating recombinant HA influenza vaccines is summarised in Figure 3.76 and 3.77. The two efficacy RCTs was deemed to be at an unclear risk of bias due to lack of clarity in one key domain. Of the 10 RCTs assessing a safety outcome of recombinant HA influenza vaccines, all studies were deemed to be at an unclear risk of bias due to lack of clarity in one or more key domains. Of note, the influence of industry funding as captured under the domain of other bias resulted in the majority of studies being deemed to be at an unclear risk of bias overall.

Figure 3.76 Risk of bias summary: review authors' judgment of each risk of bias item, presented as percentages across all included studies

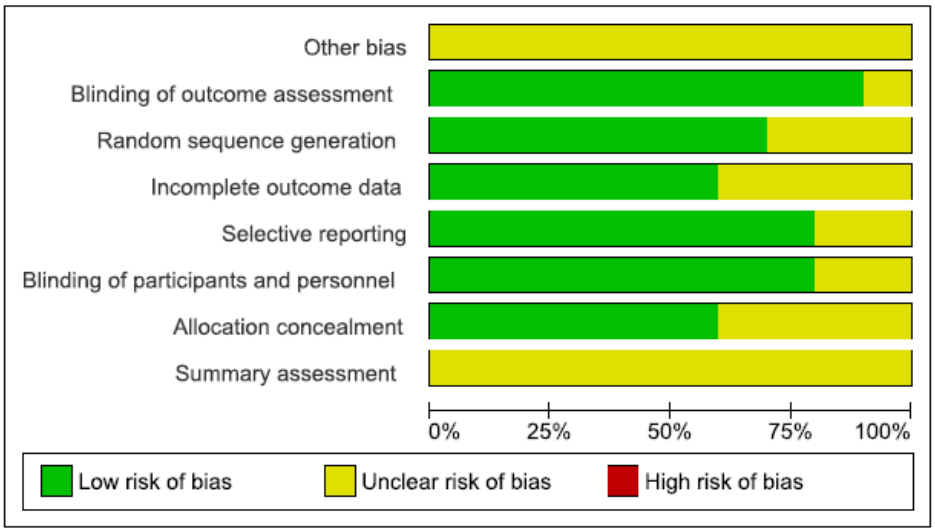
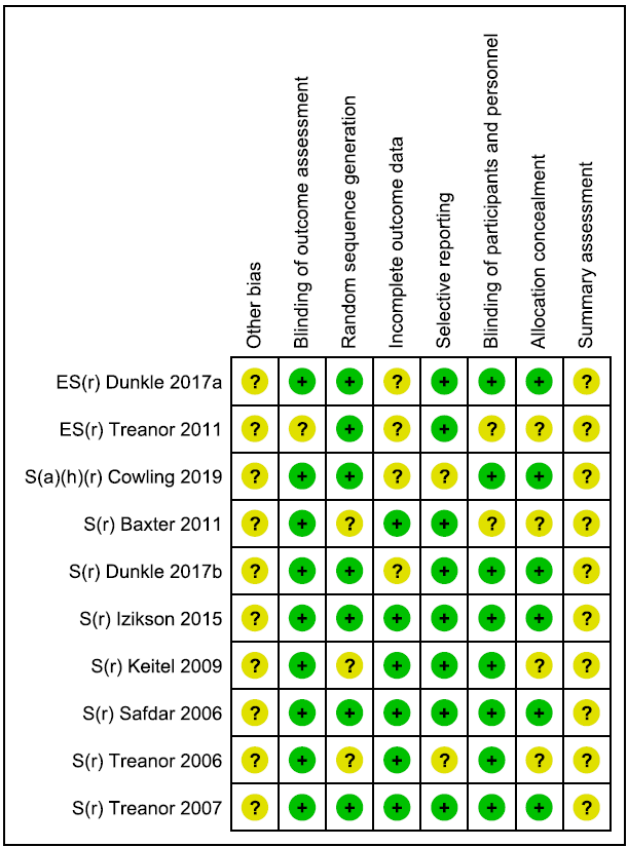


Figure 3.77 Risk of bias summary: review authors' judgments about each risk of bias item for each included study



3.6 Duration of within-season protection of vaccines

The studies included within this systematic review did not provide sufficient data to estimate the duration of within-season protection for any of the vaccines of interest. The issues precluding this analysis will be highlighted in the discussion section.

4. Discussion

This systematic review aimed to synthesise the existing evidence base for the efficacy, effectiveness and safety of a subset of influenza vaccines, which were deemed to be newer and enhanced in comparison with traditional influenza vaccines, namely: MF59® adjuvanted, cell-based, high-dose and recombinant HA. This review included 110 studies, of which five related to efficacy and safety, 35 investigated effectiveness and 67 concerned safety only, with three studies contributing additional results to already included datasets. The distribution of studies across vaccine type was 48 for adjuvanted influenza vaccines, 19 for cell-based influenza vaccines, 36 for high-dose influenza vaccines, and 10 for recombinant HA influenza vaccines. The results of this review will be discussed for each vaccine of interest with consideration towards the hierarchy of evidence available, followed by a collective narrative regarding challenges encountered during this review process and potential directives for research and reporting to mitigate such challenges in the future.

4.1 MF59® adjuvanted influenza vaccines

No relevant published study was identified which investigated the efficacy of MF59® adjuvanted influenza vaccines. While efficacy data may be reported for completed studies [141], unless peer-reviewed, they were not considered eligible for inclusion.

Twenty-two effectiveness studies, including 11 test-negative design case-control studies, presented results which were relevant to the primary outcome of laboratory-confirmed influenza. Compared with no vaccination, MF59® adjuvanted vaccines were found to be effective in preventing influenza in older adults (low-certainty evidence). The treatment effect in relation to influenza A(H3N2) was not statistically significant (very low-certainty evidence), although considerable heterogeneity existed across studies with regard to matching with the circulating strain. These findings appear largely in keeping with previous reviews of influenza vaccine effectiveness [142, 143]. The heterogeneity displayed when considering influenza A(H3N2) data specifically is not unexpected, given the known antigenic drift associated with this subtype in particular [1]. It appears to support previous directives regarding the cornerstone of influenza effectiveness being first and foremost the accuracy of prediction of circulating strains and the degree of within-season drift [144, 145]. Although adjuvanted influenza vaccines enhance immunogenicity, their vulnerability to mismatch may be similar to traditional influenza vaccines [11]. Limited evidence was presented with regards to the effectiveness of MF59® adjuvanted influenza vaccines compared with their non-adjuvanted equivalents. There were only seven studies reporting relevant data, which included both crude and adjusted outcomes and could not be synthesised. A subjective interpretation of these limited data suggests MF59® adjuvanted influenza vaccines do not appear to offer a benefit over non-adjuvanted influenza vaccines, with no statistical difference noted in any trial for all influenza strains, or by subtype, irrespective of the season.

The remaining matched case-control and cohort studies reported outcomes which were not laboratory-confirmed and were categorised as additional outcomes. A similar pattern to the above was seen with regards to influenza-related hospitalisations, whereby MF59® adjuvanted vaccines appeared superior to no vaccination, but limited data suggested no difference in effect compared with non-adjuvanted vaccines. MF59® adjuvanted vaccines were more effective than no vaccination in reducing the risk of influenza- or pneumonia-related hospitalisations, with data from two studies suggesting they may also be more effective than non-adjuvanted vaccines in this regard. Data for the remaining outcomes were limited to single studies only, with effect shown in favour of MF59® adjuvanted vaccines for influenza-related hospital encounters compared with non-adjuvanted vaccines, and influenza-like illness compared with no vaccination and non-adjuvanted vaccines. Given the nature of the studies investigating the additional outcomes outlined within this review and the inherent risk of bias, significant caution is needed when interpreting these results.

A reasonably large evidence base was presented in terms of the safety of MF59® adjuvanted influenza vaccines compared with their non-adjuvanted equivalents, with data from 27 studies. In general, the included studies demonstrated that MF59® adjuvanted influenza vaccines were associated with a higher frequency of solicited local and systemic reactions (low-moderate certainty evidence). This finding is not surprising given the potency of inflammatory action associated with the use of adjuvants in vaccines; Hervé et al. [146] discuss the reactogenicity and physical manifestations associated with adjuvants and highlight the inevitability of more solicited reactions. However, these adverse effects are noted to be largely mild to moderate, and transient in their presentation [146, 147].

Overall, there is an absence of high-quality evidence regarding the efficacy of MF59® adjuvanted influenza vaccines. While data show that they are generally more effective than no vaccination in reducing the risk of laboratory-confirmed influenza and additional proxy outcomes, their effectiveness compared with traditional vaccine comparators is uncertain and based on limited data. MF59® adjuvanted influenza vaccines are associated with more local and systemic reactions when compared with traditional influenza vaccines, which is consistent with the known effects of other adjuvanted vaccine formulations.

4.2 High-dose influenza vaccines

One efficacy study was included within this review which investigated a high-dose influenza vaccine compared with a standard-dose equivalent in older adults, for the primary outcome of laboratory-confirmed influenza. The results highlighted better protection against laboratory-confirmed influenza with the use of the high-dose vaccine (moderate-certainty evidence).

One study was identified that compared the effectiveness of a high-dose influenza vaccine with no vaccination for the primary outcome of laboratory-confirmed influenza in older adults. While the high-dose vaccine was associated with a significant reduction in laboratory-confirmed influenza B, no significant effect was seen for influenza A(H3N2), with a likely mismatch of the latter to circulating strains. The collective data for efficacy and effectiveness, albeit limited, appear to suggest that high-dose influenza vaccines provide greater protection than standard dose or no vaccination. However, the results highlight that irrespective of the vaccine type, the requirement for accurate matching is an important foundation [144, 145].

In terms of additional outcomes of interest to this review, the included studies highlight a larger effect with high-dose influenza vaccines compared with standard-dose equivalents for influenza-related hospitalisation, influenza- or pneumonia- related hospitalisation, influenza-related hospital encounters, influenza-related office visits and respiratory-related hospital admissions. Given the nature of the majority of the studies included, significant caution should be used when interpreting these results. Additionally, it is unclear how accurate these outcomes are as proxy measures given the lack of laboratory or culture-confirmed methodologies.

A reasonable evidence base was presented for the safety of high-dose influenza vaccines compared with their standard-dose counterparts. The findings of this review highlight that high-dose vaccines are likely associated with a higher frequency of local and systemic reactions (very low-moderate certainty evidence). The increase in reactions with high-dose influenza vaccines is likely attributed to the composition of these vaccines, which contain a fourfold increase in the antigens included compared to standard. Notably these symptoms are typically reported as mild and transient in nature [148].

Overall, high-dose influenza vaccines may provide better protection against laboratory- confirmed influenza and proxy outcome measures. However, the evidence base is limited and largely restricted to cohort studies so caution should be taken when interpreting these results. The safety profile of high-dose vaccines highlights that they elicit more reactions overall compared with standard-dose equivalents, which is not unsurprising given dosage differences.

4.3 Cell-based influenza vaccines

Two efficacy studies were included in this review and were in agreement with regards to cell-based vaccines being effective in the prevention of laboratory- confirmed influenza when compared with placebo in adults (moderate-certainty evidence). While it may be possible to calculate efficacy compared with traditional influenza vaccine (IIV3) based on an indirect comparison [65], only direct comparisons were considered in this review. Indirect comparisons are, in this context, typically underpowered to detect differences in effect.

Evidence for effectiveness was limited to three studies reporting data for laboratory-confirmed influenza: two in adult populations and one specifically in older adults (aged ≥65 years). Overall, results were conflicting when compared with no vaccination, with probable mismatching to circulating strains evident. One study compared cell-based vaccines with traditional influenza vaccines with no evidence of a difference in effect shown. One study reported data for additional outcomes, with a small but significant increase in effectiveness observed for cell-based vaccines compared with traditional influenza vaccines for influenza-related hospitalisation, influenza-related hospital encounters and influenza-related office visits.

Taken collectively, the efficacy and effectiveness findings in favour of cell-based influenza vaccinations compared with no vaccination is consistent with previous reviews [142, 143], albeit the condition of strain matching remains a constant [142, 144]. While it is proposed that cell-based vaccines may be more effective than traditional egg-based vaccines due to reduced antigenic mutation during vaccine production [10], there were insufficient data to examine this effect.

In general, compared with traditional influenza vaccines, no significant difference in the risk of systemic reactions was noted; however, there was evidence of a limited increased frequency of local reactions including ecchymosis and possibly pain (low-moderate certainty evidence). This is consistent with expectations given similarities in the profile of cell-based and traditional influenza vaccines [5].

Overall, the findings of this review suggest that cell-based influenza vaccines are likely to be effective compared with no vaccination when the constant caveats of influenza vaccine strain matching are applied. There are limited data to assess the effectiveness of these vaccines compared with their egg-based counterparts. The safety profile of cell-derived influenza vaccines appears largely similar to traditional influenza vaccines.

4.4 Recombinant HA influenza vaccines

Data related to efficacy or effectiveness for recombinant HA influenza vaccines were limited to two efficacy RCTs within this review. Recombinant HA was found to provide a greater protective effect against overall influenza compared with no vaccination and with traditional influenza vaccination (moderate-certainty evidence). In the latter case, it is speculated that this effect may be attributable to either the restriction of mutations seen with egg-based vaccines or the higher dose of antigen seen in this type of influenza vaccine [10, 149]. Collectively, the results of these studies appear to suggest that recombinant HA vaccines may offer better protection than no vaccination or standard influenza vaccines with some possible cross protection to drift variants.

The safety of recombinant HA influenza vaccines was assessed by 10 studies included within this review. Collectively, the findings of this review suggest that the safety profile of recombinant HA influenza vaccines is largely similar to that of traditional influenza vaccines in terms of local and systemic effects (low-moderate certainty evidence).

4.5 Challenges encountered during review process

In conducting this systematic review, numerous challenges were encountered at all stages of the process which were more impactful than anticipated. An overview of these challenges is provided to assist future updates of the review or for the conduct of similar systematic reviews.

Search and selection of studies

This review included four different influenza vaccines. The comparators were defined as one or more of: any seasonal influenza vaccine, placebo, no vaccination, or other type of vaccine. This constituted a wide range of allowed study types, and numerous potential outcomes of interest. To appropriately answer the review questions set out, the search needed to be broad to ensure it would capture all potentially relevant studies. However, this sensitivity resulted in a notable decrease in specificity, as demonstrated in the collective search strategy returning 19 822 citations, of which 110 were included in the review. The issue of balancing sensitivity with specificity, with regards to influenza vaccine reviews appears to be a common challenge with a Cochrane review seemingly encountering similar issues, identifying 16 278 citations at the end of 2016, of which only 120 were included [142].

It may be possible to refine search terms further, although extensive testing of alternate filters and search terms was conducted prior to the definitive search with little impact on the number of citations returned. However, improving specificity may be at the expense of sensitivity. The limited evidence base presented by the studies included in this review was frequently extracted from within studies where the newer and enhanced influenza vaccines formed part of a large dataset rather than being the primary vaccine of interest. Therefore, their presence was not identifiable from titles or abstracts, resulting in a large number of full-text reviews. The challenges faced in determining the eligibility of studies even after full-text review suggests that an improved search specificity may be difficult to achieve. The fact that many of the effectiveness outcomes were supported by only a single study indicates that reducing search sensitivity may further prove to be a high risk strategy given the low quantity of available evidence. Future work could use the outputs of the search presented in this review to explore refinements and their impact on search sensitivity and specificity, and text mining could further be considered to identify potentially useful search terms.

Full-text review

The process of reviewing full-text articles is a core element of any systematic review. In the context of newer and enhanced seasonal influenza vaccines, the lack of consistent terminology or clear reporting created significant challenges in this review. Many studies did not clearly report the valency of included vaccines or the adjuvant used in the case of adjuvanted vaccines. Critical information was often distributed across different sections of a paper rather than being clearly reported in the methods and results sections. In particular, reference to the degree of matching of vaccine strains to circulating strains was often reported narratively and somewhat ambiguously in the discussion section of studies rather than the results section. This resulted in a substantial degree of subjectivity in the authors' interpretation of these factors when interpreting the results of included studies.

Data extraction

The method used to present key outcomes of interest to this review were reported in a heterogeneous nature across the included studies with key results being in tables, graphs, described narratively or a combination of these methods. This is not unusual, but given the use of both adjusted and unadjusted values for a range of age groups, outcomes and comparisons, it created challenges for accurate data extraction. Some studies did not report the raw two- by two- table data used to calculate the unadjusted vaccine effectiveness. Where multiple vaccine comparisons were reported, the associated effectiveness data were sometimes either not reported or presented opaquely, presenting a missed opportunity to sufficiently answer the question of relative effectiveness in comparison to traditional influenza vaccines and potentially provide valuable data to support policy decisions overall.

Analysis of results

A number of adjuvant vaccine studies did not report whether the vaccine was trivalent or quadrivalent in either the intervention or comparator arms. These studies could then not be combined with studies that clearly stated valency, limiting the pooled analyses of such studies overall.

Where multiple studies were available for a given combination of comparison, outcome and age group, there was the potential for pooling of outcomes. The lack of consistent age groups for reporting further hampered the ability to pool data. The failure to disaggregate outcomes by vaccine type in some studies also limited the number of comparisons that could be extracted. From a comparison of adjusted and unadjusted outcomes, it was clear that the process of adjustment often had an important impact on effect estimates. For this review, it was assumed that the adjusted value was the least biased estimate of effectiveness as it accounted for differences in demography and other potentially important patient-level characteristics. Although almost all studies reported adjusted estimates, a small minority did not. While the results of those studies were included, it was with the acknowledgement that the estimates were likely to be biased. Studies that included multiple vaccine types often only reported adjusted vaccine effectiveness for the main or a restricted number of comparisons, thereby limiting the useful data that could be extracted. The covariates considered for adjustment were generally reported clearly, with age and sex used consistently in addition to a range of other covariates. What was less clear was which covariates were actually used for adjustment, as studies often reported that only those with a *p*-value of less than 0.1 were retained for adjustment, without stating which those were.

Pooling studies across a mix of matched and mismatched seasons is likely to generate misleading results. The included studies may not give a fair representation of how often the vaccine matches the circulating strains in a given season. The pooled result will also reflect neither a matched or mismatched season, but some form of 'on average' that is also not a reflection of the 'on average' probability of matching.

Interpretation of results

While there were limited data for most comparisons, this was further reduced when considering only a particular influenza season. The extent of match or mismatch to circulating strains within a season was not consistently reported, and it was unclear what constituted a 'good match' in terms of full, partial or poor matching overall. However, whether the level of matching could be converted into a dichotomous measure may not be very relevant given the limited number of studies available for subgroup analysis. As already stated, pooling across a mix of matched and mismatched seasons must be interpreted with caution as it may not reflect the true likelihood of matching.

There were insufficient data to support a network meta-analysis. As the review was of newer and enhanced seasonal influenza vaccines, only studies that included one of the four identified vaccines were included. However, those studies included a wide range of comparators – often non-adjuvanted vaccine or no vaccination. Ideally, a network meta-analysis would include the findings of studies that compared adjuvanted vaccines with no vaccination, as this would be an important component in determining the consistency of evidence across the network. This is particularly important, given that there was evidence to suggest a benefit over no vaccination, but limited evidence to suggest a benefit over traditional influenza vaccines. As such, it is recommended that a network meta-analysis should not be limited to newer and enhanced seasonal influenza vaccines, but should be undertaken as part of a review of all relevant influenza vaccines which may produce more impactful results.

There are unique regulatory and manufacturing requirements that pertain to vaccines; lot variation and/or major changes to the manufacturing process have the potential to impact vaccine performance and safety. Decisions on the requirement for comparative clinical immunogenicity trials following changes to the product composition or manufacturer (including changes to process, site or scale) are made on a case-by-case basis by the regulatory authorities [150]. Such changes should routinely be considered when drawing conclusions around the generalisability of vaccine findings.

In the context of this review, efficacy data for the cell-based vaccines are based on a product originally marketed by Novartis as Optaflu® in Europe and Flucelvax® in the US, with production of both products initially limited to a facility in Germany. Production has since been moved exclusively to the US [151, 152]. For the included cell-based vaccines, no additional immunogenicity trials were required by regulators following a review of the manufacturing sites, so it is assumed that the findings of this review were not impacted by the production changes [153].

Considerations to improve the quality of reporting

On the basis of our experience of conducting this systematic review, a number of suggestions to improve reporting can be proposed which may facilitate future evidence synthesis when considering newer and enhanced influenza vaccines:

- Studies should clearly report the key features of the study in the title and abstract (for example, types of vaccines included, study design). In the absence of consistent use of key words and MeSH terms, this would greatly facilitate searching.
- There should be clearer reporting within papers in terms of how the patient population were selected, whether influenza was laboratory-confirmed, the type of adjuvant used, and the valency of the included vaccines.
- While acknowledging that age groupings reported in effectiveness studies may reflect country-specific vaccine policy recommendations, data should also be reported according to the age groupings for the licensed indications of the included vaccines.
- Results should be reported disaggregated by vaccine type, while acknowledging that there can be issues with small numbers, for all included vaccines to enable a greater number of comparisons between the vaccines of interest to this review and traditional influenza vaccines.
- The degree of matching between vaccine and circulating strains should be explicitly reported as part of the results section, preferably as a percentage rather than as a dichotomous outcome.
- Vaccine effectiveness should be presented as both an adjusted and unadjusted outcome with adjusted comparisons explicitly stating the variables included in the final model.

4.6 Strengths and limitations

The findings of this systematic review should be interpreted with consideration of its strengths and limitations overall. A robust approach to the review process was employed with the publication of a defined protocol and adherence to guidelines to standardise conduct and reporting. To the evaluation team's knowledge, this is the first review to collectively assess the evidence base of a range of newer and enhanced seasonal influenza vaccines specifically. Immunogenicity measures were outside the scope of this systematic review, however inclusion of such factors may provide more insight to the potential benefits of these newer and enhanced influenza vaccines in future reviews. This is an active area of research, and a large number of ongoing studies (see Appendix 4) and systematic reviews [154] were identified. At least one study relevant to this review has been published since the date of search [155]. These ongoing and completed studies highlight a need to update this systematic review in the near future.

The data coverage regarding the efficacy and effectiveness of these influenza vaccines was limited in this review. Although a large body of RCT evidence was presented for safety of the newer and enhanced influenza vaccines which is likely reflective of regulatory requirements, the body of evidence for efficacy and effectiveness was extremely limited. In particular, this review was limited in its ability to answer questions regarding the relative vaccine effectiveness of these newer and enhanced influenza vaccines in comparison to their traditional counterparts, and similarly a number of primary outcomes identified in the protocol stage. It is anticipated that the implementation of the recommendations outlined above will greatly enhance future evidence synthesis in this area. Additionally, this review was unable to answer the research question regarding within-season protection duration associated with the newer and enhanced influenza vaccines due to a lack of data overall. This outcome consists of a complex interaction between a large number of factors including, age, previous vaccination history, previous infection history, circulating strain clade and research design [156]. However, it is anticipated that with the increased use of these newer and enhanced influenza vaccines, a larger data coverage will emerge. This should facilitate answers regarding this outcome, in particular with comprehensive datasets such as those collected by the I-MOVE initiative in Europe [157]. This review did not consider stratification by level of care (primary and secondary). As per the agreed protocol, all levels of care were considered collectively. However, future updates may warrant inclusion of this factor to further facilitate decision-making.

A final important consideration is the potential risk of bias of industry funding and industry affiliation. For efficacy and safety trials, industry funding falls under 'other source of bias' within the Cochrane Risk of Bias tool, as this potential source of bias is unclear. That is, while it may influence results, industry funding does not necessarily bias the results. The potential for this form of bias resulted in a large number of studies being deemed to be at an unclear risk overall. In contrast, few NRSI studies were industry-funded (17%). Such factors have been documented as potentially influencing the likelihood of publication of favourable results when considering influenza vaccines [158]. The conduct of sufficiently powered and publicly-funded trials to assess these vaccines in an effort to reduce the uncertainty regarding industry bias has been suggested as crucial for future research [142].

4.7 Conclusion

Overall the evidence base for the efficacy and effectiveness of newer and enhanced influenza vaccines appears limited at present, with a number of potentially relevant studies identified as ongoing. It is likely that the use of such vaccines provides greater protection than no vaccination at all, when the usual considerations of circulating strain matching are applied. Evidence regarding the comparability of these vaccines to traditional seasonal influenza vaccines is uncertain with a lack of available literature. The safety profiles of these vaccines are largely in keeping with that expected when considering their individual compositions and, for the most part, they appear to be well tolerated. Some suggestions are provided to enhance research conduct and reporting regarding these newer and enhanced influenza vaccines which are anticipated to improve the data coverage overall and facilitate future decision-making regarding the use of such vaccines.

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among the U.S. elderly, 2018-19. J Infect Dis. 2020.
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Appendices

Appendix 1. Electronic databases' search terms

MEDLINE (via PubMed)

#1	'influenza'/exp OR 'influenza'
#2	'influenza virus a'/exp OR 'influenza virus b'/exp
#3	flu:ab,ti OR influenza*:ab,ti
#4	#1 OR #2 OR #3
#5	'vaccine'/de
#6	'immunization'/de OR 'vaccination'/de OR 'acIIV3e immunization'/de OR 'immunoprophylaxis'/de OR 'mass immunization'/de
#7	vaccin*:ab,ti OR immuni*:ab,ti OR inocul*:ab,ti
#8	trivalent NEAR/3 influenza
#9	quadrivalent NEAR/3 influenza
#10	tetravalent NEAR/3 influenza
#11	TIV
#12	QIV
#13	fluad
#14	"Fluzone High-Dose"
#15	"Flucelvax"
#16	"FluBlok"
#17	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	#4 OR #17
#19	'influenza vaccine'/de
#20	#18 OR #19
#21	'controlled clinical trial'/exp OR 'controlled clinical trial'
#21	'trial':ab,ti
#23	'case control study' OR 'case control':ab,ti OR (case*:ab,ti AND control*:ab,ti) OR 'test-negative':ab,ti OR 'cohort analysis' OR 'cohort study':ab,ti OR 'study cohort':ab,ti OR 'cross-section*':ab,ti OR observational:ab,ti
#24	'non-randomized clinical trial'
#25	'quasi-experimental studies'
#26	'equivalence trial'
#27	non-inferiority trial'
#28	'pragmatic clinical trial'
#29	'superiority trial'
#30	'case-referent studies'
#31	'incidence studies'
#32	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33	('animal'/exp OR 'animal') NOT ('human'/exp OR 'human')
#34	#32 NOT #33
#35	#20 AND #34

Embase

#1	((Influenza, Human[MeSH Terms]) OR Influenzavirus A[MeSH Terms]) OR Influenzavirus B[MeSH Terms]
#2	(influenza*[Text Word]) OR flu[Text Word]
#3	#1 OR #2
#4	Vaccines[MeSH Terms]
#5	vaccination[MeSH Terms]
#6	immunization[MeSH Terms]
#7	(vaccin*[Text Word]) OR immuni*[Text Word]) OR inocula*[Text Word]
#8	Trivalent
#9	Quadrivalent
#10	Tetravalent
#11	TIV
#12	QIV
#13	fluad
#14	"Fluzone High-Dose"
#15	"Flucelvax"
#16	"FluBlok"
#17	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	#3 OR #17
#19	influenza vaccines[MeSH Terms]

#20	#18 OR #19
#21	controlled clinical trial[MeSH Terms]
#21	(clinical trial, phase 4[MeSH Terms]) OR clinical trial, phase iv[MeSH Terms]
#23	trial[Title/Abstract]
#24	((case control studies[MeSH Terms]) OR (case*[Title/Abstract] AND control*[Title/Abstract])) OR test negative*[Title/Abstract]
#25	(cohort studies[MeSH Terms]) OR cohort analysis[MeSH Terms]
#26	cross sectional studies[MeSH Terms]
#27	"observational study"
#28	(Non-Randomized Controlled Trials as Topic[MeSH Terms]) OR "Non-Randomized Controlled Trial"
#29	"Non-randomized clinical trial"
#30	"Quasi-Experimental Studies"
#31	"Equivalence trial"
#32	"Non-inferiority trial"
#33	"Pragmatic clinical trial"
#34	"Superiority trial"
#35	"Case-Referent Studies"
#36	"Incidence Studies"
#37	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38	(animals[MeSH Terms]) NOT humans[MeSH Terms]
#39	#37 NOT #38
#40	#20 AND #39

Cumulative Index of Nursing and Allied Health Literature (CINAHL)

S1	(MH "Influenza, Human")
S2	"influenza virus" OR "influenza*" OR "flu"
S3	S1 OR S2
S4	(MH "vaccines" OR "vaccination" OR " immunization ")
S5	"vaccin*" OR "immuni*" OR "inocula*"
S6	Trivalent N3 influenza
S7	Quadrivalent N3 influenza
S8	Tetravalent N3 influenza
S9	TIV
S10	QIV
S11	Fluad
S12	Fluzone High-Dose
S13	Flucelvax
S14	FluBIok
S15	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16	S3 AND S15
S17	(MH "Influenza Vaccine") OR (influenza vaccine or influenza vaccination or flu vaccine)
S18	S16 OR S17
S19	MH "Randomized Controlled Trials+" OR randomized controlled trials OR randomised control trials OR "randomized clinical trial" OR randomized controlled study
S20	controlled clinical trial
S21	MH "Quasi-Experimental Studies+"
S22	MH "Nonexperimental Studies+
S23	MH "Nonrandomized Trials"
S24	(case N2 control)
S25	cohort*
S26	cross-section*
S27	observational
S28	test-negative
S29	Quasi-Experimental Studies
S30	Equivalence trial
S31	Non-inferiority trial
S32	Pragmatic clinical trial
S33	Superiority trial
S34	Case-Referent Studies
S35	Incidence Studies
S36	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
S37	(MH "Animals+") NOT ((MH "Human") OR (humans or people or individuals))
S38	S36 NOT S37
S39	S18 AND S38

CENTRAL

No.	Query
#1	influenza*
#2	MeSH descriptor: [Influenza, Human] explode all trees
#3	"flu"
#4	#1 OR #2 OR #3
#5	vaccin*
#6	immuni*
#7	inocula*
#8	Trivalent NEAR influenza
#9	Quadrivalent NEAR influenza

#10	Tetravalent NEAR influenza
#11	TIV
#12	QIV
#13	Fluad
#14	Fluzone High-Dose
#15	Flucelvax
#16	FluBIok
#17	MeSH descriptor: [Vaccines] explode all trees
#18	MeSH descriptor: [Immunization] explode all trees
#19	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	MeSH descriptor: [Influenza Vaccines] explode all tress
#21	#19 OR #20
#22	#4 AND #21 in Trials

Appendix 2. Grey literature sources

Source	Access link
U.S. National Library of Medicine Clinical Trials Database	https://ClinicalTrials.gov/ct2/home
The Cochrane Library	http://onlinelibrary.wiley.com/cochranelibrary/search
Open Grey	http://www.opengrey.eu
WHO International Clinical Trials Registry Platform	https://apps.who.int/trialsearch/

Appendix 3. Excluded studies

Details (Author Year; Title; DOI)
Exclusion reason-Abstract only
Alyanak 2018; Effectiveness of influenza vaccine for prevention of influenza-associated hospitalizations among high-risk adults in the United States, 2015-2016; DOI: 10.1093/ofid/ofy210.832
Ao 2014; Safety of domestic influenza split virion vaccine for adult use; DOI: NA
Avalos 2018; Trivalent inactivated influenza vaccine (tiv) during pregnancy and risk for adverse infant neurodevelopment; DOI: 10.1002/pds.4629
Ayabe 2008; The efficacy of influenza vaccine for acute exacerbation of chronic obstructive lung disease in elderly patients; DOI: NA
Bénet 2018; Incidence of symptomatic and asymptomatic influenza among healthcare workers: A multicenter prospective cohort study; DOI: 10.1093/ofid/ofy209.065
Bobadilla-Rosado 2019; Influenza infection in the Yucatan during the year 2018; DOI: 10.4269/ajtmh.abstract2019
Boiron 2019; PIN29 Public health and economic impact of vaccination of seniors with a high dose trivalent influenza vaccine in Brazilian private health care system; DOI: 10.1016/j.jval.2019.09.1273
Bukhanova 2019; Assessment of efficacy, safety and immunogenicity of a trivalent split-virus influenza vaccine in patients with rheumatic diseases; DOI: 10.1136/annrheumdis-2019-eular.3663
Burgess 2019; Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED): Influenza-like-illness rates in year 1; DOI: 10.1093/ofid/ofz360.2477
Burgess 2019; Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED): Methods; DOI: 10.1093/ofid/ofz360.2428
Chambers 2015; Safety of seasonal influenza vaccines in pregnancy: VAMPSS update; DOI: 10.1002/pds.3838
Chung 2016; Comparison of influenza vaccine effectiveness estimates using data from the influenza incidence surveillance project and the us influenza vaccine effectiveness network, 2011-12 through 2014-15; DOI: 10.1093/ofid/ofw172.574
Coleman 2018; Department of Defense end-of-season influenza vaccine effectiveness estimates for the 2017-2018 season; DOI: NA
Colmegna 2018; Efficacy of high-dose versus standard-dose influenza vaccine in seropositive rheumatoid arthritis patients; DOI: 10.1002/art.40700
Colombo 2019; Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED): Immunogenicity sub-study; DOI: 10.1093/ofid/ofz360.2434
Comeaux 2019; Safety and immunogenicity of a seasonal influenza vaccine and AD26.RSV.pref vaccine with and without co-administration: a randomized, double-blind, placebo-controlled phase 2A study in adults aged ≥60 years; DOI: 10.1093/ofid/ofz360.2452
Cook 2018; Safety and immunogenicity of a recombinant influenza vaccine: A randomized trial; DOI: 10.1542/peds.2018-2420YYYY
Cordero 2013; Efficacy and safety of influenza vaccination during the first six months post-transplantation; DOI: 10.1111/ajt.12266
Cost 2014; Brief report: mid-season influenza vaccine effectiveness estimates for the 2013-2014 influenza season; DOI: NA
Dahi 2019; Influenza vaccine Coverage and efficacy among King Salman Armed Forces Hospital 2017-2018; DOI: 10.1016/j.jiph.2018.10.043
Donaldson 2012; Increased incidence of COPD exacerbations following influenza vaccination; DOI: 10.1136/thoraxjnl-2012-202678.034
DosSantos 2014; Safety of seasonal influenza vaccination in solid organ transplant recipients; DOI: 10.1002/pds.3701
Doyle 2018; Relative effectiveness of high-dose and standard-dose influenza vaccine against influenza-related hospitalization among older adults-United States, 2015-2017; DOI: 10.1093/ofid/ofy209.020
Dzekova-Vidimliski 2012; Clinical effectiveness of vaccination against influenza in dialysis patients; DOI: 10.1093/ndt/gfs246
Engler 2012; Incidence of myocarditis/pericarditis following smallpox versus influenza vaccination; DOI: 10.1016/S0735-1097(12)61546-0
Fernandez-Sanchez 2019; VacunaciÃ³n antigripal y antineumocÃ³cica 23 valencias en pacientes reumÃiticos en tratamiento con inmunosupresores; DOI: NA
Flannery 2017; Influenza vaccine effectiveness in the United States during the 2016-2017 season; DOI: 10.1093/ofid/ofx163.1151
Flight 2011; Clinical efficacy of seasonal influenza vaccination in adults with cystic fibrosis; DOI: 10.1136/thoraxjnl-2011-201054b.45
Galtier 2015; Influenza in patients with diabetes and obesity: Vaccine effectiveness against hospitalised influenza and complications after hospitalised influenza-like illness; DOI: 10.1007/s00125-015-3687-4
Gershon 2019; Influenza vaccine effectiveness in older patients with chronic obstructive pulmonary disease (COPD); DOI: NA
Getahun 2017; Association between influenza immunization during pregnancy and perinatal outcomes; DOI: NA

Details (Author Year; Title; DOI)
Giammanco 2005; Immunogenicity and tolerability of two subunit influenza vaccines in patients with chronic obstructive bronchopneumopathy; DOI: NA
Gorse 2017; Enhanced potency and durability of antibody response to seasonal trivalent inactivated influenza vaccine (tiv) combined with a novel water-in-oil adjuvant system at reduced hemagglutinin (HA) doses; DOI: 10.1093/ofid/ofx163.1159
Gravenstein 2016; Effectiveness of high-dose influenza vaccination on hospitalizations of older adults in US nursing homes: Results. From a cluster-randomized controlled trial; DOI: 10.1093/ofid/ofw172.1048
Gravenstein 2018; A cluster-randomized trial of adjuvanted trivalent influenza vaccine vs. standard dose in US nursing homes; DOI: 10.1093/ofid/ofy210.833
Grimaldi-Bensouda 2010; Risk of Guillain-Barré syndrome and vaccination against seasonal flu; DOI: 10.1002/pds.2019
Grimaldi-Bensouda 2011; Guillain-Barré syndrome, influenza-like illnesses and influenza vaccination during seasons with and without circulating a/H1N1 viruses; DOI: 10.1002/pds.2206
Grimaldi-Bensouda 2012; The risk of immune thrombocytopenic purpura associated with vaccines in adults: A multicenter case-control study; DOI: 10.1002/pds.3324
Grimaldi-Bensouda 2012; The risk of systemic lupus erythematosus associated with vaccines: A case-control study in France and Canada; DOI: 10.1002/pds.3324
Grimaldi-Bensouda 2019; Vaccination before first symptom of central demyelination; DOI: 10.1002/pds.4864
HakkiKaya 2016; Path to decrease hospitalizations in heart failure outpatient: Flu vaccine or not?; DOI: 10.1177/2047487316668118
Hansen 2019; Safety of recombinant influenza vaccine compared with inactivated influenza vaccine in adults; DOI: 10.1093/ofid/ofz360.2420
Hapfelmeier 2019; A large case-control study on vaccination as risk factor for multiple sclerosis; DOI: 10.1212/WNL.0000000000008012
Henaff 2019; Seasonal nosocomial influenza infection: A prospective 13 years surveillance among patients and healthcare workers in Lyon, France; DOI: 10.1186/s13756-019-0567-6
Henley 2018; Real-world effectiveness of influenza vaccination in older adults in the UK from 1997-2012: A quasi-experimental cohort study; DOI: 10.1002/pds.4629
Hilmi 2019; Miller Fischer syndrome after vaccination in The United States: A CDC/FDA vaccine adverse event reporting system study, 1999- 2017; DOI: NA
Hoppmann 2016; Vaccination and hospitalization rate in Crohn's disease: Results from a cohort; DOI: NA
Hughes 2014; High-dose vaccine reduces clinical influenza in older adults compared with standard dose; DOI: NA
Hur 2012; Safety of the 2010-2011 influenza vaccinations in the department of veteran affairs; DOI: 10.1002/pds.3324
Hur 2017; Risk of developing Guillain-Barre syndrome following influenza vaccinations in the US veterans population; DOI: 10.1002/pds.4275
Imfeld 2012; Risk of developing Alzheimer's disease in association with influenza infections; DOI: 10.1002/pds.3324
Ishigami 2018; Influenza vaccination and subsequent risk of hospitalization with pneumonia in elderly adults with and without CKD Geisinger Health System cohort; DOI: NA
Izikson 2013; Safety and immunogenicity of FluBlok, a highly purified recombinant influenza vaccine made without eggs or live influenza viruses; DOI: 10.1016/j.jaci.2012.12.717
Jamshed 2017; Randomized study comparing high-dose (HD) influenza vaccine to standard-dose (SD) influenza vaccine in patients with breast cancer age < 65 receiving chemotherapy; DOI: NA
Janackov 2012; Effects of the grippe vaccination, smoking cessation, and short acting beta agonist in COPD subjects; DOI: NA
Ju-ChiLiu 2016; Influenza vaccination reduces relative risk of dementia in patients with heart failure; DOI: 10.1002/ejhf.539
Kim 2018; Effectiveness of 23-valent pneumococcal polysaccharide vaccine and influenza vaccine against pneumococcal pneumonia among elderly patients aged 65 years and older in the republic of Korea: A case-control study; DOI: 10.1093/ofid/ofy210.751
Kissling 2016; Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study; DOI: 10.2807/1560-7917.ES.2016.21.6.30134
Klein 2018; Vaccine effectiveness of Flucelvax relative to inactivated influenza vaccine during the 2017-18 influenza season in Northern California; DOI: 10.1093/ofid/ofy229.2189
Knypinski 2019; Retrospective review of maternal and neonatal outcomes of third trimester gravidas with influenza-like illness during the 2017-2018 influenza season; DOI: 10.1016/j.ajog.2019.10.029
Kobayashi 2005; Efficacy of influenza vaccine in reducing hospital admissions among elderly nursing home residents in winter: The Hokkaido influenza study; DOI: NA
Kolhatkar 2018; Influenza vaccination via oral tablet is protective and induces a unique mucosal immune response; DOI: 10.1093/ofid/ofy210.1603
Kumar 2014; Randomized trial of a MF-59 adjuvanted influenza vaccine in kidney transplant recipients; DOI: 10.1097/01.tp.0000452133.17661.04
Kumbhani 2008; Influenza vaccination in secondary prevention from coronary ischemic events in coronary artery disease (FLUCAD); DOI: NA

Details (Author Year; Title; DOI)
Lafaurie 2019; Risk of immune thrombocytopenia induced by influenza vaccine. A nationwide population-based study in France; DOI: 10.1182/blood-2019-124720
Landi 2003; Effects of influenza vaccination on mortality among frail, community-living elderly patients: an observational study; DOI: NA
Langley 2019; A phase I randomized, observer-blind, controlled, dose escalation trial of the safety and tolerability of a single intramuscular dose of a pal adjuvant (laboratory code, FB-631) co-administered with seasonal tiv (2013-2014) to healthy adults ≥18-50 years of age; DOI: 10.1093/ofid/ofz360.2421
Lavalle 2013; Influenza vaccination was not associated with reduction of major cardiovascular events in patients with recent TIA and stroke; DOI: NA
Liao 2018; Effects of influenza vaccination on the admission outcomes of liver cancer: A nationwide matched study; DOI: 10.1159/000490877
Liu 2014; Idiopathic thrombocytopenic purpura after seasonal influenza vaccination; DOI: 10.1002/pds.3701
Lucero-Obusan 2017; Comparative effectiveness of high-dose vs. standard-dose influenza vaccines among veterans: 2015-2016 and 2016-2017 seasons; DOI: 10.1093/ofid/ofxl63.1162
Luo 2013; Comparison of the incidence of influenza like illness in pregnant women with rheumatoid arthritis and women without rheumatoid arthritis who receive an influenza vaccination; DOI: 10.1002/art.38216
Luo 2013; Incidence of influenza-like illness in pregnant women with autoimmune disease and women without autoimmune disease who do or do not receive an influenza vaccination; DOI: 10.1038/ajg.2013.268
Lytras 2017; Severe influenza; Greece 2016-2017: Vaccine failures in type A influenza and risk factors for poor outcome; DOI: 10.1093/ofid/ofx163.1525
Madhi 2014; Efficacy and immunogenicity of inactivated influenza vaccine in pregnant women: a randomized, double-blind, placebo controlled trial; DOI: 10.1016/j.ijid.2014.03.1308
Madhi 2014; Randomized, placebo-controlled trial on safety and efficacy of inactivated influenza vaccination of pregnant women in preventing illness in their infants; DOI: 10.1016/j.ijid.2014.03.480
Mannino 2010; Effectiveness of influenza vaccination with Fluad versus a sub-unit influenza vaccine; DOI: 10.1093/aje/kwq151
Manzoli 2009; Influenza vaccine effectiveness for the elderly: A cohort study involving General Practitioners from Abruzzo, Italy; DOI: NA
Maves 2019; Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED), influenza-like-illnesses (ILIS) sub-study at the marine corps recruit depot-San Diego, CA (MCRD-SD) during the 2018-2019 influenza season; DOI: 10.1093/ofid/ofz360.2433
McLean 2018; Randomized trial of high dose, adjuvanted, and standard inactivated influenza vaccine immune response against egg-and cell-propagated vaccine strains in older adults, 2016-2017 season; DOI: 10.1093/ofid/ofy210.828
McNeil 2016; Influenza vaccine effectiveness in the prevention of influenza-related hospitalization in Canadian adults over the 2011/12 through 2013/14 season: A pooled analysis from the serious outcomes surveillance (SOS) network of the Canadian influenza research network (CIRN); DOI: 10.1093/ofid/ofw194.75
Mixéu 2002; Impact of influenza vaccination on civilian aircrew illness and absenteeism; DOI: NA
Modin 2019; The flu vaccine and mortality in hypertension. a Danish nationwide cohort study; DOI: 10.1093/eurheartj/ehz748.0047
NA: Assessment of efficacy and safety of a trivalent split-virus influenza vaccine in patients with rheumatic diseases; DOI: 10.1136/annrheumdis-2018-eular.1500
Nakafero 2018; Inactivated influenza vaccine prevents respiratory infections and improves all-cause and cause-specific mortality in immunosuppressed people with autoimmune rheumatic diseases: Propensity score adjusted cohort study using data from clinical practice research datalink; DOI: 10.1002/art.40700
Nakafero 2019; Inactivated influenza vaccination does not associate with disease flares in autoimmune rheumatic diseases: A self-controlled case series study using data from the clinical practice research datalink; DOI: 10.1136/annrheumdis-2019-eular.1597
Natori 2016; A pilot randomized controlled trial of adjuvanted versus nonadjuvanted influenza vaccine in adult allogeneic hematopoietic stem cell transplant recipients; DOI: 10.1093/ofid/ofw172.1058
Natori 2017; A randomized trial of high-dose influenza vaccine in adult solid-organ transplant recipients; DOI: 10.1093/ofid/ofx180.000
Nicholls 2004; Outbreak of influenza A (H3N2) in a highly-vaccinated religious community: a retrospective cohort study; DOI: NA
Nichols 2018; 2016-2017 influenza burden of disease and end-of-season influenza vaccine effectiveness (VE) estimates for preventing influenza-related hospitalization among Canadian adults: An analysis from the Canadian immunization research network (CIRN) serious outcomes surveillance (SOS) network; DOI: 10.1093/ofid/ofy210.829
Palani 2017; Does seropositivity translate to protection against influenza? A prospective study among HCWs and patients with chronic respiratory diseases; DOI: NA
Paudel 2019; Relative vaccine efficacy of high-dose vs. standard dose influenza vaccines in preventing probable influenza in a US Medicare fee-for-service population; DOI: 10.1093/ofid/ofz360.2424

Details (Author Year; Title; DOI)
Petrie 2016; No evidence of influenza vaccine effectiveness against antigenically drifted influenza a (H3N2) viruses in a household cohort during the 2014-2015 influenza season; DOI: 10.1093/ofid/ofw172.662
Pitigoi 2012; Is seasonal influenza vaccine effective? Results of three Romanian I-move case-control studies, 2008-2012; DOI: NA
Polachek 2015; Immunogenicity and safety of vaccination against seasonal 2012 influenza virus among patients with psoriatic arthritis and psoriasis; DOI: NA
Puig-Barbera 2015; Influenza H3N2 antigenic drift in hospital admissions with influenza during the 2014-2015 season in the Valencia Hospital Network for the Study of Influenza and Respiratory Viruses Disease, Valencia (Spain); DOI: 10.1016/j.jcv.2015.07.150
Qudah 2012; Encephalitis after vaccination in United States. A report from the CDC/FDA vaccine adverse event reporting system. [1990-2010]; DOI: 10.1212/WNL.78.1
Rattigan 2019; Influence of pre-season antibody titers to influenza on influenza risk in a cohort of healthcare personnel; DOI: 10.1093/ofid/ofz360.483
Regan 2018; Birth outcomes associated with seasonal influenza vaccination during first trimester of pregnancy; DOI: 10.1111/jpc.13882_111
Rogers 2019; Prevalence of influenza-like illness in sheltered homeless populations: A cross-sectional study in Seattle, WA; DOI: 10.1093/ofid/ofz360.1996
Saade 2018; Comparative effectiveness of high-vs. standard-dose influenza vaccine on hospitalization for acute myocardial infarction in nursing-home residents: A post-hoc analysis from a large cluster-randomized trial; DOI: 10.1093/ofid/ofy210.1609
Sarker 2019; Comparison of antibody responses to vaccination with a pure hemagglutinin influenza vaccine (RHA) and licensed subvirion influenza vaccine made in eggs or cell culture in adults 60 years and older; DOI: 10.1093/ofid/ofz360.2415
Segaloff 2017; Influenza vaccination and treatment with antiviral agents among hospitalized adults in the 2014-2015 and 2015-2016 influenza seasons; DOI: 10.1093/ofid/ofx163.740
Seki 2016; Effectiveness of Influenza Vaccine in Adults Using A Test-negative, Case-control Design -2013/2014 and 2014/2015 Seasons; DOI: NA
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Exclusion reason- No relevant outcomes

Details (Author Year; Title; DOI)
Van Aalst 2020 Comparative effectiveness of high dose versus adjuvanted influenza vaccine: A retrospective cohort study 10.1016/j.vaccine.2019.09.105
Lapi 2019 Adjuvanted versus nonadjuvanted influenza vaccines and risk of hospitalizations for pneumonia and cerebro/cardiovascular events in the elderly; 10.1080/14760584.2019.1622418

**Denotes foreign language studies whose English abstracts were reviewed and, where accessible, the study texts (supported by online translation tools). Based on the combination of the English abstract and /or these unofficial translations, the studies were excluded for the provided reasons*

Appendix 4. Ongoing or completed studies

Title	Status	Study Identifier
Efficacy or effectiveness		
FLUAD vs. FLUZONE HD Influenza Vaccine in Residents of Long Term Care	Active, recruiting	NCT03694808
Study to Evaluate the Effectiveness of a High-Dose Quadrivalent Influenza Vaccine (QIV-HD) Compared to a Standard-Dose Quadrivalent Influenza Vaccine (QIV-SD) in Adults 65 Years of Age and Older	Active, recruiting	NCT04137887
Recombinant Influenza Vaccination in U.S. Nursing Homes	Active, recruiting	NCT03965195
Adjuvanted Influenza Vaccination in U.S. Nursing	Active, not recruiting	NCT02882100
Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults ≥ 65 Years of Age	Completed	NCT02587221
Flublok v. Standard Dose Vaccine Effectiveness Among Kaiser Permanente Northern California Adults 18-64 Years	Active, recruiting	NCT03694392
A Pivotal Trial to Assess the Safety and Clinical Efficacy of the M-001 as a Standalone Universal Flu Vaccine	Active, not recruiting	NCT03450915
Intradermal Influenza Vaccine With Topical Imiquimod in Elderly and Chronic Illness Patients	Active, recruiting	NCT04143451
Immunogenicity of Alternative Annual Influenza Vaccination Strategies in Older Adults in Hong Kong	Active, not recruiting	NCT03330132
Reducing the Burden of Influenza After Solid-Organ Transplantation	Active, recruiting	NCT03699839
Influenza Immunization in Adults Over Age 75	Active, recruiting	NCT02200276
Doyle JD, Beacham L, Martin ET, et al. Relative and absolute effectiveness of high-dose and standard-dose influenza vaccine against influenza-related hospitalization among older adults - United States, 2015-2017 [published online ahead of print, 2020 Feb 18. Clin Infect Dis. 2020;ciaa160. doi:10.1093/cid/ciaa160]	Completed	
Safety		
High vs. Standard Dose Flu Vaccine in Adult Stem Cell Transplant Recipients	Active, recruiting	NCT03179761
Vaccination Against Influenza to Prevent Cardiovascular Events After Acute Coronary Syndromes	Active, recruiting	NCT04001504
Study to Assess the Immune Response and the Safety Profile of a High-Dose Quadrivalent Influenza Vaccine (QIV-HD) Compared to a Standard-Dose Quadrivalent Influenza Vaccine (QIV-SD) in Europeans Adults 60 Years of Age and Older	Active, recruiting	NCT04024228
Safety, Tolerability and Immunogenicity of an Trivalent Inactivated Cell-Culture Influenza Vaccine in Healthy Adults	Completed	NCT03893669
Safety of RIV4 Versus IIV4 in Pregnant Women	Active, recruiting	NCT03969641
Recombinant Influenza Vaccine Containing Different H3 Antigens in Healthy Adults 18 to 30 Years of Age	Active, recruiting	NCT04144179
Flucelvax (TIVc or QIVc) Pregnancy Registry	Active, not recruiting	NCT03438487
FLUAD vs. Fluzone High-Dose Study	Completed	NCT03183908
Safety and Immunogenicity of Fluzone® Quadrivalent and Fluzone® High-Dose, Influenza Vaccines	Completed	NCT03617523

Appendix 5 Study characteristics for efficacy and effectiveness

Appendix 5.1 MF59® adjuvanted influenza vaccines

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Efficacy- randomised controlled trials							
No relevant studies identified.							
Effectiveness- case-control studies^							
Bella 2019 [34]	Italy Multicentre Hospitals	Adults (aged ≥ 65 years) N = 502 Cases: (n = 118, Mean age 76.3, 68 Males (57.6%) Controls: (n = 384), Mean age 77.8, 229 males (59.6%)	2017-2018	aIIV3 (Fluad)	Unvaccinated	SARI RT-PCR	Laboratory-confirmed influenza
Bellino 2019a [35]	Italy General Practice	Children and adults (aged ≥6 months) N = 2 526 Cases (n = 1 177) Controls (n = 1 349)	2018-2019	aIIV3 (Fluad)* IIV4 (Vaxigrip Tetra) IIV4 (Fluarix Tetra) IIV3 (Agrippal S1) IIV (Influpozzi Subunità)	Unvaccinated	ILI RT-PCR	Laboratory-confirmed influenza
Gasparini 2013 [68] **Matched case-control**	Italy	Older adults (aged >64 years) N = 374 Mean age = 78.1 (SD 8.2) Cases (n = 187): Mean age = 78.6 (SD 8.3), 104 Males (55.6%) Controls (n = 187): mean age = 77.7 (SD 8.0), 104 Males (55.6%)	2010–2011	aIIV3 (Inflexal V, Fluad)* Intanza	Unvaccinated	Discharge diagnosis of influenza or pneumonia (ICD-9 code) and GP record linkage Controls recruited by GPs	Hospitalisation for influenza or pneumonia
Gilca 2015 [70]	Canada Hospital	Adults (aged ≥65 years) N = 304 Median age 81.5 years (65–101) 30% were >85 years-old Cases (n = 186) Controls (n = 128)	2014-2015	aIIV3* IIV3	Unvaccinated	Respiratory symptoms RT-PCR	Laboratory-confirmed influenza
Kissling 2019 [85] **Includes data from Kissling 2017** [86]	Europe Multicentre Primary care	Children and adults (aged >0 years) 2016–17 (N= 11 007): Cases (n = 4 909), Controls (n = 6 098) 2017–18 (N=7 601): Cases (n = 1 714), Controls (n = 5 887)	2016-2017 2017-2018	aIIV3* LAIV IIV3	Unvaccinated	ILI RT-PCR	Laboratory-confirmed influenza
Mira-Iglesias 2019 [97]	Spain Hospital	Adults (aged ≥60 years) N = 1 477 Cases (n = 482): 234 Males (48.4%) Controls (n = 994): 526 Males (52.9%)	2017-2018	aIIV3	IIV3 Unvaccinated	ILI RT-PCR	Laboratory-confirmed influenza
Pebody 2020a [104]	England General practice and Hospitals	Adults (aged ≥65 years) N = 1 439 Cases (n = 428) Controls (n = 1 013)	2018-2019	aIIV3	aIIV3 and aIIV4 Unvaccinated	RT-PCR	Laboratory-confirmed influenza hospitalisation

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Pebody 2020b [105]	United Kingdom General practice	Children and adults (aged >0 years) N = 2 326 Cases (n = 773) Controls (n = 1 553)	2018-2019	aIIV3* IIV3 IIV4 LAIV	Unvaccinated	ILI RT-PCR	Laboratory-confirmed influenza
Puig-Berbera 2004 [108] **Matched case-control**	Spain Hospital	Adults (aged >64 years) N = 815 Cases (n = 290) Controls (n = 525)	2002-2003	Adjuvanted influenza vaccines (94.7%)	Non-adjuvanted influenza vaccines (3.8%) Unvaccinated	Population vaccine registry and ICD-9 code linkage	Pneumonia related hospitalisation
Puig-Berbera 2007 [109] **Matched case-control**	Spain Hospital	Adults (aged > 64 years) N = 1 301 Cases (n = 476) Controls (n = 825)	2004-2005	aIIV3 (Fluad)	Unvaccinated	Population vaccine registry and ICD-9 code linkage	Hospitalisation secondary to: Acute coronary syndrome Cerebrovascular accident Pneumonia
Rondy 2017a [113] **Includes data from Kissling 2017** [86]	Europe Multicentre Hospital	Adults (aged ≥65 years) Community- dwelling N = ,640 Cases (n = 1 099): Only A(H3N2) assessed (n = 1 073), Median age 81 (65–102), 516 males Controls (n = 1 541): Median age 80 (65–102)	2016-2017	aIIV3* Inactivated split virion influenza vaccine Inactivated subunit influenza vaccine	Unvaccinated	SARI RT-PCR	Laboratory-confirmed influenza
Rondy 2017b [114]	Europe Multicentre Hospitals	Adults (aged ≥65 years) Community- dwelling N = 1 802 Cases (n = 1,274): A(H1N1)pdm09 (n = 335), Median age 76 (65–95), 194 males Influenza B (n = 110), Median age 76 (65–94), 57 males Controls (n = 528): A(H1N1)pdm09 (n = 976), Median age 78 (65–101), 512 males Influenza B (n = 1 015) Median age 78 (65–101), 520 males	2015-2016	aIIV3* Inactivated split virion influenza vaccine Inactivated subunit influenza vaccine	Unvaccinated	SARI RT-PCR	Laboratory- confirmed influenza
Spadea 2014 [123] **Matched case-control**	Italy Hospitals	Adults (aged ≥65 years) N = 3 108 2010-2011: Cases (n = 269), Controls (n = 1 247) 2011-2012: Cases (n = 365), Controls (n = 1 227)	2010-2011 2011-2012	aIIV3	IIV3 Unvaccinated	Cases were hospitalised subjects for influenza or pneumonia with appropriate ICD-9 codes. Controls were hospitalised individuals not related to influenza or pneumonia.	Hospitalisation for influenza or pneumonia
Valenciano 2016 [132] **Includes data from Rizzo 2016**[112]	Europe Multicentre	Children and adults (aged >0 years) N = 6 579 Cases (n = 3 405): AH1N1pdm09 (n = 539) Median age 30.0, 301 males; AH3N2 (n = 1 828) Median age 28.0, 883 males; B (n = 1,038) Median age 39.0, 482 males Controls (n = 3,142): Median age 31.0, 1 532 males	2014-2015	aIIV3* Cell-derived inactivated subunit influenza vaccine Egg-derived inactivated split virion influenza vaccine Egg-derived inactivated subunit influenza vaccine	Unvaccinated	ILI RT-PCR	Laboratory-confirmed influenza
Van Buynder 2013 [133]	Canada Multicentre Community	Adults (aged ≥65 years) N = 282 Mean age 83.0 years (SE 0.51), 186 Females (66%), 160 residents of long term care facilities (57%) Cases (n = 84) Controls (n = 198)	2011-2012	aIIV3 (Fluad)	IIV3 (Fluviral) Unvaccinated	ILI Fourplex PCR	Laboratory-confirmed influenza

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Effectiveness- cohort studies							
Bellino 2019b [36]	Treviso, Italy General Practice	Adults (aged ≥65 years) 2014: N = 83 265 2015: N = 84 375 2016: N = 85 800	2014-2015 2016-2017	aIIV3 2014: n = 41 614, 18,349 males (44.1%) 2015: n= 41 857, 18,620 males (44.5%%) 2016: n = 44 250, 19 957 males (45.1%)	Unvaccinated 2014: n = 41 651, 17 905 males (43.0%) 2015: n = 42 518, 18,279 males (43.0%) 2016: n = 41 550, 17 804 males (42.8%)	Health administrative databases	Influenza-associated hospitalisation
Iob 2005 [76]	Italy Long term care facilities	Older adults (3.65% under 65 years of age) N = 3 173 Mean age 85 years (SD 10), 645 males	1998-1999	aIIV3 (n = 1 487):	IIV3 (n = 1 478): Unvaccinated (n = 208)	Physician assessment	Influenza like illness
Izurieta 2019 [78]	United States Community	Medicare beneficiaries (aged ≥65 years) N = 13 504 092	2017-18	ccIIV4 (n = 659 249): 49.6% 65-74 years, 34.3% 75-84 years, 16.1% ≥85 years HD-IIV3 (n = 8 489,159): 51.1% 65-74 years, 34.6% 75-84 years, 14.4% ≥85 years aIIV3 (n = 1 473 536): 50.6% 65-74 years, 34.1% 75-84 years, 15.2% ≥85 years	IIV3 (n = 1 018,494): 48.4% 65-74 years, 34.4% 75-84 years, 17.2% ≥85 years IIV4 (n = 1 863 654): 52% 65-74 years, 33% 75-84 years, 15% ≥85 years	Medicare database linkage and ICD-10 codes	Influenza- related hospitalisations or ED visits
Mannino 2012 [94]	Lombardo region, Italy Community	Adults (aged ≥65 years) N = 164 254	2006-2007 2007-2008 2008-2009	aIIV3 (Fluad) n = 84 665: 43.2% male	IIV3 (Agrippal) n = 79 589: 43.2% male	Record linkage with administrative databases (ICD-9 codes)	Influenza- or pneumonia-associated hospitalisation
Puig Barbera 2013 [110]	Spain Community	Adults (aged ≥65 years) N = 373 798	2010-2011	aIIV3 (n = 197 180): 22% 65–69 years, 24% 70–74 years, 24% 75–79 years, 19% 80–84 years, 13% ≥85 years 86 741 males (44%)	IIV3 (Inflexal-V) n = 176 618: 22% 65–69 years, 24% 70–74 years, 24% 75–79 years, 17% 80–84 years, 12% ≥85 years 79 887 males (45%)	Linkage Vaccine health care Information System and ICD-9 codes	Influenza-associated hospitalisation

*^Test-negative case-control design unless otherwise stated; *Denotes only data for specific vaccine available for inclusion in this review*

Key: *aIIV3 – adjuvanted trivalent inactivated influenza vaccine; HD-IIV3– high-dose trivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; ILI – influenza-like illness; LAIV – live attenuated influenza vaccine; RT PCR - real time polymerase chain reaction; SARI – Severe acute respiratory infections*

Appendix 5.2 High-dose influenza vaccines

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Efficacy- randomised controlled trials							
DiazGranados 2014b [53] **Additional results from DiazGranados 2014a** [52] **and DiazGranados 2015a** [55]	United States and Canada Multicentre	Adults (aged ≥65 years) without moderate or severe acute illnesses N = 31 989	2011-2012 Northern hemisphere 2012-2013 Northern hemisphere	HD-IIV3 (n = 15 990): Mean age 73.3 (SD 5.8), 6 780 males (42.4%)	SD-IIV3 (n = 15 993) Mean age 73.3(SD 5.8), 7 030 males (43.9%)	Nasopharyngeal swab Culture confirmed swab and/or Positive PCR	Laboratory-confirmed ILI Culture-confirmed ILI Respiratory illness All-cause hospitalisation Serious cardio-respiratory events Pneumonia events
Gravenstein 2017 [71]	United States	Adults (aged ≥65 years) who were long-stay residents of nursing homes N = 52 738 HD group (N = 26 369) SD group (N = 26 369)	2013–2014 Northern hemisphere	HD-IIV3 (N = 26 369) Mean age 83.6 (SD 8.8), 19 262 females (72%)	SD-IIV3 (N = 26 369) Mean age 83.6 (SD 8.9), 19 016 females (72%)	Medicare claims based on ICD-9 codes	Hospital admissions related to pulmonary and influenza-like conditions All-cause hospital admissions All-cause mortality
Effectiveness- case control studies							
Zimmerman 2016 [139]	United States Multicentre	Children and Adults (aged >6 months) N = 9 311 Cases (n = 2 233) Controls (n = 7 078)	2014-2015	HD-IIV3 SD-IIV3 SD-IIV4 LAIV	Unvaccinated	ARI RT-PCR	Laboratory-confirmed influenza
Effectiveness- cohort studies							
Butler 2019 [41]	United States	Adults (aged ≥65 years) undergoing in-center maintenance hemodialysis N = 225 215	2010-11 2011-12 2012-13 2013-14 2014-2015	HD-IIV3 (n = 5 776): Mean age 75.8 (SD 6.9), 3 064 males (53.0%)	SD-IIV3 (n = 219 439): Mean age 74.6 (SD 7.0) 111 827 males	Claims-based influenza definitions from the USRDS	Influenza- or pneumonia-associated hospitalisation ILI
Izurieta 2015 [79]	United States Community	Medicare beneficiaries (aged ≥65 years) N = 2 545 275	2012-2013	HD-IIV3 (Fluzone High-Dose) n = 929 730: Mean age 75.74 (SD 7.19), 391 350 males (42.1%)	Standard dose influenza vaccine (n = 1 615 545): Mean age 75.35 (SD 7.27), 656 473 males (40.63%)	Medicare database linkage and ICD-9 codes	ILI Influenza associated hospitalization or ED visit
Izurieta 2019 [78]	United States Community	Medicare beneficiaries (aged ≥65 years) N = 13 504 092	2017-18	ccIIV4 (n = 659 249); 49.6% 65-74 years, 34.3% 75-84 years, 16.1% ≥85 years HD-IIV3 (n = 8 489 159): 51.1% 65-74 years, 34.6% 75-84 years, 14.4% ≥85 years aIIV3 (n = 1 473 536): 50.6% 65-74 years, 34.1% 75-84 years, 15.2% ≥85 years	SD-IIV3 (n = 1 018 494): 48.4% 65-74 years, 34.4% 75-84 years, 17.2% ≥85 years SD-IIV4 (n = 1,863,654): 52% 65-74 years, 33% 75-84 years, 15% ≥85 years	Medicare database linkage and ICD-10 codes	Influenza- related hospitalizations or ED visits
Lu 2019 [92]	United States	Adults (aged ≥65 years) N = 19 922,180	2012-2013 2013-2014 2014-2015 2015-2016 2016-2017 2017-2018	HD-IIV3 (Fluzone high dose) n = 13 770 207: 50.3% 65–74 years, 35.90% 75–84 years, 13.8% ≥85 years, 5 745 684 males (41.7%)	SD-IIV3 (n = 6 151 913): 52.7% 65–74 years, 34.0% 75–84 years 13.30% ≥85 years n = 817 571, 2 480 066 males (40.30%)	Medicare claims database and ICD-9 codes	Influenza-related hospital encounters, (defined by inpatient stays or emergency department)

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Richardson 2015 [111]	United Statues Primary care	Adults (aged ≥65 years) N = 165 225	2010-2011	HD-IIV3 (Fluzone High-dose) n = 25 714: Mean age 75.5 (SD 7.45), 25 316 males (98.5%)	SD-IIV3 (Fluzone) n = 139 511: 13 ,945 males (98.2%), Mean age 75.0 (SD 7.43)	Linkage administrative databases and ICD- 9 codes	Influenza- or pneumonia-associated hospitalisation
Shay 2017 [120]	Spain Community located pharmacies Medicare administrative files	Adults (aged ≥65 years) Medicare beneficiaries	2012-2013 2013-2014	HD-IIV3: 2012-2013 (n = 1 039 645) 2013-2014 (n = 1 508 176)	SD-IIV3: 2012-2013 (n = 1 683 264) 2013-2014 (n = 1 877 327)	Medicare administrative databases and ICD- 9 code	Post influenza mortality Influenza-associated hospitalisation or ED visit
Young-Xu 2018 [137]	United States Veterans Health	Adults (aged ≥65 years) Presented as groups before and after matching. Results after matching taken. N = 73 773	2015-2016	HD-IIV3 (Fluzone High-dose) n = 24 682: 55% 65–74 years, 25% 75–84 years, 19% ≥85 years, 24 219 males (98%)	SD-IIV3 (n = 49 091): 66% 65–74 years, 23% 75–84 years, 10% ≥85 years, 47 984 males (97%)	Veterans Health Administration electronic medical record and ICD codes	Influenza- or pneumonia associated hospitalisation Influenza- or pneumonia related primary care physician, urgent care or ED visits
Young-Xu 2019 [138]	United States Medical centres and community-based outpatient clinics	Veterans Health Adults (aged ≥65 years N = 1 728 562 1 702 824 males (98.5%) HD-TIV recipients tended to have a higher prevalence of comorbidities.	2010-2011 2011-2012 2012-2013 2013-2014 2014-2015	HD-IIV3 (Fluzone High-Dose) n = 158 636: 34% 65–69 years, 18% 70–74 years, 17% 75–79 years, 16% 80–84 years, 14% ≥85 years	SD-IIV3 (n = 3 480 288): 32% 65–69 years, 19% 70–74 years, 18% 75–79 years, 16% 80–84 years 14% ≥85 years	VHA electronic medical records and ICD-9 codes	Influenza- or pneumonia-associated hospitalisations

Key: *aIIV3– adjuvanted trivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; ILI – influenza-like illness; LAIV – live attenuated influenza vaccine; RT PCR - real time polymerase chain reaction; SARI – Severe acute respiratory infections; SD-IIV3 – Standard dose trivalent inactivated influenza vaccine*

Appendix 5.3 Cell-based influenza vaccines

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Efficacy- randomised controlled trials							
Barrett 2011 [31]	Austria Multicentre	Healthy adults (aged 18-48 years) N = 7 520	2008-2009 Northern hemisphere	ccIIV3 (n = 3 623): Median age 31 years (range 18-49) 1 823 Males (50%)	Phosphate buffered saline (n = 3,620): Median age 30 years (range 18-49) 1 865 Males (42%)	Nasopharyngeal swabs Traditional culture methods and RT-PCR analyses	Culture-confirmed influenza infection antigenically matched to vaccine strains Culture-confirmed or RT-PCR influenza infection irrespective of match to vaccine strains by strain
Frey 2010 [65]	United States, Poland and France Multicentre	Healthy adults (aged 18-49 years) N = 11 404 Across groups: Mean age 32.7–33.0 years, 44%–45% were male	2007–2008 Northern Hemisphere	ccIIV3 (n = 3 828)	IIV3 (n = 3 676) Phosphate buffered saline (n = 3 900)	Nasal and throat specimens Cell culture and positive PCR	ILI Laboratory-confirmed Influenza
Effectiveness- case control studies							
Bruxvoort 2019 [40]	United States Hospitals utilising a certain electronic record system	Children and Adults (aged ≥4 years) N = 8 132 Individuals<65 years (n = 3 143) Adults≥ 65 years (n = 4 989)	2017-2018	ccIIV3 ccIIV4	IIV3 IIV4 Unvaccinated	Multiplex PCR	Laboratory-confirmed influenza hospitalisation
Castilla 2016 [42]	Navarra, Spain Primary healthcare centres and hospitals	Children and Adults (aged ≥6 months) N=1 213 Cases (n = 619) Controls (n= 594)	2014-2015	Cell-based influenza subunit vaccine (Optaflu)* Egg-grown influenza subunit vaccine (Chiroflu), only in those <18 years	Unvaccinated	ILI RT-PCR	Laboratory-confirmed influenza
DeMarcus 2019 [51]	United States Military treatment facility	Department of Defense healthcare beneficiaries (Children and Adults aged ≥6 months) N = 4 037 Cases (n = 1 757) Controls (n = 2 280)	2017-2018	ccIIV4 (Flucelvax)* IIV4 (FluLaval and Fluarix)	Unvaccinated	ILI RT-PCR or Viral culture	Laboratory- confirmed influenza
Effectiveness- cohort studies							
Izurieta 2019 [78]	United States Community N = 13 504 092	Medicare beneficiaries (aged ≥65 years)	2017-18	ccIIV4 (n = 659 249); 49.6% 65-74 years, 34.3% 75-84 years, 16.1% ≥85 years HD-IIV3 (n = 8 489 159): 51.1% 65-74 years, 34.6% 75-84 years, 14.4% ≥85 years aIIV3 (n = 1 473 536): 50.6% 65-74 years, 34.1% 75-84 years, 15.2% ≥85 years	IIV3 (n = 1 018 494): 48.4% 65-74 years, 34.4% 75-84 years, 17.2% ≥85 years IIV4 (n = 1 863 654): 52% 65-74 years, 33% 75-84 years, 15% ≥85 years	Medicare database linkage and ICD-10 codes	Influenza- related hospitalisations or ED visits

Key: *aIIV3 – adjuvanted trivalent inactivated influenza vaccine; ccIIV3- cell-based trivalent inactivated influenza vaccine; ccIIV4- cell-based quadrivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; ILI – influenza-like illness; LAIV – live attenuated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; RT PCR - real time polymerase chain reaction; IIV3 – trivalent inactivated influenza vaccine*

Appendix 5.4 Recombinant HA influenza vaccines

Author Year	Country Setting	Population Study size	Influenza season	Intervention vaccine	Comparator (s)	Diagnostic or confirmatory method	Clinical outcomes
Efficacy- randomised controlled trials							
Dunkle 2017a [57]	United States Multicentre Outpatients	Adults (aged ≥ 50 years) living independently without clinically significant acute illness N = 9 003	2014-2015 Northern Hemisphere	RIV4 (n = 4 328): Mean age 63 years (range 50-96), 1796 males (41.5%)	IIV4 (n = 4 344) Mean age 63 years (range 50-94), 1 807 males (41.6%)	Nasopharyngeal swabs Virus cultures and positive RT-PCR	Protocol-defined ILI Culture-confirmed influenza-like illness PCR-confirmed ILI
Treanor 2011 [127]	United States Multicentre	Healthy adults (aged 18-55 years) N = 4 648 Across groups: Mean age 32.5 years, 41% male	2007-2008	RIV3 (n = 2 344)	Saline (n = 2 304)	Subjects completed a weekly diary to record influenza symptoms. Returned to the clinic if they observed any acute respiratory symptoms or fever. Combined nasal and throat swabs for virus culture	CDC-defined ILI Laboratory-confirmed influenza
Effectiveness- Case Control Studies							
No relevant studies identified.							
Effectiveness- Cohort studies							
No relevant studies identified.							

Key: *ILI – influenza-like illness; IIV4 – quadrivalent inactivated influenza vaccine; PCR - polymerase chain reaction; RIV3- Recombinant HA trivalent inactivated influenza vaccines; RIV4- Recombinant HA quadrivalent inactivated influenza vaccine*

Appendix 6. Vaccine and circulating strain characteristics

Appendix 6.1 MF59® adjuvanted influenza vaccines

Author (Year)	Intervention Vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Efficacy- randomised controlled trials			
No relevant studies identified.			
Effectiveness- case control studies			
Bella 2019 [34]	aIIV3 (Fluad)* A/Michigan/45/2015, Victoria Lineage	Unvaccinated	**2017-2018** Co-dominated by the B (60%) and the A viruses (40%). 94% of subtyped A viruses belonged to the A/H1N1pdm09 strain, mostly characterised by the genetic subgroup 6B.1. 99% of B viruses belonged to the Yamagata Lineage.
Bellino 2019a [35]	aIIV3 (Fluad) A/Singapore/INFIMH-16-0019/2016, 3C.2a1 subclade. A/Michigan/45/2015	IIV4 (Vaxigrip Tetra) IIV4 (Fluarix Tetra) IIV3 (Agrippal S1) IIV3 (Influpozzi Subunit) A/Singapore/INFIMH-16-0019/2016, 3C.2a1 subclade. A/Michigan/45/2015 Unvaccinated	**2018-2019** Dominated by type A viruses (99.9%). Co-circulation of influenza A(H1N1)pdm09 (50.1%) and A(H3N2) viruses (49.9%). 6% A(H1N1)pdm09 viruses clustered within the 6B.1A subclade. 70.6% of A(H3N2) viruses Clustered within subclade 3C.2a1b, 5.4% in subclade 3C.2a2, 24.0% in clade 3C.3a.
Gaspirini 2013 [68]	aIIV3 (Inflexal V and Fluad) Strains not reported	IIV3 (Intanza) Strains not reported Unvaccinated	**2010-2011** A/California/07/09pdm (67%), followed by B virus (B/ Brisbane/60/2008) (23.5%) and A/H3N2 (A/Perth/16/2009) (9.3%)
Gilca 2015 [70]	aIIV3 Retention of the same three influenza vaccine antigens as were also used in 2013/14, including the A/Texas/50/2012 (H3N2)-like strain	IIV3 Retention of the same three influenza vaccine antigens as were also used in 2013/14, including the A/Texas/50/2012 (H3N2)-like strain	**2014-2015** Dominant A(H3N2) season
Kissling 2019 [85] Includes data from Kissling 2017 [86]	aIIV3 **2016-2017** A/Hong Kong/4801/2014 (H3N2)-like virus A/California/7/2009 (H1N1)pdm09-like virus **2017-2018** A/Hong Kong/4801/2014 (H3N2)-like virus A/Michigan/45/2015 (H1N1)pdm09-like virus	LAIV IIV3 **2016-2017** A/Hong Kong/4801/2014 (H3N2)-like virus A/California/7/2009 (H1N1)pdm09-like virus **2017-2018** A/Hong Kong/4801/2014 (H3N2)-like virus A/Michigan/45/2015 (H1N1)pdm09-like virus Unvaccinated	**2016-2017** Influenza A(H3N2) predominated with very little A(H1N1) pdm09 and B circulating. Influenza A(H3N2): 24% A/HongKong/4801/2014 (3C.2a clade), 74% A/Bolzano/7/2016-like (3C.2a1 clade), 1% A/Switzerland/ 9715293/2013 (3C.3a clade). **2017-2018** Influenza B/Yamagata was the main circulating strain. Both A (H1N1) pdm09 and A(H3N2) circulated. Influenza A(H3N2): 55% 74A/HongKong/4801/2014-like (3C.2a clade), 43% A/Singapore/INFIMH-16-0019/2016-like (3C.2a1 clade) and 2% A/Switzerland/9715293/2013-like (3C.3a clade). Influenza A(H1N1)pdm09: 100% A/Michigan/45/2015 (clade 6B.1)
Mira-Iglesias 2019 [97]	aIIV3 A/Michigan/45/2015(H1N1)-like A/HongKong/4801/2014(H3N2)-like B/ Brisbane/60/2008(Victoria-lineage)-like	IIV3 A/Michigan/45/2015(H1N1)-like A/HongKong/4801/2014(H3N2)-like B/ Brisbane/60/2008(Victoria-lineage)-like Unvaccinated	**2017-2018** Co-circulation of influenza A(H1N1) pdm09, A(H3N2) and B/Yamagata lineage. A(H1N1)pdm09 = 16.8%, A(H3N2) = 48.0%, B/Yamagata = 31.1%, B/Victoria = 0.2%, Not subtyped = 3.9%.
Pebody 2020a [104]	aIIV3 Strains not reported	IIV4 IIV3 Strains not reported	**2018-2019** A(H1N1)pdm09 and A (H3N2) co-circulated

Author (Year)	Intervention Vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Pebody 2020b [105]	aIIV3 A(H3N2) vaccine strain (subclade 3C.2a1) B/Victoria-lineage quadrivalent and trivalent vaccine component virus (B/Colorado/06/2017-like virus)	IIV3 IIV4 LAIV A(H3N2) vaccine strain (subclade 3C.2a1) B/Victoria-lineage quadrivalent and trivalent vaccine component virus (B/Colorado/06/2017-like virus)	**2018-2019** Influenza A(H1N1)pdm09 followed by influenza A(H3N2), with very little influenza B observed. Influenza A(H3N2): 99% subclade 3C.2a Influenza B: clade 1A of the B/Victoria lineage
Puig-Berbera 2004 [108]	Adjuvanted influenza vaccine (94.7%) Strains not reported	Non-adjuvanted influenza vaccine (3.8%) Unvaccinated Strains not reported	**2002-2003** Non-applicable
Puig-Berbera 2007 [109]	aIIV3 (Fluad) Strains not reported	Unvaccinated	**2004-2005** Non-applicable
Rondy 2017a [113] Includes data from Kissling 2017 [86]	aIIV3 The A(H3N2) vaccine component was A/Hong Kong/2014 (3c.2a).	Inactivated split virion influenza vaccine Inactivated subunit influenza vaccine The A(H3N2) vaccine component was A/Hong Kong/2014 (3c.2a) Unvaccinated	**2016-2017** A(H3N2) viruses predominated
Rondy 2017b [114]	aIIV3 A/California/7/2009 (H1N1)pdm09-like virus A/Switzerland/9715293/2013 (H3N2)-like virus B/Phuket/3073/2013-like virus (Yamagata lineage)	Inactivated split virion influenza vaccine Inactivated subunit influenza vaccine A/California/7/2009 (H1N1)pdm09-like virus A/Switzerland/9715293/2013 (H3N2)-like virus B/Phuket/3073/2013-like virus (Yamagata lineage) Unvaccinated	**2015-2016** A(H1N1)pdm09 and influenza B (mainly Victoria lineage) viruses predominated
Spadea 2014 [123]	aIIV3 Strains not reported	IIV3 Strains not reported Unvaccinated	**2010-2011** A/H1N1, Influenza B, A/H3N2 2011-2012 A/Perth/16/2009, A/Victoria/361/2011, B/Victoria/2/87 and B/Yamagata/16/88
Valenciano 2016 [132] Includes data from Rizzo 2016 [112]	Cell-derived Inactivated subunit influenza vaccine Adjuvanted influenza vaccine A/California/7/2009 (H1N1)pdm09-like virus A/Texas/50/2012 (H3N2)-like virus B/Massachusetts/2/2012-like virus	Egg-derived Inactivated split virion influenza vaccine Egg-derived Inactivated subunit influenza vaccine A/California/7/2009 (H1N1)pdm09-like virus A/Texas/50/2012 (H3N2)-like virus B/Massachusetts/2/2012-like virus Unvaccinated	**2014-2015** Predominance of A(H3N2) but with influenza A(H1N1) pdm09 and B also circulating
Van Buynder 2013 [133]	aIIV3 (Fluad) A/California/7/2009 (H1N1)-like virus A/Perth/16/2009 (H3N2)-like virus B/Brisbane/60/2008-like virus.	IIV3 (Fluviral) A/California/7/2009 (H1N1)-like virus A/Perth/16/2009 (H3N2)-like virus B/Brisbane/60/2008-like virus. Unvaccinated	**2011-2012** Not reported
Effectiveness- Cohort Studies			
Bellino 2019b [36]	aIIV3 A/California/7/2009 (H1N1), A/Texas/50/2012 (H3N2) B/Massachusetts/2/2012 (Yamagata lineage). **2015-2016** A/California/7/2009 (H1N1),A/Switzerland/9715293/2013 (H3N2), B/Phuket/3073/2013 (Yamagata lineage) **2016-2017** A/California/7/2009 (H1N1), A/Hong Kong/4801/2014 (H3N2), B/Brisbane/60/2008 (Victoria lineage)	Unvaccinated	**2014-2015** 2014-2015: A 92% (H1N1 55%, H3N2 30%), B 8% (not subtyped) 2015-2016: A 82% (H1N1 8%, H3N2 75%), B 18% (Victoria 74%), 2016-2017: A 93% (H3N2 90%), B 7% (Yamagata 88%)

Author (Year)	Intervention Vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Izurieta 2019 [78]	ccIIV4 HD-IIV3 aIIV3 IIV3: A(H1N1), A(H3N2), and a single type B (B/Victoria) lineage strain. IIV4: A(H1N1), A(H3N2), and 2 type B lineage strains.	IIV4 IIV3 IIV3: A(H1N1), A(H3N2), and a single type B (B/Victoria) lineage strain. IIV4: A(H1N1), A(H3N2), and 2 type B lineage strains.	**2017-2018** Not reported
Mannino 2012 [94]	aIIV3 (Fluad) Both vaccines contained the recommended virus strains for the respective influenza season in the Northern Hemisphere.	IIV3 Both vaccines contained the recommended virus strains for the respective influenza season in the Northern Hemisphere.	**2006-2007, 2007-2008, 2008-2009** Seasons 2006-2007 and 2008-2009 were mainly A/H3N2 epidemics. Season 2007-2008 showed mainly circulation of A/H1N1 and B viruses.
Puig Barbera 2013 [110]	aIIV3 A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like and B/Brisbane/60/2008/like,	IIV3 (Inflexal-V) A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like and B/Brisbane/60/2008/like,	**2010-2011** Predominant circulating influenza strains, A(H1N1)pdm09 and B

Denotes only data for specific vaccine available for inclusion in this review
***Key:** aIIV3 – adjuvanted trivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; LAIV – live attenuated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; SD-IIV3 – Standard-dose trivalent inactivated influenza vaccine*

Appendix 6.2 High-dose influenza vaccines

Author (Year)	Intervention vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Efficacy- randomised controlled trials			
DiazGranados 2014b [53] Additional results from DiazGranados 2014a [52] **and DiazGranados 2015a** [56]	HD-IIV3 Dose: 0.5ml 60 µg hemagglutinin 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)	SD-IIV3 Dose: 0.5ml 15 µg of hemagglutinin per strain 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)	**2011-2012** Northern Hemisphere **2012-2013** Northern Hemisphere A/H1N1, A/H3N2 and B.
Gravenstein 2017 [71]	HD-IIV3 Strains not reported	SD-IIV3 Strains not reported	**2013-2014** A(H1N1)pdm09 strain was the dominant circulating virus
Effectiveness- case control studies			
Zimmerman 2016 [139]	HD-IIV3 SD-IIV3 SD-IIV4 LAIV A/California/7/2009(H1N1), A/Texas/50/2012(H3N2) (A/Victoria/361/2011-like) B/Massachusetts/2/2012 (B/Yamagata lineage)	SD-IIV3 SD-IIV4 LAIV A/California/7/2009(H1N1), A/Texas/50/2012(H3N2) (A/Victoria/361/2011-like) B/Massachusetts/2/2012 (B/Yamagata lineage) Quadrivalent addition: B/Brisbane/60/2008 (B/Victoria lineage) Unvaccinated	**2014-2015** Influenza A/H3N2 was the dominant virus, causing disease in November 2014 through February 2015, but B/Yamagata became the dominant virus in March 2015.
Effectiveness- cohort studies			
Butler 2019 [41]	HD-IIV3 60 µg HA Strains not reported	SD-IIV3 15 µg HA Strains not reported	**2010-2011, 2011-2012, 2012-2013, 2013-2014, 2014-2015** A(H3N2) viruses were the predominant strain for all influenza seasons with the exception of 2013-2014 (H1N1).
Izurieta 2015 [79]	HD-IIV3 (Fluzone High-Dose) 60 µg HA Strains not reported	SD-IIV3 15 µg HA Strains not reported	**2012-2013** Not reported
Izurieta 2019 [78]	Cell-Cultured IIV4 HD-IIV3 aIIV3 IIV3: A(H1N1), A(H3N2), and a single type B (B/Victoria) lineage strain. IIV4: A(H1N1), A(H3N2), and 2 type B lineage strains.	IIV4 SD-IIV3 IIV3: A(H1N1), A(H3N2), and a single type B (B/Victoria) lineage strain. IIV4: A(H1N1), A(H3N2), and 2 type B lineage strains.	**2017-2018** Not reported
Lu 2019 [92]	HD-IIV3 (Fluzone High- Dose) Strains not reported	SD-IIV3 Strains not reported	2012-2013, 2013-2014, 2014-2015, 2015-2016, 2016-2017, 2017-2018 Influenza A(H3N2) dominated in 4 seasons. Influenza A(H3N2) and influenza A(H1N1)–dominated in the other seasons.
Richardson 2015 [111]	HD-IIV3 (Fluzone High-dose) 60 µg HA Strains not reported	SD-IIV3 (Fluzone) 15 µg HA Strains not reported	Not reported

Author (Year)	Intervention vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Shay 2017 [120]	HD-IIV3 **2012-2013** A/California/7/2009(H1N1)pdm09-like virus, A/Victoria/361/2011(H3N2)-like virus, and B/Wisconsin/1/2010-like virus **2013-2014** A/California/7/2009(H1N1)pdm09-like virus, A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011(A/Texas/50/2012) and a B/Massachusetts/2/2012-like virus	SD-IIV3 **2012-2013** A/California/7/2009(H1N1)pdm09-like virus, A/Victoria/361/2011(H3N2)-like virus, and B/Wisconsin/1/2010-like virus **2013-2014** A/California/7/2009(H1N1)pdm09-like virus, A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011(A/Texas/50/2012) and a B/Massachusetts/2/2012-like virus	**2012-2013** **2013-2014** Influenza B viruses circulated in both seasons, representing 20%–30% of influenza detections. H1N1 H3N2
Young-Xu 2018 [137]	HD-IIV3 (Fluzone High-Dose) 60 µg HA Strains not reported	SD-IIV3 15 µg HA Strains not reported	**2015-2016** Not reported
Young-Xu 2019 [138]	HD-IIV3 (Fluzone High-Dose) 60 µg per strain Strains not reported	SD–IIV3 15 µg per strain Strains not reported	**2010-2011, 2011-2012, 2012-2013, 2013-2014, 2014-2015** Not reported

Key: *aIIV3 – adjuvanted trivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; LAIV – live attenuated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; SD-IIV3 – Standard dose trivalent inactivated influenza vaccine*

Appendix 6.3 Cell-based influenza vaccines

Author (Year)	Intervention vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Efficacy-randomised controlled trials			
Barrett 2011 [31]	ccIIV3 Dose: 0.5ml 15µg hemagglutinin A-H1N1: A/Brisbane/59/2007 A-H3N2: A/Uruguay/716/2007 (A/Brisbane/10/2007-like) B: B/Florida/4/2006	Phosphate buffered saline Dose: 0.5ml	**2008-2009** Northern Hemisphere 63 (86%) of the specimens identified as A/H1N1, six (8%) as A/H3N2, and four (5%) as B.
Frey 2010 [65]	ccIIV3 Dose: 0.5ml 15mg of hemagglutinin A/Solomon Islands/3/2006 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, B/Malaysia/2506/2004-like	*IIV3* Dose: 0.5ml 15mg of hemagglutinin A/Solomon Islands/3/2006 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, B/Malaysia/2506/2004-like *Phosphate buffered saline* Dose: 0.5ml	**2007–2008** Northern Hemisphere A/H1N1, A/H3N2 and B.
Effectiveness- case control studies			
Bruxvoort 2019 [40]	ccIIV3 ccIIV4 Strains not reported	IIV3 IIV4 Strains not reported Unvaccinated	**2017-2018** Influenza A(H3N2)-predominant season. Other Influenza A and Influenza B also circulating.
Castilla 2016 [42]	Cell-based influenza subunit vaccine (Optaflu) A/California/7/2009(H1N1)pdm09-like A/Texas/50/2012(H3N2)-like B/Massachusetts/2/2011-like	Egg-grown influenza subunit vaccine (Chiroflu), only in those <18 years A/California/7/2009(H1N1)pdm09-like A/Texas/50/2012(H3N2)-like B/Massachusetts/2/2011-like Unvaccinated	**2014-2015** 81 influenza A(H3N2) viruses characterised were 13A/Samara/73/2013-like (group 3C.3), 14 A/Newcastle/22/2014-like (group 3C.3b), 33 A/HongKong/5738/2014-like (group 3C.2a) and A/Switzerland/9715283/2013-like (group 3C.3a). Of the characterised A(H3N2) strains, 67% belonged to drifted genetic subgroups3C.2a and 3C.3a. All 17 B viruses were B/Phuket/3073/2013-like (lineage Yamagata), and the 2 A(H1N1)pdm09 viruses were A/SouthAfrica/3626/2013-like.
DeMarcus 2019 [51]	ccIIV4 (Flucelvax) IIV4 (FluLaval and Fluarix) Strains not reported	IIV4 (FluLaval and Fluarix) Strains not reported Unvaccinated	2017-2018. Influenza A(H3N2) was the predominant strain until week 4 when influenza B outcompeted A(H3N2); low levels of influenza A(H1N1)pdm09.
Effectiveness- cohort studies			
Izurieta 2019 [78]	cc IIV4 HD-IIV3 aIIV3 IIV3: A(H1N1), A(H3N2), and a single type B (B/Victoria) lineage strain. IIV4: A(H1N1), A(H3N2), and 2 type B lineage strains.	IIV4 SD IIV3 IIV3: A(H1N1), A(H3N2), and a single type B (B/Victoria) lineage strain. IIV4: A(H1N1), A(H3N2), and 2 type B lineage strains.	**2017-2018** Not reported

Key: *aIIV3 – adjuvanted trivalent inactivated influenza vaccine; ccIIV3- cell-based trivalent inactivated influenza vaccine; ccIIV4- cell-based quadrivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; LAIV – live attenuated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; SD-IIV3 – standard-dose trivalent inactivated influenza vaccine*

Appendix 6.4 Recombinant HA influenza vaccines

Author (Year)	Intervention vaccine Included strains	Comparator Included strains (if applicable)	Season Circulating strains
Efficacy- randomised controlled trials			
Dunkle 2017a [57]	RIV4 Dose: 0.5 ml 45 µg of recombinant hemagglutinin, 180 µg of protein A/California/7/2009 (H1N1)-like, A/Texas/50/2012 (H3N2), B/ Massachusetts/2/2012, and B/Brisbane/60/2008.	IIV4 Dose: 0.5 ml 15 µg of hemagglutinin, 60 µg of protein A/California/7/2009 (H1N1)-like, A/Texas/50/2012 (H3N2), B/ Massachusetts/2/2012, and B/Brisbane/60/2008.	**2014-2015** Predominantly H3N2 viruses
Treanor 2011 [127]	RIV3 Dose: 45 mcg of each purified rHA0 formulated with 0.005% Tween®-20 in 10 mM sodium phosphate buffer A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004	Saline	**2007-2008** Eight isolates in the study (<5% of the total) were antigenically identical to the strains contained in the vaccine. All of these viruses were A/Wisconsin/67/2005-like H3N2 viruses. The remaining 111 influenza A viruses were characterised as antigenic variants including 12 H1N1 viruses antigenically resembling H1 drift variant A/Brisbane/59/2007, 41 H3N2 viruses antigenically resembling the H3 drift variant A/Brisbane/10/2007, 42 H3N2 viruses that could not be identified as either A/Wisconsin-like or A/Brisbane-like. Fifty-eight of the 59 influenza B viruses (98%) were antigenically similar to B/Florida/04/2006.
Effectiveness- case control studies			
No relevant studies identified.			
Effectiveness- cohort studies			
No relevant studies identified.			

Key: *HA- Hemagglutinin; IIV4 – quadrivalent inactivated influenza vaccine; RIV3- Recombinant HA trivalent inactivated influenza vaccine; RIV4- Recombinant HA quadrivalent inactivated influenza vaccine*

Appendix 7. Study characteristics for safety

Appendix 7.1 MF59® adjuvanted influenza vaccines

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Randomised controlled trials					
Baldo 2007 [30]	Italy General Practice	Adults (aged 18-60 years) with chronic medical conditions* N = 238	aIIV3 (Fluad) n = 120: Mean age 51.4 (SD 12.1), 67 males (55.8%)	IIV3 (n = 118): Mean age 50.7 (SD 12.7), 53 males (44.9%)	Severe adverse events Local adverse events Systemic adverse events
Cowling 2019 [48]	Hong Kong	Adults (aged 65–82 years) Community dwelling N = 1 861	aIIV3 (Fluad) n = 508: 200 males (39%) HD-IIV3 (Fluzone HD) n = 510: 183 males (36%) Recombinant HA influenza vaccine (Flublok) n = 335: 140 males (42%)	IIV4 (FluQuadri) n = 508: 207 males (41%)	Local adverse events Systemic adverse events Serious adverse events
de Bruijn 2006 [49]	Netherlands	Adults (aged ≥61 years) N = 386 Approximately 50% aged >70 years	aIIV3 (Fluad) n = 130: Mean age 70.3	Virosomal influenza vaccine (Invivac) n = 129: Mean age 69.8 Subunit influenza vaccine (Influvac) n = 127: Mean age 70.5	Mortality Serious adverse events Local adverse events Systemic adverse events
Della Cioppa 2014 [50]	Germany, Poland and Belgium Multicentre	Healthy Adults (aged ≥65 years) N = 270	Two groups of aIIV3 (Fluad) n = 90: Group 1 (n = 47) Mean age 68.5 (SD 3.1), 42% male; Group 2 (n = 43) Mean age 69.0 (SD 3.5), 46% male	Two groups of Intradermal low-dose IIV3 (n = 93): Group 1 (n = 47) Mean age 68.3 (SD 3.5), 49% male; Group 2 (n = 46) Mean age 69.6 (SD 5.1), 48% male Two groups of Intramuscular IIV3 (n = 87): Group 1 (n = 44) Mean age 69.2 (SD 3.6), 40% male; Group 2 (n = 43) Mean age 69.2 (SD 4.0), 56% male	Serious adverse events Any adverse event
Durando 2008 [59]	Italy Multicentre Outpatient	Adults (aged 18-65) N = 256 Grouped by HIV serostatus	aIIV3 (Fluad) Seronegative (n = 81): Mean age 31.4 (SD 7.5), 66 males (81.5%) aIIV3 (Fluad) Seropositive (n = 46): Mean age 41.0 (SD 5.7), 40 males (86.9%)	IIV3 (Aggripal) Seronegative (n = 80): Mean age 32.5 (SD 7.1), 71 males (88.7%) IIV3 (Aggripal) Seropositive (n = 49): Mean age 40.1 (SD 6.4), 39 males (79.6%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Essink 2020 [62]	United States Multicentre	Adults (aged ≥65 years) N = 1 778 Mean age 72.5 (SD 5.5), 771 males (43.3%)	aIIV4 (n = 889): Mean age 72.4 (SD 5.5), 372 males (41.8%)	aIIV3 (Fluad) n = 445: Mean age 72.4 (SD 5.6), 196 males (44.0%) aIIV3 (alternate B strain) n =444: Mean age 72.6 (SD 5.5), 203 males (45.7%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Frey 2003 [64]	United States Multicentre Research centres	Adults (aged 18-64 years) N = 301	aIIV3 (Fluad) n = 150	IIV3 (Fluzone) n = 151	Local adverse events Systemic adverse events
Frey 2014 [66]	United States, Philippines, Panama and Columbia Multicentre	Adults (aged ≥65 years) N = 7 109	aIIV3 (Fluad) n = 3,479: Mean age 71.9 (SD 5.3), 36% male	IIV3 (Agriflu) n = 3,482: Mean age 71.8 (SD 5.3), 34% male	Mortality Local adverse events Systemic adverse events

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Gabutti 2005 [67]	Italy Hospital	Adults (aged 18-65 years) HIV seropositive N = 40	aIIV3 (Fluad) n = 18: Age 40.2 (95% CI 35.5 to 44.9), 14 males (77.8%)	IIV3 (Aggripal) n = 19: Age 37.1 (95% CI 34.5 to 39.7), 14 males (73.7%)	Serious adverse events Local adverse events Systemic adverse events
Gasparini 2001 [69]	Italy Multicentre Outpatients	Adults (aged ≥65 years) N = 308	aIIV3 (Fluad) n = 204: Mean age 75.9, 91 males (45%)	IIV3 (Aggripal) n = 104: Mean age 75.4, 46 males (44%)	Serious adverse events Local adverse events Systemic adverse events
Kumar 2016 [87]	Canada Outpatients	Adult kidney transplant recipients N= 68 Median age 49.7 (range 21.6-78.8), 47 males, median time from transplantation to vaccination 8.10 (range 0.73-33)	aIIV3 (Fluad) n = 34: Median age 48.6 (range 21.6-74.6), 20 males, median time from transplantation to vaccination 9.32 (range 0.76-22.6)	IIV3 (Agriflu) n = 34: Median age 51.5 (range 28.4-78.8), 27 males, median time from transplantation to vaccination 7.00 (range 0.73-33)	Local adverse events Systemic adverse events
Li 2008 [88]	China	Adults (aged ≥60 years) N = 600	aIIV3 (Fluad) n = 400	IIV3 (Agriflu) n = 200	Serious adverse events Local adverse events Systemic adverse events
Magnani 2005 [93]	Italy	Adult heart transplant recipients N = 58 Median age 55, 46 males, time since transplant 30)	aIIV3 (Fluad) n = 21	IIV3 (Agrippal) n = 21 Unvaccinated n = 16	Systemic adverse events
Minutello 1999 [96]	Italy Community	Adults (aged ≥65 years) N = 92	aIIV3 (Fluad) n = 46: Mean age 71.5 years (range 65±81), 43.5% male	IIV3 (Agrippal S1) n = 46: Mean age 73.4 years (range 65±90), 56.5% male	Serious adverse events Local adverse events Systemic adverse events
Natori 2017 [99]	Canada Tertiary care centre	Adult allogeneic hematopoietic stem cell transplant recipients N= 73 Median age 54 (range 22–74), 40 males	aIIV3 (Fluad) n = 35: Median age 54.5 (range 23–74), 23 males	IIV3 (Influvac) n = 38: Median age 52.5 (range 22–69), 17 males	Local adverse events Systemic adverse events
Pregliasco 2001 [107]	Italy Nursing homes	Institutionalized elderly adults (aged >64 years) N = 635 Median age 86 (range 65-106), 207 males	aIIV3 (Fluad) n = 207: Median age 86	IIV3 (Inflexal) n = 213: Median age 86 IIV3 (Inflexal V) n =215: Median age 86	Mortality Local adverse events Systemic adverse events
Ruf 2004 [115]	Germany, Multicentre	Adults (aged ≥60 years) N = 827 Mean age 67.9 years (SD 6.3), more females than male subjects in TIV group. Reactogenicity analysis n = 815 (≥65 years n = 491)	aIIV3 (Fluad) n = 273	IIV3 (Fluarix) n = 272 IIV3 (Inflexal V) n = 270	Local and general symptoms Serious adverse events
Scheifele 2013 [118]	Canada	Adults (aged ≥65 years) N = 922 Mean age 73.8 years, 371 males (40.7%)	aIIV3 (Fluad) n = 306: Mean age 73.8 years, 122 males (40.5%)	Intradermal IIV3 (Intanza) n = 306: Mean age 73.7 years, 124 males (40.9%) IIV3 (Agriflu) n = 310: Mean age 73.9 years, 125 males (40.7%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Seo 2014 [119]	South Korea, Multicentre Community	Healthy, independently-living adults (aged ≥65 years) N = 354	aIIV3 (Fluad) n = 118: Median age 71 (65–88), 36 males (32.4%),	IIV3 (Agrippal) n= 118: Median age 73 (65–88), 44 males (38.9%) Intradermal split vaccine n = 118: Median age 72 (65–86), 36 males (32.4%)	Local adverse events Systemic adverse events

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Sindoni 2009 [121]	Italy Social community settings	Adults (aged ≥65 years) Social community settings N = 195	aIIV3 (Fluad) n =96: Mean age 79.04 (SD 8.29), 26 males	IIV3 (Agrippal) n = 99: Mean age 80.29 (SD 7.78), 25 males	Serious adverse events Local adverse events Systemic adverse events
VanDamme 2009 [134]	Belgium and France Multicentre Outpatients	Adults (aged ≥65years) N = 795 Mean age 74.3 (SD 6.4), 370 males (46.5%)	aIIV3 (Fluad) n = 397: Mean age 74.7 (SD 6.6), 176 males (44.3%)	Intradermal IIV3 (Intanza) n = 398: Mean age 73.9 (SD 6.3), 194 males (48.7%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Non-randomised studies					
Lindert 2019 [89]	United States Phase I through III trials	Healthy, independently living adults (aged ≥65 years) N = 10 952	aIIV3 (Fluad) First-dose RCTs: aIIV3 (n = 5,754) Mean age 72.9 (SD 6.2) 38.9% male Revaccination pooling: Year2: aIIV3 (n = 492) mean age 76.5 (SD 7.5), 42.9% male Year 3: aIIV3 (n = 150)	IIV3 First-dose RCTs: IIV3 (n = 5,198) Mean age 72.8 (SD 6.2), 37.1% male Revaccination pooling: Year2: IIV3 (n = 330) Mean age 77.3 (SD 7.7), 41.2% male Year 3: IIV3 n= 87	Adverse events Serious adverse events Adverse events leading to withdrawal Adverse events leading to hospitalisation Mortality
Otten 2020 [102]	Berlin, Germany Clinical trial	Adults (aged ≥65 years) 2/6 groups received licensed aTIV: Group 1 (n=28), mean age 69.7, 14 males (50%) Group 5 (n=28), mean age 70.0, 17 males (60.7%)	aIIV3 (Fluad)	Non-applicable	Local adverse events Systemic adverse events Mortality
Panatto 2020 [103]	Italy Multicentre General practitioner	Adults (aged ≥65 years) 2015-2016: 1 060 doses 2016-2017: 1 046 doses 20172018: 1 045 doses	aIIV3 (Fluad)	Non-applicable	Local adverse events Systemic adverse events
Tsai 2011 [130]	Clinical trials and pharmaco-vigilance databases		aIIV3 (Fluad) ccIIV3 (Optaflu)	Non-adjuvanted vaccine	Narcolepsy
Villa 2013 [135]	Northern Italy Local health authorities	Adults (aged ≥65 years) N = 107 661	aIIV3 (Fluad): 88,449 doses, mean age 76.5 years	IIV3 (Agrippal): 82,539 doses, mean age 74.9 years	AESIs AESIs leading to hospitalisation

Key: *aIIV3 – adjuvanted trivalent inactivated influenza vaccine; AESI - adverse event of special interest; HD-IIV3- high-dose trivalent inactivated influenza vaccine; HIV- Human Immunodeficiency Virus; IIV4- quadrivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; SD-IIV3- standard-dose trivalent inactivated influenza vaccine*

Appendix 7.2 High-dose influenza vaccines

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Randomised controlled trials					
Chang 2019 [43]	United States Multicentre	Adults (aged ≥65 years) N = 2 670	HD-IIV4 (n = 1 680): Mean age 72.9 (SD 5.66), 703 males (41.8%)	Two HD-IIV3 pooled for analysis: HD-IIV3 1 (n = 423): Mean age 72.8 (SD 5.82), 172 males (40.7%) HD-IIV3 2 (n = 430): Mean age 73.2 (SD 5.50), males (44.4%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Colmegna 2020 [46]	Canada Multicentre	Adults with Rheumatoid Arthritis N = 279	HD-IIV3 (Fluzone HD) n = 138: Mean age 59.7 (SD 13.9), 29 males (21%)	SD-IIV4 (Fluzone) n = 136: Mean age 62.9 (SD 11.8), 27 males (20%)	Serious adverse events Local adverse events Systemic adverse events
Couch 2007 [47]	United States Multicentre	Adults (aged ≥65 years) medically stable for any underlying illness N = 414	HD-IIV3 (n = 206): Median age 73 (range 65-95), 104 males (50%)	SD-IIV3 (n = 208): Median age 72 (range 65-88), 108 males (52%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Cowling 2019 [48]	Hong Kong	Adults (aged 65–82 years) Community dwelling N = 1 861	aIIV3 (Fluad) n = 508: 200 males (39%) HD-IIV3 (Fluzone HD) n = 510: 183 males (36%) Recombinant HA influenza vaccine (Flublok) n = 335: 140 males (42%)	SD-IIV4 (FluQuadri) n = 508: 207 males (41%)	Serious adverse events Hospitalization
DiazGranados 2014b [53]	United States and Canada Multicentre	Adults (aged ≥65 years) without moderate or severe acute illnesses N = 31 989	HD-IIV3 (n = 15,990): Mean age 73.3 (SD 5.8), 6,780 males (42.4%)	SD-IIV3 (n = 15,993) Mean age 73.3(SD 5.8), 7,030 males (43.9%)	Serious adverse events Mortality
DiazGranados 2015b [56]	United States Multicentre	Adults (aged 50- 64 years) who were medically stable N= 300	HD-IIV3 (Fluzone High Dose) n = 148: Mean age 57.6 (SD 4.4), 50 males (33.8%)	SD-IIV3 (Fluzone) n = 152: Mean age 57.7 (SD 4.1), 56 males (36.8%)	Serious adverse events Mortality Local adverse events Systemic adverse events
DiazGranados 2016 [54]	United States and Canada Multicentre	Adults (aged ≥65 years) who were medically stable Year 1 N = 14 500 Reenrollment Year 2 N = 7 643	Year 1 HD-IIV3, Year 2 HD-IIV3 (n = 1,942): Mean age 74.3 (SD 5.6), 817 males (42.1%) Year 1 SD-IIV3, Year 2 HD-TIV (n = 1,881): Mean age 74.1 (SD 5.5), 795 males (42.2%) Year 1 HD-IIV3 or SD-IIV3, Year 2 HD-IIV3 (n = 3,823): Mean age 74.2 (SD 5.6), 1,612 males (42.2%) Year 1 HD--IIV3, Year 2 SD-IIV3 (n = 1891): Mean age 74.2 (SD 5.7), 821 males (43.4%)	Year 1 SD-IIV3, Year 2 SD-IIV3 (n = 1,929): Mean age 74.3 (SD 5.7), 810 males (42.0%)	Serious adverse events (death, hospitalization, considered as life-threatening or medically important, or resulting in disability)
Falsey 2009 [63]	United States Multicentre	Adults (aged ≥65 years) Community-dwelling N = 3 876 Mean age 73 (SD 6)	HD-IIV3 (n = 2,573): Mean age 73 (SD 6), 1,320 females (51%)	SD-IIV3 (n = 1,260): Mean age 73 (SD 6), 688 females (55%)	Mortality Local adverse events Systemic adverse events
Halasa 2016 [73]	United States Outpatients	Adults (aged ≥ 18 years) Hematopoietic Stem Cell Transplantation Patients N = 44 Median age 50.1 years (19.6 to 72.8), , 61.4% male	HD-IIV3 (Fluzone) n = 29: Median age 50 (range 43-59), 17 males (59%)	SD-IIV3 (Fluzone) n = 15: Median age 50 (range 44-57), 10 males (66%)	Serious adverse events Local adverse events Systemic adverse events
Jamshed 2016 [80]	United States Hospital	Adults (aged 18-64 years) Receiving chemotherapy for malignancy N = 105	HD-IIV3 (Fluzone HD) n = 54: Mean age 53.94 (SD 7.16), 23 males (38%)	SD-IIV3 (Fluzone) n = 51: Mean age 52.9 (SD 7.95), 24 males (51%)	Serious adverse events Local adverse events Systemic adverse events

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Keipp Talbot 2018 [82]	United States	Adults (aged ≥65 years) N = 31 989 Median age 72.2 years	HD-IIV3 (Fluzone HD) n = 15,992: 42.9% male	SD-IIV3 (Fluzone)n = 15,991: 43.9% female	Gastrointestinal events
Keitel 2006 [83]	United States Community	Adults (aged ≥65 years) N = 202 Median age 72.5 years (range 65-88)	HD-IIV3 per strain (n = 50)	15 ug IIV3 per strain (n = 51) 30 ug IIV3 per strain (n = 51) Placebo (n = 50)	Serious adverse events Mortality Local adverse events Systemic adverse events
McKittrick 2013 [95]	United States Outpatients	Adults (aged ≥18years) HIV infected N= 195	HD-IIV3 (Fluzone HD) n = 100: Median age 44 (range 35 to 50), 64 males (64%)	SD-IIV3 (Fluzone) n = 95: Median age 46 (range 37 to 53), 73 males (77%)	Mortality Hospitalisation Local adverse events Systemic adverse events
Nace 2015 [98]	United States Multicentre Long term care facilities	Frail adults (aged ≥65 years) Long term care facilities residents N = 187 Mean age 87 (SD 6), 59 males (32%)	HD-IIV3 (Fluzone HD) n = 89: Mean age 87 (SD 6), 32 males (36%)	SD-IIV3 (Fluzone) n = 98: Mean age 86 (SD 6), 17 males (28%)	Mortality Serious adverse events
Natori 2018 [100]	Canada	Adult (aged ≥18 years) Solid organ transplant recipients N = 172 Median age 57 (range 18–86), 121 males (70.3%), Median time from transplant to vaccination 38 months (range 12–89.5)	HD-IIV3 (Fluzone HD) n = 87: Median age 57 (range 18–86), 60 males (69.0%), Median time from transplant to vaccination 48 (range 14–95)	SD-IIV3 (Fluviral) n = 85: Median age 57(range 19–80), 61 males (71.8%), Median time from transplant to vaccination 33.5 (range 11–89.5)	Local adverse events Systemic adverse events
Noh 2019 [101]	Republic of Korea	Adults (aged 19-64 years) N = 40	HD-IIV4 (n = 30): Median age 39.5, 26.7% male	SD-IIV4 (n = 10): Median age 31.5, 40.0% male	Local adverse events Systemic adverse events
Pillet 2019 [106]	United States	Adults (aged ≥18 years) N = 750 Grouped by age: Group 1 (aged 18-49 years) n = 300 Group 2 (aged ≥50 years) n = 450	Group 1 (aged 18-49 years): HD(60 µg) IIV4 (n = 75) Group 2 (aged ≥50 years): HD(60 µg) IIV4 (n = 74)	Group 1 (aged 18-49 years): SD(15 µg)- IIV4 (n = 75) SD(30 µg)- IIV4 (n = 75) Placebo (n = 75) Group 2 (aged ≥50 years): SD(15 µg)- IIV4 (n = 75) SD(30 µg)- IIV4 (n = 75) A1OH3 adjuvanted SD(7.5 µg) IIV4 (n = 76) A1OH3 adjuvanted SD(15 µg) IIV4 (n = 76) Placebo (n = 75)	Serious adverse events Local adverse events Systemic adverse events
Sanchez 2019 [117]	Japan Outpatients	Adults (aged ≥65 years) N = 175	Intramuscular HD- IIV4 (n = 60): Mean age 70.2 (SD 3.6), 32 males (53.3%) Subcutaneous HD- IIV4 (n = 60): Mean age 70.6 (SD 3.5), 33 males (55%)	Subcutaneous SD- IIV4 (n = 55): Mean age 69.9 (SD 3.8), 30 males (54.5%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Tsang 2014 [131]	United States Multicentre	Adults (aged ≥18 years) Grouped by age (18-49 years; ≥65 years). Only those ≥65 years possessed comparisons of interest for the present review Adults (aged ≥65 years): N = 1912	HD-IIV3 (n = 320): Mean age 73.0 (SD 6.0), 137 males (42.8)	SD-IIV3 (Fluzone) n = 319: Mean age 73.4 (SD 5.9), 143 males (44.8%) 15 µg intradermal vaccine (n = 637): Mean age 73.1 (SD 6.0), 272 males (42.8%) 21 µg intradermal vaccine (n = 636): Mean age 72.9 (SD 5.9), 288 males (45.4%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Non-randomised studies					

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Arya 2019 [29]	United States Medicare	Adults (aged ≥65 years)	HD-IIV3 vaccine 60 µg HA per strain 2015-2016: n = 6 936 021 4 037 736 females (58.2%), 65–74 years n = 3 458 968 (49.9%) 75-84 years n = 2 432 437 (35.1%) 85+ years n = 1 044 616 (15.1%) 2016-2017: n = 8 100 846 4,719,542 females (58.3%), 65–74 years n = 4 058 115 (50.1%) 75-84 years n = 2 813 561 (34.7%) 85+ years n = 1 229 170 (15.2%)	SD-IIV3 and SD-IIV4 15 µg HA per strain 2015-2016: n = 6,218,036 3 707 972 females (59.6%), 65–74 years n = 2 945 163 (47.4%) 75-84 years n = 2 125 867 (34.2%) 85+ years n = 1 147 006 (18.5%) 2016-2017: n = 5 298 835 3 150 894 females (59.5%), 65–74 years n = 2,550 615 (48.1%) 75-84 years n = 1 791 917 (33.8%) 85+ years n = 956 303 (18.0%)	Self-reported Guillain Barré Syndrome
Branagan 2017 [38]	United States Academic hospital	Patient with a diagnosis of MM or another PCD n = 51 Median age 65 years, 61 males (31%)	HD-IIV3 (Fluzone High-dose) 60 µg HA per strain	Non-applicable	Adverse events
Chong 2020 [45]	New York, United states Tertiary cancer care centre	Patients with advanced cancer on immune checkpoint inhibitors N = 370	HD-IIV3 (n = 171)	SD-IIV4 (n = 163) SD-IIV3 (n = 36)	Influenza-related adverse event (any grade)
Kaka 2017 [81]	United States Minneapolis Veteran Affairs Health Care System clinics	Adults (aged ≥65 years) N = 2 709	HD-IIV3 (Fluzone High-dose) n = 1,211 532 males (99%), 65–74 years n = 371 (68%) 75–84 years n = 125 (23%) ≥85 years n = 51 (9.3%)	SD-IIV3 (n = 1,498): 539 males (99%), 65–74 years n = 385 (71%) 75–84 years n = 117 (22%) ≥85 years n = 38 (7%)	Local adverse events Systemic adverse events
Strowd 2018 [124]	United States, Single institution for patients with a diagnosis of primary CNS malignancy	Patients with primary CNS malignancy N = 27 Mean age 52.7 years (SD 12.9), 11 males (41%)	HD-IIV3 (Fluzone high-dose)	Non-applicable	Local adverse events Systemic adverse events Tolerability

Key: *aIIV3– adjuvanted trivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; ILI – influenza-like illness; LAIV – live attenuated influenza vaccine; RT PCR - real time polymerase chain reaction; SARI – severe acute respiratory infections; SD-IIV3 – standard-dose trivalent inactivated influenza vaccine*

Appendix 7.3 Cell-based influenza vaccines

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Randomised controlled trials					
Bart 2016 [32]	United States Multicentre Outpatients	Adults (aged ≥18 years) N = 2 680	ccIIV4 (n = 1 335) Mean age 57.4 (SD 17.8), 603 males (45.2%)	ccIIV3 (Optaflu) n = 669: Mean age 57.1 (SD 18.1), 277 males (41.4%) ccIIV3 (Flucelvax) n = 676: Mean age 57.2 (SD 18.0), 284 males (42.0%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Barrett 2011 [31] **Includes data reported by Ehrlich 2012b** [61]	Austria Multicentre Outpatients	Healthy adults (aged 18-48 years) N = 7 520	ccIIV3 (n=3 623) Median age 31 years (range 18–49) 1 823 males (50%)	Phosphate buffered saline (n=3 620) Median age 30 years (range 18–49) 1 865 males (42%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Choi 2017 [44]	Republic of Korea University hospitals	Adults and elderly individuals N = 1 503 Mean age 43.27 (SD 14.31), 556 males (37.0%)	ccIIV4 (n = 752): Mean age 43.36 (SD 14.46), 276 males (36.7%)	Two IIV3 First IIV3 (n = 373): Mean age 43.38 (SD 14.20), 135 males (36.2%) Second IIV3 (n = 378): Mean age 42.96 (SD 14.14), 145 males (38.4%)	Local adverse events Systemic adverse events
Ehrlich 2012a [60]	United States Multicentre	Adults (aged>50 years) N = 3 208 Grouped by age Group 1 (aged 50-64 years) Group 2 (aged ≥65 years)	ccIIV3 (n = 2 842): Group 1 (aged 50-64 years) n = 1 762 Group 2 (aged ≥65 years) n = 1 080	IIV3 (Fluzone) n = 366: Group 1 (aged 50-64 years) n = 229 Group 2 (aged ≥65 years) n = 137	Serious adverse events Mortality Local adverse events Systemic adverse events
Frey 2010 [65]	United States, Poland and France Multicentre	Healthy adults (aged 18-49 years) N=11 404 Across groups: Mean age 32.7–33.0 years, 44%–45% were male.	ccIIV3 (Optaflu) n = 3 828	IIV3 (n = 3,676) Phosphate buffered saline (n = 3,900)	Serious adverse events Local adverse events Systemic adverse events
Groth 2009 [72]	Germany	Adults (aged ≥ 18 years) N = 240 Phase 1 (n = 40): 18-40 years Phase 2 (n = 200): 18-60 years (n = 80); ≥61 years (n = 120)	ccIIV3 (n = 120): 18-60 years (n = 60) ≥61 years (n = 60)	IIV3 (Aggripal) n = 120: 18-60 years (n = 62) ≥61 years (n = 58)	Serious adverse events Mortality Local adverse events Systemic adverse events
Halperin 2002 [75]	Canada	Adults and children (aged ≥3 years) N = 940 Children (aged 3-12) n = 209: Mean age 8 (range 3–13) Adults (aged 19-50) n = 462: Mean age 33 (range 19–51), 162 males (35%) Seniors (aged ≥65 years) n = 269: Mean age 74 (range 65–100), 138 males (51%)	ccIIV3	IIV3 (Fluviral)	Local adverse events Systemic adverse events
Song 2015 [122]	Republic of Korea Multicentre	Adults (aged ≥19 years) N = 1 155 Mean age 41.6 (SD 15.2), 347 males (30%)	ccIIV3 (n = 1 050): Mean age 41.6 (SD 15.2), 318 males (30.3%) Further grouped by age for safety outcomes: Group 1 (aged 19-59 years) n = 835 Group 2 (aged ≥60 years) n = 210	IIV3 (Agrippal) n = 155: Mean age 41.1 (SD 15.2), 29 males (27.6%) Further grouped by age for safety outcomes: Group 1 (aged 19-59 years) n = 84 Group 2 (aged ≥60 years) n = 20	Serious adverse events Local adverse events Systemic adverse events
Szymczakiewicz-Multanowska 2009 [125]	Poland Multicentre	Adults (aged ≥18 years) N = 2 654 Grouped by age: Group 1 (aged 18-60 years) n = 1 300 Group 2 (aged ≥61 years) n = 1 354	ccIIV3 (n = 1 322): Group 1 (aged 18-60 years) n = 652: Mean age 38.7 (SD 12.7), 42% male Group 2 (aged ≥ 60 years) n = 678: Mean age 69.1 (SD 5.7), 42% male	IIV3 (Agrippal) n = 1,318: Group 1 (aged 18-60 years) n = 648: Mean age 38.7 (SD 12.7), 43% male Group 2 (aged ≥ 60 years) n = 676: Mean age 68.8 (SD 5.6), 43% male	Serious adverse events Mortality Local adverse events Systemic adverse events

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Szymczakiewicz-Multanowska 2012 [126] **Extension study of revaccination for Szymczakiewicz-Multanowska 2009** [125]	Poland	Adults (aged ≥18 years) N = 1 522	Revaccination ccIIV3 (Optaflu) n = 639 Cell-derived influenza vaccine with concomitant pneumococcal vaccine group (n = 78)	Revaccination IIV3 (Agrippal) n = 226 IIV3with concomitant Pneumococcal vaccine (n = 44)	Local adverse events Systemic adverse events
Non-randomised studies					
Hall 2018 [74]	United Kingdom Primary Healthcare records from general practice (THIN database) n = 497	Adults (aged ≥ 18 years) N = 4 578 Mean age 60.5 years (SD 16.5) 42.6% male, 56.9% had a history of 1≥ chronic illness	ccIIV3 (Optaflu)	Non-applicable	Severe allergic reactions (anaphylactic reactions and severe angioedema), Bell's palsy, Convulsions, Demyelination in total and Guillain Barré Syndrome alone, Paresthesia, Noninfectious encephalitis, Neuritis (optic and brachial), Vasculitis, Inflammatory bowel disease, Thrombocytopenia
Loebermann 2013 [91]	Germany University-based center	Adults (aged ≥18 years) N = 126 Mean age 54.36 (SD17.3), 56 males (44%) Aged 18–60 years n = 62: Mean age 39.76 (SD 12.0), 27 males (44%) Aged ≥61 years n = 64: Mean age 68.5 (SD 6.0), 29 males (45%)	ccIIV3 (Optaflu)	Non-applicable	Solicited local reactions Systemic reactions
Loebermann 2019 [90]	Berlin, Germany Clinical trial	Adults (aged ≥18 years) N = 126 Mean age 53.8 (SD 16.7), 55 males (44%) Aged 18 to ≤60 years, n = 63: Mean age 39.3 (SD 0.7), 25 males (40%) Aged ≥61 years, n = 63: Mean age 68.3 (SD 4.8), 30 males (48%)	ccIIV3 (Optaflu)	Non-applicable	Solicited adverse events Unsolicited adverse events
Vinnemeier 2014 [136]	Germany University Medical Center	Adults (aged ≥ 18 years) N = 126 Mean age 52.7 (SD 17.7), 62 males (49%)	ccIIV3 (Optaflu)	Non-applicable	Solicited local and systemic reactions Serious adverse events

Key: *ccIIV3- cell-based trivalent inactivated influenza vaccine; ccIIV4- cell-based quadrivalent inactivated influenza vaccine; HD-IIV3 – high-dose trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine*

Appendix 7.4 Recombinant HA influenza vaccines

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Randomised controlled trials					
Baxter 2011 [33]	United States Multicentre	Healthy adults (aged 50-64 years) N = 602 Mean age 55.8 (SD 3.67), 223 males (37%)	Recombinant HA influenza vaccine (FluBlok) n = 300: Mean age 55.9 (SD 3.71), 113 males (38%)	IIV3 (Fluzone) n = 302: Mean age 55.7 (SD 3.64), 110 males (36%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Cowling 2019 [48]	Hong Kong	Adults (aged 65–82 years) Community dwelling N = 1 861	Recombinant HA influenza vaccine (Flublok) n = 335: 140 males (42%) aIIV3 (Fluad) n = 508: 200 males (39%) HD-IIV3 (Fluzone HD) n = 510: 183 males (36%)	SD-IIV4 (FluQuadri) n = 508: 207 females (41%)	Serious adverse events Hospitalisation
Dunkle 2017a [57]	United States Multicentre (outpatients)	Adults (aged≥ 50 years) living independently without clinically significant acute illness N=9 003	Recombinant HA influenza vaccine (n=4 328) Mean age 63 years (range 50-96) 1 796 males (41.5%)	IIV4 (n=4 344) Mean age 63 years (range 50-94) 1 807 Males (41.6%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Dunkle 2017b [58]	United States Multicentre	Adults (aged 15-49 years) N = 1 350	Recombinant HA influenza vaccine (n=998): Mean age 33.3, 359 males (36%)	IIV4 (n=332): Mean age 34.0, 110 males (33%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Izikson 2015 [77]	United States Multicentre	Adults (aged ≥50 years) N = 2 640 Grouped by age: Aged 50-64 (n = 1 345) Aged ≥65 years (n = 1 295)	Recombinant HA influenza vaccine (Flublok) n = 1,319: Aged 50-64 (n = 675): Mean age 56.6, 292 males (43%) Aged ≥65 years (n = 644): Mean age 71.7, 297 males (46%)	IIV3 (AFLURIA) n = 1,321: Aged 50-64 (n = 670): Mean age 56.5, 293 males (43%) Aged ≥65 years (n = 651): Mean age 71.2, 303 males (46%)	Serious adverse events Mortality Local adverse events Systemic adverse events
Keitel 2009 [84]	United States Multicentre	Adults (aged ≥65 years) Community dwelling N = 869	Recombinant HA influenza vaccine (n = 436): Mean age 72.9 (SD 6.66), 208 males	IIV3 (Fluzone) n = 433: Mean age 73.0 (SD 6.13), 199 males	Serious adverse events Mortality Local adverse events Systemic adverse events
Safdar 2006 [116]	United States	Adults with Non-Hodgkin B Cell Lymphoma N =27 Mean age 55 years, 15 males	Recombinant HA influenza vaccine (15 µg) (n = 9) Recombinant HA influenza vaccine (45 µg) (n = 6) Recombinant HA influenza vaccine (135 µg) (n = 6)	IIV3 (n= 6)	Serious adverse events Local adverse events Systemic adverse events
Treanor 2006 [128]	United States	Adults (aged ≥18 years) Community dwelling Mean age 72 years (range 65–90), 49% male N= 399	Recombinant HA influenza vaccine (15 µg) Recombinant HA influenza vaccine (45 µg) Recombinant HA influenza vaccine (135 µg)	IIV3	Local adverse events Systemic adverse events

Author (Year)	Country Setting	Population Study size	Vaccine (s)	Comparator (s)	Safety outcomes
Treanor 2007 [129]	United States Academic medical centres	Adults (18- 49 years) N = 458 Median age 31 (range 18-49), 170 males (37%)	Recombinant HA (75 µg) influenza vaccine (n = 151): Median age 32 (range 18-49), 48 males (32%) Recombinant HA influenza vaccine (135 µg) (n = 153) Median age 30 (range 18-49), 57 males (37%)	Saline placebo (n = 154): Median age 32 (range 18-49), 65 males (42%)	Mortality Local adverse events Systemic adverse events
Treanor 2011 [127]	United States Multicentre	Adults (aged 18-55 years) N=4 648 Across groups: Mean age 32.5 years, 59% Female	Recombinant HA influenza vaccine (45 µg) (Flublok) n = 2,344	Saline (n = 2,304)	Mortality Local adverse events Systemic adverse events
Non-randomised studies					
No relevant studies identified.					

Key: *IIV3 – trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; PCR - polymerase chain reaction; RIV3- Recombinant HA trivalent inactivated influenza vaccine; RIV4- Recombinant HA quadrivalent inactivated influenza vaccines*

Appendix 8. Safety sub group analyses- older adults

Appendix 8.1 MF59® adjuvanted influenza vaccine

Adverse event	Cowling 2019 †		De Bruijn 2006		Frey 2014		Gasparini 2001		Li 2008		Minutello 1999		Pregliasco 2001‡		Ruf 2004		Scheifele 2013		Seo 2014		Sindoni 2009		Pooled RR (95%CI lower, 95%CI upper)
	aIIV3 n = 508	IIV4 n = 508	aIIV3 n = 130	IIV3 n = 129	aIIV3 n = 3 505	IIV3 n = 3 495	aIIV3 n = 204	IIV3 n = 104	aIIV3 n = 391	IIV3 n = 198	aIIV3 n = 46	IIV3 n = 46	aIIV3 n = 207	IIV3 n = 213	aIIV3 n = 273	IIV3 n = 272	aIIV3 n = 301	IIV3 n = 307	aIIV3 n = 111	IIV3 n = 113	aIIV3 n = 96	IIV3 n = 99	Indicates results distinct from main analyses
Local																							
Combined	-	-	60	24	1 122	594	-	-	94	30	-	-	4	1	-	-	-	-	-	-	48	27	1.92 (1.53, 2.40)
Pain	64	59	48	12	876	419	39	11	40	6	19	3	-	-	84	46	114	64	12	8	7	2	2.12 (1.51, 2.98)
Erythema	14	17	3	0	35	35	14	5	6	3	14	7	-	-	55	39	39	39	39	39	-	-	0.96 (0.52, 1.75)
Swelling	47	43	-	-	35	35	11	2	-	-	-	-	-	-	-	-	36	19	3	4	-	-	1.28 (0.78, 2.12)
Induration	-	-	-	-	35	35	10	3	2	5	6	6	-	-	56	40	24	14	-	-	-	-	1.12 (0.59, 2.16)
Systemic																							
Combined	-	-	41	28	1 122	909	-	-	42	19	-	-	0	2	-	-	120	121	-	-	23	18	1.18 (0.91, 1.53)
Arthralgia	-	-	1	2	280	245	10	4	-	-	0	0	-	-	9	16	38	34	6	1	-	-	1.08 (0.56, 2.06)
Chills	-	-	-	-	245	175	8	3	-	-	3	1	-	-	21	13	-	-	3	2	-	-	1.43 (1.26, 1.63)
Diarrhoea	-	-	-	-	189	175	-	-	3	4	-	-	-	-	-	-	-	-	-	-	-	-	1.06 (0.87, 1.29)
Fatigue	37	21	-	-	456	315	-	-	13	2	-	-	-	-	24	26	56	65	6	1	2	2	1.37 (0.84, 2.22)
Fever	16	7	-	-	175	105	4	2	62	15	0	0	-	-	2	4	-	-	0	0	-	-	1.66 (0.96, 2.88)
Headache	-	-	23	14	456	350	12	7	14	5	2	1	-	-	19	29	29	35	3	1	-	-	1.10 (0.80, 1.51)
Malaise	-	-	-	-	-	-	12	9	-	-	7	0	-	-	-	-	33	35	6	0	-	-	2.07 (0.17, 24.56)
Myalgia	9	14	-	-	526	315	10	4	7	1	4	0	-	-	29	21	78	58	9	1	-	-	1.60 (0.87, 2.94)
Nausea	6	1	-	-	105	105	4	2	-	-	1	0	-	-	-	-	-	-	-	-	-	-	1.38 (0.42, 4.52)
Vomiting	-	-	-	-	105	70	-	-	4	2	-	-	-	-	-	-	-	-	-	-	-	-	1.48 (1.10, 1.98)

Key: *aIIV3 – MF59 adjuvanted trivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine*

† The valency of vaccines administered to intervention and comparator groups was not the same: aIIV3 compared with IIV4.

ǂ Institutionalised elderly adults > 64 years.

Appendix 8.2 High-dose influenza vaccine

Adverse event	Couch 2007 Cowling 2019†		Cowling 2009		Falsey 2009		Keipp Talbot 2018		Keitel 2006		Tsang 2014		Pooled RR (95%CI lower, 95%CI upper)
	HD-IIV n = 206	SD-IIV3 n = 208	HD-IIV n = 508	SD-IIV n = 510	HD-IIV3 n = 2 572	SD-IIV3 n = 1 260	HD-IIV3 n = 50	SD-IIV3 n = 51	HD-IIV3 n = 50	SD-IIV3 n = 51	HD-IIV3 n = 320	SD-IIV3 n = 319	Indicates results distinct from main analyses
Local													
Combined	-	-	-	-	-	-	-	-	35	25	158	110	1.43 (1.21, 1.69)
Pain	83	41	73	59	915	306	-	-	31	21	119	58	1.62 (1.24, 2.12)
Erythema	60	58	18	17	384	136	-	-	17	13	57	49	1.23 (1.04, 1.46)
Swelling	49	38	63	43	165	45	-	-	-	-	46	24	1.59 (1.21, 2.09)
Induration	-	-	-	-	-	-	-	-	-	-	47	34	1.38* (0.91, 2.08)
Ecchymosis	-	-	-	-	-	-	-	-	-	-	20	20	1.00* (0.55, 1.82)
Systematic													
Combined	-	-	-	-	882	370	-	-	6	10	116	82	1.19 (1.09, 1.31)
Chills	-	-	-	-	-	-	-	-	-	-	29	12	2.41* (1.25, 4.64)
Diarrhoea	-	-	-	-	-	-	0	2	-	-			0.20* (0.01, 4.14)
Fatigue	-	-	25	21	-	-	-	-	-	-			1.19* (0.67, 2.09)
Fever	9	1	12	7	92	29	-	-	0	1	18	6	2.10 (0.76, 5.79)
Headache	34	27	-	-	432	181	-	-	0	1	60	42	1.25 (0.92, 1.70)
Malaise	47	36	-	-	463	176	-	-	0	1	51	43	1.25 (0.96, 1.62)
Myalgia	54	32	7	14	550	231	-	-	0	1	81	48	1.20 (0.62, 2.32)
Vomiting	-	-	-	-	-	-	3	2	-	-			1.53* (0.27, 8.77)

Key: *HD – high dose; IIV3 - trivalent inactivated influenza vaccine; IIV4 – quadrivalent inactivated influenza vaccine; SDIIV3 – standard dose trivalent inactivated influenza vaccine*
** Indicates single study analyses*
† The valency of vaccines administered to intervention and comparator groups was not the same: HD-IIV3 compared with SD-QIV.

Appendix 8.3 Cell-based influenza vaccine

Adverse event	Ehrlich 2012a		Groth 2009 †		Halperin 2002		Song 2015 ‡		Szymczakiewicz-Multanowska 2009		Pooled RR (95%CI lower, 95%CI upper)
	ccIIV3 n = 1 080	IIV3 n = 137	ccIIV3 n = 60	IIV3 N = 58	ccIIV3 n = 176	IIV3 N = 93	ccIIV3 n = 210	IIV3 N = 20	ccIIV3 n = 678	IIV3 n = 676	Indicates results distinct from main analyses
Local											
Combined	220	34	28	36	42	14	48	4	-	-	0.96 (0.56, 1.64)
Pain	177	30	6	9	-	-	33	3	64	32	1.06 (0.45, 2.49)
Erythema	39	5	13	18	10	5	12	0	72	72	0.93 (0.71, 1.22)
Swelling	40	3	8	17	8	3	3	0	23	17	1.00 (0.48, 2.10)
Induration	28	4	8	13	-	-	-	-	37	29	1.04 (0.71, 1.51)
Ecchymosis	-	-	0	2	-	-	-	-	26	25	0.96 (0.57, 1.62)
Tenderness	-	-	-	-	38	8	25	2	-	-	2.17 (1.15, 4.08)
Systemic											
Combined	-	-	24	19	62	32	35	5	-	-	1.03 (0.79, 1.34)
Arthralgia	45	2	3	1	-	-	-	-	41	44	1.11 (0.75, 1.63)
Chills	60	2	2	3	22	10	-	-	23	26	1.19 (0.43, 3.33)
Diarrhoea	-	-	-	-	5	3	2	0	-	-	0.81 (0.23, 2.89)
Fatigue	118	9	14	12	-	-	24§	2§	73	84	1.01 (0.79, 1.29)
Fever	17	0	0	1	5	4	0	0	5	5	0.92 (0.26, 3.24)
Malaise	119	7	4	6	-	-	-	-	70	75	1.07 (0.82, 1.42)
Myalgia	99	6	3	1	24	16	24	2	46	57	1.08 (0.58, 1.98)
Nausea	-	-	-	-	11	2	-	-	-	-	2.91* (0.66, 12.84)
Vomiting	-	-	-	-	1	0	1	0	-	-	0.84 (0.10, 7.15)

Key: *ccIIV3 – cell-based trivalent inactivated influenza vaccine; IIV3 – trivalent inactivated influenza vaccine*
** Indicates single study analyses*
† Adults ≥61 years of age.
‡ Adults ≥60 years of age.

Appendix 9. Supplementary GRADE assessment

Appendix 9.1 MF59® adjuvanted influenza vaccines

Safety of aIIV3 compared with IIV3

Patient or population: Adullts (aged ≥18 years)
Setting: All settings
Intervention: aIIV3
Comparison: IIV3

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with IIV3	Risk with aIIV3			
Redness-erythema	34 per 1 000	41 per 1 000 (32 to 53)	**RR 1.20** (0.93 to 1.55)	11 103 (11 RCTs)	⊕⊕⊕◯ MODERATE [a]
Swelling	22 per 1 000	29 per 1 000 (17 to 47)	**RR 1.28** (0.78 to 2.12)	9 437 (5 RCTs)	⊕⊕◯◯ LOW [a,b]
Induration	29 per 1 000	37 per 1 000 (22 to 65)	**RR 1.30** (0.75 to 2.25)	9 604 (8 RCTs)	⊕⊕◯◯ LOW [a,b]
Myalgia	81 per 1 000	139 per 1 000 (88 to 218)	**RR 1.71** (1.09 to 2.69)	10 844 (10 RCTs)	⊕⊕⊕◯ MODERATE [a]
Headache	92 per 1 000	110 per 1 000 (81 to 148)	**RR 1.19** (0.88 to 1.61)	10 087 (10 RCTs)	⊕⊕◯◯ LOW [a,c]
Shiver-chills	47 per 1 000	81 per 1 000 (57 to 114)	**RR 1.7** (1.2 to 2.4)	8 631 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]
Arthralgia	66 per 1 000	82 per 1 000 (43 to 151)	**RR 1.25** (0.66 to 2.31)	9 498 (9 RCTs)	⊕⊕◯◯ LOW [a,b]
Malaise	86 per 1 000	142 per 1 000 (47 to 438)	**RR 1.65** (0.54 to 5.09)	1 694 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Nausea	26 per 1 000	33 per 1 000 (15 to 73)	**RR 1.27** (0.57 to 2.82)	8 717 (5 RCTs)	⊕⊕◯◯ LOW [a,b]
Fatigue	86 per 1 000	127 per 1 000 (80 to 199)	**RR 1.47** (0.93 to 2.31)	10 338 (8 RCTs)	⊕⊕◯◯ LOW [a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to risk of bias (See Figures 3.22 and 3.23)
b. Downgraded one level due to imprecision
c. Downgraded one level due to inconsistency in results between studies

Appendix 9.2 High-dose influenza vaccines

Effectiveness of HD-IIV3 compared with SD-IIV3 for influenza-related outcomes

Patient or population: Older adults (aged ≥65 years)
Setting: All settings
Intervention: HD-IIV3
Comparison: SD-IIV3

Outcomes	Vaccine effectiveness (95% CI)	Number of studies (number of seasons)	Certainty of the evidence (GRADE)
Influenza- related hospitalisation	**VE 11.8%** (6.4 to 17.0)	2 observational studies (7 influenza seasons)	⊕⊕◯◯ LOW [a,b]
Influenza- or pneumonia-related hospitalisation	**VE 13.7%** (9.5 to 17.7)	3 observational studies (6 influenza seasons)	⊕⊕◯◯ LOW [c]
Influenza-related hospital encounters	**VE 13.1%** (8.4 to 17.7)	5 observational studies (6 influenza seasons)	⊕⊕◯◯ LOW [a,d]
Influenza- related office visits	**VE 3.5%** (1.5 to 5.5)	2 observational studies (3 influenza seasons)	⊕⊕◯◯ LOW [a,d]

VE: Vaccine effectiveness [(1 – Odds Ratio)*100%]

CI: Confidence interval
*Given the outcome of interest typically incorporating adjustments results are not presented as raw rates

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to risk of bias
b. Downgraded one level due to inconsistency in results
c. Downgraded two levels due to very serious risk of bias
d. Downgraded one level due to imprecision

Safety of HD-IIV compared with SD-IIV

Patient or population: Adults (aged ≥18 years)
Setting: All settings
Intervention: HD-IIV3 or HD-IIV4
Comparison: SD-IIV3 OR SD-IIV4

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with SD-IIV	Risk with HD-IIV			
Ecchymosis	45 per 1 000	45 per 1 000 (25 to 80)	**RR 1.00** (0.56 to 1.80)	938 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Induration	79 per 1 000	128 per 1 000 (87 to 188)	**RR 1.63** (1.10 to 2.39)	938 (2 RCTs)	⊕⊕◯◯ LOW [a,b]
Redness-erythema	121 per 1 000	170 per 1 000 (110 to 263)	**RR 1.41** (0.91 to 2.18)	5 625 (7 RCTs)	⊕⊕◯◯ LOW [a,b]
Swelling	53 per 1 000	116 per 1 000 (59 to 228)	**RR 2.20** (1.12 to 4.32)	5 524 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Headache	142 per 1 000	191 per 1 000 (145 to 251)	**RR 1.35** (1.02 to 1.77)	5 645 (7 RCTs)	⊕⊕◯◯ LOW [a,c]
Malaise	142 per 1 000	181 per 1 000 (153 to 215)	**RR 1.28** (1.08 to 1.51)	5 622 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]
Myalgia	174 per 1 000	241 per 1 000 (174 to 333)	**RR 1.39** (1.00 to 1.92)	5 625 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]
Shiver-chills	62 per 1 000	107 per 1 000 (66 to 174)	**RR 1.73** (1.07 to 2.81)	1 278 (4 RCTs)	⊕⊕◯◯ LOW [a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to risk of bias (See Figures 3.42 and 3.43)
b. Downgraded one level due to imprecision
c. Downgraded one level due to inconsistency in results

Appendix 9.3 Cell-based influenza vaccines

Safety of ccIIV3 compared with IIV3

Patient or population: Adults (aged ≥18 years)
Setting: All settings
Intervention: ccIIV3
Comparison: IIV3

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with IIV3	Risk with ccIIV3			
Redness-erythema	123 per 1 000	120 per 1 000 (100 to 145)	**RR 0.98** (0.81 to 1.18)	15 396 (6 RCTs)	⊕⊕⊕◯ MODERATE [a]
Swelling	48 per 1 000	52 per 1 000 (37 to 72)	**RR 1.08** (0.77 to 1.51)	15 396 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Induration	60 per 1 000	58 per 1 000 (44 to 75)	**RR 0.96** (0.74 to 1.25)	13 516 (4 RCTs)	⊕⊕◯◯ LOW [a,b]
Ecchymosis	30 per 1 000	38 per 1 000 (31 to 47)	**RR 1.27** (1.03 to 1.56)	10 308 (3 RCTs)	⊕⊕◯◯ LOW [a,c]
Chills	50 per 1 000	56 per 1 000 (32 to 98)	**RR 1.12** (0.64 to 1.95)	14 247 (5 RCTs)	⊕⊕◯◯ LOW [a,b]
Arthralgia	31 per 1 000	38 per 1 000 (28 to 51)	**RR 1.22** (0.90 to 1.66)	13 516 (4 RCTs)	⊕⊕◯◯ LOW [a,b]
Myalgia	100 per 1 000	111 per 1 000 (90 to 138)	**RR 1.11** (0.90 to 1.38)	15 396 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Malaise	86 per 1 000	95 per 1 000 (65 to 139)	**RR 1.11** (0.76 to 1.62)	14 665 (5 RCTs)	⊕⊕◯◯ LOW [a,b]
Headache	143 per 1 000	150 per 1 000 (130 to 173)	**RR 1.05** (0.91 to 1.21)	15 396 (6 RCTs)	⊕⊕⊕◯ MODERATE [a]
Fatigue	115 per 1 000	120 per 1 000 (86 to 164)	**RR 1.04** (0.75 to 1.43)	13 516 (4 RCTs)	⊕⊕◯◯ LOW [a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to risk of bias (See Figures 3.64 and 3.65)
b. Downgraded one level due to imprecision
c. Downgraded one level due to inconsistency in results

Appendix 9.4 Recombinant HA influenza vaccines

Safety of RIV compared with IIV

Patient or population: Adults (aged ≥18 years)
Setting: All settings
Intervention: RIV3 or RIV4
Comparison: IIV3 or IIV4

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with IIV	Risk with RIV			
Redness-erythema	32 per 1 000	38 per 1 000 (21 to 69)	**RR 1.18** (0.64 to 2.15)	14 895 (6 RCTs)	⊕⊕⊕◯ MODERATE [a]
Swelling	41 per 1 000	37 per 1 000 (20 to 70)	**RR 0.91** (0.48 to 1.72)	12 367 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Tenderness	292 per 1 000	257 per 1 000 (193 to 348)	**RR 0.88** (0.66 to 1.19)	13 821 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Chills	45 per 1 000	60 per 1 000 (47 to 78)	**RR 1.33** (1.03 to 1.72)	4 555 (3 RCTs)	⊕⊕◯◯ LOW [a,c]
Fatigue	64 per 1 000	57 per 1 000 (47 to 68)	**RR 0.89** (0.74 to 1.06)	14 930 (6 RCTs)	⊕⊕◯◯ LOW [a,b]
Headache	60 per 1 000	47 per 1 000 (19 to 119)	**RR 0.79** (0.32 to 1.98)	11 668 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]
Myalgia	43 per 1 000	42 per 1 000 (31 to 55)	**RR 0.97** (0.73 to 1.29)	14 269 (6 RCTs)	⊕⊕⊕◯ MODERATE [a]
Nausea	39 per 1 000	47 per 1 000 (30 to 73)	**RR 1.19** (0.76 to 1.86)	5 597 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to risk of bias (See Figrues 3.76 and 3.77)
b. Downgraded one level due to imprecision
c. Downgraded one level due to inconsistency

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