EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

TECHNICAL REPORT

Systematic review update on 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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This review was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities of the ECDC's EU/EEA NITAG Collaboration, in close cooperation with the European Commission and the European Health and Digital Executive Agency (HaDEA). The commissioning and production of this review was coordinated by Karam Adel Ali (ECDC) and Kate Olsson (ECDC).

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Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
CI	Confidence interval
ED	Emergency department
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HD	High-dose influenza vaccine
HSP	Henoch-Schönlein purpura
ICU	Intensive care unit
IP	Inpatient
ITT	Intention-to-treat
ITP	Idiopathic thrombocytopenic purpura
mRNA	messenger RNA
NITAG	National Immunization Technical Advisory Group
NRSI	Non-randomised study of the effects of interventions
OR	Odds Ratio
PCR	Polymerase chain reaction
PRESS	Peer Review of Electronic Search Strategies
PROSPERO	Prospective Register of Systematic Reviews
RCT	Randomised controlled trial
RoB	Risk of Bias
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
RR	Risk Ratio
rVE	Relative vaccine effectiveness
SAE	Serious adverse events
SD	Standard-dose influenza vaccine (tri- or quadrivalent egg-based standard-dose influenza vaccine containing 15 µg HA)
SoF	Summary of findings
VE	Vaccine efficacy/effectiveness
WHO	World Health Organization

Executive summary

Seasonal influenza is a respiratory infectious disease that spreads globally through annual epidemics and occasional pandemics. Vaccination is the most effective means for preventing influenza infection. However, the effectiveness of influenza vaccines varies to some degree from season to season, and is influenced by factors such as the health status and immune competence of the recipient, and the degree of match between circulating vaccine strains and the vaccine production process. The intrinsic factors that influence vaccine response result in the effectiveness of standard influenza vaccines being suboptimal in specific population groups. The response to standard influenza vaccine is reduced, especially among groups that are at higher risk of a severe disease outcome, such as the elderly and people with immunocompromising conditions. Therefore, in recent years, newer and/or enhanced influenza vaccines have been developed in an attempt to further improve vaccine effectiveness.

In 2020, ECDC conducted a systematic review of the efficacy, effectiveness and safety of newer and/or enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over, which covered literature up to 7 February 2020 (herein referred to as the primary review). In this report, we present an update of the 2020 primary systematic review, to take into account more recent evidence on the efficacy, effectiveness and safety of newer and/or enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over, with a search period from 1 January 2020 to 24 July 2023.

For this update a total of 1 561 new entries in databases were retrieved. After title/abstract and full-text screening, a total of 17 new studies (seven studies on efficacy/effectiveness, 10 studies on safety) were included in the updated review. These 17 newer studies were added to the 42 studies (10 studies on efficacy/effectiveness, 32 studies on safety) which were identified in the primary review, forming a total evidence body of 59 studies analysed. The current report describes the entire body of evidence from both the primary review and this update review. Risk of bias was assessed to be low-to-moderate in all efficacy/effectiveness studies and low-to-serious in safety studies.

Relative vaccine effectiveness (rVE) was used to describe the effect of the newer and/or enhanced influenza vaccines compared to the standard vaccines. We considered studies that reported data on at least one of the following newer and/or enhanced seasonal tri- or quadrivalent influenza vaccines:

- MF59-adjuvanted trivalent or quadrivalent vaccine[1];
- high-dose trivalent or quadrivalent inactivated vaccine[2];
- trivalent or quadrivalent inactivated cell-based vaccine[3];
- recombinant trivalent or quadrivalent HA vaccine[4];
- quadrivalent mRNA-based vaccine[5].

[1]E.g. Fluad/Fluad Tetra, produced by Seqirus
[2]E.g. Fluzone/Fluzone Quadrivalent produced by Sanofi Pasteur
[3]E.g. Flucelvax/Flucelvax tetra produced by Seqirus
[4]E.g. Flublok/Flublok Quadrivalent produced by Sanofi Pasteur
[5]E.g. mRNA-1010 by Moderna, MRT5407 and MRT4113 by Sanofi Pasteur.

Valid comparators were standard influenza vaccines (tri- or quadrivalent egg-based standard-dose influenza vaccine) or one of the above-mentioned newer and/or enhanced seasonal tri- or quadrivalent influenza vaccines (i.e. head-to-head comparison between newer and/or enhanced vaccines).

For the MF59-adjuvanted vaccine, rVE estimates against laboratory-confirmed influenza (all strains) ranged between -30% (95%CI: -146 to 31%) and 88% (95%CI: 51 to 100) (seven NRSI; low certainty of evidence). Metanalysis was not performed due to the heterogeneity of the estimates. The rVE estimate against laboratory-confirmed influenza-related hospitalisation (all strains) was 59.2% (95%CI: 14.6 to 80.5%) (one NRSI; moderate certainty). No data were available for rVE against influenza-related death. No increased risk was detected for MF59-adjuvanted vaccine-related serious adverse events (three RCT, two NRSI; low certainty of evidence). Overall, for the MF59-adjuvanted vaccine, certainty was assessed as being low for the outcome laboratory-confirmed influenza and moderate for influenza-related hospitalisation. No assessment was possible for influenza-related death due to lack of data. For serious adverse events, certainty of evidence was low.

For the high-dose vaccine, the rVE estimate against laboratory-confirmed influenza (all strains) was 24.2% (95%CI: 9.7 to 36.5%) in one RCT (moderate certainty of evidence) and ranged from -9% (95%CI: -158 to 54%) to 19% (95%CI: -27 to 48%) in one NRSI, depending on the outcome. The rVE estimate against laboratory-confirmed influenza-related hospitalisation (all strains) was 27% (95%CI: -1 to 48%) (one NRSI; low certainty). No data were available for rVE against influenza-related death. No increased risk was detected for high-dose vaccine-related serious adverse events (six RCT, three NRSI; low certainty of evidence). Overall, for high-dose vaccine, certainty of evidence was moderate for the outcome laboratory-confirmed influenza. Certainty was assessed to be low for influenza-related hospitalisation. No assessment was possible for influenza-related death due to lack of data. For serious adverse events, certainty of evidence was low.

For the cell-based vaccine, rVE estimates against laboratory-confirmed influenza ranged from -5.8% (95%CI: -36.1 to 17.7%) (influenza A) to 21.4% (95%CI: -7.3 to 42.4%) (influenza B) (two NRSI; low certainty of evidence). The rVE estimate against laboratory-confirmed influenza-related hospitalisation (all strains) was 8.5% (95%CI: -75.9 to 52.3%) (one NRSI; low certainty of evidence). No data were available for rVE against influenza-related death. No increased risk was detected for cell-based vaccine-related serious adverse events (one RCT; low certainty of evidence). Overall, for the cell-based vaccine, certainty of evidence was low for the outcome laboratory-confirmed influenza. Certainty was low for influenza-related hospitalisation. No assessment was possible for influenza-related death due to lack of data. For serious adverse events, certainty of evidence was low.

For the recombinant vaccine, the rVE estimate against laboratory-confirmed influenza (all strains) was 30% (95%CI: 10 to 47%) in one RCT (moderate certainty of evidence) and ranged between 3% (95%CI: -31 to 28%) and 19% (95%CI: -27 to 48%) in one NRSI, depending on the outcome. Relative VE against laboratory-confirmed influenza-related hospitalisation (all strains) was -7.3% (95%CI: -52.1 to 24.4%) (18−49 years of age) and 16.3% (95%CI: -8.7 to 35.5%) (50−64 years of age) (one RCT; certainty of evidence not assessed due to lack of information). No data were available for rVE against influenza-related death. No increased risk was detected for recombinant vaccine-related serious adverse events (two RCT, two NRSI; low certainty of evidence). Overall, for the recombinant vaccine, certainty of evidence was assessed to be moderate for laboratory-confirmed influenza. No assessments were possible for influenza-related hospitalisation (not enough information, only conference abstract available) and influenza-related death (no data). For serious adverse events, certainty of evidence was low.

No data on rVE or safety of the mRNA-based vaccine were available.

Overall, low-to-moderate relative vaccine effectiveness was found for the MF59-adjuvanted vaccine, the high-dose vaccine and the recombinant vaccine for laboratory confirmed influenza. Low-to-moderate relative vaccine effectiveness was also found for the MF59-adjuvanted vaccine and the high-dose vaccine for laboratory-confirmed influenza-related hospitalisation. In this update of the 2020 primary systematic review, the evidence on rVE of newer and/or enhanced influenza vaccines compared to standard vaccines is still limited. No data was found on head-to-head comparison between the different new and/or enhanced vaccines. A larger evidence base is available on safety, demonstrating an overall favourable safety profile for all vaccines included in the review. Further studies are needed to allow more substantial conclusions on the potential benefits of the newer and/or enhanced influenza vaccines.

Summary of findings

Standard vaccines are defined as any vaccine other than MF-59 adjuvanted, high-dose vaccine, cell-based vaccine, recombinant vaccines and m-RNA vaccines.

Table 1. Summary of findings on relative effectiveness and safety of MF59-adjuvanted influenza vaccine versus standard influenza vaccine in adults

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Assessment
		With standard influenza vaccine	MF59-adjuvanted influenza vaccine	**Difference**		
Laboratory confirmed influenza. No. of participants: 10 492 (seven observational studies)	**rVE-range: -30** (-146 to 31) **to 88** (51 to 100)	NA.	NA	NA	⊕⊕◯◯ Low[a,b]	MF59-adjuvanted influenza vaccines may or may not reduce laboratory-confirmed influenza infection in adults compared to standard vaccine.
Influenza-related hospitalisation (laboratory confirmed) No. of participants: 512 (one observational study)	**rVE 59.2** (14.6 to 80.5)	NA	NA	NA	⊕⊕⊕◯ Moderate[a]	MF59-adjuvanted influenza vaccines probably reduce hospitalisation related to laboratory-confirmed influenza infection in adults compared to standard vaccine.
Influenza-related death (laboratory confirmed)	-	-	-	-	-	No data reported.
Serious adverse event (SAE) Number of participants: 8 504 (three RCTs)	**RR 0.95** (0.19 to 4.72)	0.1%	**0.1%** (0 to 0.3)	**0.0% fewer** (0.1 fewer to 0.3 more)	⊕⊕◯◯ Low[c,d]	MF59-adjuvanted influenza vaccines may result in little-to-no difference in serious adverse events (SAEs) compared to the standard vaccine.
Idiopathic thrombocytopenic purpura	-	-	-	-	-	No data reported.
Narcolepsy/cataplexy	-	-	-	-	-	No data reported.
Guillain–Barré syndrome (GBS)	-	-	-	-	-	No data reported.

*__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; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

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. Residual confounding cannot be excluded.
b. Heterogeneous point estimates between the studies.
c. High risk of bias in two out of three studies.
d. Wide confidence interval.

Table 2. Summary of findings on relative effectiveness and safety of high-dose influenza vaccine versus standard influenza vaccine in adults

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Assessment
		With standard influenza vaccine	High-dose influenza vaccine	Difference		
Laboratory confirmed influenza (lab confirmed) assessed with PCR Number of participants: 31 989 (one RCT)	**rVE 24 (11 to 36)**	1.9%	**1.4**% (1.2 to 1.7)	**0.5**% **fewer** (0.7 fewer to 0.2 fewer)	⊕⊕⊕◯ Moderate[a]	High-dose influenza vaccines probably slightly reduce laboratory-confirmed influenza infection in adults.
Influenza-related hospitalisation (laboratory confirmed) assessed with PCR Number of participants: 1 107 (one NRSI)	**rVE 27** (-1 to 48)	NA	NA	NA	⊕⊕◯◯ Low[b,c]	High-dose influenza vaccines may slightly reduce hospitalisation related to laboratory-confirmed influenza infection in adults.
Influenza-related death (laboratory confirmed)	-	-	-	-	-	No data reported.
Serious adverse events (SAE) Number of participants: 9 034 (six RCTs)	**RR 1.02** (0.42 to 2.46)	0.2%	**0.2**% (0.1 to 0.6)	**0.0**% **fewer** (0.1 fewer to 0.4 more)	⊕⊕◯◯ Low[c,d]	High-dose influenza vaccines may result in little to no difference in serious adverse events (SAEs) related to vaccination.
Idiopathic thrombocytopenic purpura	-	-	-	-	-	No data reported.
Narcolepsy/cataplexy	-	-	-	-	-	No data reported.
Guillain–Barré syndrome (GBS)	-	-	-	-	-	No data reported.

*__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; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

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.
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⊕◯◯◯ **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. One RCT with moderate risk of bias.
b. Residual confounding cannot be excluded.
c. Wide confidence interval.
d. Moderate risk of bias for three out of six studies.

Table 3. Summary of findings on relative effectiveness and safety of cell-based influenza vaccine versus standard influenza vaccine in adults

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Assessment
		With standard influenza vaccine	With cell-based influenza vaccine	Difference		
Laboratory-confirmed influenza (lab-confirmed) assessed with PCR. Number of participants: 1 025 097 (two observational studies)	**rVE-range -5.8** (-36.1 to 17.7) **to 21.4** (-7.3 to 42.4)	NA	NA	NA	⊕⊕◯◯ Low[a]	Cell-based influenza vaccines may or may not reduce laboratory-confirmed influenza infection in adults.
Influenza-related hospitalisation (lab-confirmed) assessed with PCR. Number of participants: 1 741 (one observational study).	**rVE 8.5** (-75.9 to 52.3)	NA	NA	NA	⊕⊕◯◯ Low[a,b]	Evidence is uncertain as to whether cell-based influenza vaccines reduce hospitalisation related to laboratory-confirmed influenza infection in adults.
Influenza-related death (laboratory confirmed).	-	-	-	-	-	No data reported.
Serious adverse events (SAE) Number of participants: 3 208 (one RCT)	**RR 0.39** (0.02 to 9.49)	NA	NA	NA	⊕⊕◯◯ Low[b]	Cell-based influenza vaccines may or may not decrease serious adverse events (SAEs) related to vaccination.
Idiopathic thrombocytopenic purpura	-	-	-	-	-	No data reported.
Narcolepsy/cataplexy	-	-	-	-	-	No data reported.
Guillain–Barré syndrome (GBS)	-	-	-	-	-	No data reported.

*__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; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

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.
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⊕◯◯◯ **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. Residual confounding cannot be excluded.
b. Wide confidence interval.

Table 4. Summary of findings on relative effectiveness and safety of recombinant influenza vaccine versus standard influenza vaccine in adults

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Assessment
		With standard influenza vaccine	With recombinant influenza vaccine	Difference		
Laboratory confirmed influenza (lab-confirmed) assessed with PCR Number of participants: 8 855 (one RCT).	**rVE 30** (10 to 47)	**3.1%**	**2.2%** (1.7 to 2.8)	**0.9% fewer** (1.5 fewer to 0.3 fewer)	⊕⊕⊕◯ Moderate[a]	Recombinant influenza vaccines probably slightly reduce laboratory-confirmed influenza infection in adults.
Influenza-related hospitalisation (lab-confirmed) assessed with PCR Number of participants: 1 630 328 (one RCT)	-	Certainty of the evidence could not be assessed due to lack of information.		-	-	NA
Influenza-related death (laboratory confirmed)	-	-	-	-	-	No data reported.
Serious adverse events (SAE) Number of participants: 907 (two RCTs).	**RR 3.04** (0.32 to 29.10)	NA	NA	NA	⊕⊕◯◯ Low[b]	Recombinant influenza vaccines may or may not result in an increase in serious adverse events (SAEs) related to vaccination.
Idiopathic thrombocytopenic purpura Number of participants: 42 684 (one observational study).	**OR 0.52** (0.15 to 1.50)	NA	NA	NA	⊕⊕◯◯ Low[c,d]	Recombinant influenza vaccines may or may not result in a decrease in idiopathic thrombocytopenic purpura related to vaccination.
Narcolepsy/cataplexy Number of participants: 305 659 (one observational study).	**OR 0** (0 to 6)	NA	NA	N.A.	⊕◯◯◯ Very low[d,e]	Evidence is uncertain for the effect of recombinant influenza vaccines on narcolepsy/cataplexy related to vaccination.
Guillain–Barré syndrome (GBS) Number of participants: 305 659 (one observational study).	**OR 0.00** (0.00 to 16.07)	NA	NA	N.A.	⊕◯◯◯ Very low[d,e]	Evidence is uncertain for the effect of recombinant influenza vaccine on Guillain–Barré syndrome related to vaccination.

*__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; **OR:** odds ratio; **RR:** risk ratio; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

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. One RCT with moderate risk of bias.
b. Two RCTs with moderate risk of bias.
c. Residual confounding cannot be excluded.
d. Wide confidence interval.
e. No adjustment for co-morbidities, even though there was a significant difference between the groups.

1. Background

Influenza is a respiratory infectious disease that spreads globally through seasonal epidemics and occasional pandemics [1, 2]. The virus is mainly transmitted between individuals through droplets, indirect contact, and aerosols [3]. Influenza viruses belong to the *Orthomyxoviridae* family, which consists of RNA viruses that are categorised into four distinct types [2]. In humans, the most commonly observed types are influenza A and B, which are responsible for the majority of infections.

Before the emergence of the novel coronavirus (SARS-CoV-2) in December 2019, influenza was considered to have one of the greatest impacts on disability-adjusted life years of all infectious diseases in Europe [4]. During the 2017−2018 influenza season in Europe, the estimated all-cause influenza-attributable mortality was 25.4 (95% CI 25.0 to 25.8) per 100 000 population [5]. The burden of seasonal influenza is influenced by various factors such as the circulating strain[s], including antigenic drift; immunity in the population after previous infection and the extent of vaccination coverage [6].

Vaccination is the most effective means for preventing influenza infection. However, the effectiveness of influenza vaccines varies to some degree from season to season and is influenced by factors such as the health status and immune competence of the recipient, the degree of match between circulating vaccine strains and vaccine production process [1]. As a result, the effectiveness of standard influenza vaccines is known to be suboptimal in specific population groups [7]. The response to standard influenza vaccine is reduced, especially among groups that are at higher risk of a severe disease outcome, such as the elderly and people with immunocompromising conditions. Consequently, there are many efforts and ongoing developments to increase the effectiveness of influenza vaccination, particularly for these groups of people. Newer and enhanced influenza vaccines, such as high-dose, recombinant, cell-based or MF59-adjuvanted seasonal influenza vaccines, have been developed in an attempt to improve vaccine effectiveness [7].

In 2020, a systematic review of the efficacy, effectiveness and safety of newer and/or enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged ≥ 18 years was conducted by the Irish Health Information and Quality Authority (HIQA) under contract to the European Centre for Disease Prevention and Control (ECDC). The review covered data published up to 7 February 2020 [8-12]. The aim of the systematic review (herein referred to the primary review) was to assess and synthesise the available evidence on the efficacy, effectiveness and safety of newer and/or 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. While the safety profiles of these vaccines were generally consistent with expectations, based on their individual compositions, and were well-tolerated, the overall evidence for the efficacy and effectiveness of newer and/or enhanced inactivated influenza vaccines was limited at that time. However, the primary review identified a number of potentially relevant studies that were still ongoing. This emphasised the need to update the systematic review in order to complement the evidence available on efficacy, effectiveness and safety of newer and/or enhanced seasonal influenza and include new developments, such as messenger RNA (mRNA)-based influenza vaccine, to facilitate and support future decision-making on the use of such vaccines.

2. Objectives

The aim of this systematic review update is to review, assess and synthesise the recent literature (published up to the date of the last search on 24 July 2023) on newer and/or enhanced inactivated seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥ 18 years of age [8].

The following key questions are addressed:

- What is the efficacy, effectiveness and safety of trivalent and quadrivalent egg-based MF59-adjuvanted seasonal influenza vaccine[6] by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent and quadrivalent egg-based high-dose seasonal influenza vaccine[7] by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent and quadrivalent cell-based seasonal influenza vaccine[8] by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of trivalent and quadrivalent recombinant HA seasonal influenza vaccine[9] by influenza type, subtype (clade if available), age and risk group?
- What is the efficacy, effectiveness and safety of a quadrivalent messenger RNA (mRNA)-based influenza vaccine[10] by influenza type, subtype (clade if available), age and risk group?

The protocol for this systematic review and meta-analyses has been developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2020 statement (http://www.prisma-statement.org/). This review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023441114 [13].

[6] E.g. Fluad/Fluad Tetra produced by Seqirus.
[7] E.g. Fluzone/Fluzone Quadrivalent produced by Sanofi Pasteur.
[8] E.g. Flucelvax/Flucelvax Tetra produced by Seqirus.
[9] E.g. Flublok/Flublok Quadrivalent produced by Sanofi Pasteur.
[10] E.g. mRNA-1010 by Moderna, MRT5407 and MRT4113 by Sanofi Pasteur

3. Review methods

3.1 Types of studies

We considered randomised controlled trials (RCTs) with randomisation either at the individual or cluster level. Non-randomised studies (NRSI) were also considered, as long as they had a control group. This included:

- studies in which participants (individuals or clusters of individuals) are allocated to different groups (intervention and control group) using methods that are not random;
- observational studies (i.e. prospective and retrospective cohort studies using a longitudinal or cross-sectional design, case control studies and test-negative design studies). In observational studies the allocation to the group is not determined by the study investigators, but by the nature of other factors outside the control of the investigator;
- any in-human studies of the above-described study designs. Study reports should preferably have been published in a peer-reviewed journal, however, non-peer reviewed data were also considered, if sufficient information on study methods and results was available.

3.2 Types of participants

We considered studies performed in subjects ≥18 years, irrespective of health status or setting.

3.3 Types of interventions

We considered studies that applied at least one of the following newer and/or enhanced seasonal tri- or quadrivalent influenza vaccines:

- adjuvanted trivalent or quadrivalent vaccine[11];
- high-dose trivalent or quadrivalent inactivated vaccine[12];
- trivalent or quadrivalent inactivated cell-based vaccine[13];
- recombinant trivalent or quadrivalent HA vaccine[14];
- quadrivalent mRNA-based vaccine[15].

3.4 Types of comparators

Valid comparators were tri- or quadrivalent standard influenza vaccines or one of the above-mentioned newer and/or enhanced seasonal tri- or quadrivalent influenza vaccines (head-to-head comparison between newer and/or enhanced vaccines).

3.5 Types of outcome measures

3.5.1 Timing of outcome measurement

We extracted end-of-season outcome measure estimates for each season reported. If end of season estimates were not available, we extracted interim or partial season estimates.

3.5.2 Primary outcome measures

Efficacy and effectiveness outcomes

We assessed the following primary efficacy and effectiveness outcomes:

- laboratory-confirmed influenza (a positive laboratory diagnosis by PCR, virus culture or antigen detection);
- influenza-related hospitalisation (laboratory-confirmed by PCR, virus culture or antigen detection);
- influenza-related death (laboratory-confirmed by PCR, virus culture or antigen detection).

[11]E.g. Fluad/Fluad Tetra, produced by Seqirus
[12]E.g. Fluzone/Fluzone Quadrivalent produced by Sanofi Pasteur
[13]E.g. Flucelvax/Flucelvax tetra produced by Seqirus
[14]E.g. Flublok/Flublok Quadrivalent produced by Sanofi Pasteur
[15]E.g. mRNA-1010 by Moderna, MRT5407 and MRT4113 by Sanofi Pasteur.

Safety outcomes

We assessed the following primary safety outcomes:

- serious adverse events (requiring intervention to prevent disability or permanent damage, resulting in disability or permanent damage, initial or prolonged hospital care, congenital anomaly/birth defect, life-threatening, or resulting in death).

3.5.3 Secondary outcome measures

Efficacy and effectiveness outcomes

We assessed the following secondary efficacy and effectiveness outcomes:

- influenza-related ICU admissions (laboratory-confirmed by PCR, virus culture or antigen detection);
- influenza-associated pneumonia/lower respiratory tract disease (laboratory-confirmed by PCR, virus culture or antigen detection);
- influenza-associated cardiovascular disease (laboratory-confirmed by PCR, virus culture or antigen detection);
- influenza-like illness (ILI) (symptoms of influenza only). Internationally accepted case definitions to be used (e.g. WHO, US CDC, EU[16]).

Safety outcomes

We assessed the following secondary safety outcomes:

- Systemic adverse events (e.g. malaise, nausea, fever, arthralgia, myalgia, rash, headache and more generalised and serious signs, such as neurological harm). After consultation with the experts of the Influenza Working Group, it was decided to focus the analysis on headache and fever as the most relevant and mainly reported events.
- Local adverse events (e.g. pain, erythema, oedema/swelling, induration). After consultation with the experts of the Influenza Working Group, it was decided to focus the analysis on pain and swelling as the most relevant and mainly reported local adverse events.
- Adverse pregnancy outcomes after vaccination during pregnancy: spontaneous abortion, foetal death, stillbirth, pre-term birth (less than 37 weeks), pre-eclampsia and eclampsia.
- Adverse neonatal outcomes after vaccination during pregnancy: congenital malformations (minor and major), neonatal death, and small-for-gestational-age.

3.6 Search methods for identification of studies

3.6.1 Literature searches

Comprehensive systematic literature searches for relevant studies were conducted by following the recommendation of PRESS (Peer Review of Electronic Search Strategies) [14]. The full electronic search strategies were peer-reviewed by an information specialist and validated by checking whether the strategy identified studies already known.

For this update of a systematic review [8] a search for literature published after 1 January 2020 (date of last search of primary review: 7 February 2020) was conducted on 24 July 2023 [8]. No language filters were applied. For each database, the date of the search, the search strategy as well as the number of search results were documented. Search strategies for the databases mentioned below were adapted from the (initial) Medline strategy. The complete search strategies are reported in Annex 1.

3.6.2 Searches for published studies

Searches for published studies were conducted in the following electronic data sources:

- Medline (ALL) (via Ovid);
- Embase (via Ovid).

3.6.2 Searches for unpublished and ongoing studies

Searches for ongoing studies or unpublished completed studies were performed in ClinicalTrials.gov (www.clinicaltrials.gov).

[16] WHO definition: an acute respiratory infection with: measured fever of ≥38°C and cough with onset within the last 10 days. US CDC definition: fever (temperature of 37.8°C or greater) and a cough and/or a sore throat in the absence of a known cause other than influenza. EU definition: sudden onset of at least one among: fever, feverishness, headache, malaise, myalgia, and at least one among: cough, sore throat, shortness of breath.

3.6.3 Supplementary searches

We used relevant studies and/or systematic reviews to search for additional references via the Pubmed similar articles function (https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020_190.html) and forward citation tracking. Reference lists of studies included were reviewed and experts in the field were contacted to enquire about any further relevant studies or unpublished data that may not have been retrieved by the electronic searches. In addition, a search was conducted in sources, including websites of regulatory agencies (European Medicines Agency (EMA) and the US Food and Drug Administration (FDA)).

3.7 Data collection and analysis

3.7.1 Study selection and management

Titles and abstracts of the citations identified by the searches were independently screened by two reviewers (title and abstract screening), and full texts of all potentially relevant articles were obtained. Full texts were also independently checked for eligibility by two reviewers, and reasons for exclusion were documented (full text screening). Any disagreement was resolved by consensus, moderated by a third reviewer. The Covidence® software was used for literature screening.

3.7.2 Data extraction

Two pairs of review authors extracted the following study data and tabulated all relevant information:

- Study characteristics including:
  - author and year of publication
  - study design;
  - start and end of study;
  - Sample size (total and for each study arm);
  - funding sources;
  - conflict of interest disclosures.
- Setting including:
  - setting (outpatients, inpatients, long-term care facilities, etc.)
  - influenza season and dominant influenza strain/clade, if match to vaccine-strain/clade;
  - geographical setting.
- Characteristics of the participants including:
  - age;
  - sex;
  - comorbidities;
  - geographical area;
  - pregnancy.
- Ascertainment of vaccination status including:
  - self-reported;
  - medical chart review;
  - immunisation registry.
- Characteristics of the intervention/exposure including:
  - type of vaccine (inactivated adjuvanted, high-dose, cell-based, recombinant, mRNA by brand);
  - type of virus.
- Characteristics of the comparator including:
  - type of comparison intervention
    - standard influenza vaccines (standard trivalent, quadrivalent by brand);
    - new/enhanced influenza vaccines (inactivated adjuvanted, high-dose, cell-based, recombinant, mRNA by brand).
- Outcome measures including:
  - reported outcomes and results including method of laboratory confirmation (PCR, virus culture or antigen detection);
  - outcome description including unit of measurement;
  - time between vaccination and outcome measurement (follow-up);
  - NRSI: where adjusted data (including covariates adjusted for) were available, these data were used; where adjusted data were not available, we extracted the unadjusted data as reported in the study;
  - RCT: we used unadjusted data;
  - cluster-RCT: we used adjusted data, where available.

Data extraction forms were piloted for different study designs. Disagreements in extracted data between the two reviewers were resolved through discussion until consensus was reached, involving a third reviewer if necessary. If necessary, authors of studies were contacted to provide any missing information or clarify any issues.

3.7.3 Assessment of risk of bias in the studies included

Risk of bias of each study included study was independently assessed by pairs of two authors by outcome level. Any disagreement was resolved by consensus, moderated by a third reviewer.

Bias in an RCT was evaluated according to the revised Cochrane risk of bias tool for randomised trials (RoB 2) considering the following domains: (i) bias arising from the randomisation process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing outcome data; (iv) bias in measurement of the outcome; and (v) bias in selection of the reported result. These domains were judged as having 'low risk of bias', 'some concerns' or 'high risk of bias' [15, 16].

Bias in a NRSI was evaluated according to the 'Risk of Bias in Non-randomised Studies of Interventions' tool [ROBINS-I] considering the following domains: (i) bias due to confounding (e.g. age, socioeconomic differences); (ii) bias in selection of participants into the study (e.g. inception bias); (iii) bias in measurement of the intervention; (iv) bias due to departures from intended interventions; (v) bias due to missing data; (vi) bias in measurement of outcomes; (vii) bias in selection of the reported result; and (viii) overall bias [17]. Domains were judged as 'low,' 'moderate', 'serious', 'critical' or 'unclear' risk of bias.

Funnel plots for small study effects were constructed and visually inspected if ≥ ten studies were available addressing the same outcome [18].

3.7.4 Unit of analysis

The unit of analysis was the individual study participant.

3.7.5 Dealing with missing data

For RCTs, data were analysed - if possible - on intention-to-treat (ITT) basis or according to recently developed recommendations for systematic reviewers for addressing missing data in clinical studies [19].

3.7.6 Measures of treatment effect

Relative vaccine estimates (in terms of efficacy or effectiveness) were expressed in percentage and calculated as follows: $vaccine\ efficacy\ or\ effectiveness = [1 - vaccine\ effect\ ratio] \times 100$. We thereby used the vaccine effect ratio as reported in the primary study (e.g. odds ratio (OR), risk ratio (RR), hazard ratio (HR), or incidence rate ratio (IRR)). The precision of the vaccine effect estimates (in terms of efficacy or effectiveness) was summarised with the corresponding 95% confidence interval (CI).

3.7.7 Assessment of heterogeneity

Heterogeneity was evaluated and statistically quantified, where appropriate, based on I^2 and the statistical test chi square and visual inspection of the forest plot [19]. The following thresholds were used to interpret an I^2:

- 0% to 40%: might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- ≥ 75 %: considerable heterogeneity.

3.7.8 Data synthesis

Where appropriate, meta-analyses were conducted separately for each intervention (type of influenza vaccine) and separately for RCTs and NRSIs. Effect estimates were pooled by applying the inverse variance method. For metanalysis the fixed-effects model was used as primary model. Random-effects models were used as sensitivity analysis. For all meta-analyses the Mantel-Haenszel method was used.

Outcomes derived from a NRSI rated as critical (by using ROBINS-I) were not included in the meta-analysis to avoid misleading conclusions [20]. Meta-analyses were conducted with RevMan Web.

In general, if pooling was not considered to be appropriate, a narrative synthesis was prepared.

3.7.9 Subgroup analysis

We planned to conduct the following subgroup analyses using the random-effects model, if sufficient data were available:

- Characteristics of the population (see suggested analyses, Section 3.3.1)
  - Age (18-64, 65-74, 75-84, 65+, 85+ years);
  - Pregnancy (pregnant or not);
  - Comorbidities (≥1 versus none);
  - Immunocompromising condition or therapy (≥1 vs. none);
  - Pre-existing cardio-pulmonary diseases (≥1 versus none).
- Characteristics of the setting (see suggested analyses, Section 3.4)
  - Geographical location (e.g. low- and middle-income versus high-income countries);
  - Community-based study versus hospital-based versus nursing homes.

3.7.10 Sensitivity analysis

We planned to conduct sensitivity analyses according to the following characteristics, if data allowed:

- Risk of bias (exclusion of RCTs with a high risk (RoB 2), and exclusion of NRSI with serious or critical risk (ROBINS-I));
- Meta-analysis model (random-effects versus fixed-effects);
- Exclusion of studies with inexplicably high or low effects;
- Ascertainment of vaccination status (exclusion of studies with self-reported vaccination status);
- Study design (RCT versus NRSI; prospective versus retrospective);
- Type of publication [peer-reviewed versus non-peer-reviewed studies).

3.8 Summary of findings and certainty of the evidence assessment

3.8.1 Summary of findings table

We used the GRADEpro GDT to create a summary of findings table. We included the following primary outcomes:

- laboratory-confirmed influenza;
- influenza-related hospitalisation;
- influenza-related death;
- serious adverse events (requiring intervention to prevent disability or permanent damage, resulting in disability or permanent damage, initial or prolonged hospital care, congenital anomaly/birth defect, life-threatening, or resulting in death).

3.8.2 Assessment of certainty in the evidence

The certainty of evidence of selected patient-relevant outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [21]. The following prioritised outcomes were considered (i.e. primary outcomes defined under 3.1.4).

Efficacy/effectiveness

- laboratory-confirmed influenza (a positive laboratory diagnosis by PCR, virus culture or antigen detection);
- influenza-related hospitalisation (laboratory-confirmed by PCR, virus culture or antigen detection);
- influenza-related mortality (laboratory-confirmed by PCR, virus culture or antigen detection).

Safety

- Serious adverse events (requiring intervention to prevent disability or permanent damage, resulting in disability or permanent damage, initial or prolonged hospital care, congenital anomaly/birth defect, life-threatening, or resulting in death).

In brief, the GRADE assessment considers five domains different aspects including:

- study limitations (risk of bias);
- imprecision (when 95% confidence intervals are wide and/or are close to null effect around the point estimate or evidence was derived from only a few studies with a small number of participants);
- inconsistency (i.e. differences in effect estimates across studies that assessed the same comparison);
- indirectness (i.e. differences in patient characteristics, differing [co-] intervention, differing extent to which the intervention of interest is optimally conducted, differing comparator, and differences in measurement of outcome);
- Publication bias.

These domains were considered in addition to the underlying study design to rate the certainty of evidence for each outcome. For each of the considered domains, we downgraded our certainty by one level, in the event of serious concerns, or by two levels in the event of very serious concerns, resulting in the overall rating of high, moderate, low or very low for each evaluated outcome. In accordance with the GRADE guidelines for NRSI assessed with ROBINS-I, we started with a high certainty of evidence [22]. The narrative statements ('what happens'-column] were informed by GRADE guidelines 26 [23].

4. Review results

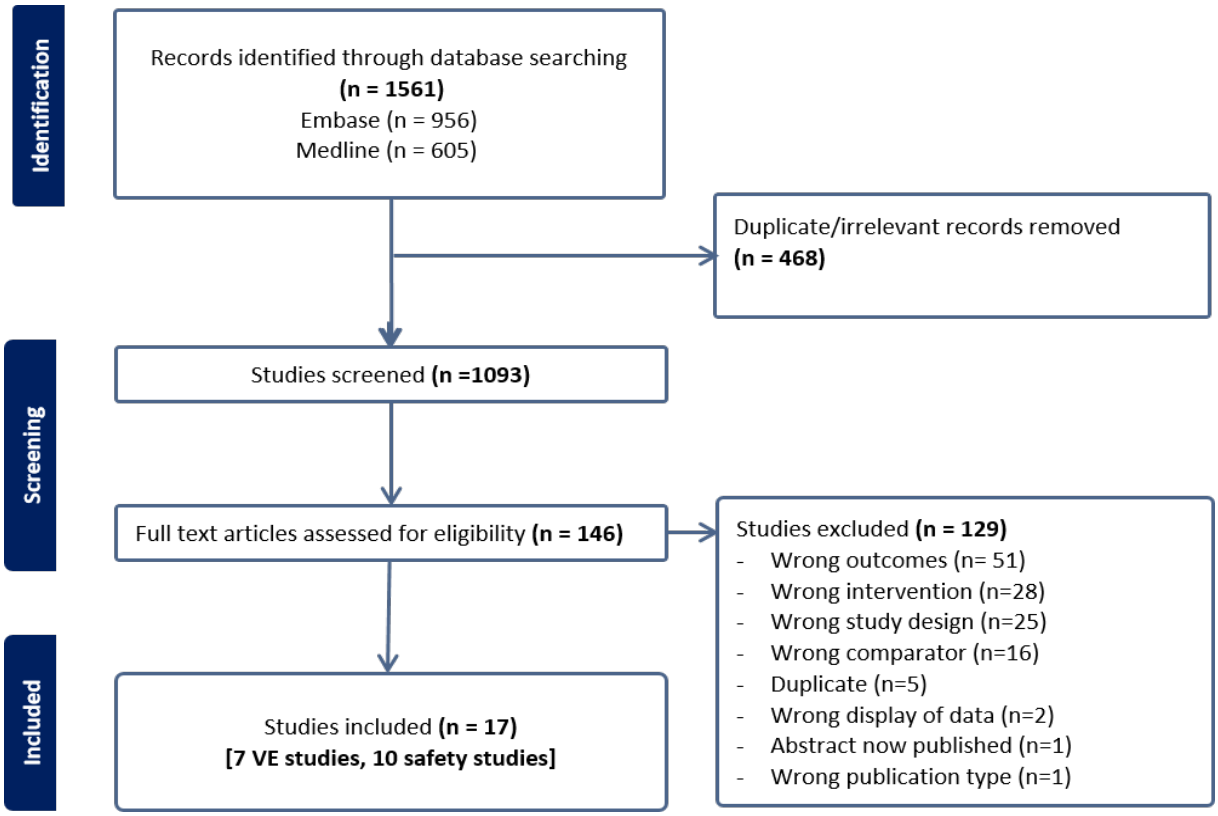
4.1 Description of studies

4.1.1 Results of the search

The literature search in the above-mentioned sources identified 1 561 records. No additional records were identified via searches of reference lists. After removing duplicates, 1 093 records remained. During title and abstract screening, we judged 947 records to be irrelevant. From the remaining 146 records, we excluded 129 records during full-text screening (see Annex 2 for records and exclusion reasons]. Finally, we included 17 new studies in this update of the systematic review. Of those, seven studies reported data on vaccine efficacy or effectiveness and 10 studies provided data on safety. The flow of records is illustrated in Figure 1.

In the primary review [8], a total of 110 studies were included. Of those studies, 10 studies on efficacy/effectiveness and 32 studies on safety met the inclusion criteria for this update review and were further considered. The evidence body for this updated systematic review therefore comprised 59 studies (42 studies from the primary review, plus the 17 studies from the updated review). The entire body of evidence will be described below.

Figure 1. PRISMA flow diagram of the update search



4.1.2 Characteristics of included studies

Efficacy/effectiveness studies

Details of studies that reported effectiveness data and were found in the update search are set out in Table 5. We included one cluster-RCT and six NRSI, two of which were retrospective cohort studies, while the other four had a test-negative design. The studies were performed in the USA or Italy and had about 500 to ≥1 million. participants. They reported rVE estimates for one to four influenza seasons between 2015/2016 and 2019/2020. Two studies investigated the high-dose influenza vaccine, another two studies reported rVE estimates for the cell-based vaccine and the recombinant vaccine. One study assessed the MF59-adjuvanted vaccine. No study reported on an mRNA-based influenza vaccine. Three studies reported a total of 10 rVE estimates against laboratory-confirmed influenza. The other four studies provided a total of 12 rVE estimates against laboratory-confirmed influenza-related hospitalisation. We did not identify rVE estimates for the other efficacy/effectiveness outcomes defined in the protocol.

In the primary review [8], there were a total of 10 studies identified that provided estimates of rVE against laboratory-confirmed outcomes compared to standard vaccine. For details on these studies, see Table 6 and Annex 5 (Appendix 5.1 to Appendix 5.4) in the primary review [8]. Seven of these studies reported rVE data on the MF59-adjuvanted vaccine, all of which were rVE estimates against laboratory-confirmed influenza. One study reported rVE of the high-dose vaccine against laboratory-confirmed influenza. One study reported rVE of the cell-based vaccine against laboratory-confirmed influenza. Another study reported this outcome for the recombinant vaccine. We did not identify rVE estimates for the other efficacy/effectiveness outcomes defined in the protocol of the primary review.

Table 5. Key characteristics of vaccine efficacy/effectiveness studies of update

Study	Intervention (Comparison)	Study design	Country	Funding	Setting	Outcome	Influenza season	Population	Number vacc	Mean age in years [SD]	Female sex %
Balasubramani 2020 [24]	HD-3v (vs. SD-3/4v)	Test-negative	USA	Non-industry funded	Outpatient	Influenza infection	2015-16, 2016-17, 2017-18, 2018-19	≥65 years	2 993	HD 73.6 (6.9) SD 73.3 (7.0)	HD 62.3 SD 61.4
Doyle 2021 [25]	HD-3v (vs. SD-3/4v)	Test-negative	USA	Non-industry funded	Inpatient	Influenza-related hospitalisation	2015-16, 2016-17	≥65 years	1 107	NA	57.3
Klein 2020 [26]	Cell-based-3v (vs. SD-3/4v)	Retrospective cohort	USA	Non-industry funded	Outpatient	Influenza infection	2017-18	4-64 years	1 016 965	NA	Cell-based 56.9 SD 56.4
Martin 2021 [27]	Cell-based-3v (vs. SD-3/4v)	Retrospective cohort	USA	Non-industry funded	Inpatient	Influenza-related hospitalisation	2017-18	≥18 years	2 350	NA	NA
Zimmerman 2023 [28]	Recombinant- 4v (vs. SD-3/4v)	Test-negative	USA	Industry funded	Outpatient	Medically attended outpatient influenza	2018-19, 2019-20	≥18 years, high-risk condition, immuno-compromised	1 553	51.5 [18.8]	65.6
Hsiao 2022 [29]	Recombinant- 4v (vs. SD-4v)	RCT	USA	Industry funded	Inpatient	Influenza-related hospitalisation	2018-19, 2019-20	≥18-64 years	1 630 328	NA	NA
Domnich 2022 [30]	MF59-3v (vs. SD-4v)	Test-negative	Italy	Non-industry funded	Inpatient	Influenza-related hospitalisation	2018-19, 2019-20	≥65 years	512	Cases78.9 (7.5) Controls79.6 (7.6)	Cases 50.6 Controls 41.0

HD= high-dose influenza vaccine;
NA= not applicable;
SD= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); 3v/4v= tri-/quadrivalent.

Table 6. Key characteristics of vaccine efficacy/effectiveness studies of primary review, included in the evidence body of the update review

Study	Intervention (Comparison)	Study design	Country	Setting	Outcome	Influenza season	Population	Number vacc
Van Buynder 2013 [31]	MF59-3v (vs. SD-3v)	Case-control	Canada	Multicentre	Laboratory-confirmed influenza	2011–2012	Adults aged ≥65 years	282
Mira-Iglesias 2019 [32]	MF59-3v (vs. SD-3v)	Case-control	Spain	Hospital	Laboratory-confirmed influenza	2017–2018	Adults aged ≥60 years	1 477
Pebody 2020a [33]	MF59-3v (vs. SD-3v/4v)	Case-control	United Kingdom	General practice and hospitals	Laboratory-confirmed influenza hospitalization	2018–2019	Adults aged ≥65 years	1 439
Pebody 2020b [34]	MF59-3v (vs. SD-3v/4v)	Case-control	United Kingdom	General practice	Laboratory-confirmed influenza	2018–2019	Children and adults aged >0 years	2 326
Bellino 2019 [35]	MF59-3v (vs. SD-3v/4)	Case-control	Italy	General practice	Laboratory-confirmed influenza	2018–2019	Children and adults aged ≥6 months	2 526
Rondy 2017a [36]	MF59-3v (vs. SD-3v)	Case-control	Europe	Multicentre, hospital	Laboratory-confirmed influenza	2016–2017	Adults aged ≥65 years	640
Rondy 2017b [37]	MF59-3v (vs. SD-3v)	Case-control	Europe	Multicentre, hospital	Laboratory-confirmed influenza	2015–2016	Adults aged ≥65 years	1 802
Diaz Granados 2014 [38]	HD-3v (vs. SD-3v)	RCT	United States and Canada	Multicentre	Laboratory-confirmed ILI	2011–2013	Adults aged ≥65 years	31 989
Bruxvoort 2019 [39]	Cell-based-3/4 vs SD-v3/4	Case control	United States	Hospital	Laboratory-confirmed influenza hospitalisation	2017–2018	Children and Adults (aged ≥4 years)	8 132
Dunkle 2017a [40]	Recombinant- 4v vs. SD-4v	RCT	United States	Multicentre, outpatients	Culture-confirmed influenza-like illness, PCR-confirmed ILI	2014–2015	Adults (aged ≥ 50 years)	9 003

HD=*high-dose influenza vaccine;*
NA*= not applicable;*
SD*= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA);* ***3v/4v****= tri-/quadrivalent.*

Safety studies

Details of studies that reported safety data and were found in the update search are provided in Table 7. We identified five RCTs. In addition, five NRSI (both retrospective cohort studies) were identified. The studies were performed in Australia, Belgium, Germany, Japan, France, Italy, the Netherlands, Poland, Taiwan and the USA and had about 40 to 1 024 160 participants. Six studies investigated the high-dose influenza vaccine. Two studies provided data for the recombinant and two other studies for the MF59-adjuvanted vaccine. No study was reported on an mRNA-based influenza vaccine. One study reported data of a head-to-head comparison between the MF59-adjuvanted and the high-dose influenza vaccine. Nine studies reported on serious adverse events. For systemic reactions, six studies gave data on fever and four studies reported on headaches. With regard to local reactions, six studies reported data on pain at the injection site and three on swelling.

In the primary review [8], there were 32 studies identified which reported data on the above-mentioned safety outcomes, as compared to standard vaccine. Study characteristics are reported in Table 8 and Appendix 7.1-Appendix 7.4 of the primary review [8]. Twelve of these studies reported safety data on the MF59-adjuvanted vaccine and seven studies had estimates for high-dose vaccine. For the cell-based vaccine, six studies reported safety estimates, while seven studies were available for the recombinant vaccine.

Table 7. Key characteristics of vaccine safety studies for update

Study	Intervention (Comparison)	Study design	Country	Type of funding	Population	Number vaccinated	Mean age in years (SD)	Female sex - %	Safety outcomes available
Caldera 2020 [41]	HD-3v (vs. SD-4v)	RCT	USA	Non-industry funded	Patients with inflammatory bowel disease on anti-tumour necrosis factor alpha agents 18–64 years	40	Median (IQR) HD 29 (25 to 45) SD 43 (32 to 52)	HD 36 SD 33	Local and systemic reactions
Chen 2022 [42]	HD-4v (vs. SD-4v)	RCT	Taiwan	Industry-funded	≥ 65 years	165	71.4 (5.52)	HD 57.3 SD 55.4	Local and systemic reactions SAE
Layton 2020 [43]	HD-3v (vs. SD)	Retrospective cohort	USA	Not reported	≥ 65 years with end-stage renal disease	520 876	74.7 (7.0)	49.5	Local and systemic reactions SAE
Pepin 2021 [44]	HD-4v (vs. SD-4v)	RCT	Belgium, France, Germany, Italy, Poland, the Netherlands	Industry-funded	≥ 60 years	1 533	66.6 (5.97)	50.4	Unsolicited non-serious injection-site AE Unsolicited non-serious systemic AE, SAE, AESI
Sanchez 2023 [45]	HD-4v (vs. SD-4v)	RCT	Japan	Industry-funded	>60 years	2 100	HD 68.2 (4.9) SD 68.4 (5.0)	HD 46.3 SD 47.9	Local and systemic reactions SAE
Pillsbury 2020 [46]	HD-3v (vs. MF59)	Retrospective cohort	Australia	Non-industry funded	≥65 years	47 307	Median (IQR) 71 (68-76)	54.0	Local and systemic reactions SAE
Schmader 2021 [47]	MF59 (vs. HD)	RCT	USA	Non-industry funded	≥65 years	757	Median age (range) 72 (65-97)	55.0	Local and systemic reactions SAE
de Lusignan 2022 [48]	MF59 (vs. SD-4v)	Retrospective cohort	UK	Non-industry funded	0–100 years	1 024 160	NA	NA	Local and systemic reactions SAE
Hansen 2020 [49]	Recombinant-3v (vs. SD-3v)	Retrospective cohort	USA	Industry-funded	≥18 years, pregnant women included	305 659	NA	Rec 52.7 SD 55.3	SAEs Fever
Hsiao 2022 [50]	Recombinant-4v (vs. SD-4v)	Prospective cohort	USA	Industry-funded	Chinese adults 18 to64 years, pregnant women included	42 684	18–65 years	63.8	SAEs Fever

***AE**= adverse event;*
***AESI**= adverse event;*
***HD=** high-dose; influenza vaccine;*
***NA**= not applicable;*
***SAE**= serious adverse event;*
***SD**= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); **3v/4v**= tri-/quadrivalent*

Table 8. Key characteristics of vaccine safety studies of primary review, included in the evidence body of the update review

Study	Intervention (Comparison)	Study design	Country	Population	Number vaccinated	Safety outcomes available
Cowling 2020 [51]	MF59-3v (vs. SD-4v)	RCT	Hong Kong	Community dwelling Adults aged 65–82 years	1 861	Local adverse events, systemic adverse events, serious adverse events
Cowling 2020 [51]	Recombinant-3v (vs. SD-4v)	RCT	Hong Kong	Community dwelling Adults aged 65–82 years	1 861	Serious adverse events, hospitalisation
de Bruijn 2006 [52]	MF59-3v (Subunit influenza vaccine)	RCT	Netherlands	Adults aged ≥61 years	386	Mortality, serious adverse events, local adverse events, systemic adverse events
Durando 2008 [53]	MF59-3v (vs. SD-3v)	RCT	Italy	Healthy Adults aged ≥65 years	270	Serious adverse events, any adverse event
Frey 2003 [54]	MF59-3v (vs. SD-3v)	RCT	United States	Adults aged 18–64 years	301	Local adverse events, systemic adverse events
Frey 2003 [54]	MF59-3v (vs. SD-3v)	RCT	United States, Philippines, Panama and Columbia	Adults aged ≥65 years	7 109	Mortality, local adverse events, systemic adverse events
Gasparini 2001 [55]	MF59-3v (vs. SD-3v)	RCT	Italy	Adults aged 18–65 years, HIV seropositive	308	Serious adverse events, local adverse events, systemic adverse events
Li 2008 [56]	MF59-3v (vs. SD-3v)	RCT	China	Adults aged ≥60 years	600	Serious adverse events, local adverse events, systemic adverse events
Minutello 1999 [57]	MF59-3v (vs. SD-3v)	RCT	Italy	Adults aged ≥65 years	92	Serious adverse events, local adverse events, systemic adverse events
Ruf 2004 [58]	MF59-3v (vs. SD-3v)	RCT	Germany	Adults aged ≥60 years	827	Local and general symptoms, serious adverse events
Scheifele 2013 [59]	MF59-3v (vs. SD-3v)	RCT	Canada	Adults aged ≥65 years	922	Serious adverse events, mortality, local adverse events, systemic adverse events
Seo 2014 [60]	MF59-3v (vs. SD-3v)	RCT	South Korea	Healthy, independently-living adults aged ≥65 years	354	Local adverse events, systemic adverse events
Sindoni 2009 [61]	MF59-3v (vs. SD-3v)	RCT	Italy	Adults [aged ≥65 years]	195	Serious adverse events, local adverse events, systemic adverse events
Couch 2007 [62]	HD-v3 (vs. SD-3v)	RCT	United States	Adults aged ≥65 years	414	Serious adverse events, mortality, local adverse events, systemic adverse events
DiazGranados 2015b [63]	HD-v3 (vs. SD-3v)	RCT	United States	Adults aged 50–64 years	300	Serious adverse events, mortality, local adverse events, systemic adverse events
Falsey 2009 [64]	HD-v3 (vs. SD-3v)	RCT	United States	Adults aged ≥65 years	3 876	Mortality, local adverse events, systemic adverse events
Keitel 2006 [65]	HD-v3 (vs. SD-3v)	RCT	United States	Adults aged ≥65 years	202	Serious adverse events, mortality, local adverse events, systemic adverse events

Study	Intervention (Comparison)	Study design	Country	Population	Number vaccinated	Safety outcomes available
Tsang 2014 [66]	HD-v3 (vs. SD-3v)	RCT	United States	Adults aged ≥65 years	1 912	Serious adverse events, mortality, local adverse events, systemic adverse events
Noh 2019 [67]	HD-4v (vs. SD-4v)	RCT	Republic of Korea	Adults aged 19-64 years	40	Local adverse events, systemic adverse events
Pillet 2019 [68]	HD-4v (vs. SD-4v)	RCT	United States	Adults aged ≥18 years	750	Serious adverse events, local adverse events, systemic adverse events
Ehrlich 2012 [69]	Cell-based-3v (vs. SD-3v)	RCT	United States	Adults aged>50 years	3 208	Serious adverse events, mortality, local adverse events, systemic adverse events
Frey 2010 [70]	Cell-based-3v [vs. SD-3v]	RCT	United States, Poland and France	Healthy adults aged 18-49 years	11 404	Serious adverse events, local adverse events, systemic adverse events
Groth 2009 [71]	Cell-based-3v (vs. SD-3v)	RCT	Germany	Adults aged ≥ 18 years	240	Serious adverse events, mortality, local adverse events, systemic adverse events
Halperin 2002 [72]	Cell-based-3v (vs. SD-3v)	RCT	Canada	Adults and children aged ≥3 years	940	Local adverse events, systemic adverse events
Song 2015 [73]	Cell-based-3v (vs. SD-3v)	RCT	Republic of Korea	Adults aged ≥19 years	1 155	Serious adverse events, local adverse events, systemic adverse events
Szymczakiewicz-Multanowska 2009 [74]	Cell-based-3v (vs. SD-3v)	RCT	Poland	Adults aged ≥18 years	2 654	Serious adverse events, mortality, local adverse events, systemic adverse events
Dunkle 2017a [75]	Recombinant-3v (vs. SD-4v)	RCT	United States	Adults aged≥ 50 years	9 003	Serious adverse events, mortality, local adverse events, systemic adverse events
Dunkle 2017b [40]	Recombinant-3v (vs. SD-4v)	RCT	United States	Adults aged 15–49 years	1 350	Serious adverse events, mortality, local adverse events, systemic adverse events
Baxter 2011 [76]	Recombinant-3v (vs. SD-3v)	RCT	United States	Healthy adults aged 50–64 years	602	Serious adverse events, mortality, local adverse events, systemic adverse events
Izikson 2015 [77]	Recombinant-3v (vs. SD-3v)	RCT	United States	Adults aged ≥50 years	2 640	Serious adverse events, mortality, local adverse events, systemic adverse events
Keitel 2009 [78]	Recombinant-3v (vs. SD-3v)	RCT	United States	Adults aged ≥65 years	869	Serious adverse events, mortality, local adverse events, systemic adverse events
Treanor 2006 [79]	Recombinant-3v (vs. SD-3v)	RCT	United States	Adults aged ≥18 years	399	Local adverse events, systemic adverse events

***AE**= adverse event;*
***AESI**= adverse event;*
***HD=** high-dose; influenza vaccine;*
***NA**= not applicable;*
***SAE**= serious adverse event; **SD**= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); **3v/4v**= tri-/quadrivalent.*

4.2 Risk of bias in the studies included

4.2.1 Overall risk of bias by study

Since risk of bias either varied by outcome in single studies, or only one outcome was reported for a given study, we did not assess risk of bias at study level.

4.2.2 Overall risk of bias by outcome

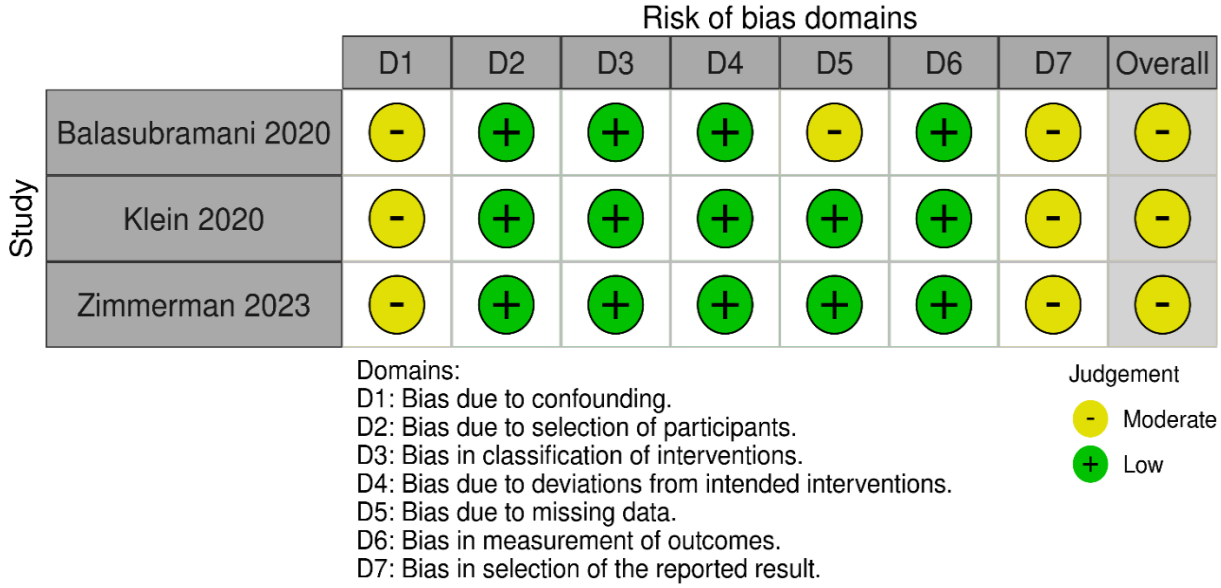
Efficacy/ effectiveness studies

Across the six NRSI that were identified in the update search as reporting data on effectiveness outcomes, overall risk of bias was moderate for each outcome and study, respectively. The main reason for this assessment was that residual confounding (domain 1) could not be excluded in all studies (see Table 9 and Table 10 for details).

Risk of bias could not be assessed for the cluster-RCT [29] since data were only presented in a conference abstract and not enough information was given.

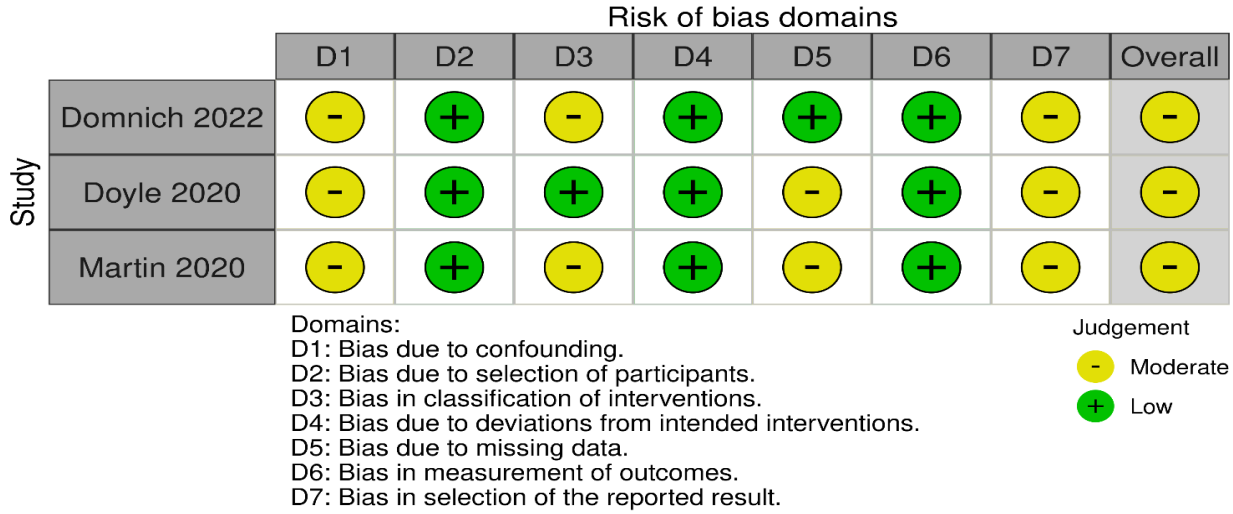
Outcome: laboratory confirmed influenza

Table 9. Risk of bias VE-studies (assessed with ROBINS-I); outcome: laboratory confirmed influenza



Outcome: laboratory confirmed hospitalisation

Table 10. Risk of bias in VE-studies (assessed with ROBINS-I); outcome: laboratory confirmed hospitalisation

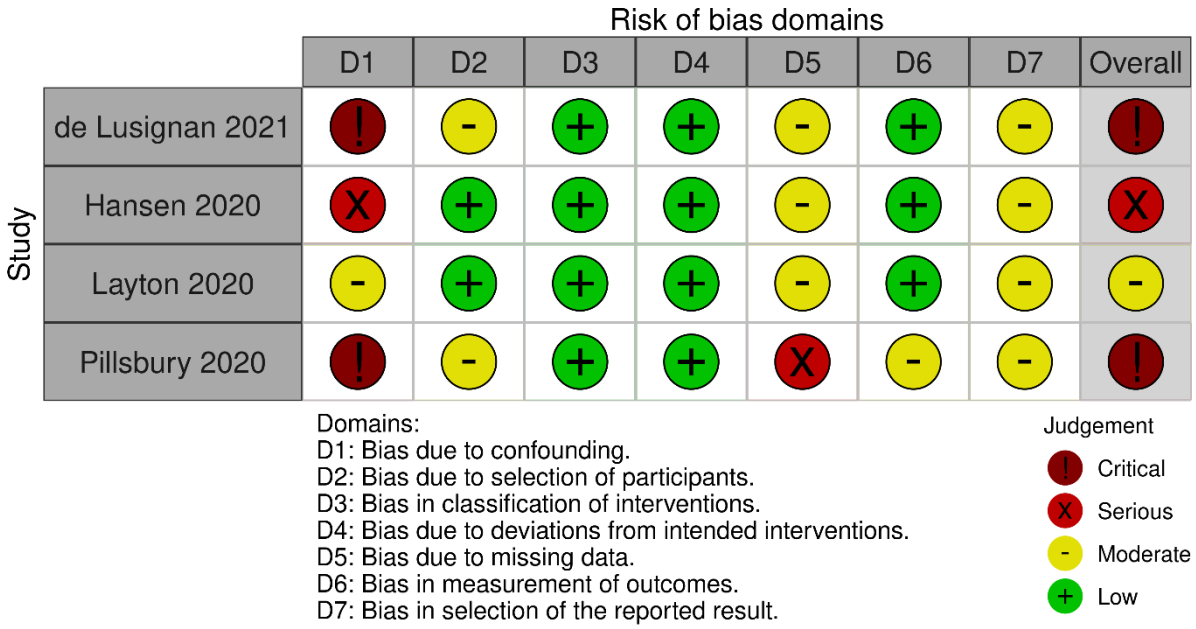


Safety studies

The overall risk of bias was moderate to critical in the five NRSI studies that were identified in the update search reporting data on safety outcomes [see Table 11]. The main reason for this assessment was that residual confounding (domain 1) could not be excluded in all studies. For two studies confounding was assessed as critical, since only unadjusted data was reported (see Table 11-9). Risk of bias assessments for the main safety outcomes (SAE, pain, swelling, headache, fever) are displayed here, whereas other safety outcomes can be found in Annex 3 [Table 25–28].

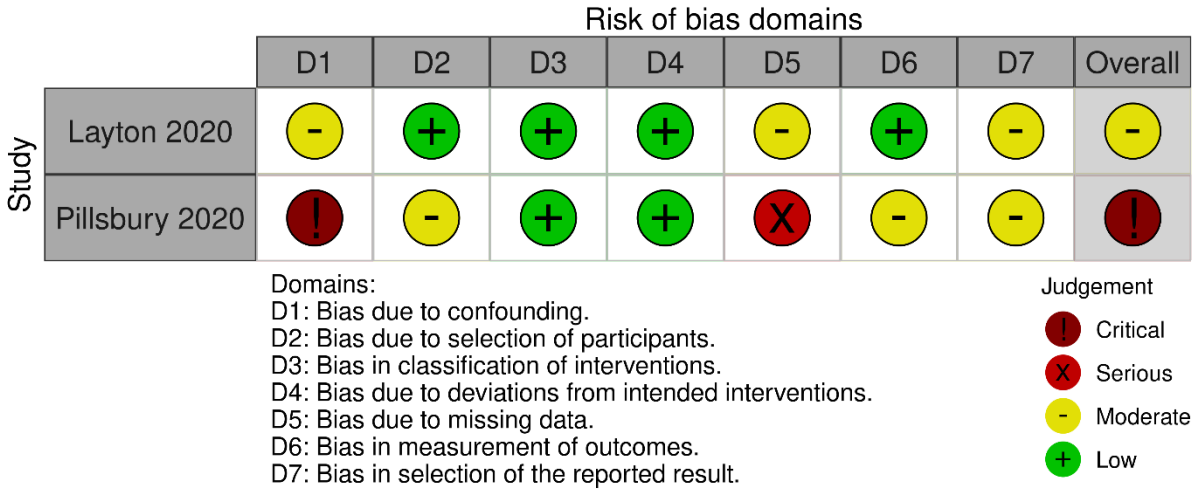
Outcome: SAE

Table 11. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: SAE (serious adverse events)



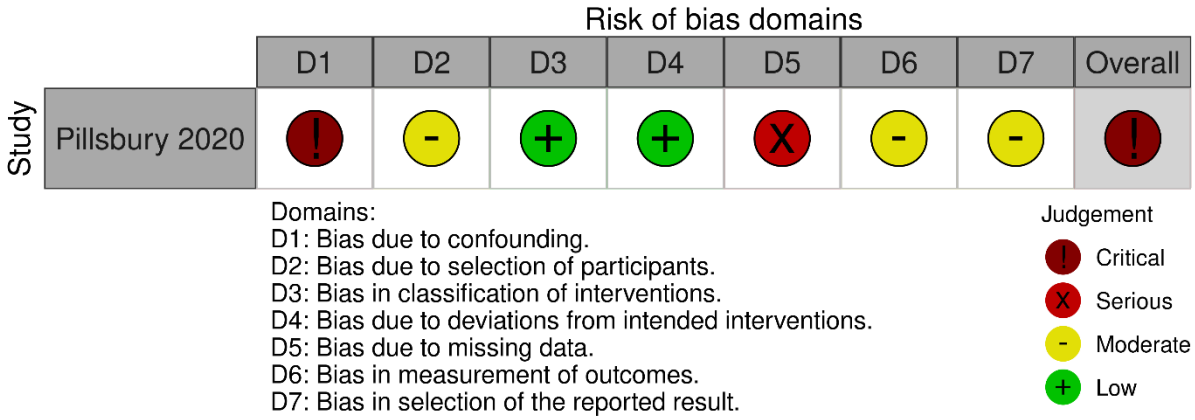
Outcome: pain

Table 12. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome:



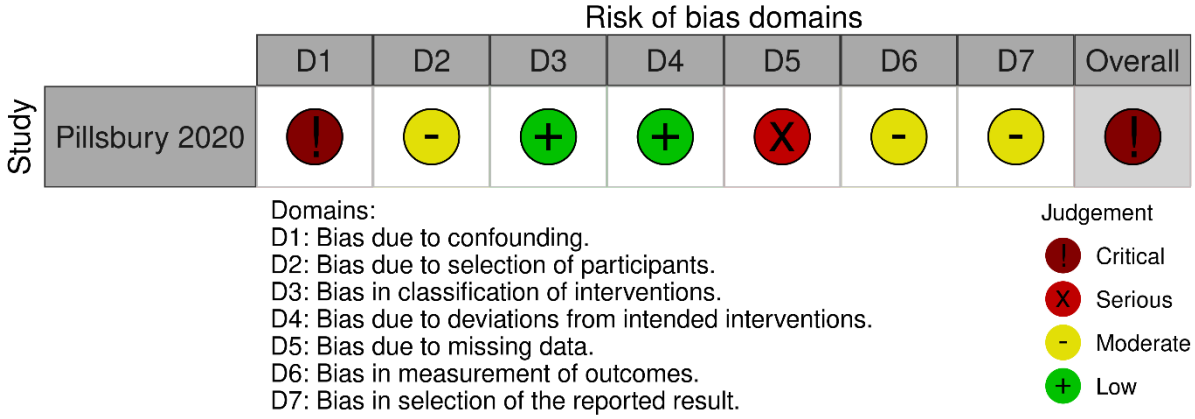
Outcome: swelling

Table 13. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome:



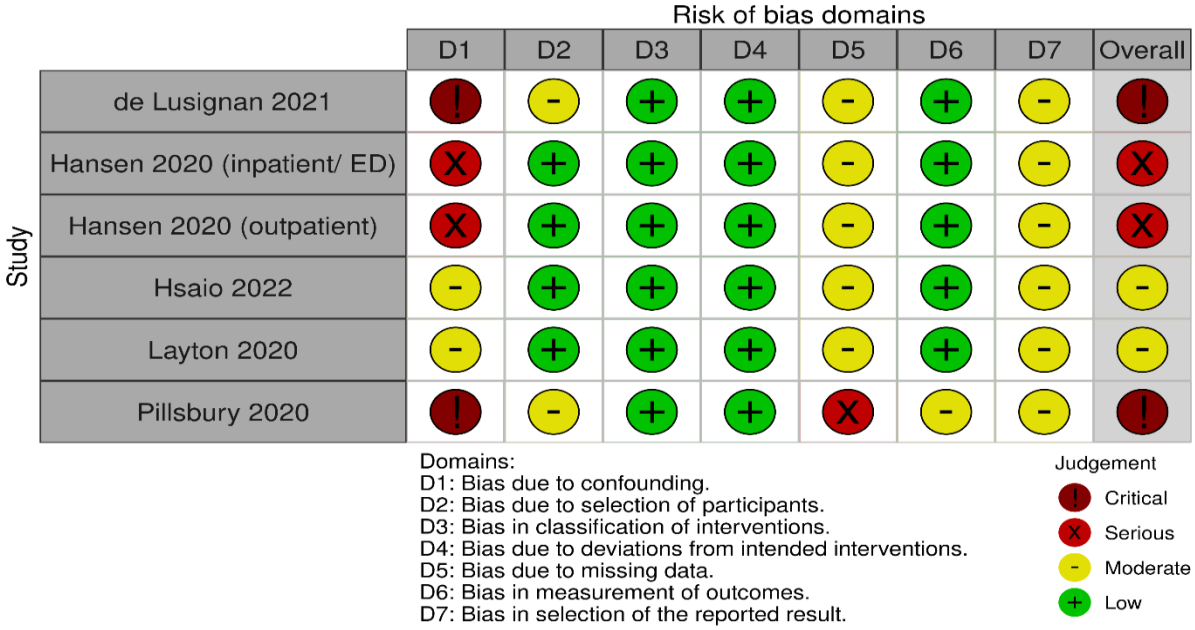
Outcome: headache

Table 14. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome:



Outcome: fever

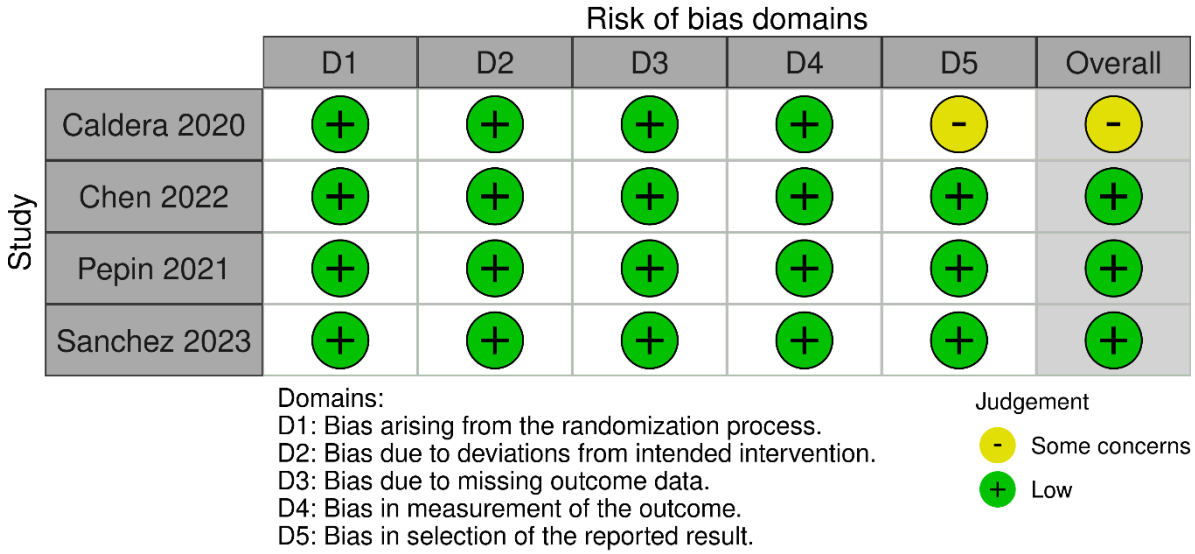
Table 15. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome:



For the five RCTs that reported safety outcomes the overall risk of bias was low regarding some concerns for each safety outcome. The main reason for this assessment was that in these modified double-blind study designs, with different volumes of the administered vaccines, a risk of unblinding by administrator could not be excluded (see Tables 16, 17, 18, 19 and 20 for details). Since these outcomes are based on subjective reporting by the study participants, knowledge of study arm allocation could have biased outcome assessment. Risk of bias assessments for the main safety outcomes (SAE, pain, swelling, headache, fever) are displayed here, and two more safety outcomes can be found in Annex 4 (Table 37).

Outcome: SAE

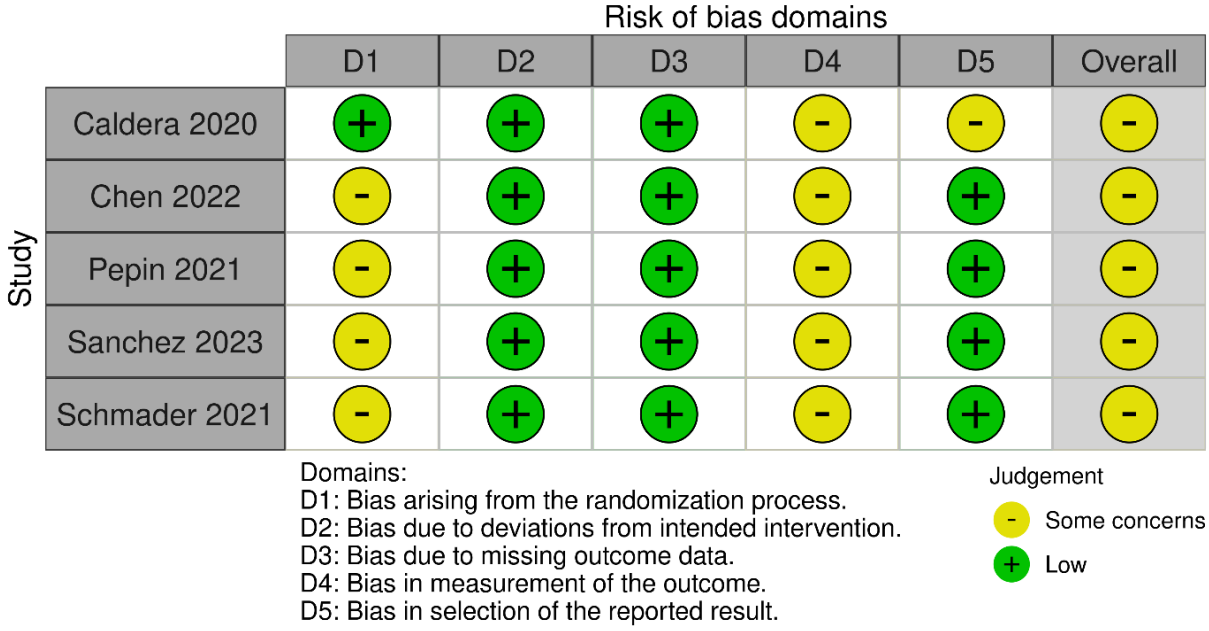
Table 16. Risk of bias in RCT safety-studies (assessed with RoB2); outcome: SAE (serious adverse events)



Outcome: pain

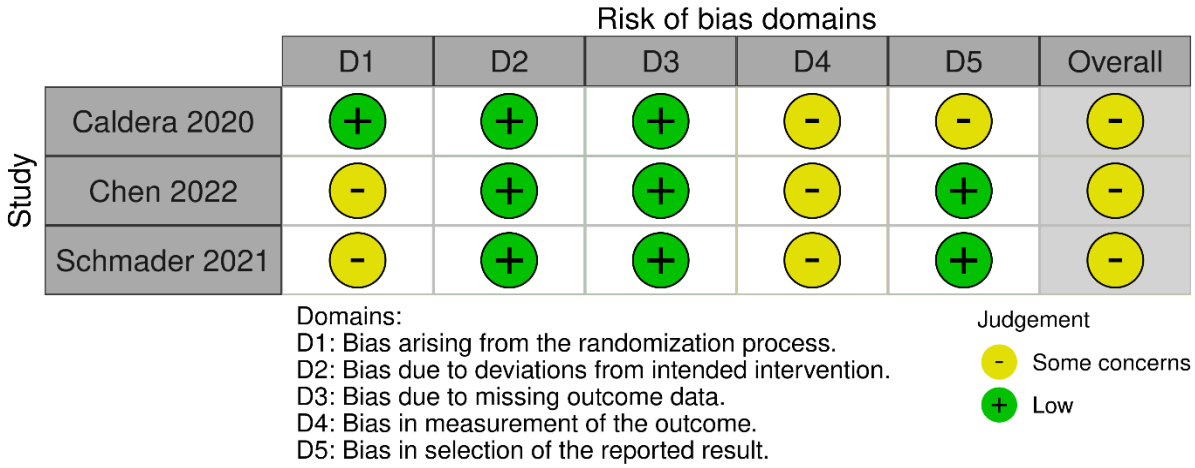
Table 17. Risk of bias in RCT safety-studies (assessed with RoB 2); outcome:

.



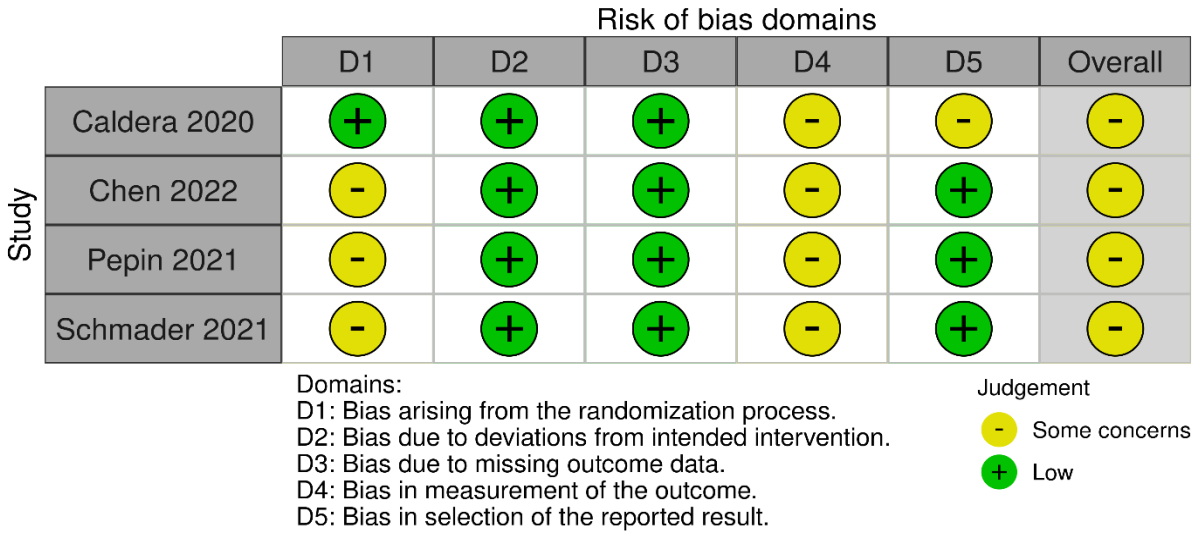
Outcome: swelling

Table 18. Risk of bias in RCT safety-studies (assessed with RoB 2); outcome:



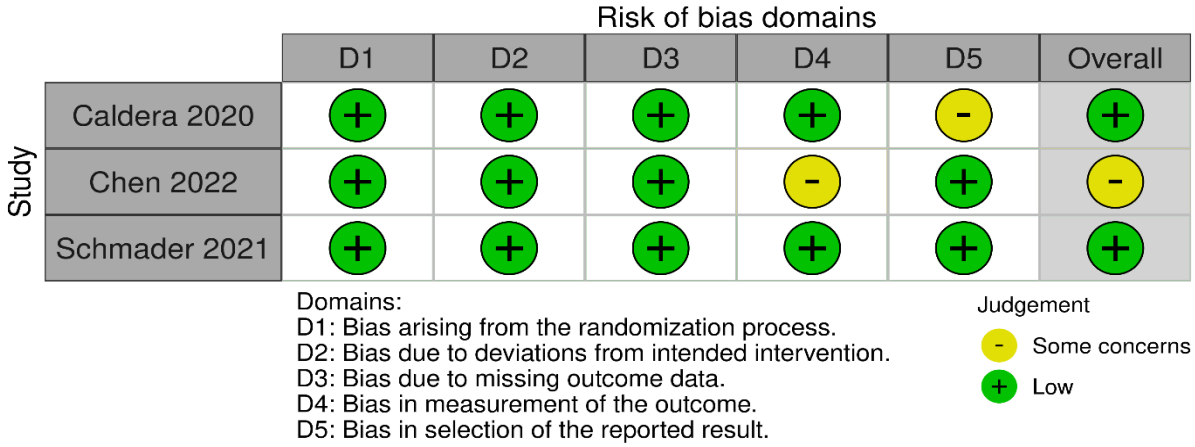
Outcome: headache

Table 19. Risk of bias in RCT safety-studies (assessed with RoB 2); outcome:



Outcome: fever

Table 20. Risk of bias in RCT safety-studies (assessed with RoB 2); outcome:



4.3 Effects of interventions

4.3.1 MF59-adjuvanted influenza vaccine

Efficacy/effectiveness

Primary efficacy/effectiveness outcomes

Laboratory-confirmed influenza

In the primary review, seven studies [all NRSI] were included, reporting a total of 13 estimates (Table 21). VE estimates were highly heterogenous and ranged from -30 to 88%, with only two estimates being statistically significant. Due to heterogeneity, metanalysis was not performed.

In the update, no additional studies were identified.

Table 21. Relative effectiveness of MF59-adjuvanted influenza vaccine versus standard influenza vaccine, for laboratory confirmed influenza

Study	Study design	rVE	95% CI	Season
All strains				
Van Buynder 2013	NRSI	42%	-8 to 69%	2011–2012
Mira-Iglesias 2019	NRSI	19%	-10 to 41%	2017–2018
Pebody 2020a	NRSI	30%	-83 to 73%	2018–2019
Pebody 2020b	NRSI	16%	-176 to 75%	2018–2019
Bellino 2019a	NRSI	-1%	-122 to 59%	2018–2019
A [H1N1]				
Mira-Iglesias 2019	NRSI	-3%	-126 to 53%	2017–2018
Pebody 2020a	NRSI	3%	-358 to 79%	2018–2019
A [H3N2]				
Rondy 2017b	NRSI	88%	51 to 100%	2015–2016
Rondy 2017a	NRSI	-30%	-146 to 31%	2016–2017
Mira-Iglesias 2019	NRSI	20%	-17 to 46%	2017–2018
Pebody 2020a	NRSI	43%	-134 to 86%	2018–2019
B				
Rondy 2017b	NRSI	87%	30 to 100%	2015–2016
Mira-Iglesias 2019	NRSI	6%	-58 to 44%	2017–2018

Influenza-related hospitalisation

No studies matching the inclusion criteria of this update were identified in the primary review. Two additional studies were reported there [80, 81] which used ICD-codes (not laboratory-confirmed) for outcome assessment.

In the update, we identified one NRSI [30]. The authors reported rVE against hospitalisation due to influenza (laboratory-confirmed) from two consecutive seasons [2018–2020]. Relative VE against all strains was 59.2% (95%CI: 14.6 to 80.5%). For influenza A, rVE was 63.7% (95%CI: 22.8 to 82.9%).

Influenza-related death

No studies reported on this outcome, either in the primary review or in the update.

Secondary efficacy/effectiveness outcomes

Influenza related ICU admissions

No studies reported on this outcome, either in the primary review or in the update.

Influenza associated pneumonia/lower respiratory tract disease

No studies were identified matching the inclusion criteria of this update. In the primary review, two additional studies were reported [82, 83] which used ICD-codes (not laboratory-confirmed) for outcome assessment.

Influenza-associated cardiovascular disease

No studies reported on this outcome, either in the primary review or in the update.

Influenza-like illness

No studies matching the inclusion criteria of this update were identified. In the primary review, one additional studies was reported [84] which used a case definition not covered by the protocol of this review.

Safety

Primary safety outcomes

Serious adverse events

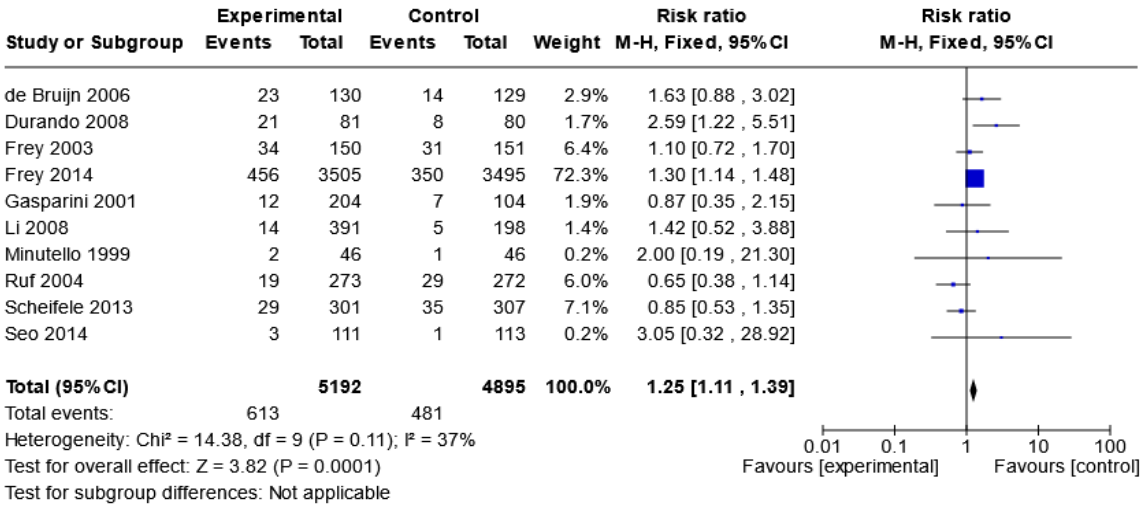
In the primary review, three RCTs and two NRSI were identified as reporting serious adverse events [SAE]. In the RCTs [56, 85, 86], a total of three SAE were identified in the MF59-adjuvanted vaccine group, including two cases of Guillain-Barré-Syndrome, and three SAE were found in the standard vaccine group. The NRSIs reported no cases of narcolepsy in both study groups (MF59-adjuvanted vaccine and standard vaccine) [87] and no group difference in hospitalised SAE [88]. No additional studies were identified in the update. The pooled relative risk of SAE after vaccination with MF59-ajuvanted influenza vaccine compared to standard influenza vaccine was 0.95 (95%CI: 0.19 to 4.72; fixed-effects model).

Secondary safety outcomes

Systemic adverse events

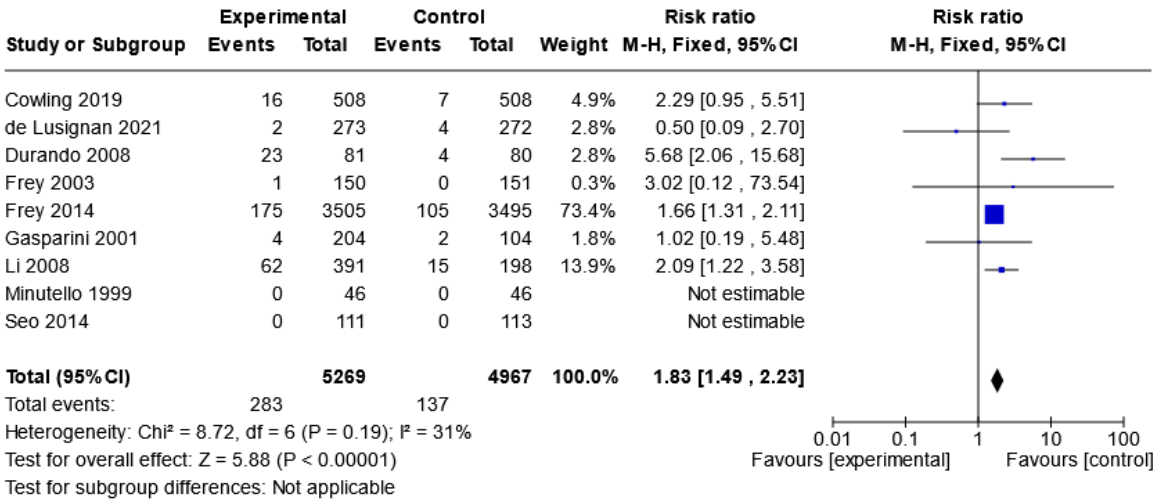
In the basic review, 10 RCTs were included which reported on headache after vaccination. A funnel plot and visual inspection for small study effects was performed (Annex 4). No evidence for publication bias could be found. The pooled risk ratio was 1.25 (95%CI: 1.11 to 1.39) in the fixed--effects model and 1.19 (95%CI: 0.88 to 1.61) according to the random effects model (Figure 2). The figure of the random-effects model is shown in Annex 5 (Figure 21). No additional studies were identified in the update.

Figure 2. Relative risk of headache after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (fixed-effects model)



Nine RCTs were included in the primary review reporting on fever after vaccination. The pooled risk ratio was 1.83 (95%CI: 1.49 to 2.23) in the fixed effects model and 1.97 (95%CI: 1.07 to 3.61) according to the random effects model (Figure 3). The figure of the random effects model is shown in Annex 5 (Figure 22). No additional studies were identified in the update.

Figure 3. Relative risk of fever after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (fixed-effects model)

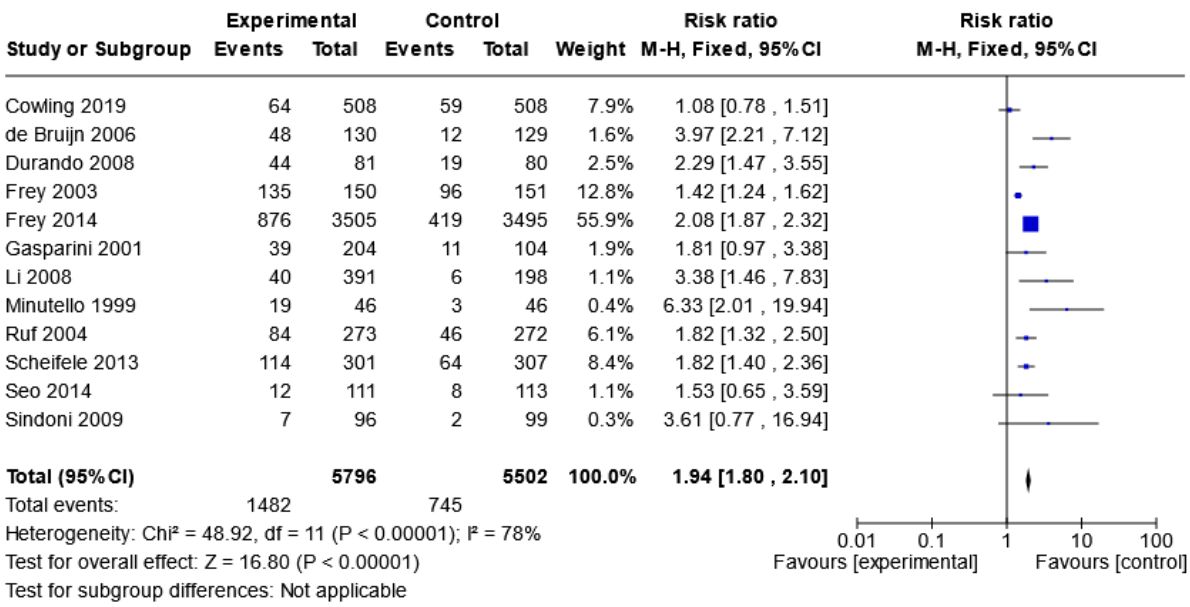


Local adverse events

In the primary review, 12 RCTs reported on pain at the injection site after vaccination. A funnel plot and visual inspection for small study effects was performed (Annex 4). No evidence for publication bias could be found.

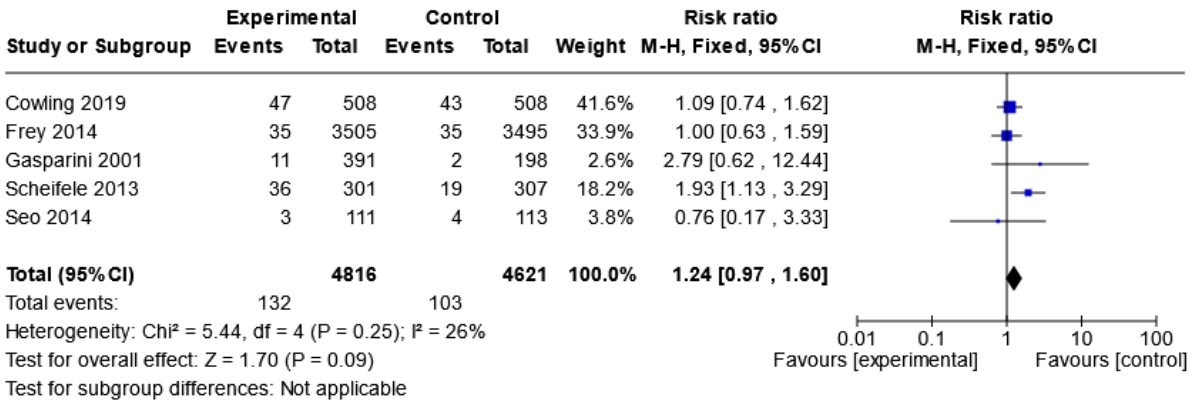
The pooled risk ratio of the fixed effects model was 1.94 (95%CI: 1.80 to 2.10) and 2.02 (95%CI: 1.53 to 2.67) according to the random effects model (Figure 4). The figure of the random effects model is shown in Annex 5 (Figure 23). No additional studies were identified in the update.

Figure 4. Relative risk of pain after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (fixed-effects model)



Swelling at the injection site was reported in five RCTs included in the primary review. The pooled risk ratio was 1.24 (95%CI: 0.97 to 1.60) in the fixed effects model and 1.28 (95%CI: 0.78 to 2.12) according to the random effects model (Figure 5). The figure of the random effects model is shown in Annex 5 (Figure 24). No additional studies were identified in the update.

Figure 5. Relative risk of swelling after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (fixed-effects model)



Adverse pregnancy outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

Adverse neonatal outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

4.3.2 High-dose influenza vaccine

Efficacy/effectiveness

Primary efficacy/effectiveness outcomes

Laboratory-confirmed influenza

In the primary review, one RCT was included that reported an rVE of 24.2% (95%CI: 9.7 to 36.5%) against laboratory-confirmed influenza (all strains) during two consecutive seasons (2011−2013) [38].

In the update, we identified one NRSI [24] which reported rVE estimates against influenza A for four consecutive seasons (2015−2019). Relative VE ranged between -9% and 19%, with none of the estimates being statistically significant (see Table 22).

Influenza-related hospitalisation

No studies matching the inclusion criteria of this update were identified in the primary review. There were two additional studies [80, 81] which used ICD-codes (not laboratory-confirmed) for outcome assessment.

In the update, we identified one NRSI [25]. Relative VE against hospitalisation due to influenza (laboratory-confirmed) was reported for two consecutive seasons against influenza A, B and all strains separately. Relative VE against all strains was 27% (95%CI: -1 to 48). None of the rVE estimates ranging between 22 and 44% were statistically significant (see Table 22).

Table 22. Relative vaccine effectiveness of high-dose versus standard influenza vaccine against laboratory-confirmed influenza and influenza-related hospitalisation (laboratory-confirmed)

Study	Study design	rVE	95% CI	Season
Laboratory confirmed influenza				
All strains				
Diaz-Granados 2014	RCT	24.2%	9.7 to 36.5%	2011-2013
A				
Balasubramani 2020	NRSI	10%	-15 to 30%	2015-2019
Balasubramani 2020	NRSI	-9%	-158 to 54%	2015-2016
Balasubramani 2020	NRSI	2%	-69 to 43%	2016-2017
Balasubramani 2020	NRSI	6%	-55 to 43%	2017-2018
Balasubramani 2020	NRSI	19%	-27 to 48%	2018-2019
Influenza-related hospitalisation (lab-confirmed)				
All strains	NRSI	27%	-1 to 48%	2015-2017
Doyle 2020	NRSI	24%	-46 to 61%	2015-2016
Doyle 2020	NRSI	27%	-8 to 50%	2016-2017
A				
Doyle 2020	NRSI	22%	-15 to 46%	2015-2017
B				
Doyle 2020	NRSI	44%	-13 to 73%	2015-2017

Influenza-related death

No studies reported on this outcome, either in the primary review or in the update.

Secondary efficacy/effectiveness outcomes

Influenza related ICU admissions

No studies reported on this outcome, either in the primary review or in the update.

Influenza associated pneumonia/lower respiratory tract disease

No study was identified matching the inclusion criteria for this update. In the primary review, three additional studies were reported [89-91] which used ICD-codes or claims data (neither being laboratory-confirmed) for outcome assessment.

Influenza-associated cardiovascular disease

No studies reported on this outcome, either in the primary review or in the update.

Influenza-like illness

No study was identified matching the inclusion criteria of this update. In the primary review, one additional study was reported [91] which used a case definition derived from claims data not covered by the protocol of this review.

Safety

Primary safety outcomes

Serious adverse events

In the primary review, six SAEs, including neuropathy, cranial nerve VI palsy, shock, Crohn's disease, myasthenia gravis and encephalomyelitis, were reported in three RCTs after high-dose vaccine administration [63, 64, 92]. One NRSI reported no increased risk of Guillain-Barré syndrome in the primary analysis [93].

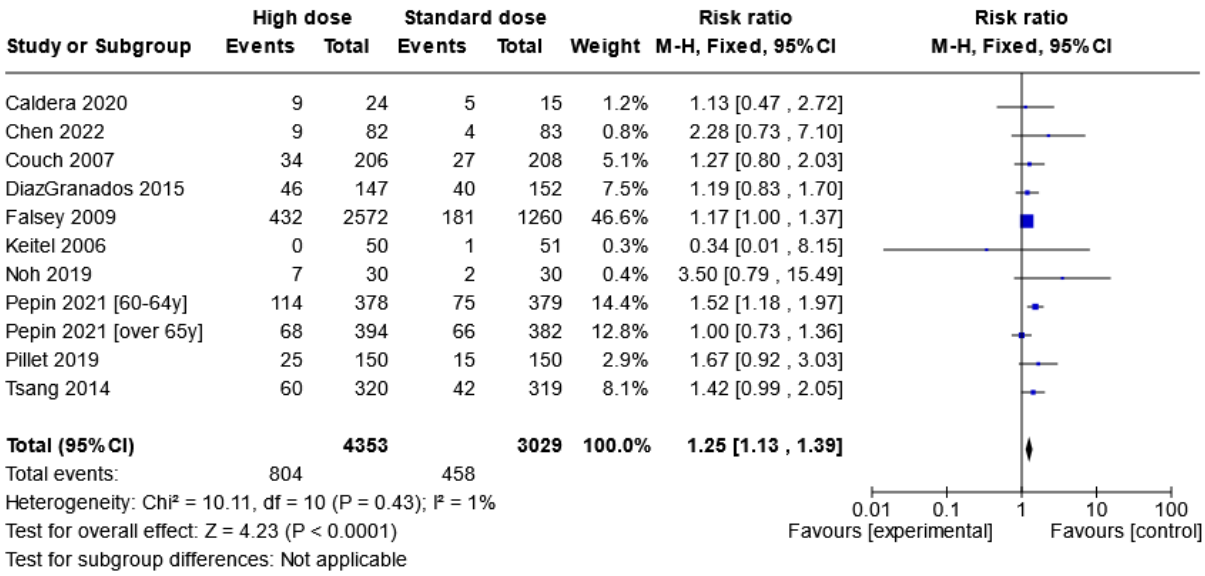
In the update, we identified three RCTs and one NRSI reporting data on serious adverse events. Two of the RCTs (Chen 2022, Sanchez 2023) did not observe SAEs in their study groups. One RCT [44] reported five SAEs [60-64 years: 1; ≥65 years: 4] in the high-dose vaccine group and seven SAEs [60−64 years: 2; ≥65 years: 5] in the standard vaccine group. One NRSI [43] did not find an increased risk of seizure (RR: 1.03 [95% CI: 0.81 to 1.32]), encephalopathy (RR: 0.94 [95% CI: 0.78 to 1.14]) or short-term death (RR: 1.09 [95% CI: 0.8 to 1.48]) after high-dose vaccine, compared to standard vaccine. The pooled relative risk of SAE after vaccination with high-dose influenza vaccine compared to standard influenza vaccine was 1.02 (95%CI: 0.42 to 2.46; fixed-effects model).

Secondary safety outcomes

Systemic adverse events

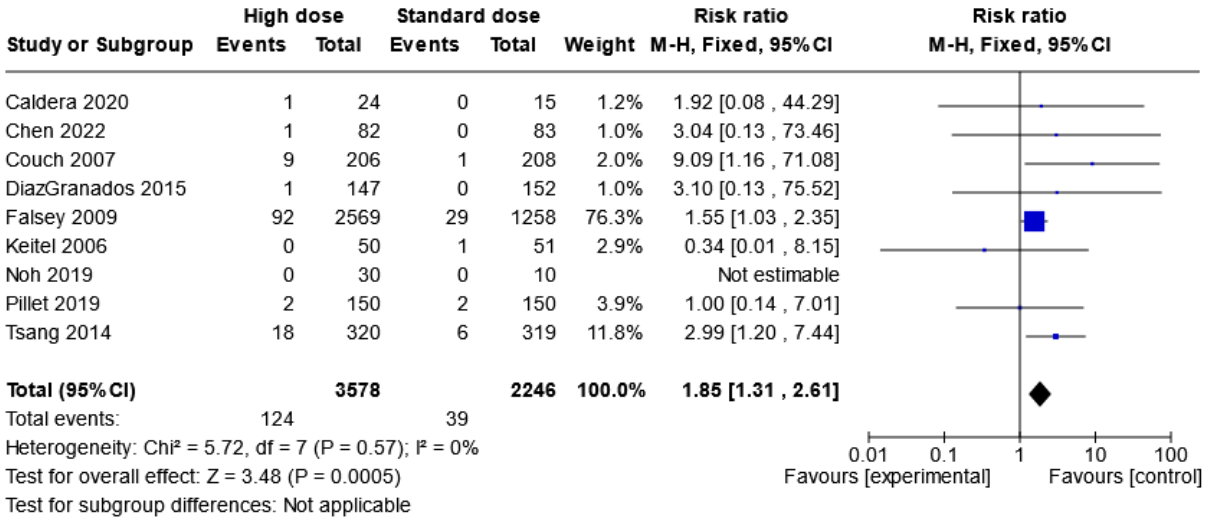
For headaches, the primary review included data from seven RCTs that resulted in a pooled RR of 1.24 (95%CI: 1.09 to 1.40; fixed effects model; random-effects model: 1.36; 95%CI: 1.02 to 1.77). In the update, we identified three additional RCTs [41, 42, 44] which provided four estimates. Adding these data to the evidence base led to an updated pooled RR of 1.25 (95%CI: 1.13 to 1.39; fixed effects model; random effects model: 1.53 [95%CI: 0.92 to 2.55]) (see Figure 6). A funnel plot and visual inspection for small study effects was performed (Annex 4). No evidence for publication bias could be found. The figure of the random-effects model is shown in Annex 5 (Figure 25).

Figure 6. Relative risk of headache after vaccination with high-dose influenza vaccine versus standard influenza vaccine (fixed-effects model)



Fever was reported in seven RCTs in the primary review. The pooled RR was 1.83 (95%CI: 1.29 to 2.60) by fixed effects model and 2.06 (95%CI: 0.84 to 5.06) by random effects model. In the update, three additional studies (two RCT, one NRSI] were found [41-43]. Adding the RCT data to the evidence base resulted in an updated pooled RR of 1.85 (95%CI: 1.31 to 2.61; fixed effects model; random effects model: 1.78 [95%CI: 1.25 to 2.54]) (see Figure 7). The figure of the random effects model is shown in Annex 5 (Figure 26). In addition, the NRSI [43] reported an RR of 0.92 (95%CI: 0.78 to 1.08).

Figure 7. Relative risk of fever after vaccination with high-dose influenza vaccine versus standard influenza vaccine (fixed-effects model)

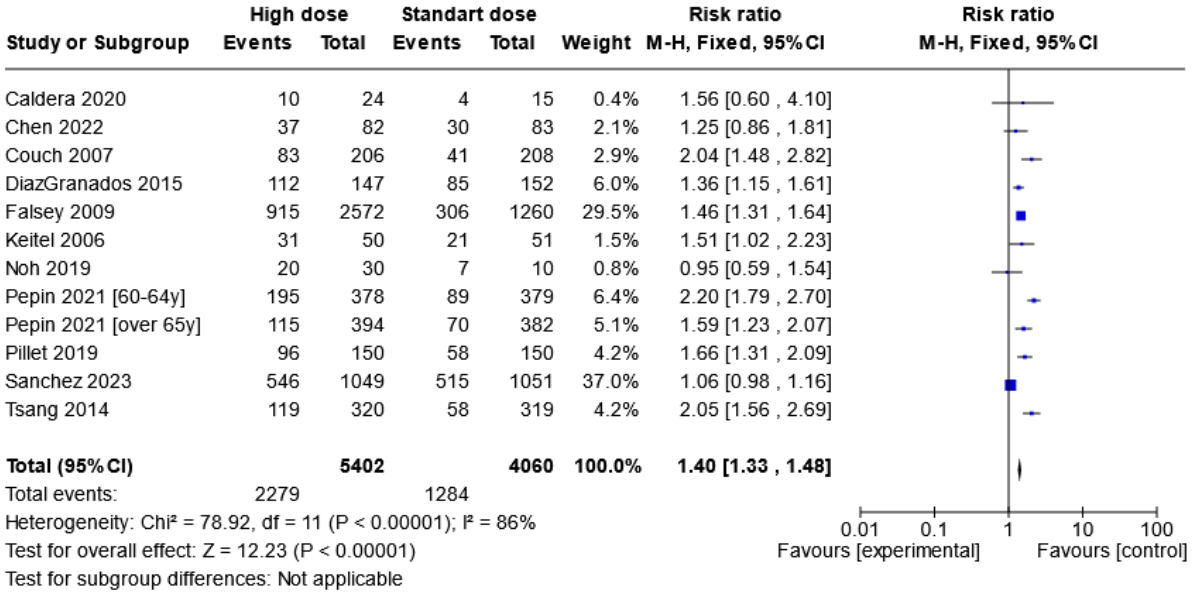


Local adverse events

Pain at the injection site after vaccination was reported in seven RCTs in the primary review. Pooled RR after high-dose vaccine compared to standard vaccine was 1.55 (95%CI: 1.43 to 1.67) using the fixed effects model and 1.56 (95%CI: 1.26 to 1.93) according to the random effects model. The figure of the random effects model is shown in Annex 5 (Figure 27).

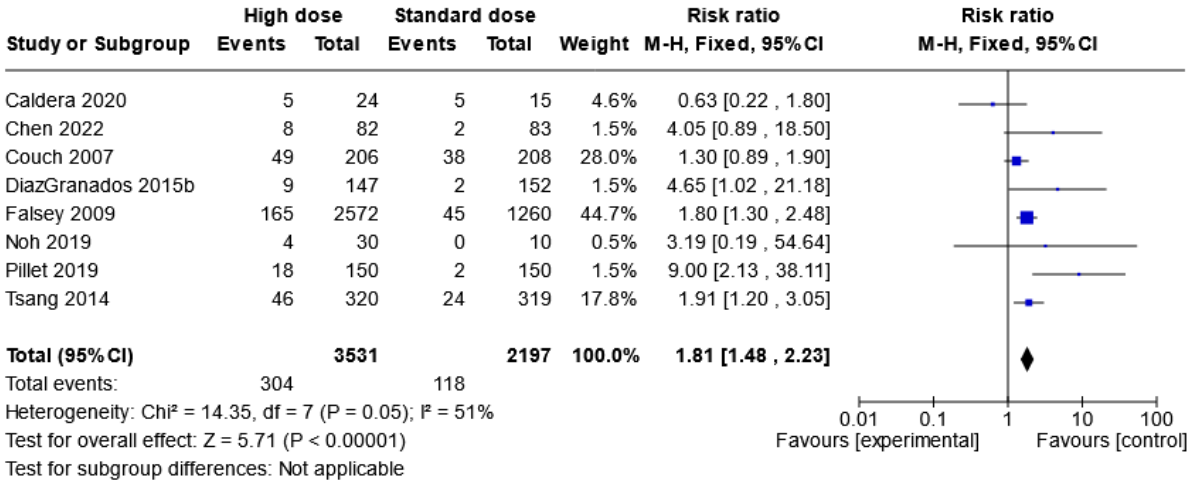
The update identified five additional studies (four RCTs, one NRSI) reporting six estimates. After adding the RCT data to the evidence base, the updated pooled RR was 1.40 (95%CI: 1.33 to 1.48); fixed effects model; random effects model: 1.52 (95%CI: 1.29 to 1.80) (see Figure 8). The NRSI [43] reported an RR of 1.23 (95%CI: 1.12 to 1.34). A funnel plot and visual inspection for small study effects was performed (Annex 4). No evidence for publication bias could be found.

Figure 8. Relative risk of pain after vaccination with high-dose influenza vaccine versus standard influenza vaccine (fixed-effects model)



Injection site swelling after vaccination was reported in six RCTs in the primary review. The pooled RR across these studies was 1.84 (95%CI: 1.49 to 2.27) according to the fixed effects model and 2.20 (95%CI: 1.12 to 4.32) using the random effects model. In the update, two additional RCTs were identified [41, 42]. Adding their data to the evidence base resulted in an updated pooled RR of 1.81 (95%CI: 1.48 to 2.23; fixed effects model; random effects model: 1.85 [95%CI: 1.27 to 2.71]) (see Figure 9). The figure of the random effects model is shown in Annex 5 (Figure 28).

Figure 9. Relative risk of swelling after vaccination with high-dose influenza vaccine versus standard influenza vaccine (fixed-effects model)



Adverse pregnancy outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

Adverse neonatal outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

4.3.3 Cell-based influenza vaccine

Efficacy/effectiveness

Primary efficacy/effectiveness outcomes

Laboratory-confirmed influenza

In the primary review, one NRSI [39] was included reporting rVE against laboratory-confirmed influenza (all strains and A/H3N2) for two seasons (2014–2015 and 2017–2018). In the update, we identified one additional NRSI [26] which reported rVE estimates against influenza A and B for one season (2017–2018). Relative VE in these two studies ranged between -5.8% and 21.4%, with none of the estimates being statistically significant (see Table 23 for details).

Influenza-related hospitalisation

No studies matching the inclusion criteria of this update were identified in the primary review. One additional study was reported there [80] which used ICD-codes (not laboratory-confirmed) for outcome assessment.

In the update, we identified one NRSI [27]. Relative VE against hospitalisation due to influenza (laboratory-confirmed) was reported for one season [2017–2018], against influenza A and B separately. None of the rVE estimates, ranging between 1.8 and 24.9%, were statistically significant (see Table 23).

Table 23. Relative vaccine effectiveness of cell-based versus standard influenza vaccine influenza vaccine against laboratory-confirmed influenza and influenza-related hospitalisation (laboratory-confirmed)

Study	Study design	rVE	95% CI	Season
Laboratory confirmed influenza				
All strains				
Bruxvoort 2019	NRSI	6%	-46-39%	2014-2015
A [H3N2]				
Bruxvoort 2019	NRSI	4%	-70-37%	2014-2015
A				
Klein 2020	NRSI	-5.8%	36.1-17.7%	2017-2018
B				
Klein 2020	NRSI	21.4%	-7.3-42.4%	2017-2018
Influenza-related hospitalisation [lab-confirmed]				
All strains				
Martin 2021	NRSI	8.5%	-75.9-52.3%	2017-2018
A				
Martin 2021	NRSI	24.9%	-78.8-68.5%	2017-2018
B				
Martin 2021	NRSI	1.8%	-254-72.8%	2017-2018

Influenza-related death

No studies reported on this outcome, either in the primary review or in the update.

Secondary efficacy/effectiveness outcomes

Influenza related ICU admissions

No studies reported on this outcome, either in the primary review or in the update.

Influenza associated pneumonia/lower respiratory tract disease

No studies reported on this outcome, either in the primary review or in the update.

Influenza-associated cardiovascular disease

No studies reported on this outcome, either in the primary review or in the update.

Influenza-like illness

No studies reported on this outcome, either in the primary review or in the update.

Safety

Primary safety outcomes

Serious adverse events

In the primary review, one SAE (hypersensitivity) was reported in one RCT after cell-based vaccine administration [69]. The relative risk of SAE after vaccination with cell-based influenza vaccine compared to standard influenza vaccine was 0.39 (95%CI: 0.02 to 9.49; fixed-effects model).

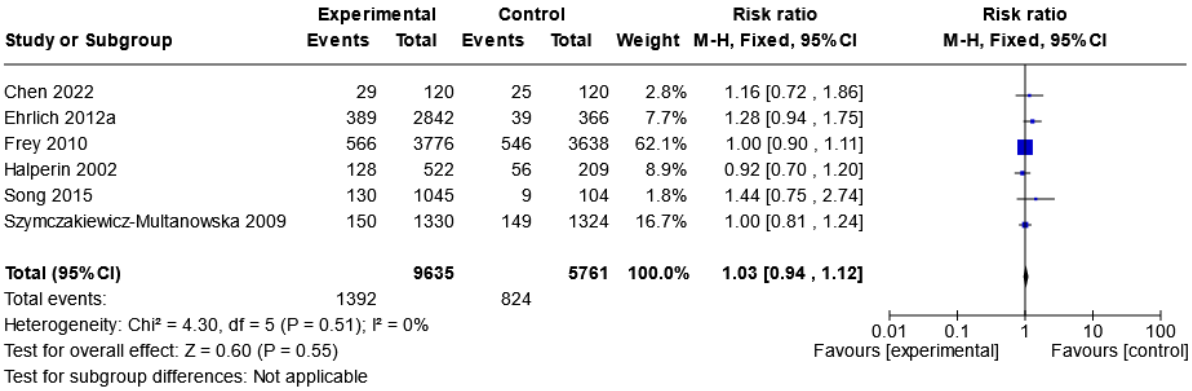
No additional data were identified in the update.

Secondary safety outcomes

Systemic adverse events

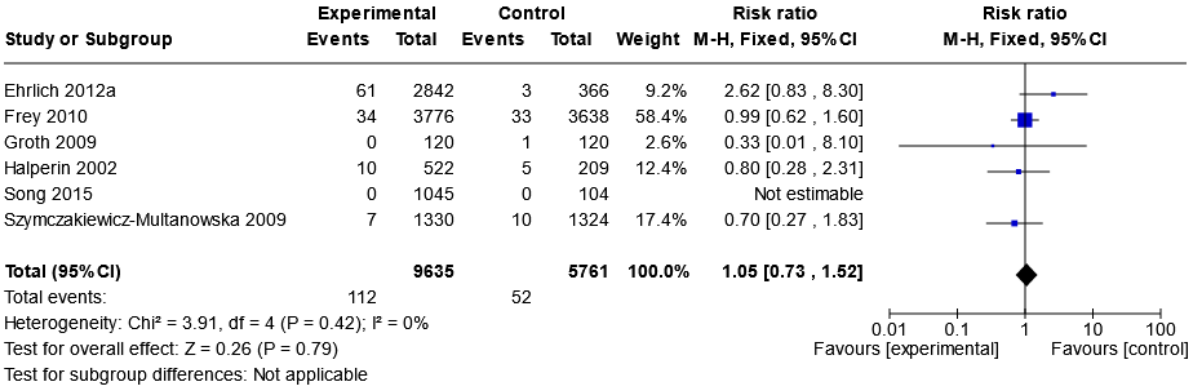
In the primary review, headaches were reported from six RCTs. Pooled RR was 1.03 (95%CI: 0.94 to 1.12; fixed effects model; random-effects model: 1.05; 95%CI: 0.91 to 1.21) (see Figure 10). The figure of the random effects model is shown in Annex 5 (Figure 29). No additional studies were identified in the update.

Figure 10. Relative risk of headache after vaccination with cell-based influenza vaccine versus standard influenza vaccine (fixed-effects model)



Six RCTs were identified in the primary review which provided data on fever after vaccination. Using a fixed effects model, the pooled RR was 1.05 (95%CI: 0.73 to 1.52); using a random effects model, pooled RR was 1.01 (95%CI: 0.51 to 2.0) (see Figure 11). The figure of the random effects model is shown in Annex 5 (Figure 30). No additional studies were identified in the update.

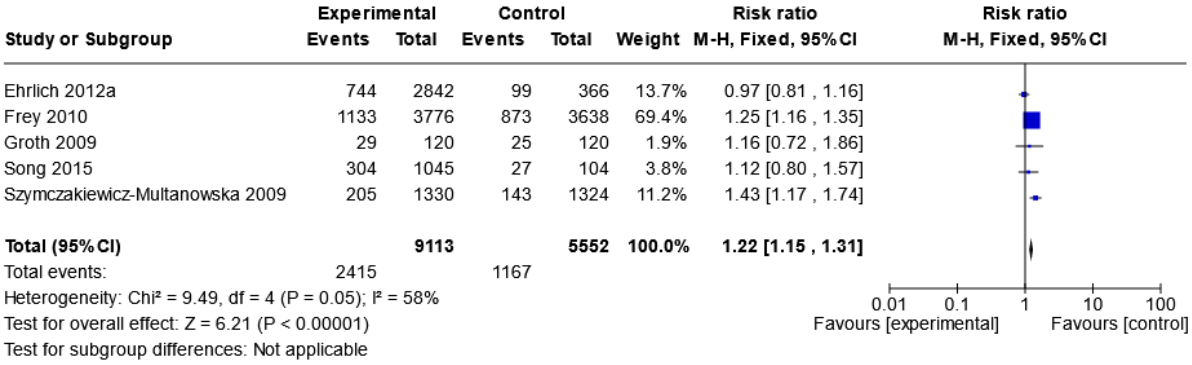
Figure 11. Relative risk of fever after vaccination with cell-based influenza vaccine versus standard influenza vaccine (fixed-effects model)



Local adverse events

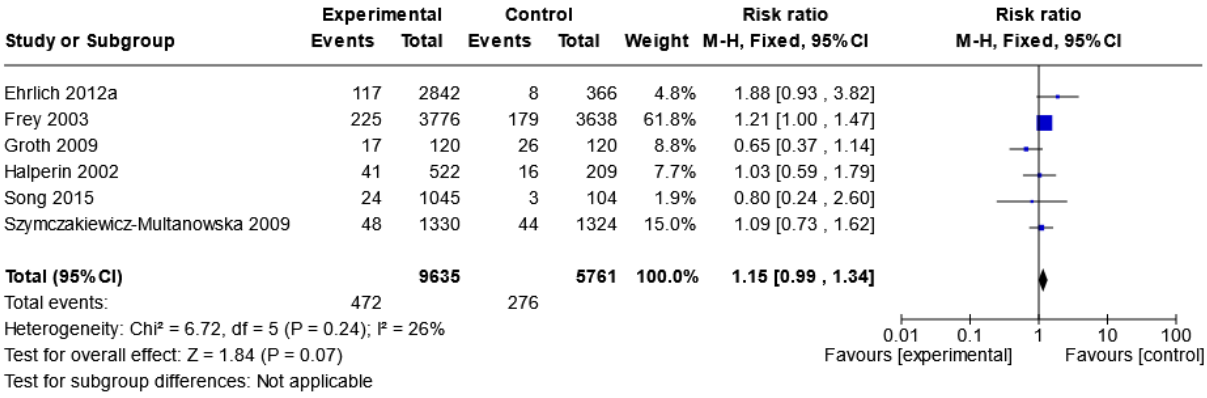
For pain at the injection site after vaccination, the primary review reported data from five RCTs, with a pooled RR of 1.22 (95%CI: 1.15 to 1.31, fixed effects model; random effects model: 1.19 [95%CI: 0.98 to 1.44]) (see Figure 12). The figure of the random effects model is shown in Annex 5 (Figure 31). No additional data were identified in the update.

Figure 12. Relative risk of pain after vaccination with cell-based influenza vaccine versus standard influenza vaccine (fixed-effects model)



In the primary review swelling at the injection site after vaccination was reported in six RCTs. Using a fixed effects model, the RR was 1.15 (95%CI: 0.99 to 1.34), while the RR using a random effects model was 1.08 (95%CI: 0.77 to 1.51) (Figure 13). The figure of the random effects model is shown in appendix E [Figure 32]. No additional data were identified in the update.

Figure 13. Relative risk of swelling after vaccination with cell-based influenza vaccine versus standard influenza vaccine (fixed-effects model)



Adverse pregnancy outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

Adverse neonatal outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

4.3.4 Recombinant influenza vaccine

Efficacy/ effectiveness

Primary efficacy/ effectiveness outcomes

Laboratory-confirmed influenza

In the primary review, one RCT was included that reported rVE estimates from one season [2014−2015] for all strains and influenza A and B separately [40]. Relative VE against all strains was 30% (95%CI: 10 to 47%), 36% (95%CI: 14 to 53%) against influenza A and 4% (95%CI: -42 to 56%) against influenza B.

In the update, we identified one NRSI [28] which reported rVE estimates (all strains) during two consecutive seasons [2018−2019]. Relative VE ranged between -3% and 6%, with none of the estimates being statistically significant (see Table 24 for details).

Influenza-related hospitalisation

No studies matching the inclusion criteria of this update were identified in the primary review.

In the update, we identified one cluster-RCT [29] which reported rVE data for two separate age groups obtained during two consecutive seasons [2018−2020]. Relative VE was -7.3% (95%CI: -52.1 to 24.4%) for the age group 18−49 years and 16.3% (95%CI: -8.7 to 35.5%) for the age group 50−64 years (Table24).

Table 24. Relative vaccine effectiveness of recombinant versus standard influenza vaccine against laboratory-confirmed influenza and influenza-related hospitalisation (laboratory-confirmed)

Study	Study design	rVE	95% CI	Season
Laboratory confirmed influenza				
All strains				
Dunkle 2017	RCT	30%	10-47%	2014-2015
Zimmerman 2023	NRSI	3%	-31-28%	2018-2020
Zimmerman 2023	NRSI	6%	-48-40%	2018-2020
Zimmerman 2023	NRSI	-3%	-52-30%	2018-2020
A				
Dunkle 2017	RCT	36%	14-53%	2014-2015
B				
Dunkle 2017	RCT	4%	-42-56%	2014-2015
Influenza-related hospitalisation (lab-confirmed)				
Age 18-49 years				
Hsiao 2022	RCT	-7.3%	-52.1-24.4%	2018-2020
Age 50-64 years				
Hsiao 2022	RCT	16.3%	-8.7-35.5%	2018-2020

Influenza-related death

No studies reported on this outcome, either in the primary review or in the update.

Secondary efficacy/ effectiveness outcomes

Influenza related ICU admissions

No studies reported on this outcome, either in the primary review or in the update.

Influenza associated pneumonia/lower respiratory tract disease

No studies reported on this outcome, either in the primary review or in the update.

Influenza-associated cardiovascular disease

No studies reported on this outcome, either in the primary review or in the update.

Influenza-like illness

No studies reported on this outcome, either in the primary review or in the update.

Safety

Primary safety outcomes

Serious adverse events

In the primary review, two RCTs reported two SAE (syncope; pericardial effusion) after administration of the recombinant vaccine [76, 94]. The pooled relative risk of SAE after vaccination with recombinant influenza vaccine compared to standard influenza vaccine was 3.04 (95%CI: 0.32 to 29.10; fixed-effects model).

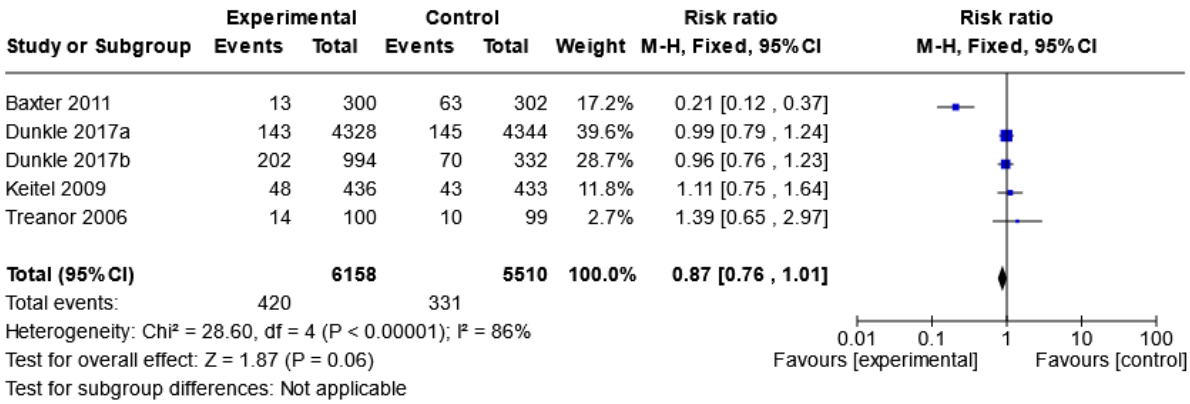
In the update, two NRSI were identified which reported on various SAEs. One NRSI [50] reported no significantly increased risk of death (OR 0.49 [95%CI: 0.21 to 1.05]), idiopathic thrombocytopenic purpura (OR 0.90 [95%CI: 0.03 to 11.81]), non-infectious pleural effusion (OR 1.76 [95%CI: 0.05 to 68.70]) and convulsion (OR 0.90 [95%CI: 0.03 to 11.81]) after recombinant vaccine, compared to standard vaccine. The other NRSI [49] found no increased risk of Guillain-Barré syndrome in inpatient or emergency department settings (OR 0 [95%CI: 0 to 16.07]) or in outpatients (OR 0 [95%CI: 0 to 112.6]). Furthermore, they did not detect an increased risk of non-infectious pleural effusion (OR 0 [95%CI: 0 to 4.8]) or narcolepsy/cataplexy (OR 0 [95%CI: 0 to 6]).

Secondary safety outcomes

Systemic adverse events

Headache after administration of the recombinant vaccine was reported by five RCTs in the primary review. According to the fixed effects model, pooled RR was 0.87 (95%CI: 0.76 to 1.01), while it was 0.79 (95%CI: 0.32 to 1.98) using the random effects model (Figure 14). The figure of the random effects model is shown in Annex 5.

Figure 14. Relative risk of headache after vaccination with recombinant influenza vaccine versus standard influenza vaccine (fixed-effects model)

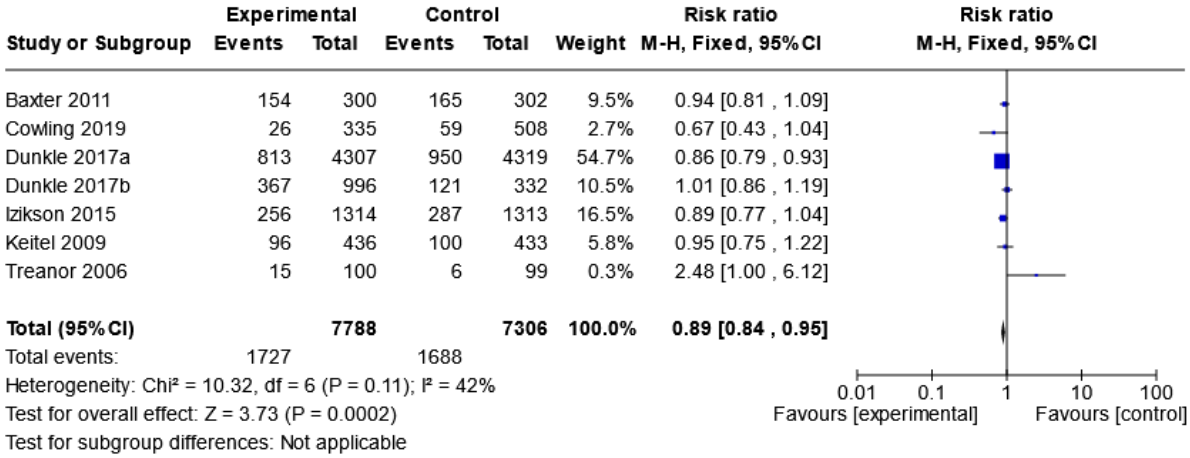


In the primary review, no studies were included that reported on fever. In the update, we identified two NRSI which reported data on this outcome [49, 50]. Neither studies found an increased risk of fever (RR 0 [95%CI: 0 to 1.47) [50]; RR inpatients: 0.38 (95%CI: 0.14 to 0.9); RR outpatients: 1.02 (95%CI: 0.6 to 1.74) [49].

Local adverse events

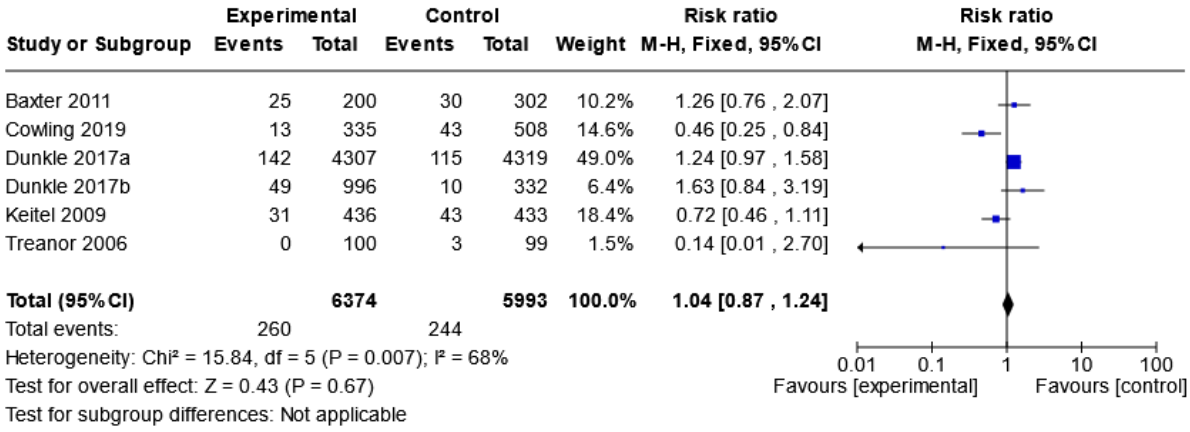
Seven RCTs were identified by the primary review reporting data on pain at the injection site. Pooled RR was 0.89 (95%CI: 0.84 to 0.95) by fixed effects model and 0.04 (95%CI: 0.73 to 1.21) by random effects model. The figure of the random effects model is shown in Annex 5 (Figure 34). No additional data were identified in the update.

Figure 15. Relative risk of pain after vaccination with recombinant influenza vaccine versus standard influenza vaccine (fixed-effects model)



Data on injection site swelling were provided by six RCTs in the primary review. According to the fixed effects model, pooled RR was 1.04 (95%CI: 0.87 to 1.24) and 0.91 (95%CI: 0.48 to 1.72) using the random effects model. The figure of the random effects model is shown in Annex 5 (Figure 35). No additional data were identified in the update.

Figure 16. Relative risk of swelling after vaccination with recombinant influenza vaccine versus standard influenza vaccine (fixed-effects model)



Adverse pregnancy outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

Adverse neonatal outcomes after vaccination during pregnancy

No studies reported on this outcome, either in the primary review or in the update.

4.3.5 mRNA-based influenza vaccine

Efficacy/effectiveness

Primary efficacy/effectiveness outcomes

Laboratory-confirmed influenza

No studies reported on this outcome.

Influenza-related hospitalisation

No studies reported on this outcome.

Influenza-related death

No studies reported on this outcome.

Secondary efficacy/effectiveness outcomes

Influenza related ICU admissions

No studies reported on this outcome.

Influenza associated pneumonia/lower respiratory tract disease

No studies reported on this outcome.

Influenza-associated cardiovascular disease

No studies reported on this outcome.

Influenza-like illness

No studies reported on this outcome.

Safety

Primary safety outcomes

Serious adverse events

No studies reported on this outcome.

Secondary safety outcomes

Systemic adverse events

No studies reported on this outcome.

Local adverse events

No studies reported on this outcome.

Adverse pregnancy outcomes after vaccination during pregnancy

No studies reported on this outcome.

Adverse neonatal outcomes after vaccination during pregnancy

No studies reported on this outcome.

4.4 Subgroup analysis

Subgroup analysis was not performed due to lack of data.

5. Discussion

This systematic review update included a total of 59 studies. This included the 17 studies [seven on efficacy/effectiveness, 10 on safety] from this update review and the 42 studies [10 on efficacy/effectiveness, 32 on safety] from the primary review (that met the inclusion criteria for this updated review). Risk of bias of the newly identified studies varied, from moderate in effectiveness studies to low-to-serious in safety studies.

For the MF59-adjuvanted vaccine, rVE against laboratory-confirmed influenza was -30% (95%CI: -146 to 31%) to 88% (95%CI: 51 to 100%) (seven NRSI; low certainty of evidence). Relative VE against laboratory-confirmed influenza-related hospitalisation (all strains) was 59.2% (95%CI: 15.6 to 80.5%) (one NRSI; moderate certainty]. No data were available for VE against influenza-related death. No increased risk was detected regarding MF59-adjuvanted vaccine related serious adverse events (three RCT, two NRSI; low certainty of evidence).

The high-dose vaccine showed rVE against laboratory-confirmed influenza of 24.2% (95%CI: 9.7 to 36.5%) in one RCT (moderate certainty of evidence) and -9% (95%CI: -158 to 54%) to 19% (95%CI: -27 to 48%) in one NRSI. Relative VE against laboratory-confirmed influenza-related hospitalisation (all strains) was 27% (95%CI: -1 to 48%) (one NRSI; low certainty). No data were available for rVE against influenza-related death. No increased risk was detected regarding high-dose vaccine related serious adverse events (six RCT, three NRSI; low certainty of evidence).

Relative cell-based vaccine efficacy against laboratory-confirmed influenza ranged from -5.8% (95%CI: -36.1 to 17.7%) (influenza A) to 21.4% (95%CI: -7.3 to 42.4%) (influenza B) (two NRSI; low certainty). Relative VE against laboratory-confirmed influenza-related hospitalisation (all strains) was 8.5% (95%CI: -75.9 to 52.3%) (one NRSI; low certainty). No data were available for VE against influenza-related death. No increased risk was detected regarding cell-based vaccine related serious adverse events [one RCT; low certainty of evidence].

For the recombinant vaccine, rVE against laboratory-confirmed influenza ranged from 30% (95%CI: 10 to 47%) in one RCT (moderate certainty) and 3% (95%CI: -31 to 28%) to 19% (95%CI: -27 to 48%) in one NRSI. Relative VE against laboratory-confirmed influenza-related hospitalisation was -7.3% (95%CI: -52.1 to 24.4%) (18-49 years of age) to 16.3% (95%CI: -8.7 to 35.5%) (50−64 years of age) (one RCT; certainty of evidence not assessed due to lack of information). No data were available for rVE against influenza-related death. No increased risk was detected regarding high-dose vaccine related serious adverse events (two RCT, two NRSI; low certainty of evidence).

No studies were found investigating efficacy, effectiveness or safety of mRNA-based vaccines.

Overall completeness and applicability of evidence

The aim of this update of an existing primary systematic review [8] was to re-assess the evidence on the efficacy/effectiveness and safety of newer and/or enhanced influenza vaccines by updating the search, and by narrowing the focus of the research question to comparison with standard vaccines or head-to-head comparison between the enhanced vaccines, allowing for new technologies [mRNA-based vaccines]. In addition, the intention was to overcome some methodological weaknesses in the primary review. For example, we no longer included effectiveness outcomes which had not been laboratory-confirmed, with the exception of influenza-like illness [ILI] where we included studies that used internationally accepted outcome definitions (e.g. by WHO or US CDC). The main reason for this decision was that non-randomised studies (observational studies) which do not use laboratory-confirmed outcomes to assess influenza vaccine effectiveness have been shown to be prone to healthy vaccine bias as well as confounding by indication [95]. Moreover, it has been demonstrated that these forms of bias cannot be eliminated by statistical procedures to control for confounding [95]. Consequently, studies using non-laboratory confirmed ICD-codes or claims data (or compound outcomes derived from such data) which were included in the primary review [80-83, 89, 90, 96-101] were not used in this update.

While new data accumulated since 2020 were reassuring in terms of the safety of the vaccines, the evidence base regarding the efficacy/effectiveness of these vaccines against laboratory-confirmed outcomes has not been substantially improved. On the contrary, for two of the new vaccines (i.e. high-dose vaccine and recombinant vaccine) findings from recent NRSI contradicted previous findings from RCTs regarding VE against laboratory-confirmed influenza. For the high-dose vaccine, the RCT by Diaz-Granados et al. [38] described a relative VE (compared to standard vaccine) of more than 20%, whereas the recent test-negative study by Balasubramani [24], which was assessed to be of moderate risk of bias, did not observe a statistically significant relative VE in any of the four consecutive influenza seasons investigated. Similarly, for the recombinant vaccine, Dunkle et al. [40] found a relative VE of 30% in their RCT, whereas the recent test-negative study by Zimmerman et al. [28] (moderate risk of bias) did not find any effect over two consecutive seasons. While the GRADE certainty of evidence assessments was still based on the RCT data (since in both cases the evidence base from the NRSI was judged to be weaker due to confounding and imprecision), the evidence available at this stage is still limited. Nevertheless, a review of the evidence summarised in this report may help contribute as one of the elements for decision making.

There was one exception where the evidence base on VE had substantially improved. The test-negative design study by Domnich [30] provides, for the first time, rVE estimates against laboratory-confirmed influenza-related hospitalisation for the MF59-adjuvanted vaccine.

After the date of the last search of this update, a study on the relative effectiveness of recombinant influenza vaccine versus standard-dose influenza vaccine was published [102]. This cluster RCT described a rVE of 15.3% (95%CI: 5.9 to 23.8) against laboratory-confirmed influenza. However, due to the cut-off date for inclusion of results in this current systematic review, the full set of results from the study could not be included in this update. Nevertheless, some data on the rVE against influenza-related hospitalisation presented in this RCT have already been published as a congress abstract and are included in this update [29].

The new studies identified in this update which investigated rVE were all assessed to have moderate risk of bias. Compared to the primary review where a substantial number of NRSI included had serious risk of bias, we observed a considerable increase in overall study quality, particularly regarding the consideration of confounders. However, there is still a lack of data regarding a number of laboratory-confirmed outcomes for all vaccines investigated in this review update. The same applies to the head-to-head comparison between the enhanced vaccines, where only one study was identified reporting safety data, but no rVE data were found. Moreover, we identified substantial evidence gaps regarding the safety of these vaccines during pregnancy. Even those studies that included pregnant women did not present appropriate information to be included in our review [49, 50]. It is worth mentioning that recombinant and cell-based vaccines are the only newer and/or enhanced influenza vaccines licenced for women of childbearing age. Furthermore, the planned sub-group analyses (e.g. strain, clade, season) could not be performed due to heterogeneity of studies and outcomes and sparse data per vaccine and outcome. Finally, no data on rVE or safety of the mRNA-vaccines have bee made available to date.

Certainty of the evidence

For this systematic review update, we assessed the certainty of the evidence for the primary efficacy/effectiveness and safety outcomes. Results are summarised below for each of the vaccines investigated.

For the MF59-adjuvanted vaccine, certainty was assessed as being low for the outcome laboratory-confirmed influenza and moderate for influenza-related hospitalisation [one NRSI, downgraded for risk of bias]. No assessment was possible for influenza-related death due to lack of data. For serious adverse events, certainty of evidence was low.

For the high-dose vaccine, certainty of evidence was moderate for the outcome laboratory-confirmed influenza (one RCT; downgraded due to risk of bias). Certainty was assessed to be low for influenza-related hospitalisation. No assessment was possible for influenza-related death due to lack of data. For serious adverse events, certainty of evidence was low.

For the cell-based vaccine, certainty of evidence was low for the outcome laboratory-confirmed influenza (two NRSI, downgraded due to risk of bias and inconsistency). Certainty was low for influenza-related hospitalisation (one NRSI; downgraded by one for risk of bias and one for imprecision). No assessment was possible for influenza-related death due to lack of data. For serious adverse events, certainty of evidence was low.

For the recombinant vaccine, certainty of evidence was assessed to be moderate for laboratory-confirmed influenza (one RCT; downgraded due to risk of bias). No assessments were possible for influenza-related hospitalisation (not enough information) or influenza-related death (no data). For serious adverse events, certainty of evidence was low.

Due to lack of data, no certainty of the evidence assessment was possible for the mRNA-based vaccine.

Potential biases in the review process

Regarding potential biases in the study identification process, there is a small chance that our search missed potentially relevant studies. However, this appears unlikely since the search string was built upon the successful strategy of the primary review and was assessed by an experienced information specialist. During the screening process, there remains a small possibility that we overlooked laboratory-confirmed outcomes in studies which were therefore excluded. However, we think that this is unlikely since the review process was conducted by pairs of experienced reviewers and a senior reviewer was involved in every case of uncertainty. Finally, risk of bias assessment is always subjective to some extent and therefore other reviewers might have come to different assessment conclusions. We tried to minimise subjectivity by having pairs of reviewers conduct independent assessments and allowing for an in-depth team discussion of the results of the risk of bias judgements.

Agreements and disagreements with other studies or reviews

As discussed in detail above, the main comparison for this update is the primary review [8] which basically arrived at the same conclusions. We are aware of another systematic review published in 2021 [data cut: 15 July 2020] which analysed the MF59-adjuvanted vaccine [103]. This review came to more favourable conclusions regarding the relative effectiveness of this vaccine. However, the authors also included non-laboratory-confirmed outcomes. It should also be noted that the review was co-authored by representatives of the manufacturer, which constitutes a conflict of interest.

6. Conclusions

This systematic review update shows that the evidence on relative efficacy/effectiveness of newer and/or enhanced influenza vaccines, compared to standard influenza vaccines, is still limited. No efficacy/effectiveness data was found on head-to-head comparison between the enhanced vaccines. Low-to-moderate relative vaccine effectiveness was found for the MF59-adjuvanted vaccine, the high-dose vaccine and the recombinant vaccine for laboratory confirmed influenza. Low-to-moderate relative vaccine effectiveness was also found for the MF59-adjuvanted vaccine and the high-dose vaccine for laboratory-confirmed influenza-related hospitalisation. A larger evidence base is available on safety (although certainty of evidence was generally low), demonstrating an overall favourable safety profile for all vaccines. The risk of bias was low-to-moderate in all efficacy/effectiveness studies and low-to-serious in safety studies. Further studies are needed, particularly regarding laboratory-confirmed outcomes and safety data, to allow more substantial conclusions on the potential benefits of these vaccines.

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Annex 1. Search strategies

Medline (Ovid)

Date run: 24.07.2023

#	Searches	Results
1	Influenza, Human/	57851
2	Influenza A virus/ or exp Influenza B virus/	25030
3	influenza.ti.	79308
4	1 or 2 or 3	97222
5	vaccines/ or vaccines, attenuated/ or vaccines, inactivated/ or vaccines, subunit/ or vaccines, synthetic/ or nucleic acid-based vaccines/ or mrna vaccines/ or vaccines, conjugate/ or vaccines, virosome/ or vaccines, virus-like particle/ or vaccines, live, unattenuated/ or viral vaccines/ or influenza vaccines/	112523
6	exp Vaccination/ or Immunization/ or Immunotherapy, Active/	160514
7	[vaccin* or immuni* or inocul*].ti,ab,kf.	834488
8	5 or 6 or 7	870327
9	4 and 8	39133
10	influenza vaccines/	26853
11	[[vaccin* or immuni* or inocul*] adj4 influenza].ti,ab,kf.	29925
12	9 or 10 or 11	46127
13	[[trivalent or quadrivalent or tetravalent or tetra*] adj8 vaccin*].ti,ab,kf.	6642
14	[[[high adj2 dose*] or highdose] adj8 vaccin*].ti,ab,kf.	1079
15	[TIV or QIV].ti,ab,kf.	1075
16	[cell adj3 vaccin*].ti,ab,kf.	11331
17	[[adjuvant* or squalene* or emulsion*] adj8 vaccin*].ti,ab,kf.	16599
18	[recombinant adj6 vaccin*].ti,ab,kf.	15694
19	[MF59* or "MF-59"].ti,ab,kf.	732
20	Nucleic Acid-Based Vaccines/ or mRNA Vaccines/	1137
21	[[gene or genetic or nucleic acid or RNA or mRNA] adj3 vaccin*].ti,ab,kf.	13577
22	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	59710
23	12 and 22	6639
24	[fluad or fluzone or flucelvax or flublok or supemtek or optaflu].ti,ab,kf,nm.	271
25	[[cell-based or cell-derived or cellular or "whole cell" or "whole cells"] adj3 vaccin* adj6 influenza].ti,ab,kf.	125
26	[aIIV3 or "aIIV4 HD-IIV3" or "HD-IIV4" or ccIIV3 or ccIIV4 or RIV3 or RIV4 or aQIV].ti,ab,kf.	80
27	23 or 24 or 25 or 26	6732
28	limit 27 to yr="2020 -Current"	1408
29	animals/ not humans/	5107621
30	[rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset* or equine or uquines or "ex vivo" or "in vitro"].ti. and [Animal Experimentation/ or models, biological/ or disease models, animal/ or exp In Vitro Techniques/ or cytological techniques/ or exp cell culture techniques/]	402856
31	29 or 30	5213363
32	28 not 31	1229
33	[randomized controlled trial or controlled clinical trial].pt.	687755
34	[randomized or randomised or placebo or randomly or trial or groups].ab.	3535662
35	33 or 34	3676435
36	32 and 35	384
37	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/	6599991

38	[[control and [group* or study]] or [time and factors] or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*].mp.	8617974
39	37 or 38	11344166
40	32 and 39	617
41	[case adj2 control].ti,ab,kf.	160691
42	[[test-negative or test-negativity] adj6 [study or studies or design*]].ti,ab,kf.	755
43	41 or 42	161027
44	32 and 43	40
45	36 or 40 or 44	719
46	comment.pt.	1014506
47	editorial.pt.	658111
48	case reports.pt.	2347767
49	[case adj [study or studies or series or report or reports]].ti.	415260
50	46 or 47 or 48 or 49	3912415
51	45 not 50	709
52	[["COVID-19" or "SARS-CoV-2" or "Coronavirus Disease 2019"] not "influenza"].ti.	292163
53	exp covid-19/ or SARS-CoV-2/	239107
54	52 or 53	339554
55	51 not 54	605

Embase (via Ovid)

Date run: 24.07.2023

#	Searches	Results
1	exp influenza/	116528
2	influenza.ti.	92329
3	exp Influenza virus A/ or influenza virus B/	25654
4	1 or 2 or 3	154279
5	vaccine/	85225
6	conjugate vaccine/ or inactivated vaccine/ or live vaccine/ or nucleic acid vaccine/ or recombinant vaccine/ or subunit vaccine/ or virosome vaccine/ or virus like particle vaccine/ or virus vaccine/	54768
7	immunization/ or vaccination/ or active immunization/ or immunoprophylaxis/ or mass immunization/	347400
8	[vaccin* or immuni* or inocul*].ti,ab,kf.	1051488
9	5 or 6 or 7 or 8	1125136
10	4 and 9	58931
11	[[vaccin* or immuni* or inocul*] adj4 influenza].ti,ab,kf.	38268
12	influenza vaccine/	46635
13	11 or 12	58440
14	10 or 13	76555
15	[[trivalent or quadrivalent or tetravalent or tetra*] adj8 vaccin*].ti,ab,kf.	8775
16	[[[high adj2 dose*] or highdose] adj8 vaccin*].ti,ab,kf.	1408
17	[TIV or QIV].ti,ab,kf.	1556
18	[[cell-based or cell-derived or cellular or "whole cell" or "whole cells"] adj3 vaccin* adj6 influenza].ti,ab,kf.	161
19	[cell adj3 vaccin*].ti,ab,kf.	14947
20	cell-based vaccine/	353
21	[[adjuvant* or squalene* or emulsion*] adj8 vaccin*].ti,ab,kf.	20599
22	[recombinant adj6 vaccin*].ti,ab,kf.	18356
23	recombinant vaccine/	8001

24	[aIIV3 or "aIIV4 HD-IIV3" or "HD-IIV4" or ccIIV3 or ccIIV4 or RIV3 or RIV4 or aQIV].ti,ab,kf.	89
25	[MF59 or "MF-59"].ti,ab,kf.	885
26	exp rna vaccine/ or nucleic acid vaccine/	16297
27	[[gene or genetic or nucleic acid or RNA or mRNA] adj3 vaccin*].ti,ab,kf.	16815
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	86613
29	14 and 28	10275
30	[fluad or fluzone or flucelvax or flublok or supemtek or optaflu].ti,ab,kf.	338
31	[aIIV3 or "aIIV4 HD-IIV3" or "HD-IIV4" or ccIIV3 or ccIIV4 or RIV3 or RIV4 or aQIV].ti,ab,kf.	89
32	[[cell-based or cell-derived or cellular or "whole cell" or "whole cells"] adj3 vaccin* adj6 influenza].ti,ab,kf.	161
33	30 or 31 or 32	543
34	29 or 33	10369
35	limit 34 to yr="2020 -Current"	2620
36	[rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset* or equine].ti. and [exp animal experiment/ or exp in vitro study/ or exp biological model/]	1749669
37	animal experiment/ not [human experiment/de or human/]	2550346
38	exp in vitro study/ not exp in vivo study/	3539450
39	exp veterinary study/ not [human experiment/de or human/]	84
40	36 or 37 or 38 or 39	6226442
41	35 not 40	2102
42	randomized controlled trial/	777203
43	controlled clinical trial/	470881
44	random*.ti,ab.	1965836
45	randomization/	98226
46	intermethod comparison/	298666
47	placebo*.ti,ab.	370124
48	[compare or compared or comparison].ti.	631873
49	[[evaluated or evaluate or evaluating or assessed or assess] and [compare or compared or comparing or comparison]].ab.	2753018
50	[open adj1 label].ti,ab.	107633
51	[[double or single or doubly or singly] adj1 [blind or blinded or blindly]].ti,ab.	277996
52	double blind procedure/	211385
53	[parallel adj1 group*].ti,ab.	32449
54	[crossover or "cross over"].ti,ab.	125039
55	[[assign* or match or matched or allocation] adj6 [alternate or group or groups or intervention or interventions or patient or patients or subject or subjects or participant or participants]].ti,ab.	457167
56	[assigned or allocated].ti,ab.	488550
57	[controlled adj8 [study or design or trial]].ti,ab.	456608
58	[volunteer or volunteers].ti,ab.	287193
59	human experiment/	634989
60	trial.ti.	404863
61	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	6360891
62	exp cohort analysis/	1023923
63	exp comparative study/	1705484
64	controlled study/ or exp case control study/ or exp controlled clinical trial/	9942972
65	clinical study/ or exp case control study/ or exp clinical trial/ or exp community trial/ or exp intervention study/ or exp major clinical study/ or exp postmarketing surveillance/ or exp prospective study/ or exp retrospective study/	7381597
66	[[control or controlled or compare* or compara*] adj8 [group or groups or population or populations or intervention or interventions or patient or patients or subject or subjects or participant or participants or program* or vaccin*]].ti,ab,kf.	3487545
67	[control or controlled or compare* or compara*].ti,ab,kf. and [epidemiology/ or observational study/]	220940

68	[[control or controlled or compare* or compara* or evaluat*] adj8 stud*].ti,ab,kf.	2821254
69	follow up/ or follow-up.ti,ab,kf.	2578286
70	cohort.ti,ab,kf.	1330861
71	[case adj2 control].ti,ab,kf.	214060
72	[[test-negative or test negativity] adj4 [study or studies or design*]].ti,ab,kf.	866
73	62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	17357049
74	61 or 73	18738508
75	41 and 74	1315
76	comment/ or editorial/	742623
77	limit 75 to [editorial or erratum or letter or note]	39
78	exp case study/	104758
79	[case adj [study or studies or series or report or reports]].ti.	534084
80	76 or 77 or 78 or 79	1346968
81	75 not 80	1256
82	[["COVID-19" or "SARS-CoV-2" or "Coronavirus Disease 2019"] not "influenza"].ti.	316922
83	[exp Severe acute respiratory syndrome coronavirus 2/ or exp coronavirus disease 2019/] not [exp influenza/ or exp Influenza virus A/ or influenza virus B/]	347784
84	82 or 83	402127
85	81 not 84	956

Annex 2. Publications excluded by full text

Wrong outcomes (n= 51)

1. Belongia EA, Levine MZ, Olaiya O, Gross FL, King JP, Flannery B, McLean HQ. Clinical trial to assess immunogenicity of high-dose, adjuvanted, and recombinant influenza vaccines against cell-grown A(H3N2) viruses in adults 65 to 74 years, 2017-2018. Vaccine. 2020;38(15):3121-8.
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3. Boikos C, Fischer L, O'Brien D, Vasey J, Sylvester GC, Mansi JA. Relative Effectiveness of Adjuvanted Trivalent Inactivated Influenza Vaccine Versus Egg-derived Quadrivalent Inactivated Influenza Vaccines and High-dose Trivalent Influenza Vaccine in Preventing Influenza-related Medical Encounters in US Adults >= 65 Yea. Clinical Infectious Diseases. 2021;73(5):816-23.
4. Boikos C, Imran M, Nguyen VH, Ducruet T, Sylvester GC, Mansi JA. Effectiveness of the adjuvanted influenza vaccine in older adults at high risk of influenza complications. Vaccines. 2021;9(8):862.
5. Boikos C, Imran M, Nguyen VH, Ducruet T, Sylvester GC, Mansi JA. Effectiveness of the Cell-Derived Inactivated Quadrivalent Influenza Vaccine in Individuals at High Risk of Influenza Complications in the 2018-2019 United States Influenza Season. Open Forum Infectious Diseases. 2021;8(7):ofab167.
6. Boikos C, McGovern I, Ortiz JR, Puig-Barbera J, Versage E, Haag M. Relative Vaccine Effectiveness of Adjuvanted Trivalent Influenza Vaccine over Three Consecutive Influenza Seasons in the United States. Vaccines. 2022;10(9):1456.
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10. Cocchio S, Gallo T, Zotto SD, Clagnan E, Iob A, Furlan P, et al. Preventing the risk of hospitalization for respiratory complications of influenza among the elderly: Is there a better influenza vaccination strategy? a retrospective population study. Vaccines. 2020;8(3):1-11.
11. Davidson H, Han L, McConeghy K, Saade E, Canaday D, Mor V, Gravenstein S. Can adjuvanted influenza vaccine given as standard of care reduce the risk for influenza outbreaks in nursing homes? evidence from a cluster-randomized trial of 823 nursing homes. Journal of the American Geriatrics Society. 2020;68(SUPPL 1):S217.
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16. Gravenstein S, McConeghy K, Davidson H, Han L, Canaday D, Saade E, Mor V. Secondary analysis comparative effectiveness of adjuvanted vs non-adjuvanted influenza vaccine on reducing hospital days in a long-term care population. Journal of the American Geriatrics Society. 2020;68(SUPPL 1):S218.

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38. Pelton S, Postma M, Divino V, Mould-Quevedo JF, DeKoven M, Krishnarajah G. Pin3 Relative Vaccine Effectiveness of Quadrivalent Cell-Based versus Egg-Based Influenza Vaccines Among Adults 50−64 Years Old: A US Observational Cohort Study. Value in Health. 2020;23(Supplement 1):S168.
39. Pelton SI, Divino V, Postma MJ, Shah D, Mould-Quevedo J, DeKoven M, Krishnarajah G. A retrospective cohort study assessing relative effectiveness of adjuvanted versus high-dose trivalent influenza vaccines among older adults in the United States during the 2018-19 influenza season. Vaccine. 2021;39(17):2396-407.
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49. van Aalst R, Gravenstein S, Mor V, Mahmud SM, Wilschut J, Postma M, Chit A. Comparative effectiveness of high dose versus adjuvanted influenza vaccine: A retrospective cohort study. Vaccine. 2020;38(2):372-9.
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Wrong intervention (n=28)

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Wrong study design (n=25)

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Wrong comparator (n=16)

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Duplicate (n=5)

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Wrong display of data (n=2)

1. de Lusignan S, Tsang RSM, Amirthalingam G, Akinyemi O, Sherlock J, Tripathy M, et al. Adverse events of interest following influenza vaccination, a comparison of cell culture-based with egg-based alternatives: English sentinel network annual report paper 2019/20. The Lancet Regional Health Europe. 2021;2(101777707):100029.
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Abstract meanwhile published as manuscript (n=1)

1. Liu C, Schmader K, Harrington T, Roundtree W, Auerbach H, Walter E, et al. Comparative safety of adjuvanted versus high-dose inactivated influenza vaccines in older adults. Journal of the American Geriatrics Society. 2020;68(SUPPL 1):S140.

Wrong publication type (n=1)

1. Fischer L, O'Brien D, Vasey J, Sylvester GC, Mansi JA. Relative effectiveness of AIIV3 versus IIV4 and HD-IIV3 in preventing influenza-related medical encounters in adults >=65 years of age at high risk for influenza complications during the U.S. 2017-2018 and 2018-2019 influenza seasons. Open Forum Infectious Diseases. 2020;7(SUPPL 1):S844.

Annex 3. Risk of bias assessment

Additional outcomes in NRSI safety-studies

Table 25. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: anaphylaxis

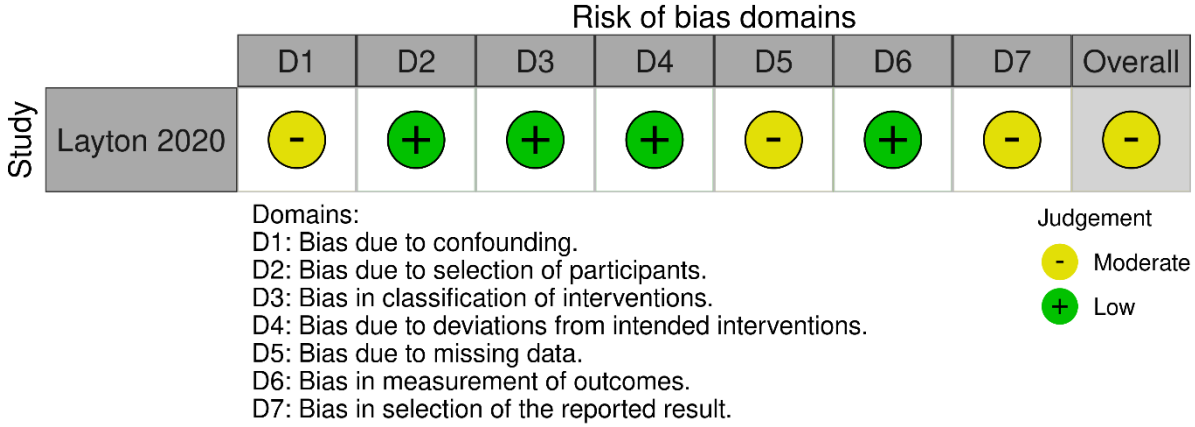


Table 26. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: angioedema

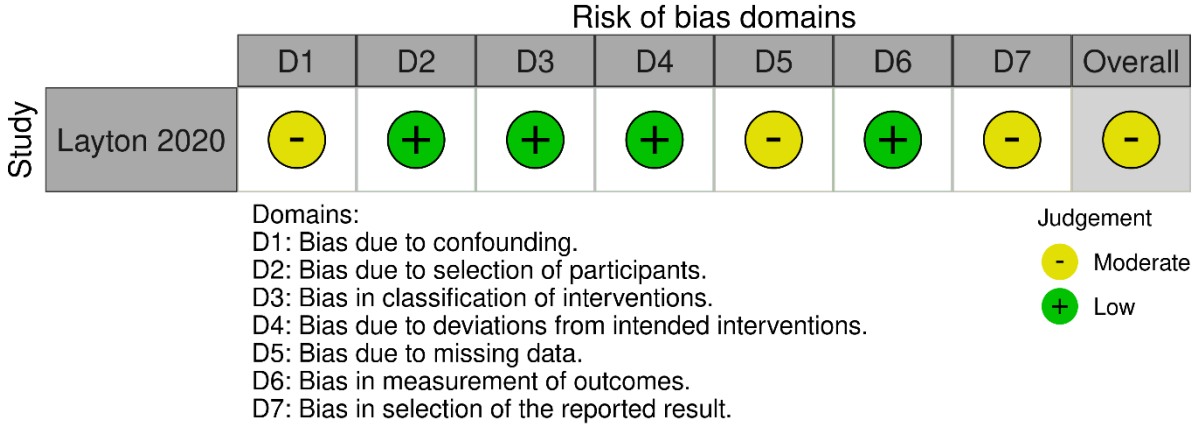


Table 27. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: asthma

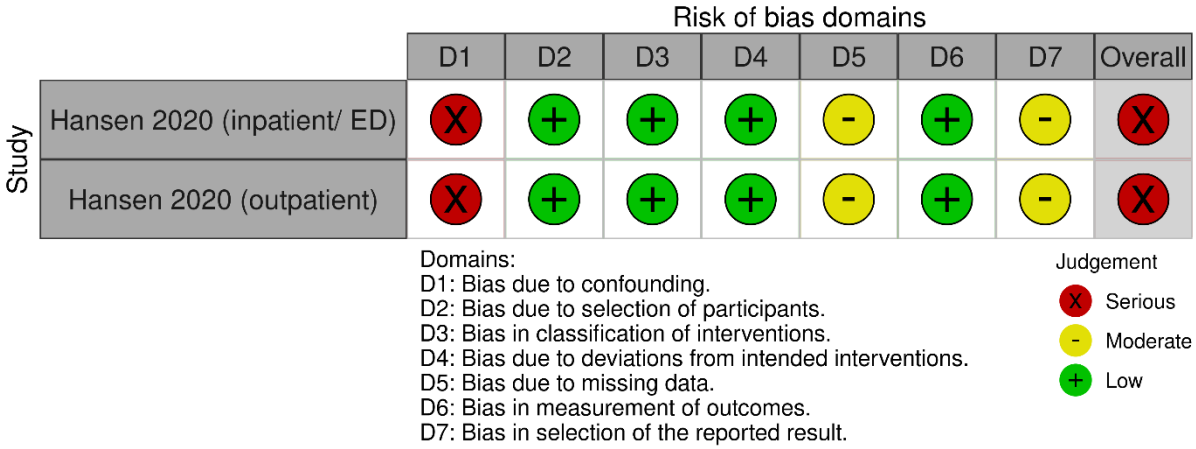


Table 28. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: death

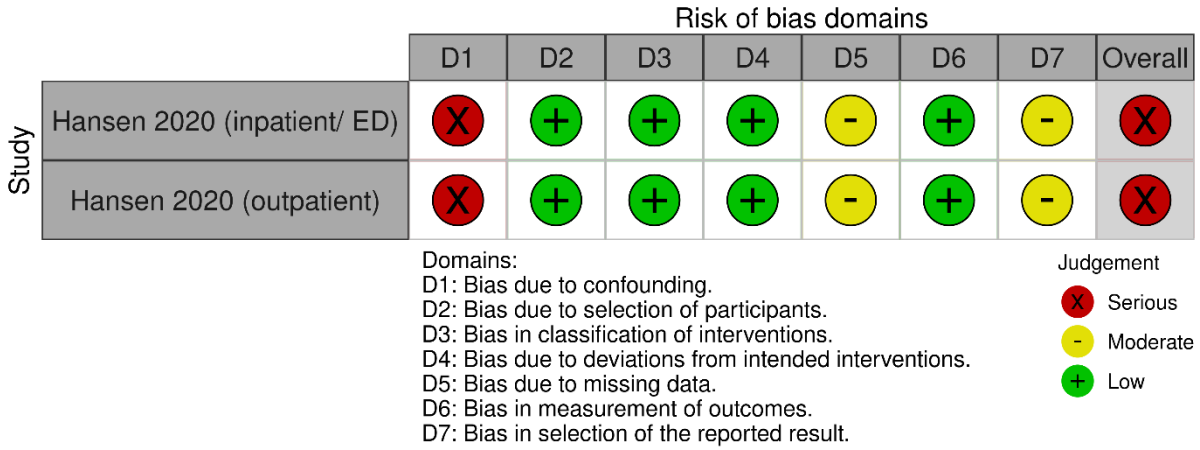


Table 29. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: encephalopathy

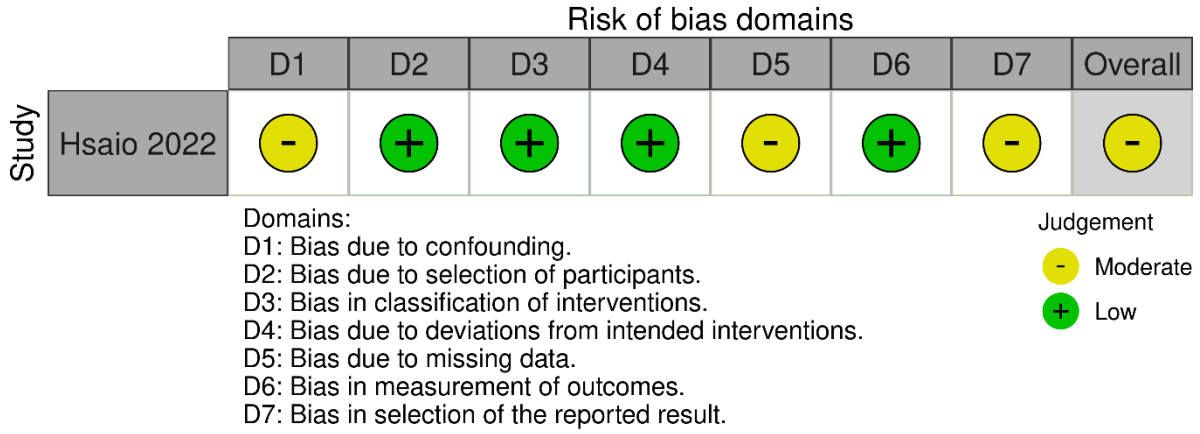


Table 30. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: idiopathic thrombocytopenic purpura/Henoch-Schönlein purpura

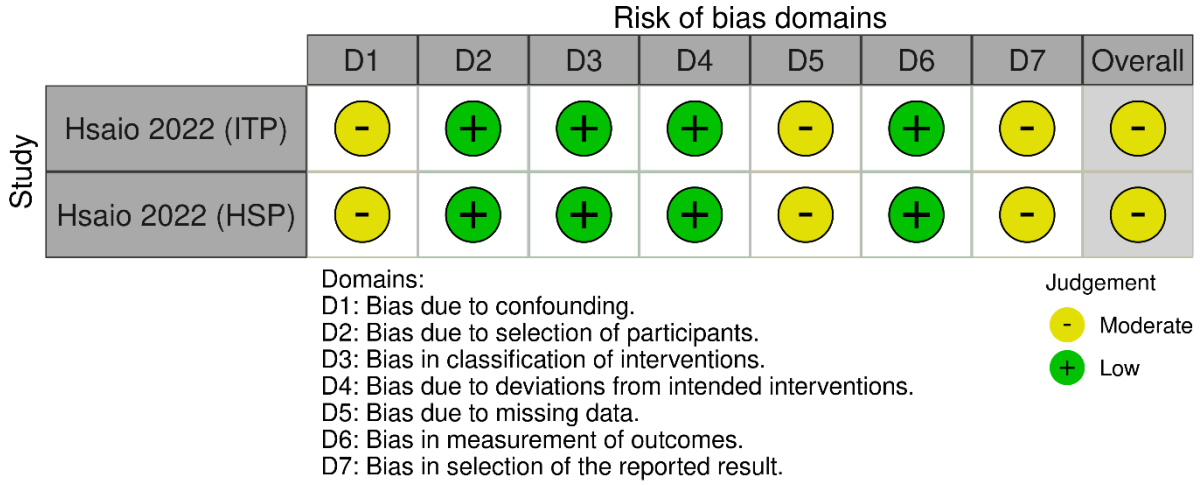


Table 31. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: narcolepsy/cataplexy

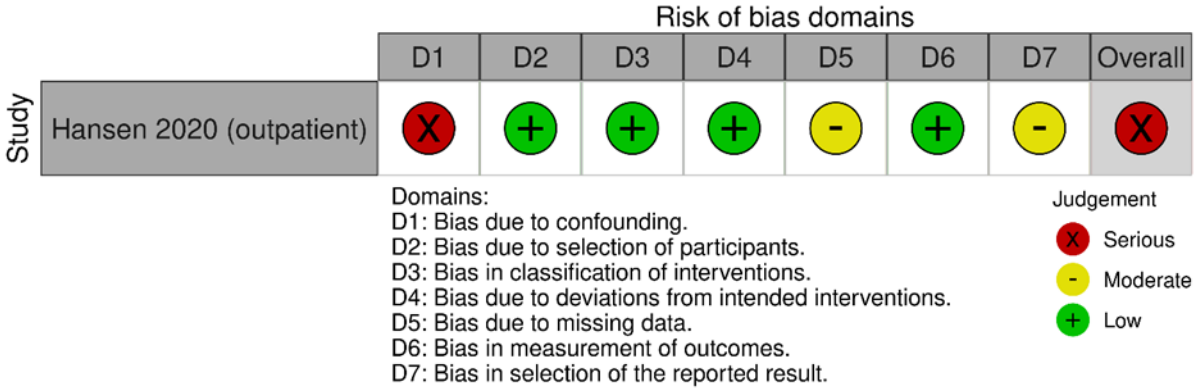


Table 32. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: non-infectious pleural effusion

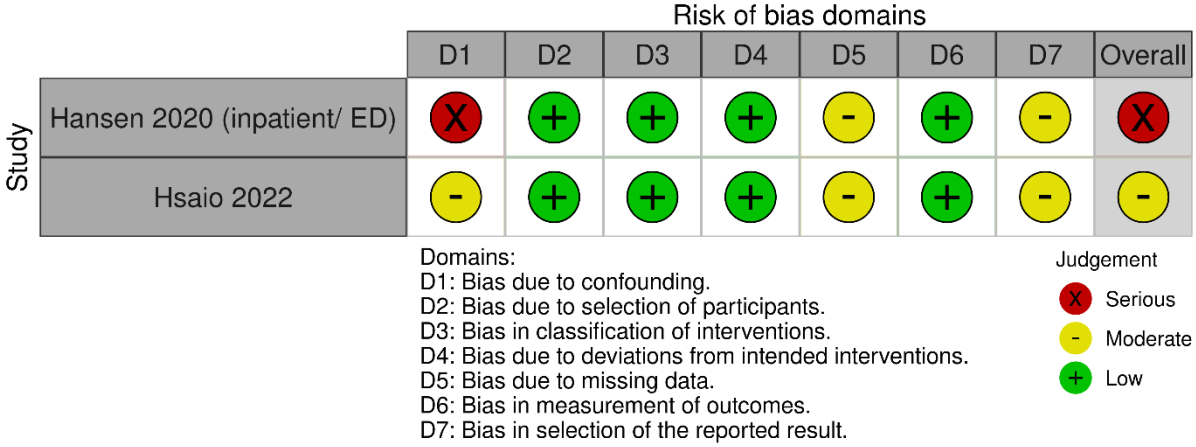


Table 33. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: acute non-infectious pericarditis

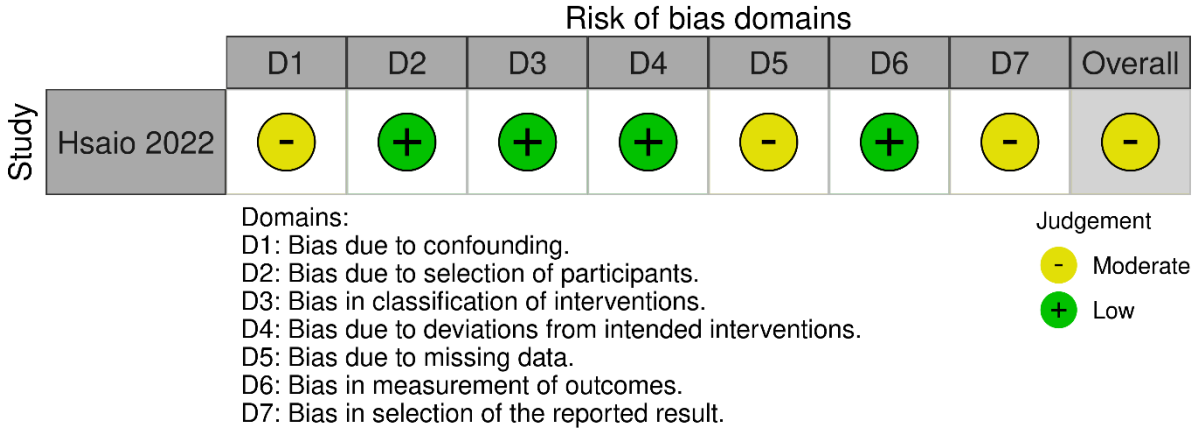


Table 34. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: seizure/ convulsion

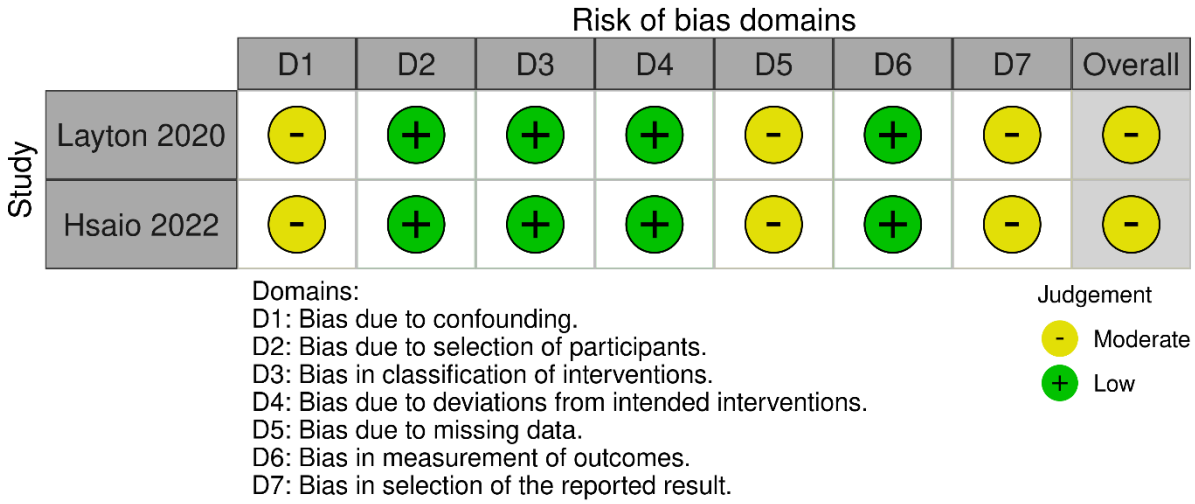
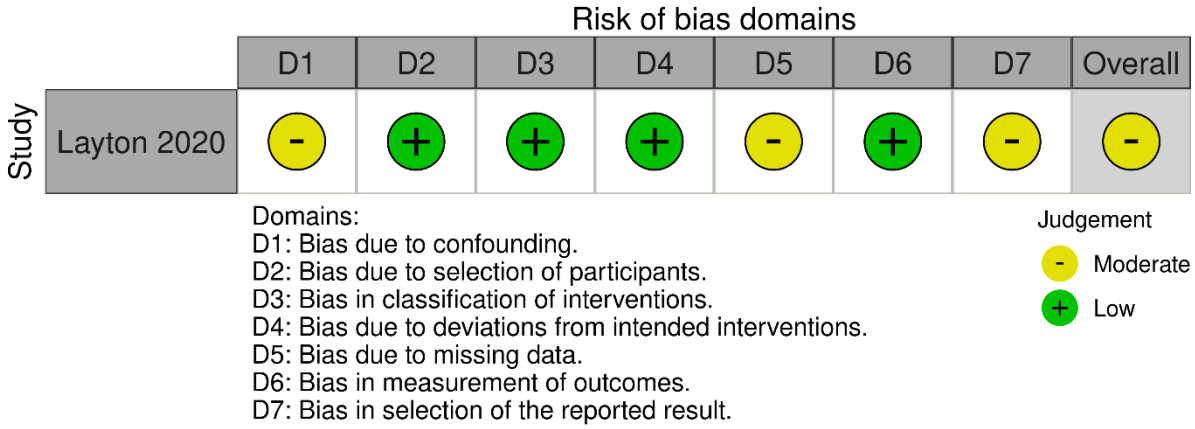


Table 35. Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: short-term mortality



RCT safety-studies

Table 36. Risk of bias in RCT safety-studies (assessed with RoB 2); outcome: AESI

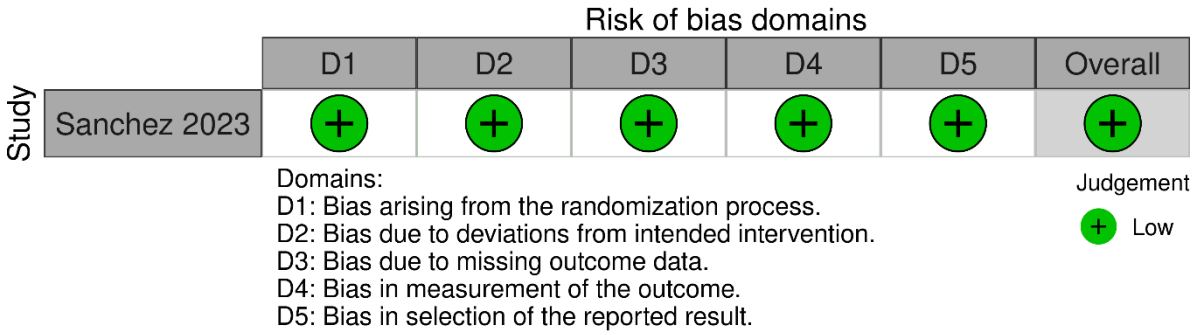
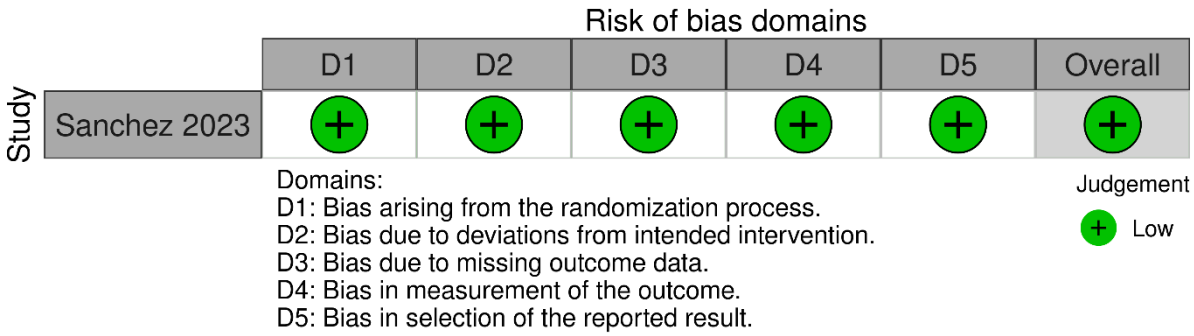


Table 37. Risk of bias in RCT safety-studies (assessed with RoB 2); outcome: death



Annex 4. Funnel plots

For comparisons of outcomes with 10 or more studies, funnel plots were constructed and visually inspected for small study effects. No evidence of publication bias was detected in any of the plots.

MF59-adjuvanted influenza vaccine versus standard influenza vaccine

Figure 17. Funnel plot for safety outcome headache after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (10 studies)

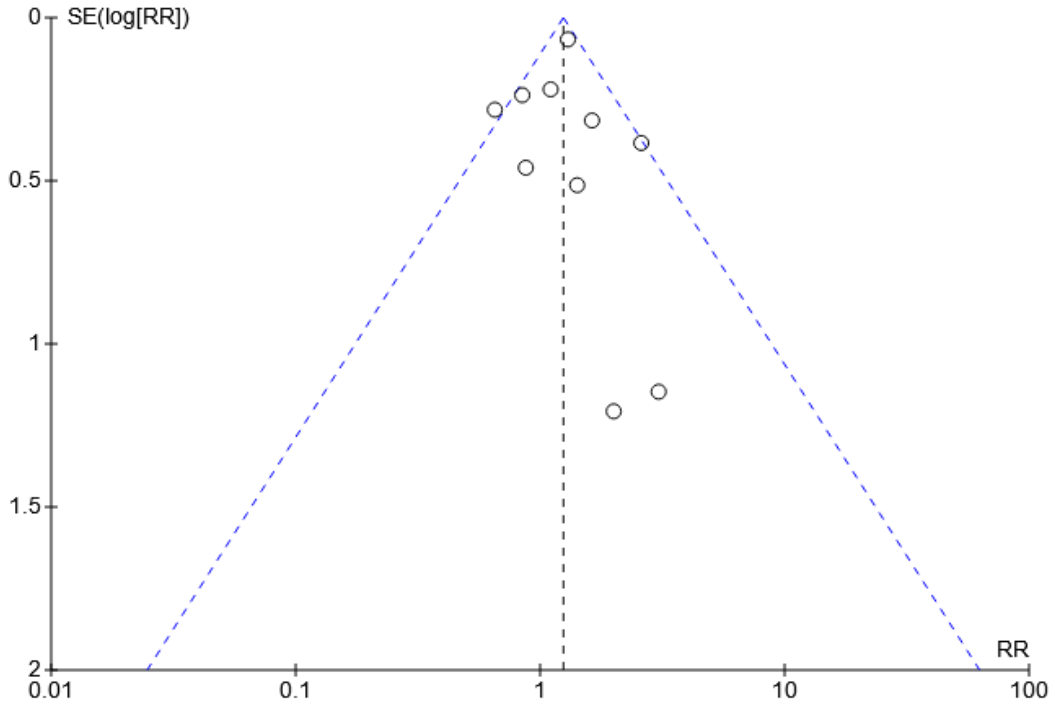


Figure 18. Funnel plot for safety outcome pain after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (12 studies)

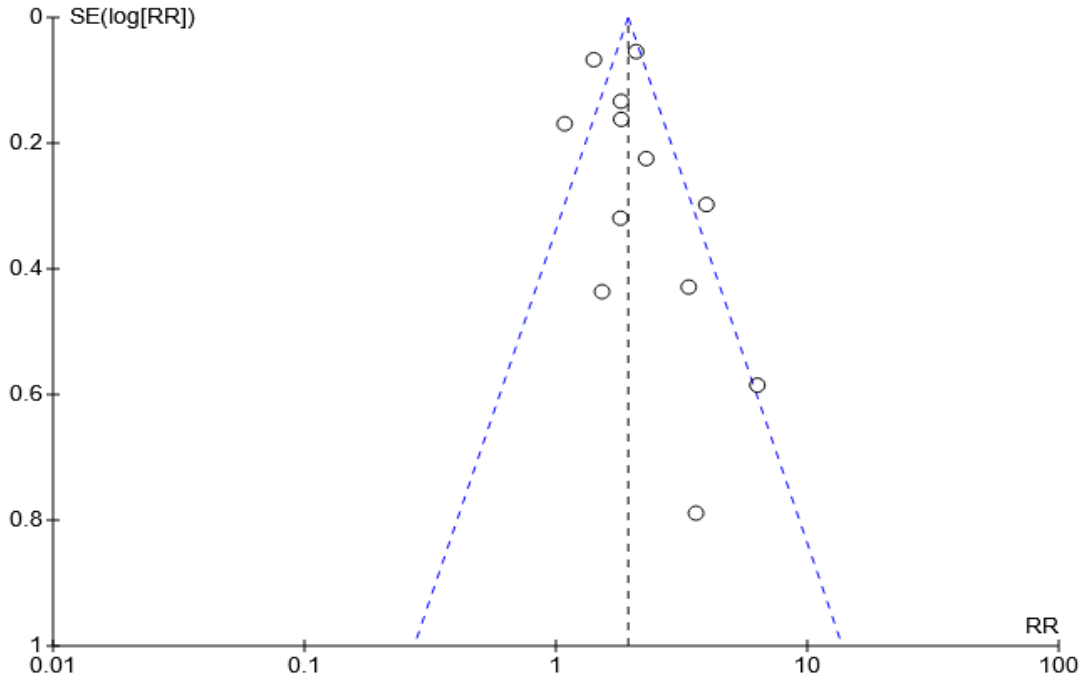


Figure 19. Funnel plot for safety outcome headache after vaccination with high-dose influenza vaccine versus standard influenza vaccine (11 studies)

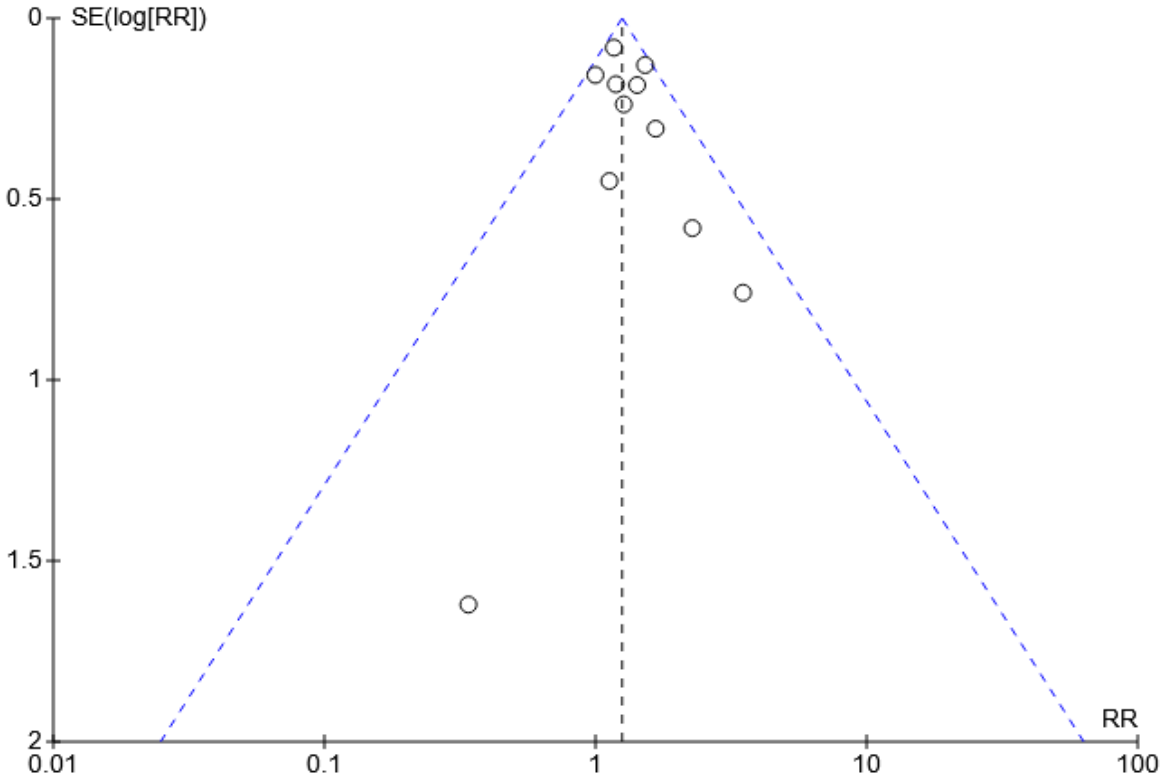
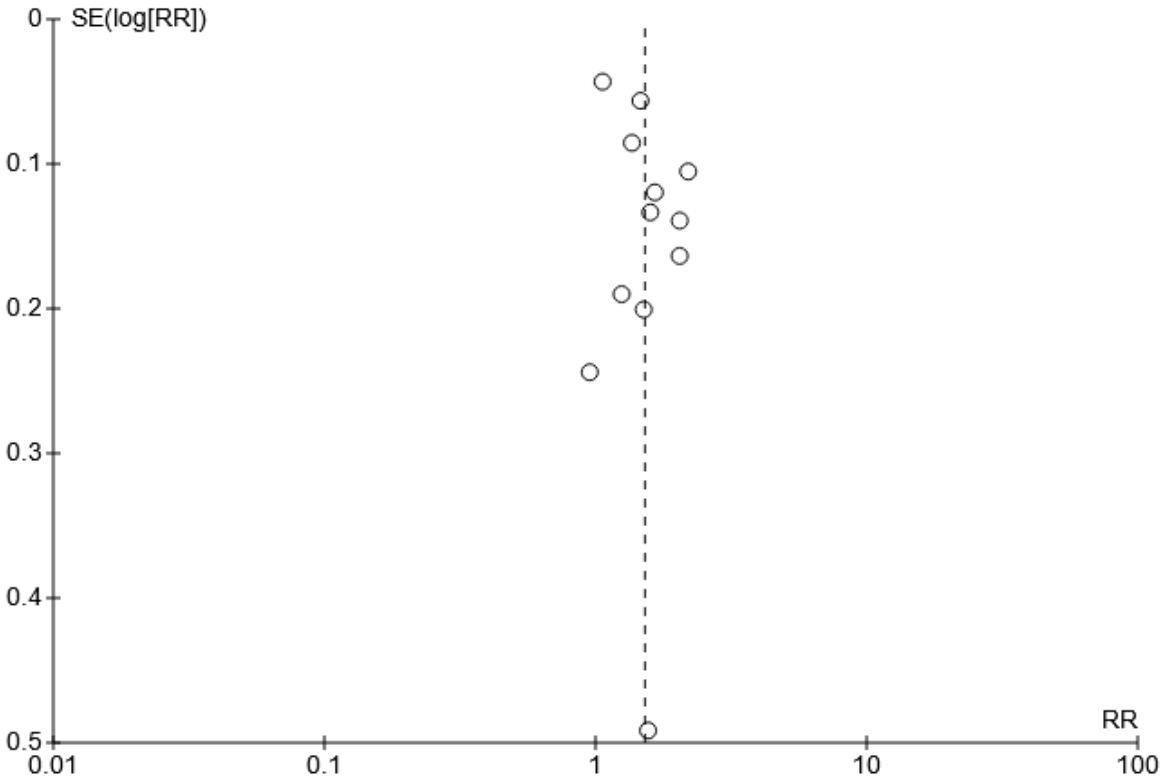


Figure 20. Funnel plot for safety outcome pain after vaccination with high-dose influenza vaccine versus standard influenza vaccine (12 studies)



Annex 5. Random effects models

Figure 21. Relative risk of headache after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (random-effects model)

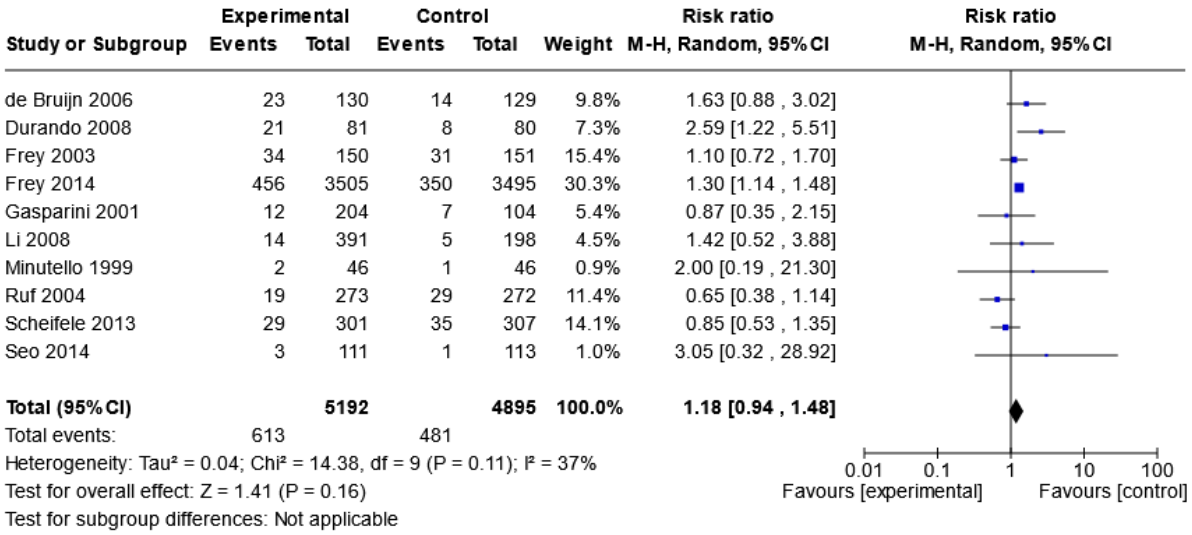


Figure 22. Relative risk of fever after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (random-effects model)

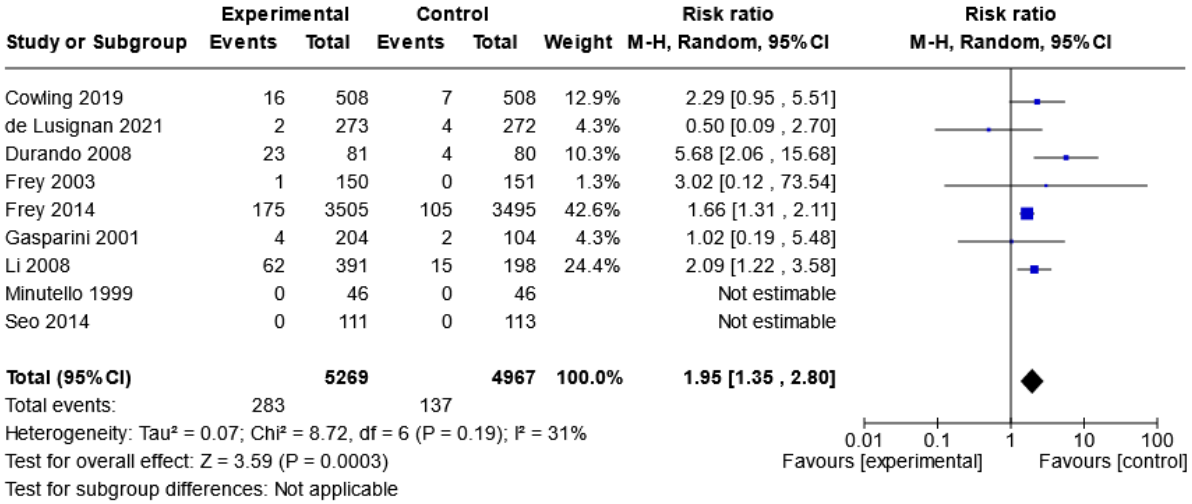


Figure 23. Relative risk of pain after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (random-effects model)

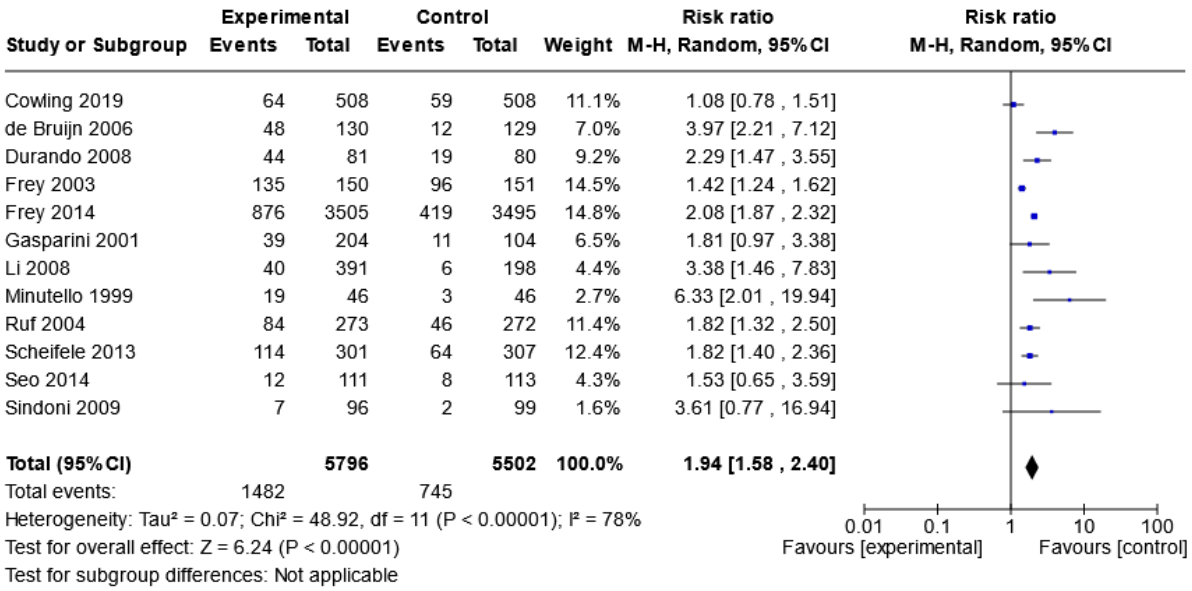


Figure 24. Relative risk of swelling after vaccination with MF59-adjuvanted influenza vaccine versus standard influenza vaccine (random-effects model)

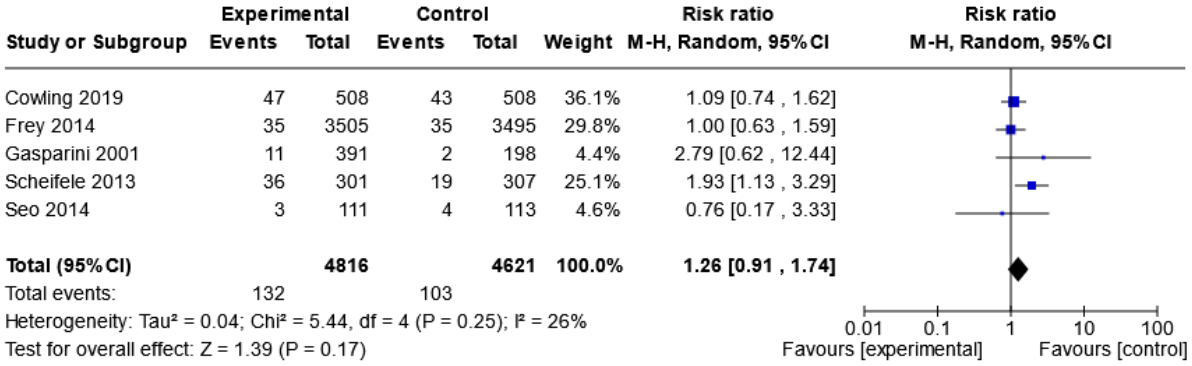


Figure 25. Relative risk of headache after vaccination with high-dose influenza vaccine versus standard influenza vaccine (random-effects model)

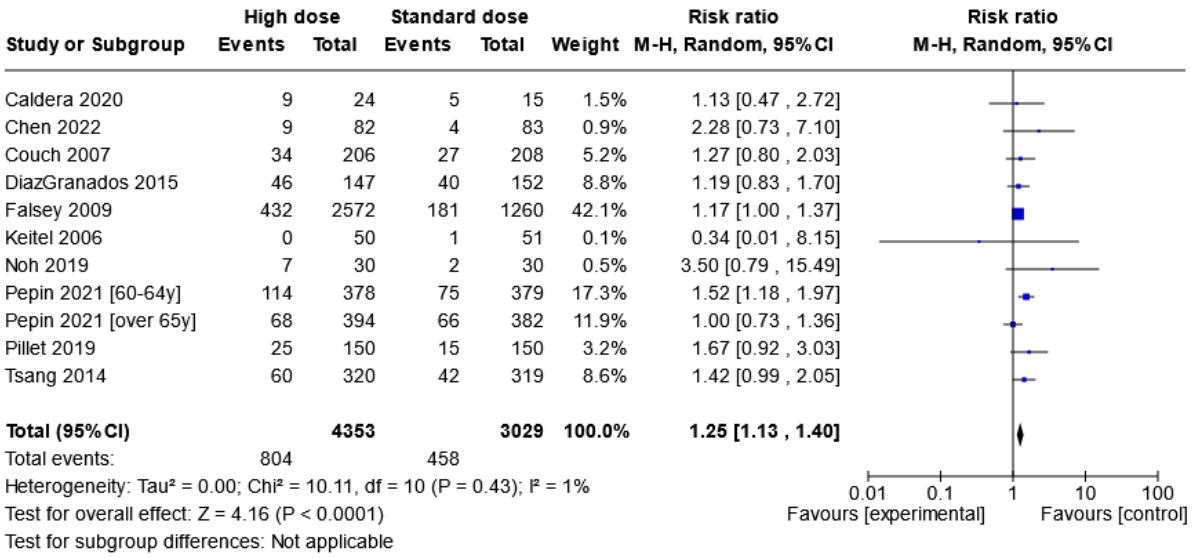


Figure 26. Relative risk of fever after vaccination with high-dose influenza vaccine versus standard influenza vaccine (random-effects model)

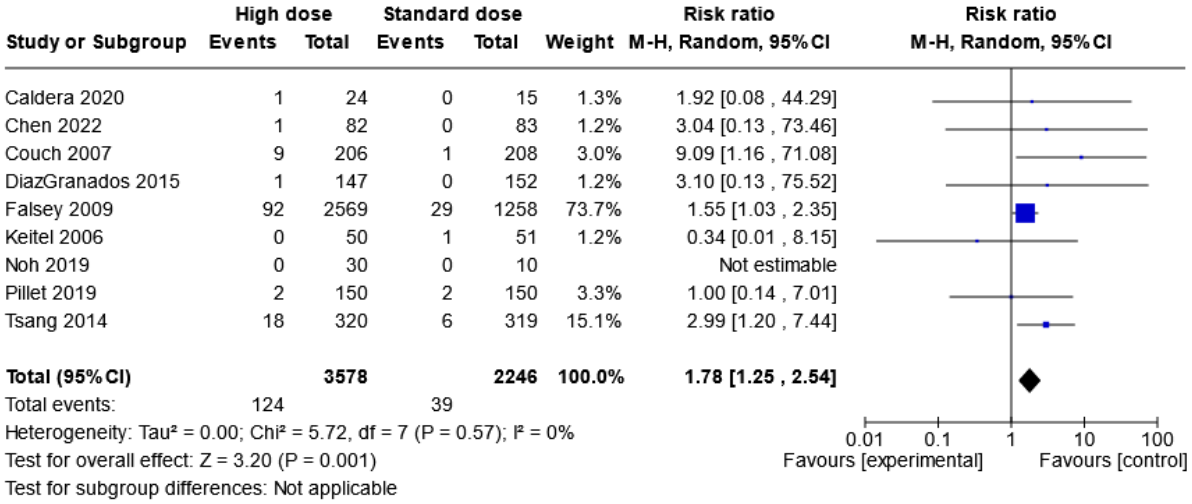


Figure 27. Relative risk of pain after vaccination with high-dose influenza vaccine versus standard influenza vaccine (random-effects model)

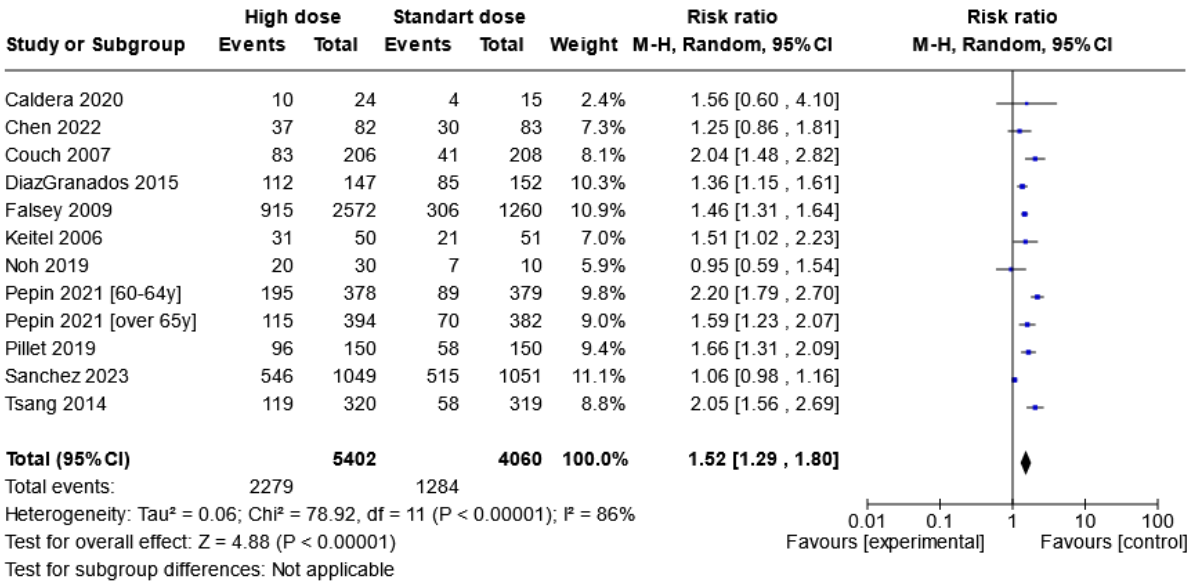


Figure 28. Relative risk of swelling after vaccination with high-dose influenza vaccine versus standard influenza vaccine (random-effects model)

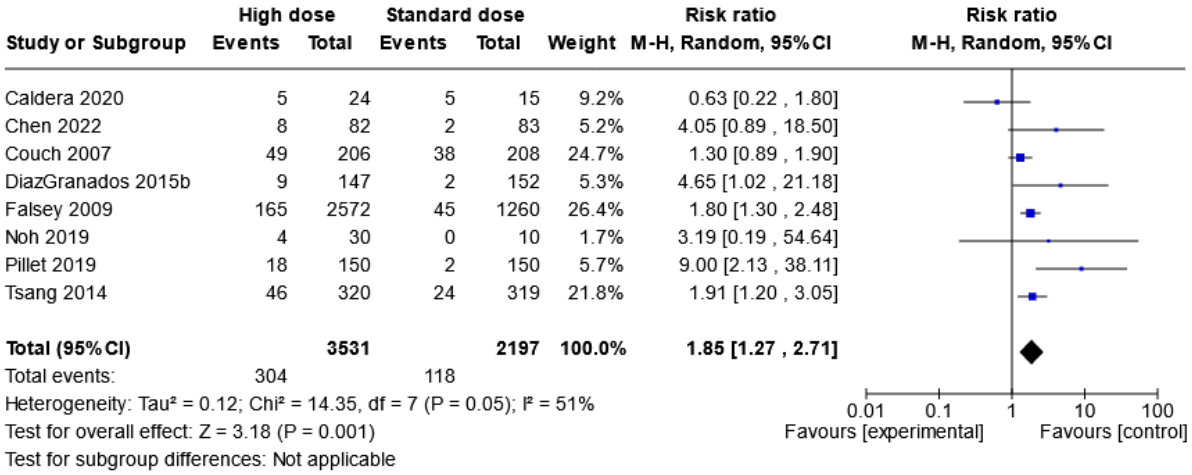


Figure 29. Relative risk of headache after vaccination with cell-based influenza vaccine versus standard influenza vaccine (random-effects model)

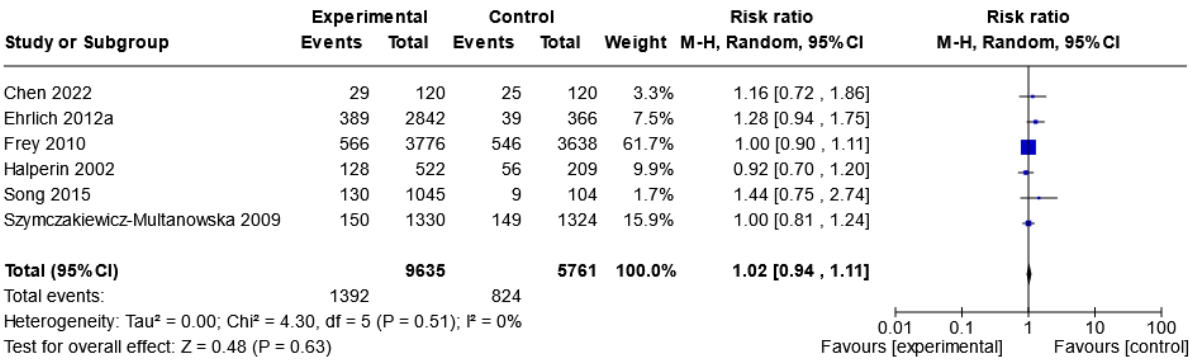


Figure 30-Relative risk of fever after vaccination with cell-based influenza vaccine versus standard influenza vaccine (random-effects model)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Ehrlich 2012a	61	2842	3	366	10.4%	2.62 [0.83 , 8.30]
Frey 2010	34	3776	33	3638	61.0%	0.99 [0.62 , 1.60]
Groth 2009	0	120	1	120	1.4%	0.33 [0.01 , 8.10]
Halperin 2002	10	522	5	209	12.3%	0.80 [0.28 , 2.31]
Song 2015	0	1045	0	104		Not estimable
Szymczakiewicz-Multanowska 2009	7	1330	10	1324	15.0%	0.70 [0.27 , 1.83]
Total (95% CI)		**9635**		**5761**	**100.0%**	**1.00 [0.69 , 1.45]**
Total events:	112		52			

Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

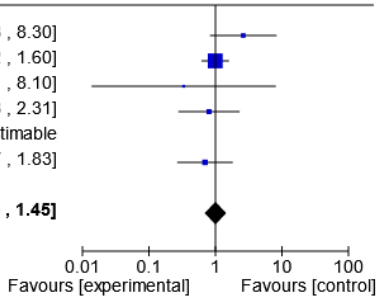


Figure 31. Relative risk of pain after vaccination with cell-based influenza vaccine versus standard influenza vaccine (random-effects model)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Ehrlich 2012a	744	2842	99	366	23.9%	0.97 [0.81 , 1.16]
Frey 2010	1133	3776	873	3638	35.4%	1.25 [1.16 , 1.35]
Groth 2009	29	120	25	120	7.1%	1.16 [0.72 , 1.86]
Song 2015	304	1045	27	104	11.8%	1.12 [0.80 , 1.57]
Szymczakiewicz-Multanowska 2009	205	1330	143	1324	21.8%	1.43 [1.17 , 1.74]
Total (95% CI)		**9113**		**5552**	**100.0%**	**1.19 [1.03 , 1.37]**
Total events:	2415		1167			

Heterogeneity: Tau² = 0.01; Chi² = 9.49, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Not applicable

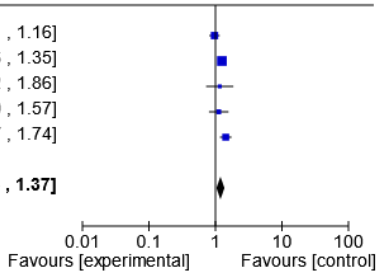


Figure 32. Relative risk of swelling after vaccination with cell-based influenza vaccine versus standard influenza vaccine (random-effects model)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Ehrlich 2012a	117	2842	8	366	8.3%	1.88 [0.93 , 3.82]
Frey 2003	225	3776	179	3638	43.4%	1.21 [1.00 , 1.47]
Groth 2009	17	120	26	120	12.4%	0.65 [0.37 , 1.14]
Halperin 2002	41	522	16	209	12.4%	1.03 [0.59 , 1.79]
Song 2015	24	1045	3	104	3.2%	0.80 [0.24 , 2.60]
Szymczakiewicz-Multanowska 2009	48	1330	44	1324	20.2%	1.09 [0.73 , 1.62]
Total (95% CI)		**9635**		**5761**	**100.0%**	**1.10 [0.88 , 1.37]**
Total events:	472		276			

Heterogeneity: Tau² = 0.02; Chi² = 6.72, df = 5 (P = 0.24); I² = 26%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

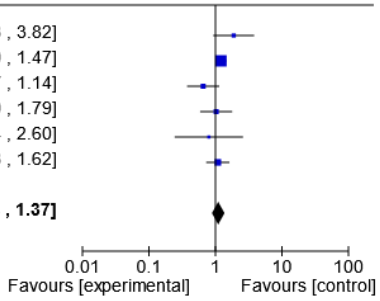


Figure 33. Relative risk of headache after vaccination with recombinant influenza vaccine versus standard influenza vaccine (random-effects model)

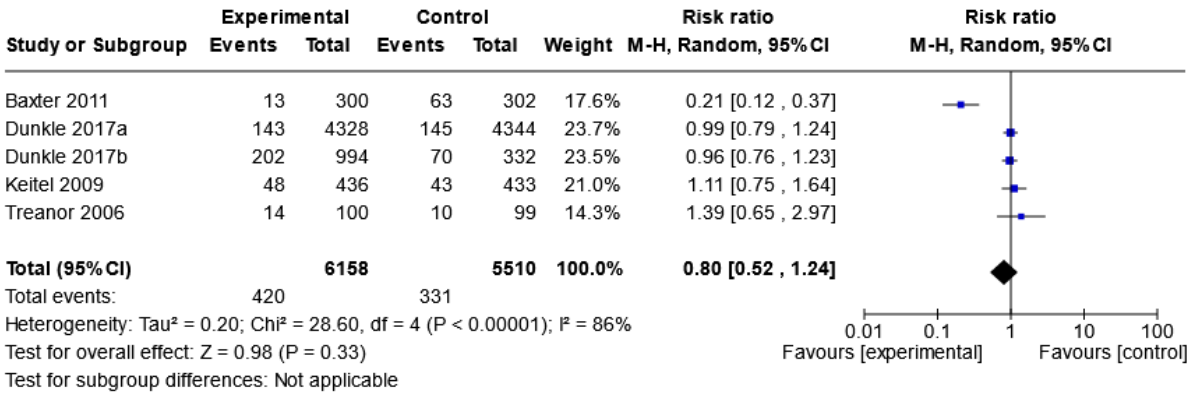


Figure 34. Relative risk of pain after vaccination with recombinant influenza vaccine versus standard influenza vaccine (random-effects model)

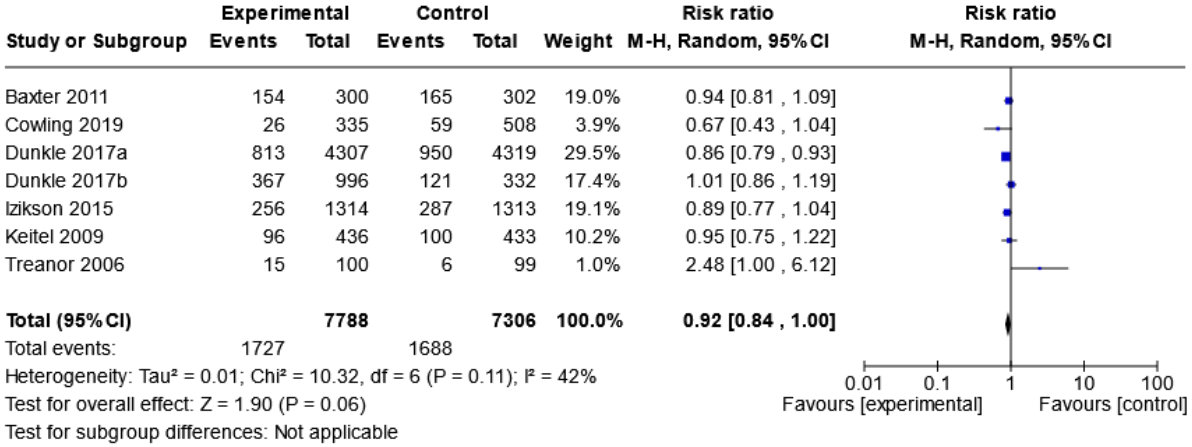
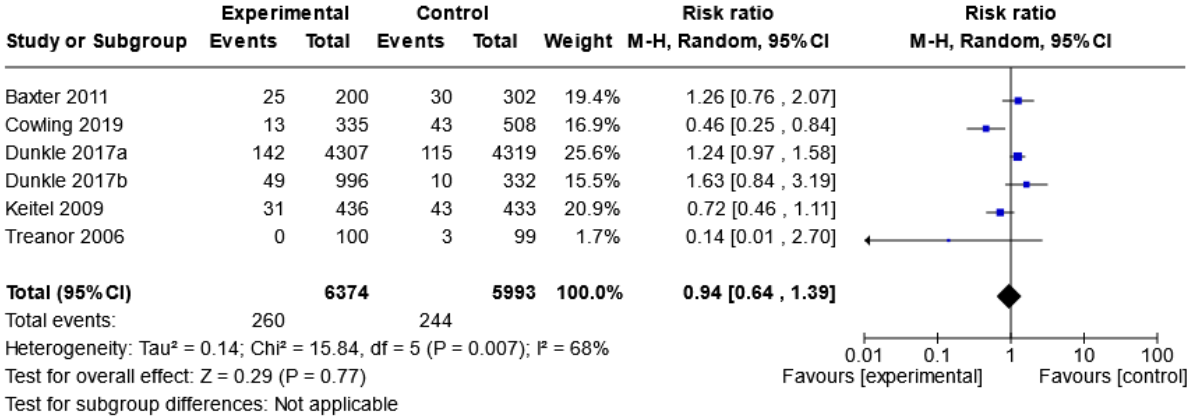


Figure 35. Relative risk of swelling after vaccination with recombinant influenza vaccine versus standard influenza vaccine (random-effects model)



Annex 6. Differences to study protocol

There are several differences between the study protocol and the current review.

- The literature search was restricted to Medline and Embase.
- Metanalysis was performed using RevMan Web and the Mantel-Haenszel method was used.
- For detection of possible publication bias (small study effects), visual inspection funnel plots were used.
- In order not to undermine the systematic character of this review, personal communication with investigators was only undertaken to clarify published study data. The PROSPERO protocol was changed accordingly on 4 December 2023.

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