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REVIEW

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Systematic review of the efficacy, effectiveness and safety of MF59® adjuvanted seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age

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Abstract

The most effective means of preventing seasonal influenza is through vaccination. In this systematic review, we investigated the efficacy, effectiveness and safety of MF59® adjuvanted trivalent and quadrivalent influenza vaccines to prevent laboratory-confirmed influenza. A systematic literature search was conducted in electronic databases and grey literature sources up to 7 February 2020.

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, Confidence interval; FEM, Fixed-effect model; GRADE, Grading of recommendations assessment, development and evaluation; HA, Haemagglutinin; HIQA, Health Information and Quality Authority; ICD, International classification of diseases; ILI, Influenza-like illness; NITAG, National immunisation technical advisory group; NRSI, Non-randomised studies of intervention; PICO, Participants, intervention, comparison, outcomes; PRISMA, Preferred reporting items for systematic reviews and meta analyses; RCT, Randomised controlled trial; REM, Random-effects model; ROBINS-I, Risk of bias in non-randomised studies of interventions; RR, Risk ratio; SAE, Serious adverse event; VE, Vaccine effectiveness; WHO, World Health Organization.

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Randomised controlled trials and non-randomised studies of interventions (NRSIs) were eligible for inclusion. The search returned 28,846 records, of which 48 studies on MF59® adjuvanted vaccines met our inclusion criteria. No efficacy trials were identified. In terms of vaccine effectiveness (VE), MF59® adjuvanted trivalent influenza vaccines were effective in preventing laboratory-confirmed influenza in older adults (aged ≥65 years) compared with no vaccination (VE = 45%, 95% confidence interval (CI) 23%–61%, 5 NRSIs across 3 influenza seasons). By subtype, significant effect was found for influenza A(H1N1) (VE = 61%, 95% CI 44%–73%) and B (VE = 29%, 95% CI 5%–46%), but not for A(H3N2). In terms of relative VE, there was no significant difference comparing MF59® adjuvanted trivalent vaccines with either non-adjuvanted trivalent or quadrivalent vaccines. Compared with traditional trivalent influenza vaccines, MF59® adjuvanted trivalent influenza vaccines were associated with a greater number of local adverse events (RR = 1.90, 95% CI 1.50–2.39) and systemic reactions (RR = 1.18, 95% CI 1.02–1.38). In conclusion, MF59® adjuvanted trivalent influenza vaccines were found to be more effective than 'no vaccination'. Based on limited data, there was no significant difference comparing the effectiveness of MF59® adjuvanted vaccines with their non-adjuvanted counterparts.

KEYWORDS
Fluad, influenza vaccines, MF59

1 | INTRODUCTION

Seasonal influenza is an infectious respiratory disease caused by influenza viruses that circulate in annual epidemics worldwide.[1] Seasonal influenza is largely transmitted between humans through droplet transmission, indirect contact and aerosol transmission.[2] Influenza viruses are from the *Orthomyxoviridae* family of ribonucleic acid viruses and are classified as four specific types, with Influenza A and B known to cause most human infections.[1,3] Influenza A is further categorised into subtypes based on the presence of specific haemagglutinin (HA) and neuraminidase proteins on the surface of the virus, with A(H1N1) and A(H3N2) commonly circulating.[3] Influenza B comprises two specific lineages, Victoria and Yamagata.

The scale of the effect of seasonal influenza is dependent on a number of factors including the predominantly circulating strains, vaccination coverage and the mutation of the virus relative to previous seasons.[4] All-cause influenza-attributable mortality was estimated to be 25.4 (95% Confidence interval (CI) 25.0–25.8) per 100,000 population in the 2017–2018 influenza season in Europe Prior to the emergence of a novel coronavirus (SARS-CoV-2) in December 2019,influenza was reported to have the highest burden of all infectious diseases in Europe in terms of disease-adjusted life years.[5]

The most effective means to prevent influenza infection is through strain-specific vaccination.[6] To facilitate strain-specific vaccination, the WHO issues recommendations to vaccine manufacturers regarding vaccine strain inclusion, based on predictions of the likely circulating strains based on global surveillance data.[6,7] Recommendations are issued for the composition of both trivalent (two A strains and one B strain) and quadrivalent (two A strains and two B strains) vaccines and include specific viral subtyping for influenza A.[6,8] However, due to antigenic drift, whereby genetic changes arise from ongoing evolution of the virus, antigenic mismatch between the virus strains contained in the vaccine and those in circulation in the seasonal epidemic can occur. Accurate predictive matching of vaccine strains to those that circulate is a key determinant of vaccine effectiveness (VE).[6-8]

The response to traditional influenza vaccines can be suboptimal.[8] Newer and enhanced influenza vaccines have been developed in an attempt to improve VE, particularly in the elderly for whom there is evidence of immunosenescence. Strategies to enhance the immune response include the use of adjuvants and higher doses of HA per vaccine strain.

Adjuvantation aims to increase immunogenicity, resulting in comparatively higher levels of HA inhibition antibodies and an enhanced immunological response.[8] Emulsions have a long history of use as adjuvants, including the oil-in-water emulsion MF59®.[9] A seasonal MF59® adjuvanted vaccine was first licensed in 1997.[10] While a number of studies have confirmed their immunogenicity and safety, relatively less is known about their efficacy and real-world effectiveness, evidence that is essential to guide influenza vaccine policy internationally.

In this series of systematic reviews, we investigated the efficacy, effectiveness and safety of newer and enhanced influenza vaccines

for the prevention of laboratory-confirmed influenza in individuals aged 18 years or older. 'Efficacy' refers to the estimate of effect (level of protection against laboratory-confirmed influenza) reported in randomised controlled trials (RCTs), while 'effectiveness' refers to the estimate of effect reported in non-randomised study designs that better reflect real-world clinical settings, such as case control and cohort studies. 'Safety' in this review refers to any data on adverse events reported in clinical studies, including local and systemic adverse reactions.

The aim of this current review was to determine the efficacy, effectiveness and safety of MF59® adjuvanted trivalent and quadrivalent egg-based seasonal influenza vaccines by influenza type, subtype, age and risk group.

2 | METHODS

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[11] The proposed methodology for this systematic review was registered on PROSPERO (ID = CRD42020156800).

2.1 | Eligibility criteria

The population for this study was adults (persons age 18 years and older), irrespective of health status or setting. The interventions of interest were MF59® adjuvanted trivalent and quadrivalent egg-based seasonal influenza vaccines. The main efficacy and effectiveness outcomes were laboratory-confirmed influenza and influenza-related mortality and hospitalisation. Safety outcomes included local and systemic events. Eligible studies included RCTs, non-randomised controlled trials, quasi-experimental, prospective and retrospective cohort, case control, test-negative design and analytical cross sectional studies. The population, intervention, comparison, outcomes and study design (PICOS) criteria for inclusion of studies in this systematic review are provided in supporting information S1. No restrictions were placed on language or date of publication.

2.2 | Exclusion criteria

Animal studies, case studies, immunogenicity studies, studies conducted during pandemic periods and studies that included pandemic, prepandemic or zoonotic vaccines were excluded. Adjuvants other than MF59® were not considered.

2.3 | Search strategy

Electronic searches were conducted in Embase, MEDLINE (via PubMed), Cumulative Index to Nursing and Allied Health (CINAHL) and The Cochrane Library. The search terms and detailed search strategy are provided in the supporting information S1. The search strategy was designed to identify a range of influenza vaccines including MF59® adjuvanted influenza vaccines. Searches were conducted on the 26 September 2019 and updated on 7 February 2020 prior to analyses. Forward citation searching was applied to included studies. A search of grey literature sources was conducted in an attempt to source any unpublished or ongoing studies which may be relevant to future iterations of this systematic review.

Two reviewers independently reviewed the titles and available abstracts in Covidence® to identify studies for full-text review. Full texts were evaluated and data extracted by two reviewers independently. Data extraction was carried out using an agreed data extraction form. Where disagreements occurred in study identification or data extraction, discussions were held to reach consensus and where necessary, a third reviewer was involved. Where additional data were required, study authors were contacted by email. For safety outcomes, data relating to the influenza season, vaccine strains and circulating strains were not deemed to be relevant and therefore were not extracted.

2.4 | Assessment of risk of bias in included studies

Two reviewers independently assessed the included studies for risk of bias, using validated critical appraisal tools. Disagreements were resolved through discussion and, where necessary, the assistance of a third reviewer was involved.

The Cochrane Risk of Bias tool was used to assess RCTs.[12] Certain domains within the risk of bias tool were designated as key domains to enable a summary assessment of risk of bias within and between studies.[13] For efficacy studies, the designated key domains were: funding sources (other bias), random sequence generation, and incomplete outcome data. For safety studies, the designated key domains were: funding sources (other bias), blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data.

Non-randomised studies of interventions (NRSIs) were assessed for risk of bias using the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool.[14] Results were presented in tabular form with the agreed consensus of risk of bias for each of the seven included domains and the overall risk of bias for each study denoted by the highest risk of bias score in any singular domain, as per the ROBINS-I methodology.[14] Where adjusted and unadjusted estimates were extracted from a study the risk of bias was assessed for each outcome.

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

2.5 | Measures of treatment effect

For test-negative design (case-control) studies, the outcome was defined as VE which was uniformly expressed as (1 – Odds Ratio)

*100%, where a value of 100% indicates prevention of all cases of influenza and 0% indicates prevention of no cases of influenza. For cohort studies, the outcome was defined as VE expressed using either a risk ratio, incidence risk ratio, or hazard ratio in place of the odds ratio. Where studies reported both unadjusted and adjusted VE, the adjusted figure was used in the results as it was considered the less biased estimate of treatment effect.

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

2.6 | Data synthesis

Where two or more studies reported an outcome, pooling was considered. Meta-analysis was conducted using the Mantel-Haenszel method for fixed effect and the Sidik-Jonkman estimator combined with the Hartung and Knapp adjustment for random effects.[15,16] Given the clinical heterogeneity across studies, preference was for a random-effects model (REM). As the estimate of between study variance is considered to be unreliable when there are few studies available for pooling,[17,18] a fixed effect model was used when less than four studies were available for pooling. For adjusted VE, pooling was on the basis of the log odds ratio and variance, with the exponential of the pooled result re-expressed as VE.

2.7 | Assessment of heterogeneity

Potential statistical heterogeneity was assessed on the basis of the I^2 statistic in line with the Cochrane methodology.[13] The I^2 value was interpreted based on the magnitude and direction of effects, and on the strength of evidence for heterogeneity based on the chi-squared statistic. Where multiple studies were available for a given outcome and there was evidence of heterogeneity, consideration was given to subgroup analysis and meta-regression to identify potential sources of heterogeneity. Subgroup analysis was considered where studies could be meaningfully grouped based on consistently provided data. Meta-regression was only considered if there were 10 or more studies available reporting a given outcome.

2.8 | GRADE and 'summary of findings' table

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[19] The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) were interpreted by two reviewers to assess the quality of the body of evidence for each outcome of interest. New guidance regarding the assessment of NRSIs was incorporated, whereby these types of studies are not penalised for their design and begin the assessment as a high certainty of evidence like their RCT counterparts.[20] As a broad range of safety outcomes were assessed by the included studies, a number were chosen which were thought to best reflect this outcome as a whole and which were relatively consistent across the vaccines of interest within this review: combined local reactions, pain, combined systemic reactions, and fever. Summary of findings tables were generated using the GRADEpro® software.

3 | RESULTS

The collective search strategy for this series of systematic reviews resulted in 26,844 records, with 2 further records being identified from additional sources. Following the removal of duplicates, 19,822 records were screened for relevance. Of 868 studies meriting full-text review, 758 were excluded based on predefined eligibility criteria. Forty-eight studies provided results concerning MF59® adjuvanted influenza vaccines.[10,21-67] Of these, 22 related to VE[10,21-41] and 26 related to vaccine safety.[42-67] The PRISMA diagram for study selection is provided in Figure 1 and the GRADE 'Summary of Findings' assessments in Tables 1 and 2 (additional GRADE assessments, the characteristics of included studies and details of the circulating strains associated with these studies are provided in supporting information S1).

Where issues with missing data were encountered, the study authors were contacted. No imputation of missing data was used. Given the small numbers of studies available for most comparisons, there was limited power to explore sources of heterogeneity and a risk of identifying spurious associations.

The following sections report the results of this review for each outcome relating to efficacy, effectiveness and safety of MF59® adjuvanted influenza vaccines.

4 | EFFICACY

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

5 | EFFECTIVENESS

Twenty-two studies contained results relevant to the effectiveness of MF59® adjuvanted influenza vaccines.[10,21-41] 17 were case-control studies[21-37] comprising 15 unique datasets[21-24,26-32,34-37] and five were cohort studies.[10,38-41]

5.1 | Effectiveness against laboratory-confirmed influenza

Eleven studies provided data relevant to the primary outcome of laboratory-confirmed influenza.[21,22,24,25,27-29,33,34,36,37] All related to

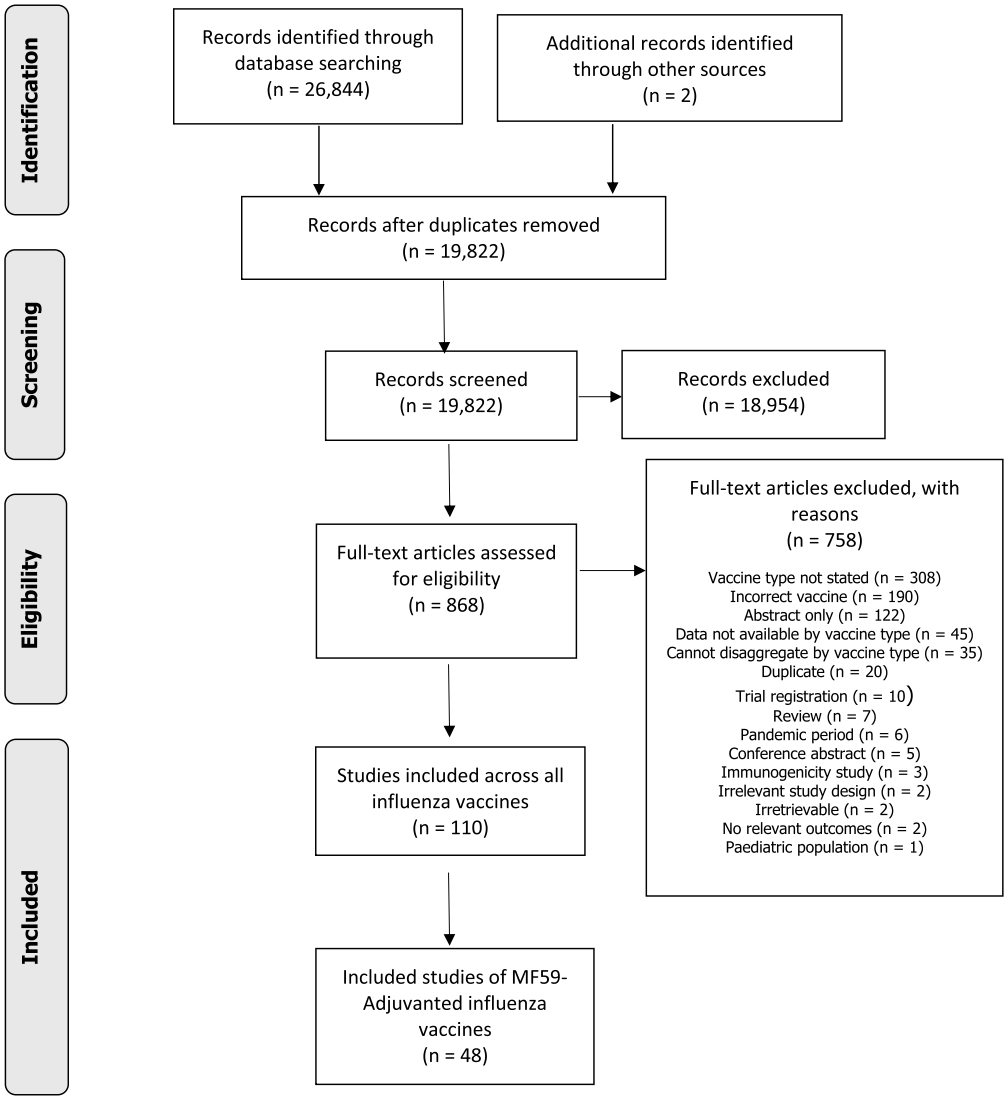

FIGURE 1 PRISMA diagram of study selection

of MF59® adjuvanted trivalent influenza vaccines and were of test-negative case-control design in older adult populations (aged ≥65 years), with the exception of one study which also presented data for adults over the age of 18 years.[29] For each relevant comparison Table 3 outlines the type of influenza, comparator, VE, and degree of matching to circulating strains, as interpreted from the narrative within each individual study, subcategorised by the influenza season.

5.2 | Effectiveness against any influenza type/subtype

Six studies presented data regarding the effectiveness of MF59® adjuvanted trivalent influenza vaccines against any influenza type.[21,22,27-29,37] In older adults (aged ≥65 years) across all influenza seasons, MF59® adjuvanted vaccines were significantly more effective than no vaccination (VE = 44.9%, 95% CI 22.7%–60.8%, REM, I^2 = 62.7%, low-certainty evidence)[21,27-29,37] (Figure 2). Crude estimates from a single study which presented data for an adult population (aged ≥18 years) did not show a significant difference between MF59® adjuvanted trivalent vaccines and no vaccination (VE = 51%, 95% CI -54%–84%).[29] In terms of relative VE, there was no significant difference comparing MF59® adjuvanted trivalent with non-adjuvanted trivalent or quadrivalent influenza vaccines in adult or older adult populations (*n* = 5 studies, Table 3).[22,27-29,37]

5.3 | Effectiveness against influenza A(H1N1)

Four studies presented data regarding the effectiveness of MF59® adjuvanted trivalent influenza vaccines against influenza A(H1N1) in older adults (aged ≥65 years).[21,25,27,28] Compared with no

TABLE 1 GRADE 'summary of findings': effectiveness

Effectiveness of MF59® adjuvanted trivalent influenza vaccine compared with no vaccination for prevention of laboratory-confirmed influenza in older adults (aged ≥65 years)			
Patient or population: Older adults (aged ≥65 years)			
Setting: Any setting			
Intervention: MF59® adjuvanted inactivated influenza vaccine			
Comparison: No vaccination			
Outcomes	**Vaccine effectiveness[a] (95% CI)**	**Number of studies**	**Certainty of the evidence (GRADE)**
Influenza (any)	**VE 44.9%** (22.7–60.8)	5 observational studies (across 3 seasons: 2011-12; 2017-18; 2018-19)	⨁⨁◯◯ LOW[b,d]
Influenza A(H1N1)	**VE 61.2%** (43.7–73.3)	4 observational studies (across 2 seasons: 2017-18; 2018-19)	⨁⨁◯◯ LOW[b,d]
Influenza A(H3N2)	**VE 10.6%** (−24.5–35.7)	8 observational studies (across 5 seasons: 2014-15; 2015-16; 2016-17; 2017-18; 2018-19)	⨁◯◯◯ VERY LOW[b,c,d]
Influenza B	**VE 28.5%** (5.4–46.0)	5 observational studies (across 3 seasons: 2014-15; 2015-16; 2017-18)	⨁⨁◯◯ LOW[b,d]

Note: 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.

Abbreviations: CI, confidence interval; GRADE, grading of recommendations assessment, development and evaluation; VE, vaccine effectiveness [(1 – odds ratio)*100%].

[a]Given the outcome of interest typically incorporating adjustments results are not presented as raw rates. Total participant numbers for vaccine of interest were not presented by all included studies.

[b]Downgraded one level for risk of bias.

[c]Downgraded one level due to inconsistency in results.

[d]Downgraded one level due to imprecision.

vaccination, MF59® adjuvanted vaccines were significantly more effective in preventing influenza A(H1N1) (VE = 61.2%, 95% CI 43.7%–73.3%, REM, I^2 = 14.5%, low-certainty evidence; Figure 3).[21,25,27,28] Individual studies were frequently subject to large uncertainty due to small sample sizes and/or rare events. In terms of relative VE, two studies found no significant difference comparing MF59® adjuvanted trivalent with non-adjuvanted trivalent or quadrivalent influenza vaccines (Table 3).[27,28]

5.4 | Effectiveness against influenza A(H3N2)

Seven studies presented data regarding the effectiveness of MF59® adjuvanted trivalent influenza vaccines against influenza A(H3N2) in older adults (aged ≥65 years).[24,25,27,28,33,34,36] There was no significant difference between MF59® adjuvanted vaccines and no vaccination (VE = 10.6%, 95% CI -24.5%–35.7%, REM, I^2 = 48.5%, very low-certainty evidence) across five influenza seasons (Figure 4).[24,25,27,28,33,34,36] There was considerable heterogeneity in terms of the matching of vaccine strains to circulating strains across the influenza seasons included in the analyses. Four studies compared MF59® adjuvanted trivalent with non-adjuvanted trivalent or quadrivalent influenza vaccines, with three showing no significant difference (Table 3).[27,28,33,34] Individual studies were frequently subject to large uncertainty due to small sample sizes and/or rare events.

5.5 | Effectiveness against influenza B

Five studies investigated the effectiveness of MF59® adjuvanted trivalent influenza vaccines against influenza B in older adults (aged ≥65 years).[21,25,27,34,36] Across all influenza seasons there was significant effect in favour of MF59® adjuvanted vaccines compared with no vaccination (VE = 28.5%, 95% CI 5.4%–46.0%, REM, I^2 = 0%, low-certainty evidence; Figure 5).[21,25,27,34,36] Two studies compared MF59® adjuvanted trivalent with non-adjuvanted trivalent influenza vaccines with conflicting results shown, and both studies reported crude estimates only (Table 3).[27,34]

TABLE 2 GRADE 'summary of findings': safety

Safety of MF59® adjuvanted trivalent influenza vaccine compared with traditional trivalent influenza vaccine					
Patient or population: Adults (aged ≥18 years)					
Setting: Safety in any setting					
Intervention: MF59® adjuvanted trivalent inactivated influenza vaccine					
Comparison: Trivalent inactivated influenza vaccine					
	Anticipated absolute effects[a] (95% CI)				
Outcomes	**Risk with non-adjuvanted trivalent vaccine**	**Risk with adjuvanted trivalent vaccine**	**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**
Combined local events	172 per 1000	**327 per 1000** (258–411)	**RR 1.90** (1.50–2.39)	8043 (4 RCTs)	⨁⨁⨁◯ MODERATE[b]
Pain	135 per 1000	**274 per 1000** (207–362)	**RR 2.02** (1.53–2.67)	11,298 (12 RCTs)	⨁⨁⨁◯ MODERATE[b]
Combined systemic events	67 per 1000	**80 per 1000** (69–93)	**RR 1.18** (1.02–1.38)	8651 (5 RCTs)	⨁⨁⨁◯ MODERATE[b]
Fever	30 per 1000	**58 per 1000** (32–107)	**RR 1.97** (1.07–3.61)	10,236 (9 RCTs)	⨁⨁◯◯ LOW[b,c]

Note: 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.

Abbreviations: CI, confidence interval; GRADE, grading of recommendations assessment, development and evaluation; RR, risk ratio.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Downgraded one level due to serious risk of bias.

[c]Downgraded one level due to imprecision.

TABLE 3 Effectiveness of MF59® adjuvanted trivalent influenza vaccines against laboratory-confirmed influenza

Author	**Comparator**	**Vaccine effectiveness (1- odds ratio)**	**95%CI (lower)**	**95%CI (upper)**	**Strain mismatch[c]**
All influenza strains					
2011–2012 season					
Van Buynder 2013[37]	Unvaccinated	0.58	0.05	0.82	Not reported
Van Buynder 2013[37]	Trivalent non-adjuvanted	0.42[a]	−0.08	0.69	Not reported
2017–2018 season					
Bella 2019[21]	Unvaccinated	0.48	0.19	0.67	B
Mira-Iglesias 2019[27]	Unvaccinated	0.10	−0.24	0.35	B and H3N2
Mira-Iglesias 2019[27]	Trivalent non-adjuvanted	0.19[a]	−0.10	0.41	B and H3N2
2018–2019 season					
Pebody 2020a[28]	Trivalent/quadrivalent non-adjuvanted	0.30	−0.83	0.73	Well-matched
Pebody 2020b[b29]	Unvaccinated	0.51[a]	−0.54	0.84	Well-matched
Pebody 2020a[28]	Unvaccinated	0.54	0.40	0.65	Well-matched
Pebody 2020b[29]	Unvaccinated	0.62	0.03	0.85	Well-matched
Pebody 2020b[b29]	Quadrivalent non-adjuvanted	0.16[a]	−1.76	0.75	Well-matched
Bellino 2019a[22]	Quadrivalent non-adjuvanted	−0.01	−1.22	0.58	Probable mismatch B

(Continues)

TABLE 3 (Continued)

Author	Comparator	Vaccine effectiveness (1- odds ratio)	95%CI (lower)	95%CI (upper)	Strain mismatch[c]
Influenza A(H1N1)					
2017–2018 season					
Bella 2019[21]	Unvaccinated	0.68	0.09	0.88	Not reported
Kissling 2019[25]	Unvaccinated	0.73	−0.19	0.94	Mismatch
Mira-Iglesias 2019[27]	Unvaccinated	0.34	−0.35	0.68	Not reported
Mira-Iglesias 2019[27]	Trivalent non-adjuvanted	−0.03[a]	−1.26	0.53	Not reported
2018–2019 season					
Pebody 2020a[28]	Trivalent/quadrivalent non-adjuvanted	0.03	−3.58	0.79	Well-matched
Pebody 2020a[28]	Unvaccinated	0.66	0.51	0.76	Well-matched
Influenza A(H3N2)					
2014–2015 season					
Gilca 2015[24]	Unvaccinated	−0.39	−1.42	0.20	Not reported
Valenciano 2016[36]	Unvaccinated	−0.28	−1.85	0.42	Mismatch
2015–2016 season					
Rondy 2017b[34]	Trivalent non-adjuvanted	0.88[a]	0.51	1.00	Not reported
Rondy 2017b[34]	Unvaccinated	0.94[a]	0.65	1.00	Not reported
2016–2017 season					
Rondy 2017a[33]	Trivalent non-adjuvanted	−0.30[a]	−1.46	0.31	Well-matched
Rondy 2017a[33]	Unvaccinated	−0.02[a]	−0.93	0.46	Well-matched
Kissling 2019[26]	Unvaccinated	0.46	0.06	0.69	Mismatch
2017–2018 season					
Kissling 2019[25]	Unvaccinated	0.53	−1.51	0.91	Mismatch
Mira-Iglesias 2019[27]	Unvaccinated	−0.24	−0.88	0.18	Mismatch
Mira-Iglesias 2019[27]	Trivalent non-adjuvanted	0.20[a]	−0.17	0.46	Mismatch
2018–2019 season					
Pebody 2020a[28]	Trivalent/quadrivalent non-adjuvanted	0.43	−1.34	0.86	Well-matched
Pebody 2020a[29]	Unvaccinated	0.40	0.05	0.62	Well-matched
Influenza B					
2014–2015 season					
Valenciano 2016[36]	Unvaccinated	0.08	−1.74	0.69	Not reported
2015–2016 season					
Rondy 2017b[34]	Trivalent non-adjuvanted	0.87[a]	0.30	1.00	Mismatch
Rondy 2017b[34]	Unvaccinated	0.92[a]	0.60	1.00	Mismatch
2017–2018 season					
Bella 2019[21]	Unvaccinated	0.45	0.09	0.66	Mismatch
Kissling 2019[25]	Unvaccinated	0.01	−0.75	0.44	Mismatch
Mira-Iglesias 2019[27]	Unvaccinated	0.30[a]	−0.11	0.56	Mismatch
Mira-Iglesias 2019[27]	Trivalent non-adjuvanted	0.06[a]	−0.58	0.44	Mismatch

Abbreviation: CI, confidence interval.

[a]Denotes unadjusted estimate of vaccine effectiveness.

[b]Denotes adult (≥18 years) population. Population is older adults ≥65 years in all other studies.

[c]Interpreted from narrative provided by included studies.

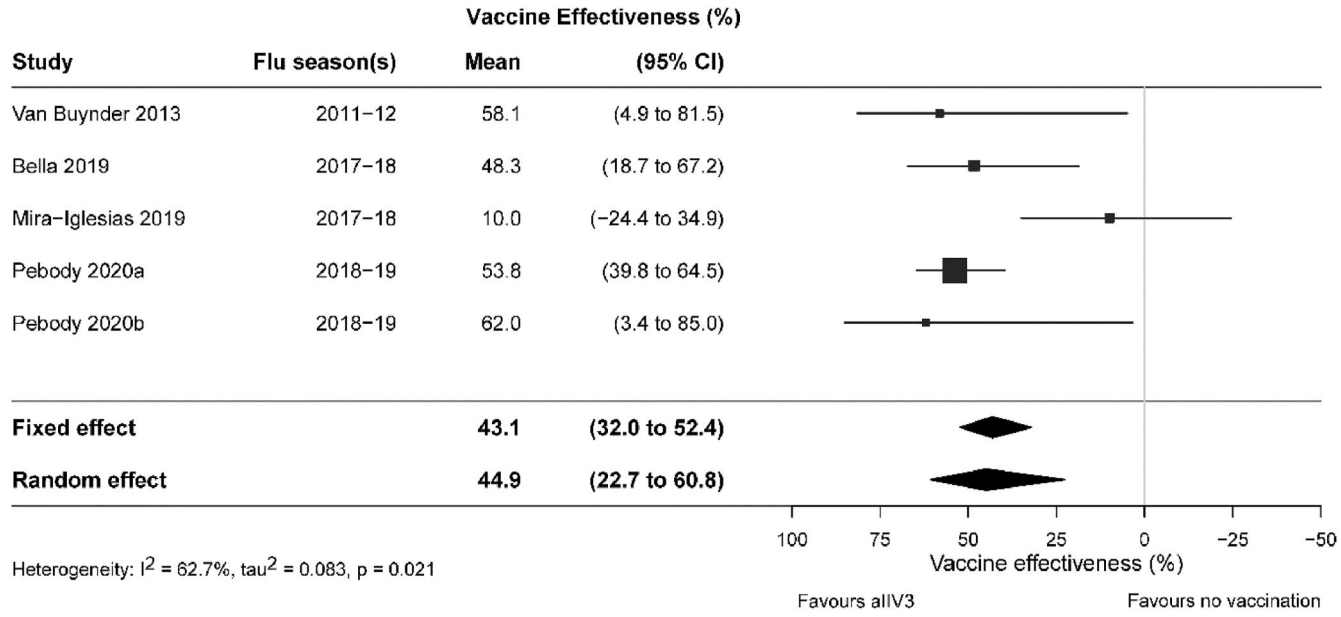

FIGURE 2 Vaccine effectiveness (VE) of MF59® adjuvanted trivalent influenza vaccines versus no vaccination against any influenza, adults aged 65 years and older. Caption: Fixed and random effects meta-analysis of VE of adjuvanted trivalent influenza vaccine versus no vaccination against any influenza type/subtype in older adults (≥65 years)

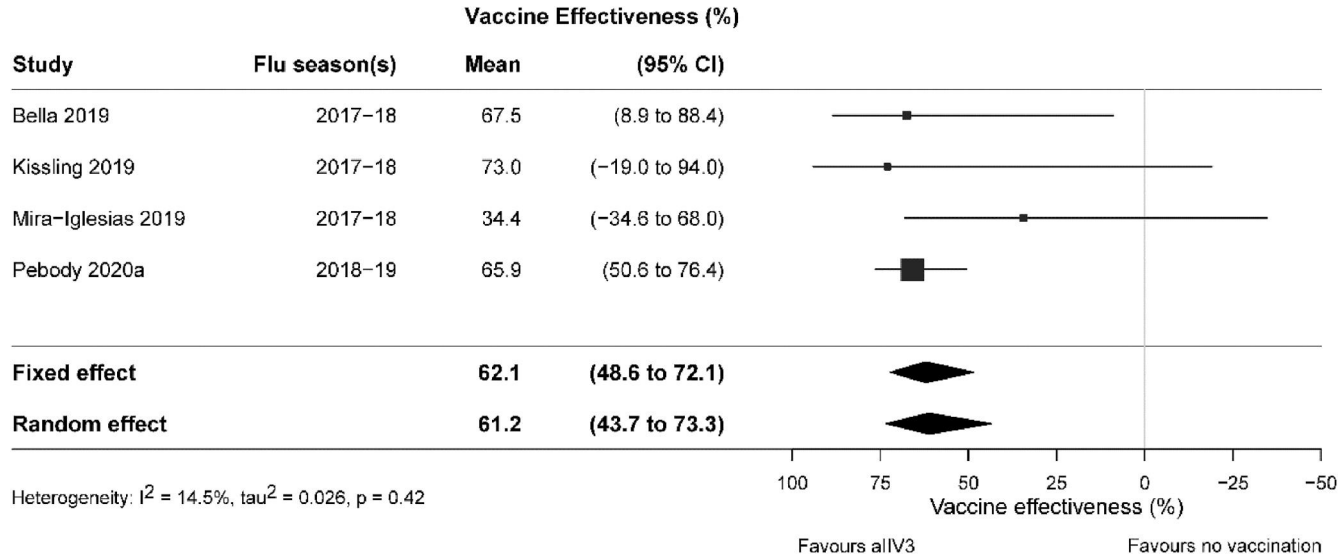

FIGURE 3 Vaccine effectiveness (VE) of MF59® adjuvanted trivalent influenza vaccines versus no vaccination against influenza A(H1N1), adults aged 65 years and older. Caption: Fixed and random effects meta-analysis of VE of adjuvanted trivalent influenza vaccine versus no vaccination against influenza A(H1N1) in older adults (≥65 years)

6 | ADDITIONAL OUTCOMES

Nine studies presented data related to additional outcomes relevant to this review; influenza-related hospitalisation, pneumonia-related hospitalisation, influenza- or pneumonia-related hospitalisation, influenza-related hospital encounters, influenza-like illness and influenza-related office visits (Table 4).[10,23,30,31,35,38-41] Of these, four were case-control studies,[23,30,31,35] five were cohort studies[10,38-41] and all investigated MF59® adjuvanted trivalent influenza vaccines in older (aged ≥65 years) adult populations.

6.1 | Influenza-related hospitalisation

Three cohort studies presented data related to the effectiveness of MF59® adjuvanted trivalent influenza vaccines in preventing influenza-related hospitalisations.[38,39,41] One study found MF59® adjuvanted vaccines to be significantly more effective than no vaccination across three influenza seasons (Table 4).[38] Two studies compared the effectiveness of MF59® adjuvanted to non-adjuvanted trivalent influenza vaccines for this outcome with no significant difference shown.[39,41]

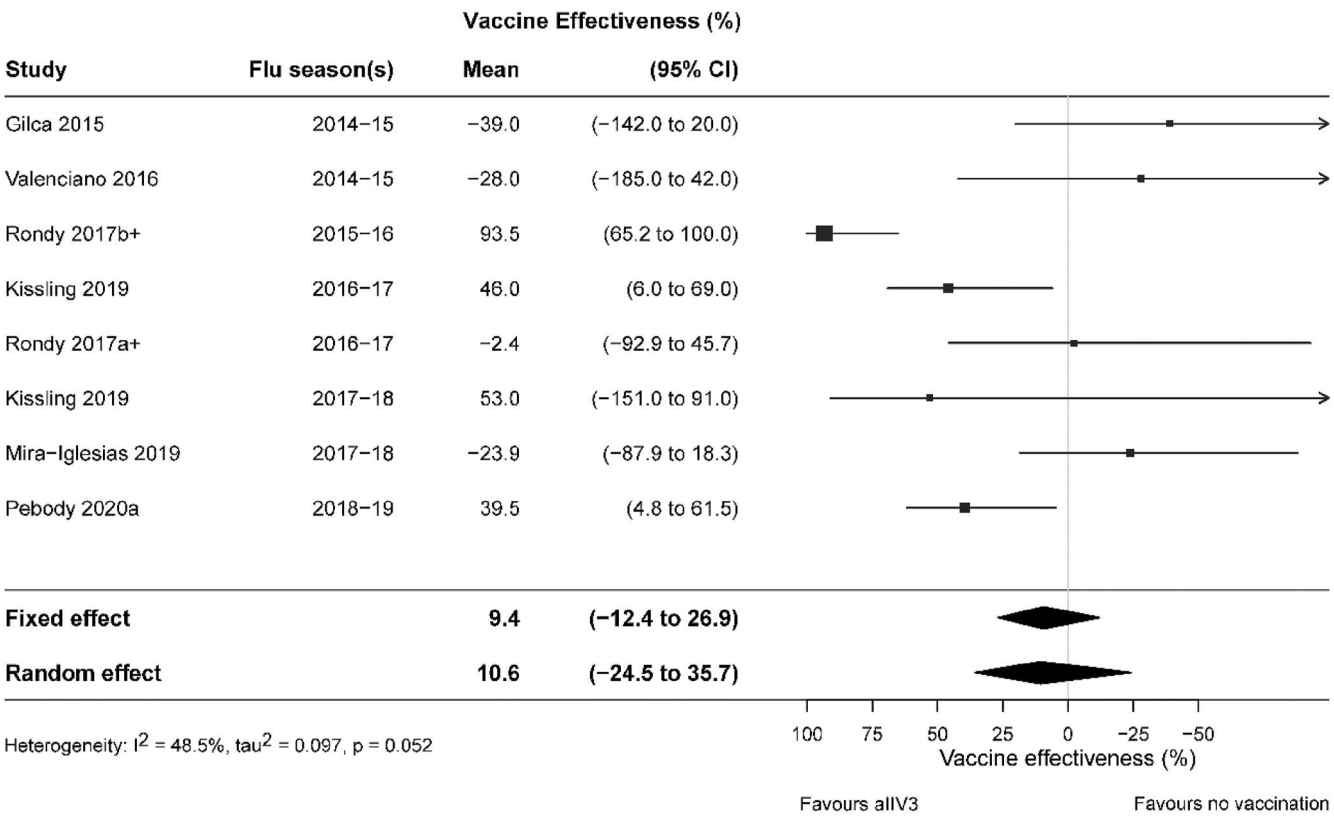

FIGURE 4 Vaccine effectiveness (VE) of MF59® adjuvanted trivalent influenza vaccines versus no vaccination against Influenza A(H3N2), adults aged 65 years and older. Caption: Fixed and random effects meta-analysis of VE of adjuvanted trivalent influenza vaccine versus no vaccination against influenza A(H3N2) in older adults (≥65 years)

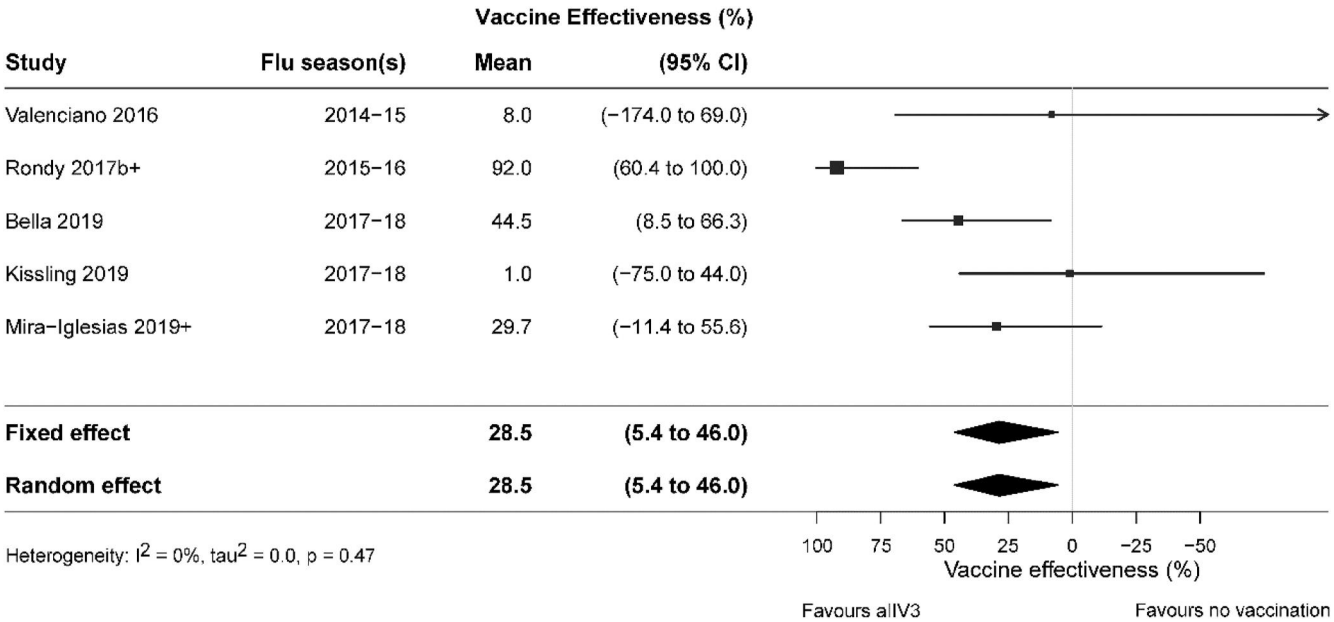

FIGURE 5 Vaccine effectiveness (VE) of MF59® adjuvanted trivalent influenza vaccines versus no vaccination against influenza B, adults aged 65 years and older. Caption: Fixed and random effects meta-analysis of VE of adjuvanted trivalent influenza vaccine versus no vaccination against influenza B in older adults (≥65 years)

TABLE 4 Effectiveness of MF59® adjuvanted influenza vaccines for additional outcomes

Author	Season	Comparator	Vaccine effectiveness (1- risk ratio)	95%CI lower	95%CI higher	Strain mismatch[b]
Influenza-related hospitalisation						
Bellino 2019b[38]	2014–2015	Unvaccinated	0.12	0.03	0.20	Not reported
Bellino 2019b[38]	2015–2016	Unvaccinated	0.16	0.07	0.24	B
Bellino 2019b[38]	2016–2017	Unvaccinated	0.15	0.06	0.23	Not reported
Puig-Barbera 2013[41]	2010–2011	Trivalent non-adjuvanted	0.06	−1.38	0.63	Well-matched
Izurieta 2019[39]	2017–2018	Trivalent non-adjuvanted	0.03	−0.01	0.06	Not reported
Influenza- or pneumonia-related hospitalisation						
Mannino 2012[40]	2006–2009	Trivalent non-adjuvanted	0.25	0.02	0.43	Mismatch
Gasparini 2013[23]	2010–2011	Unvaccinated	0.88	0.00	0.99	Well-matched
Spadea 2014[35]	2010–2011	Trivalent non-adjuvanted	0.48	0.29	0.62	Well-matched
Spadea 2014[35]	2011–2012	Trivalent non-adjuvanted	0.49	0.30	0.60	Mismatch
Pneumonia-related hospitalisation						
Puig-Barbera 2004[30]	2002–2003	Unvaccinated	0.48	0.20	0.66	Not reported
Puig-Barbera 2007[31]	2004–2005	Unvaccinated	0.69	0.29	0.86	Not reported
Influenza-related hospital encounters						
Iziureta 2019[39]	2017–2018	Trivalent non-adjuvanted	0.04	0.01	0.06	Not reported
Influenza-related office visits						
Iziureta 2019[39]	2017–2018	Trivalent non-adjuvanted	−0.07	−0.10	−0.04	Not reported
Influenza like illness						
Iob 2005[10]	1998–1999	Unvaccinated	0.20[a]	0.14	0.31	Well-matched
Iob 2005[10]	1998–1999	Trivalent non-adjuvanted	0.76[a]	0.59	0.97	Well-matched

Abbreviation: CI, confidence interval.

[a]Denotes unadjusted estimate of vaccine effectiveness.

[b]Interpreted from narrative provided by included studies.

6.2 | Influenza- or pneumonia-related hospitalisations

Three studies presented data related to the effectiveness of MF59® adjuvanted trivalent vaccines in preventing influenza- or pneumonia-related hospitalisations compared with no vaccination (one case control study[23]) or non-adjuvanted trivalent vaccines (one case control study[35] and one cohort study[40]). Regardless of the comparator, all included studies displayed a significant effect in favour of MF59® adjuvanted vaccines (Table 4).[23,35,40]

6.3 | Pneumonia-related hospitalisations

Two case control studies presented data specifically concerning the effectiveness of MF59® adjuvanted trivalent influenza vaccines in preventing pneumonia-related hospitalisations compared with no vaccination; a significant effect in favour of MF59® adjuvanted vaccines was found in both studies (Table 4).[30,31]

6.4 | Influenza-related hospital encounters or office visits

One cohort study presented data relating to the effectiveness of MF59® adjuvanted compared with non-adjuvanted trivalent influenza vaccines for the prevention of influenza-related hospital encounters or office visits with a small, but statistically significant difference highlighted in favour of MF59® adjuvanted vaccines for hospital encounters (VE = 4%, 95% CI 1%–6%), but not for office visits (VE = −7%, 95% CI -10% to −4%, Table 4).[39]

6.5 | Influenza-like illness

One case control study presented data that related to the effectiveness of MF59® adjuvanted trivalent influenza vaccines for the prevention of influenza-like illness compared with no vaccination and with non-adjuvanted trivalent vaccines for long-term care facility residents (Table 4).[10] A significant effect in favour of MF59®

adjuvanted vaccines was found for both comparisons. However, these results should be interpreted with caution as they are crude estimates and the unvaccinated population represent a small portion of residents who refused vaccination.

7 | SAFETY

Twenty-six studies concerned the safety of MF59® adjuvanted influenza vaccines.[42-67] Of these, 21 were RCTs[42-61,65] and five were NRSIs.[62-64,66,67]

7.1 | Serious adverse events

Three RCTs[49,53,61] and two NRSIs[66,67] reported vaccine-related serious adverse events (SAEs) comparing MF59® adjuvanted trivalent with non-adjuvanted trivalent influenza vaccines. Frey et al.[49] reported four SAEs; one in the MF59® adjuvanted group (bronchitis) and three in the non-adjuvanted group (asthmatic crisis, chronic obstructive pulmonary disease [unspecified issue] and Guillain–Barré syndrome). One death attributable to respiratory depression secondary to Guillain–Barré syndrome in the MF59® adjuvanted group was considered possibly vaccine-related. Li et al.[53] reported a SAE of high fever in a recipient of a MF59® adjuvanted vaccine. A third study reported a case of facial herpes zoster that was deemed by the investigator to be possibly vaccine-related.[61] Tsai et al.[66] reported no cases of narcolepsy in either vaccine group and found no increase in adverse sleep-related events in MF59® adjuvanted vaccine recipients. Villa et al.[67] noted no difference in the rate of hospitalisation for adverse events related to vaccination between MF59® adjuvanted and non-adjuvanted trivalent influenza vaccine groups.

7.2 | Local reactions

Twelve studies possessed sufficient data to enable a quantitative synthesis of local reactions, all of which compared MF59® adjuvanted with non-adjuvanted trivalent influenza vaccines in adult populations.[43,44,46,48,49,51,53,55,58-60,65] MF59® adjuvanted vaccines were associated with a greater number of combined local reactions (RR = 1.90, 95% CI 1.50–2.39, four RCTs, moderate-certainty evidence), with pain in particular being more frequently reported in recipients of MF59® adjuvanted vaccines (RR = 2.02, 95% CI 1.53–2.67, 12 RCTs, moderate-certainty evidence; supporting information S1). No significant difference between MF59® adjuvanted and non-adjuvanted vaccines was noted for redness, swelling or induration based on the remaining pooled analyses (low-moderate certainty of evidence). Similar results were displayed for older adults within sub-group analyses (supporting information S1).

In terms of studies that were excluded from pooled analyses, in agreement with the results of the pooled analyses, local injection site reactions were typically more frequent with adjuvanted compared with non-adjuvanted vaccines in older adults.[43,45,61,62,65]

7.3 | Systemic reactions

Twelve studies reported sufficient data to enable quantitative synthesis of systemic reactions with all comparing MF59® adjuvanted with non-adjuvanted trivalent influenza vaccines in adult populations.[43,44,46,48,49,51,53,55,58-60] The relative risk of combined systemic reactions (RR = 1.18, 95% CI 1.02–1.38, five RCTs, moderate-certainty evidence), myalgia (RR = 1.71, 95% CI 1.09–2.69, 10 RCTs, moderate-certainty evidence), fever (RR = 1.97, 95% CI 1.07–3.61, nine RCTs, low-certainty evidence) and chills (RR = 1.70, 95% CI 1.20–2.40, seven RCTs, moderate-certainty evidence) were significantly higher compared with MF59® adjuvanted vaccines, however no significant difference were noted for arthralgia, malaise, headache, nausea or fatigue (low-moderate certainty evidence; supporting information S1). Similar results were found for older adults within sub-group analyses (supporting information S1).

In terms of studies which were excluded from the pooled analyses, in general the frequency of systemic adverse events was similar for recipients of adjuvanted and non-adjuvanted vaccines.[43,45,61,62,65] Panatto et al.[64] highlighted chills and fatigue as the most frequently experienced systemic adverse events in a surveillance study of MF59® adjuvanted vaccine recipients.

7.4 | Safety of MF59®adjuvanted influenza vaccines in at-risk populations

Six studies included in this review were deemed to include at-risk populations including: a diagnosis of HIV,[46,50] transplant recipients,[54,56] institutionalised older adults,[57] and those receiving regular medical care.[42]

For local reactions, one study reports that local reactions were more common in those receiving MF59® adjuvanted compared with non-adjuvanted vaccines in individuals who receive regular medical care.[42]

For systemic reactions, there was no significant difference in rates between MF59® adjuvanted and non-adjuvanted vaccines for individuals who receive regular medical care,[42] institutionalised older adults[57] or haematopoietic stem cell transplantation recipients.[56] Shivers and fever were more commonly reported among HIV-seropositive patients vaccinated with MF59® adjuvanted compared with non-adjuvanted trivalent influenza vaccines.[46,50] Among heart-transplant recipients, there was no difference in the frequency of acute myocardial rejection or early side effects for recipients of adjuvanted vaccines compared with non-adjuvanted.[54]

8 | RISK OF BIAS

Fifteen (71.4%) of the included RCTs investigating the safety of MF59® adjuvanted influenza vaccines were deemed to be at an unclear risk of bias due to lack of clarity in one or more of the key domains assessed,[42-45,47,51-60] with the remaining six (28.6%) studies deemed to be at a high risk of bias due to a high risk of bias in one or more of the key domains (Figure 6 and supporting information S1).[46,48-50,61,65] Of note, the influence of industry funding, as captured under the domain of other bias, resulted in the majority of studies being deemed to be at an unclear risk of bias overall.

Of 14 assessed outcomes from test-negative design case-control studies, four (28.6%) were assessed to be at a low risk of bias,[27-29,36] four (28.6%) at moderate risk[21,25,37,38] and six (42.8%) at a high risk of bias[24,27,29,33,34,37] (supporting information S1). Areas of poor reporting included adequate control of confounding variables and selection bias. Of note, a number of studies provided adjusted and unadjusted outcomes depending on the comparator investigated and have been assessed separately in these instances. Four (44.4%) NRSIs investigating additional outcomes were deemed to be at a low risk of bias,[30,31,39,41] one (11.1%) at a moderate risk,[38] three (33.3%) at a serious risk and,[23,35,40] one (11.1%) at a critical risk of bias.[10] Areas of poor reporting included confounding variables, selection bias and missing data. Two studies presented data relating to safety with both deemed to be at a serious risk of bias.[66,67]

9 | DISCUSSION

To our knowledge, this is the first systematic review to assess the efficacy, effectiveness and safety of MF59® adjuvanted influenza vaccines in individuals ≥18 years of age. Overall, there is an absence of high-quality evidence regarding the efficacy of MF59® adjuvanted influenza vaccines. Twenty-two effectiveness studies,[10,21-41] including 11 test-negative design case-control studies,[21,22,24,25,27-29,33,34,36,37] presented results which were relevant to the primary outcome of laboratory-confirmed influenza. Compared with no vaccination, MF59® adjuvanted trivalent vaccines were found to be effective in preventing influenza in older adults.[21,27-29,37] Limited evidence was presented with regards to the effectiveness of MF59® adjuvanted influenza vaccines compared with their non-adjuvanted equivalents for the prevention of laboratory-confirmed influenza. Only seven studies reported relevant data,[22,27-29,37,39,41] which included both crude and adjusted outcomes and could not be synthesised. All studies included older adults (≥65 years) except for one study[29] that included adults ≥18 years. A subjective interpretation of these limited data suggests MF59® adjuvanted influenza vaccines do not appear to offer a benefit over non-adjuvanted influenza vaccines. No statistical difference was noted in any observational study, including by subtype, irrespective of season.

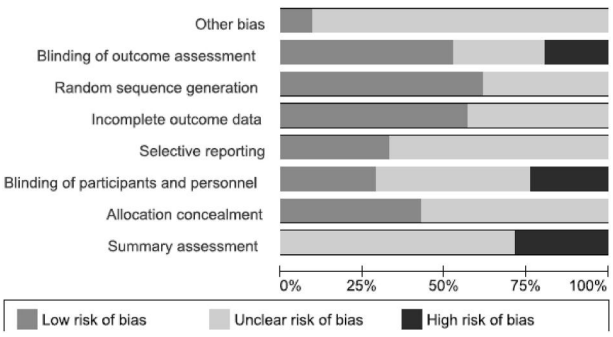

FIGURE 6 Risk of bias graph. Caption: Risk of bias graph displays review authors' judgement of each risk of bias item, presented as percentages across all included studies

Our effectiveness findings concur with prior reviews that were limited to elderly populations, whereby MF59® adjuvanted vaccines appear to offer benefit compared with no vaccination.[68,69] Immunogenicity measures were outside the scope of this review, however prior meta-analyses have suggested enhanced immunogenicity associated with MF59® adjuvanted compared with non-adjuvanted influenza vaccines, including significantly higher antibody titres.[70,71] Limited relative effectiveness data from this review, however, suggest MF59® adjuvanted influenza vaccines do not appear to offer a real-world benefit over their non-adjuvanted counterparts.

While the treatment effect in relation to influenza A(H3N2) was not statistically significant, many studies were not powered to detect a difference by subtype, and considerable heterogeneity existed across studies with regard to matching with the circulating strain. These findings appear largely in keeping with previous reviews of influenza VE.[72,73] The heterogeneity displayed when considering influenza A(H3N2) data specifically is not unexpected, given the known antigenic drift associated with this subtype in particular.[1] Although adjuvanted influenza vaccines enhance immunogenicity, their vulnerability to mismatch may be similar to traditional influenza vaccines.[8] It appears to support previous directives regarding the cornerstone of influenza effectiveness being first and foremost the accuracy of prediction of circulating strains and the degree of within-season drift.[74,75]

Any outcome that was not laboratory-confirmed was categorised as an additional outcome. A similar pattern was seen with regards to influenza-related hospitalisations, whereby MF59® adjuvanted vaccines appeared superior to no vaccination, but limited data suggested no difference in effect compared with non-adjuvanted vaccines. MF59® adjuvanted vaccines were also more effective than no vaccination in reducing the risk of influenza- or pneumonia-related hospitalisations, with data from two studies suggesting they may also be more effective than non-adjuvanted vaccines. Given the nature of the studies investigating these proxy outcomes and the inherent risk of bias, significant caution is needed when interpreting these results.

A reasonably large evidence base was presented in terms of the safety of MF59® adjuvanted influenza vaccines compared with their non-adjuvanted equivalents, with data from 27 studies. In general, the included studies demonstrated that MF59® adjuvanted influenza

vaccines were associated with a higher frequency of solicited local and systemic reactions. This finding is not surprising given the potency of inflammatory action associated with the use of adjuvants in vaccines; Hervé et al.[76] discuss the reactogenicity and physical manifestations associated with adjuvants and highlight the inevitability of more solicited reactions. However, these adverse effects are noted to be largely mild to moderate, and transient in their presentation.[76,77]

9.1 | Clinical and research implications

Likely reflective of regulatory requirements, a large volume of evidence was retrieved relating to the safety of MF59® adjuvanted influenza vaccines. However, there was an absence of efficacy data, and while VE demonstrated effect compared with 'no vaccination', limited and heterogenous data limited our ability to assess relative VE. The greater potential for adverse events associated with MF59® adjuvanted influenza vaccines has implications when considering the benefit-harm balance, and may favour non-adjuvanted vaccines. While the risks and benefits are not equivalent, benefits and harms could be directly compared through a composite measure such as quality-adjusted life years, a potential area of future research.

There is a need for robust trials to address the dearth of relative efficacy data, uncertainty in terms of matched/mismatched vaccine strain seasons included in effectiveness studies, and lack of clarity and consistency in terms of outcomes reported. In light of the difficulties encountered in conducting this review, we have proposed recommendations to improve the reporting of these studies for future assessments. While a number of relative effectiveness studies comparing MF59® adjuvanted with standard vaccines were identified, no comparative effectiveness studies with newer/enhanced vaccines were retrieved. Comparisons with high dose influenza vaccines in particular would improve policy decision-making, especially in older age groups.

9.2 | Strengths and limitations

The findings of this systematic review should be interpreted with consideration of its overall strengths and limitations. A robust approach to the review process was employed with the publication of a defined protocol and adherence to guidelines to standardise conduct and reporting.

It is notable that no efficacy trials were identified. Relative VE studies were limited by low numbers, lack of adjustment for confounders in some studies leading to a potentially biased estimate, and frequent mis-match of vaccine with circulating viral strains. All studies but one investigated the effectiveness in older adults, limiting the conclusions that can be drawn in younger age groups. Small sample sizes were particularly an issue when comparing vaccine types, such as the relative effectiveness of MF59® adjuvanted compared with traditional vaccines. Power calculations of VE studies are frequently for the main comparison only (vaccinated vs. unvaccinated). Future VE studies should include sample size calculations in the study design phase, not only for the primary outcome, but also for secondary outcomes included in the subgroup analysis (e.g. age-group, virus subtypes and vaccine types).

This review was unable to answer the research question regarding within-season protection duration associated with MF59® adjuvanted influenza vaccines due to a lack of data overall. This outcome consists of a complex interaction between a large number of factors including, age, previous vaccination history, previous infection history, circulating strain clade and research design.[78] However, it is anticipated that with the increased use of these newer and enhanced influenza vaccines, a larger data coverage will emerge. This should facilitate answers regarding this outcome, in particular with comprehensive datasets such as those collected by the I-MOVE initiative in Europe.[79]

A final consideration is the potential risk of bias of industry funding and industry affiliation. The potential for this form of bias resulted in a large number of studies being deemed to be at an 'unclear' risk overall. Such factors have been documented as potentially influencing the likelihood of publication of favourable results when considering influenza vaccines.[80] The conduct of sufficiently powered and publicly-funded trials to assess these vaccines in an effort to reduce the uncertainty regarding industry bias has been suggested as crucial for future research.[72]

9.3 | Conclusions

In conclusion, the evidence base for the efficacy and effectiveness of the MF59® adjuvanted influenza vaccines is limited at present. MF59® adjuvanted trivalent influenza vaccines were found to be more effective than 'no vaccination', however there was no significant difference comparing MF59® adjuvanted trivalent vaccines with either non-adjuvanted trivalent or quadrivalent vaccines. Pooled analyses of effectiveness data comparing adjuvanted with non-adjuvanted vaccines was restricted by limited study numbers, statistical and clinical heterogeneity.

MF59® adjuvanted influenza vaccines were associated with a higher frequency of local and systemic reactions compared with their non-adjuvanted counterparts. With consideration to the benefit-harm balance, further evidence is likely needed before recommending MF59® adjuvanted over non-adjuvanted influenza vaccines.

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AUTHOR CONTRIBUTIONS

All authors attest they meet the ICMJE criteria for authorship. Eamon O. Murchu, Conor Teljeur, Kari Johansen, Laura Comber, Liam Marshall, Michelle O'Neill, Máirín Ryan, Patricia Harrington, Sarah Hawkshaw: Writing original draft, reviewing, editing, investigation, formal analysis. Pasi Penttinen, Kari Johansen, Nathalie Nicolay, Annasara Carnahan, Jaime Jesús Pérez, Anna Hayman Robertson, Jorgen de Jonge, Tyra Krause, Ole Wichmann, Richard Pebody, Hanna Nohynek, Ioanna Pavlopoulou, Marta Soler-Soneira: Idea conception, protocol development, reviewing, editing, expert input.

ETHICS STATEMENT

Ethics approval was not necessary.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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