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Review

Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis

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ABSTRACT

Background: In the elderly, traditional influenza inactivated vaccines are often only modestly immunogenic, owing to immunosenescence. Given that adjuvantation is a means of enhancing the immune response, the trivalent inactivated vaccine adjuvanted with MF59 (MF59-TIV) was specifically designed to overcome this problem. Considering that, for ethical reasons, the absolute effectiveness of an influenza vaccine in the elderly cannot be demonstrated in placebo-controlled studies, the present study aimed to assess the effectiveness of MF59-TIV in preventing influenza-related outcomes in the elderly.
Methods: We conducted a systematic review of observational studies aimed at evaluating the effectiveness of MF59-TIV against influenza-related outcomes. Results of single studies were pooled whenever possible.
Results: Of the 1993 papers screened, 11 (6 case-control, 3 cohort and 2 prospective case-control) studies were identified. Hospitalization due to pneumonia/influenza and laboratory-confirmed influenza were reported in more than one study, while other outcomes (influenza-like illness, cardio- and cerebrovascular accidents) were investigated only by one study each. Pooled analysis of four case-control studies showed an adjusted MF59-TIV effectiveness of 51% (95% CI: 39–61%) against hospitalizations for pneumonia/influenza among community-dwelling seniors. Pooled results of the adjusted vaccine effectiveness against laboratory-confirmed influenza were also high (60.1%), although the 95% CI passed through zero (−1.3 to 84.3%). Other single community-based studies showed very high effectiveness of MF59-TIV in preventing hospitalizations for acute coronary [87% (95% CI: 35–97%)] and cerebrovascular [93% (95% CI: 52–99%)] events. MF59-TIV proved highly effective [94% (95% CI: 47–100%] in reducing influenza-like illness among institutionalized elderly. Furthermore, MF59-TIV displayed greater efficacy than non-adjuvanted vaccines in preventing hospitalizations due to pneumonia/influenza [adjusted risk ratio 0.75 (95% CI: 0.57–0.98)] and laboratory-confirmed influenza [adjusted odds ratio 0.37 (0.14–0.96)].
Conclusions: Our results suggest that MF59-TIV is effective in reducing several influenza-related outcomes among the elderly, especially hospitalizations due to influenza-related complications.

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1. Introduction

The elderly are particularly vulnerable to seasonal influenza; indeed, approximately 90% of all influenza-related deaths occur among senior citizens [1]. Vaccination remains the most effective public health measure to reduce the impact of seasonal influenza [2,3]. In this regard, the European Union Council encourages individual countries to reach a vaccination coverage rate of at least 75% in the elderly [4]. However, traditional trivalent inactivated vaccines (TIVs) often induce only a modest immune response in the elderly, owing to immunosenescence [5].

Adjuvantation is a well-known means of increasing vaccine potency. Moreover, adjuvanted vaccines may induce a more rapid and broader (i.e. towards heterologous serotypes) immune response [6]. The first adjuvant used for seasonal influenza vaccines was the squalene-based adjuvant microfluidized emulsion 59 (MF59), an oil-in-water emulsion. Its immuno-stimulatory properties have been extensively demonstrated; it activates local immune cells at the injection site, and promotes transition from monocytes to dendritic cells and recruitment of antigen-presenting cells and antigen uptake [7]. Italy was the first country in which a seasonal TIV vaccine adjuvanted with MF59 (MF59-TIV) was licensed (in 1997) [8].

The immunogenicity and safety of MF59-TIV have been studied in several pooled analyses [9–11]. The early paper by Podda [9] reported that, compared with non-adjuvanted TIVs, MF59-TIV induced significantly higher levels of immunogenicity in terms of geometrical mean ratios, and seroconversion and seroprotection rates for both primary and subsequent immunizations. In that study, MF59-TIV was judged to be well tolerated (most adverse events being mild), although several local and systemic reactions were more common in recipients of the adjuvanted vaccine [9]. The latter finding was later confirmed by an integrated analysis of safety outcomes [10], in which subjects vaccinated with MF59-TIV showed a higher risk than those vaccinated with non-adjuvanted TIV [weighted risk ratio 1.34 (95% CI: 1.28–1.40)] in terms of solicited local and systemic reactions within 3 days of immunization. A more recent systematic review by Camilloni et al. [11] suggested that the immunogenicity of MF59-TIV was high in the elderly, and in most instances satisfied the Committee for Medicinal Products for Human Use (CHMP) criteria.

Although randomized controlled trials (RCTs) in which the primary endpoints are immunogenicity and/or efficacy are advantageous in terms of rigorous control for biases and prospective monitoring of disease attack rates, observational studies are able to estimate in-field vaccine effectiveness (VE), thereby providing additional useful insights into the "real world" impact of a vaccine [12]. Furthermore, the absolute VE of a seasonal influenza vaccine in the elderly cannot be demonstrated in placebo-controlled studies for ethical reasons, since immunization of this age-class is highly recommended [8]. The present systematic review aimed to analyze the VE of seasonal MF59-TIV in preventing several influenza-related outcomes in the elderly.

2. Methods

2.1. Eligibility criteria

As a guideline for reporting, the MOOSE (meta-analysis of observational studies in epidemiology) checklist [13] was consulted.

Observational studies investigating the effectiveness of MF59-TIV in elderly populations were potentially eligible. Both cut-offs (60 and 65 years) for defining the elderly were acceptable [14]. Study populations were classified, in accordance with the study settings, as community-dwelling subjects, those institutionalized in long-term care facilities, and mixed.

The primary endpoint was the absolute VE, which was defined as the proportional reduction in the risk of influenza-related outcomes among vaccinees (in comparison with non-vaccinated subjects), as recorded in observational studies [12,15]. Influenza-related outcomes included: laboratory-confirmed influenza [through real-time polymerase chain reaction (RT-PCR) or culture], influenza-like illness (ILI), outpatient visits for influenza and pneumonia, hospitalizations for all respiratory pathologies, for influenza and pneumonia, for cardio- and cerebrovascular accidents, and mortality following hospitalization for influenza and pneumonia [15–17]. Our secondary endpoint was the relative VE, which was assessed by comparing influenza-related outcomes in subjects vaccinated with MF59-TIV with those of recipients of other influenza vaccines [18].

Owing to the fact that MF59-TIV was first authorized for human use in Italy in 1997 [8] and the first clinical trials were conducted in the early 1990s [19], our search was limited to the period starting from 01/01/1990. The last automatic search was performed on 26/04/2016. No language restrictions were applied.

2.2. Search strategy

A comprehensive search was performed in MEDLINE via OVID, Web of Science and Cochrane Library. The search strategy was adapted from [17,20], and is reported in Appendix, Table S1. Reference lists of included studies were manually checked by an expert. The vaccine manufacturer was asked to suggest relevant studies.

2.3. Study selection and data extraction

Once duplicates had been removed, titles and abstracts obtained from the automatic search were independently screened by two investigators (AD and LA). Subsequently, full texts of potentially eligible studies were assessed by applying a set of inclusion and exclusion criteria.

The following inclusion criteria were applied: (i) use of commercially available formulations of MF59-TIV; (ii) study population aged $\geqslant$60/65 years, regardless of setting; (iii) study period determined by influenza or ILI surveillance systems; (iv) case-control or cohort design; (v) studies reporting at least one of the above-mentioned influenza-related outcomes. Exclusion criteria were

formulated as follows: (i) non-original research, case reports and similar; (ii) animal studies; (iii) cross-sectional design; (iv) studies of any design aimed to evaluate immunogenicity, vaccine efficacy, tolerability and safety of MF59-TIV; (v) number of subjects vaccinated with MF59-TIV < 50; (vi) influenza diagnosed by means of serology; (vii) studies on subjects with particular chronic conditions (e.g. immunosuppression); (viii) absence of separate data for subjects of different ages (e.g. elderly and non-elderly adults) or vaccinated with different vaccines. However, if the majority ($\geqslant$90%) of study participants belonged to a group of interest, the study was included.

Data from selected studies were extracted by two reviewers (AD and LA), each working independently, and were inserted into an *ad hoc* database. The following information was gathered: first author and year of publication, study location, influenza season, study aim, study design, sample size, setting, age of vaccinees, comparator vaccines (if any), influenza-related outcome/s used, unadjusted and adjusted estimates of VE with 95% confidence intervals (CIs), and potential confounders. If a study reported VE estimates in different periods of the influenza season, only the estimate calculated close to the peak was recorded.

During the process of study selection and data extraction, any disagreement between the two investigators was settled by consensus and/or consultation of the third investigator (RG).

2.4. Quality assessment of included studies

The Newcastle-Ottawa scale (NOS) [21] was used to assess the quality of case-control and cohort studies. Evaluation was carried out independently by two authors, and the inter-rater agreement was quantified by means of Cohen's κ. Any between-rater disagreement was settled by consensus. Studies were categorized as being at low ($\leqslant$1 inadequate item on the NOS), medium (2–3 inadequate items on the NOS), high (>3 inadequate items on the NOS) or very high (no description of methods) risk of bias [17].

2.5. Data analysis

VE was expressed as [1-odds ratio (OR)]·100% and [1-risk ratio (RR)]·100% for case-control and cohort studies, respectively. VE was deemed statistically significant when its 95% CI did not pass through zero. The relative VE was expressed as an appropriate measure of effect size (OR and RR for case-control and cohort studies, respectively).

The meta-analysis of ORs (vaccinated with MF59-TIV vs non-vaccinated) was carried out in order to obtain pooled estimates of VE. To this end, a random-effects model using the DerSimonian-Laird weighting method was first implemented. If

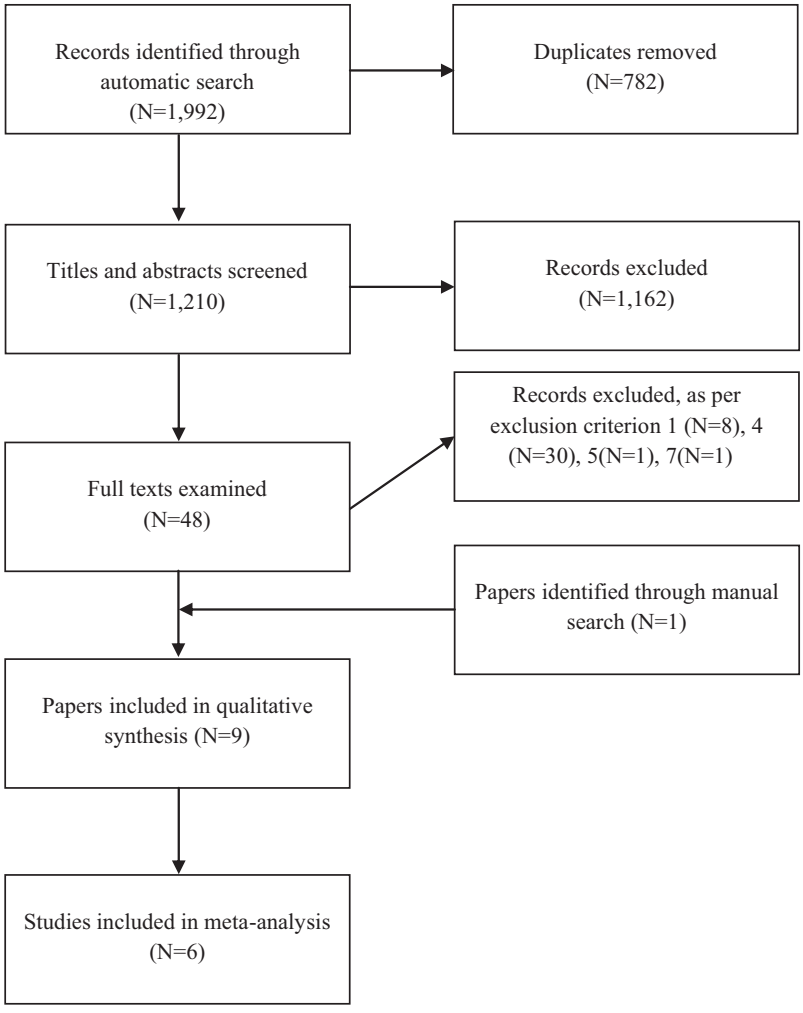

Fig. 1. Flowchart of the study selection process.

the observed heterogeneity was low, i.e. with an $I^2 < 40\%$, a fixed-effects model using the inverse variance method for weighting was re-applied. Unadjusted and adjusted effect sizes (ESs) were pooled separately. Meta-analysis was not performed when I^2 was over 85% [22]. A "leave-one-out" sensitivity analysis was carried out in order to ascertain that the pooled estimates were not driven by single studies. We planned *a priori* to conduct a subgroup analysis and/or meta-regression, in order to highlight those study characteristics that were significantly associated with heterogeneity among studies. Assessment of publication bias through Doi plot and LFK index was also planned, but could not be carried out. All analyses were performed in MetaXL 5.0 [23].

3. Results

3.1. Characteristics of studies included

Of the 1993 records screened, 9 papers (8 [24–26,28–32] and 1 [27] retrieved through automatic and manual searches, respectively), corresponding to 11 studies [24–32] (one paper [26] reported results of three studies), met the inclusion criteria (Fig. 1). The vaccine manufacturer agreed with the list of studies included. Taken together, the 11 studies enrolled 546,015 person-seasons. Of these, 52.3% were vaccinated with MF59-TIV. Six studies were case-control [24,26,30,32], three were cohort [25,28,31], and two were prospective community-based case-control studies [27,29]. Six studies were conducted in Spain [24,26,27,31], four in Italy [25,28,30,32], and the remaining one in Canada [29]. Most studies ($N = 9$) were conducted in the community setting [24,26–28,30–32]; the study by Iob et al. [25] was the only one carried out in long-term care facilities. The Canadian study [29] had a mixed population (56.7% of subjects living in long-term care facilities). Across the selected studies, the most frequent influenza-related outcome was hospitalization for pneumonia and influenza [24,26,28,30–32], followed by laboratory-confirmed influenza [27,29], ILI [25], hospitalization for acute coronary syndrome [26] and cerebrovascular accidents [26]. Five studies [25,28–31] compared the effectiveness of MF59-TIV with that of other adjuvanted and non-adjuvanted vaccines. All included studies were judged (once consensus had been reached) to be at medium risk of bias, although inter-rater agreement was low ($\kappa = 0.2$). The characteristics of the studies included are reported in Table 1.

Table 1
Characteristics of studies included.

Study design	Primary study aim	Country (influenza season)	Age of subjects, years	Setting	Influenza-related outcome	Sample size (person-seasons)	Ref.
Case-control	To estimate effectiveness of MF59-TIV in preventing hospital admissions for pneumonia	Spain (2002/03)	⩾65	Community	Emergency hospitalization for pneumonia (ICD-9-MC codes 480–487)	815 (290 cases and 525 controls), 486 of whom vaccinated	[24]
Prospective	To compare adjuvanted and non-adjuvanted vaccines in preventing ILI	Italy (1998/99)	23–100[a]	Long-term care facilities	Influenza-like illness	3173, of whom 1487 vaccinated with MF59-TIV	[25]
Case-control	To estimate the effectiveness of MF59-TIV in preventing hospitalizations for acute coronary syndrome	Spain (2004/05)	⩾65	Community	Hospitalizations for acute coronary syndrome (ICD-9-MC codes 410–411.89, 413)	402 (144 cases and 258 controls), 295 of whom vaccinated	[26]
Case-control	To estimate the effectiveness of MF59-TIV in preventing hospitalizations for cerebrovascular accidents	Spain (2004/05)	⩾65	Community	Hospitalizations for cerebrovascular accidents (ICD-9-MC codes 431–436)	380 (134 cases and 246 controls), 275 of whom vaccinated	[26]
Case-control	To estimate the effectiveness of MF59-TIV in preventing hospitalizations for pneumonia	Spain (2004/05)	⩾65	Community	Hospitalizations for pneumonia (ICD-9-MC codes 480–487)	519 (198 cases and 321 controls), 401 of whom vaccinated	[26]
Prospective case-control	To estimate seasonal influenza vaccine effectiveness in preventing laboratory-confirmed influenza-related hospitalizations	Spain (2010/11)	⩾18[b,c]	Community	Laboratory-confirmed influenza (RT-PCR)	826, of whom 113[c] vaccinated with MF59-TIV	[27]
Prospective	To compare adjuvanted and non-adjuvanted vaccines in preventing hospitalizations for influenza and pneumonia	Italy (2006/07, 2007/08, 2008/09)	⩾65	Community	Hospitalization for pneumonia and influenza (ICD-9-MC codes 480–487)	164,254, of whom 84,665 vaccinated with MF59-TIV	[28]
Prospective case-control	To evaluate adjuvanted and non-adjuvanted vaccines, compared with no vaccination, in preventing laboratory-confirmed influenza	Canada (2011/12)	⩾65	Mixed	Laboratory-confirmed influenza (RT-PCR)	282 (84 cases and 198 controls), 165 of whom vaccinated with MF59-TIV	[29]
Case-control	To evaluate the effectiveness of seasonal adjuvanted vaccines available in Italy in the elderly	Italy (2010/11)	⩾65	Community	Hospitalization for pneumonia and influenza (ICD-9-MC codes 480–487)	374 (187 cases and 187 controls), 88 of whom vaccinated with MF59-TIV	[30]
Retrospective	To compare adjuvanted and virosomal vaccines in preventing influenza-related hospitalizations	Spain (2010/11)	⩾65	Community	Hospitalization for pneumonia and influenza (ICD-9-MC codes 487–488.89)	373,398, of whom 197,180 vaccinated with MF59-TIV	[31]
Case-control	To evaluate and compare effectiveness of non-adjuvanted (2010/11) and adjuvanted vaccines (2011/12) in reducing hospitalizations for per influenza or pneumonia	Italy (2011/12)[d]	⩾65	Community	Hospitalization for pneumonia and influenza (ICD-9-MC codes 480–487)	1592 (365 cases and 1227 controls), 519 of whom vaccinated	[32]

[a] Subjects aged <65 years accounted for only 3.65%.
[b] Subjects vaccinated with MF59-TIV were all aged ⩾65 years.
[c] Data derived from personal communication of the corresponding author.
[d] Study also considered the 2010/11 season, when, however, a non-adjuvanted vaccine was used.

3.2. MF59-TIV effectiveness

In the Canadian study [29], which involved a mixed study population of both community and long-term care facility residents, the VE of MF59-TIV in preventing laboratory-confirmed influenza was 35% and 58% on univariable and multivariable analyses, respectively. When a subgroup analysis of community-dwelling subjects was undertaken, VE exceeded 70%: 73% and 72% in unadjusted and adjusted models, respectively [29]. By contrast, in one Spanish study [27], the VE of MF59-TIV in preventing laboratory-confirmed influenza did not reach an $\alpha < 0.05$ (Table 2). Pooled analyses of these two studies revealed a significant unadjusted VE of 58.8% (95% CI: 10.7–81.0%). When adjusted estimates were pooled, VE slightly increased to 60.1%; however, although the ES was large, the 95% CI passed through zero (−1.3 to 84.3%). No heterogeneity was found (both $I^2 = 0\%$) (Fig. 2A).

Among four case-control community-based studies [24,26,30,32], unadjusted VE in preventing hospitalization for pneumonia and influenza ranged from 9% [24] to 95.2% [30]; this range narrowed (from 48% [24] to 88% [30]) when considering the adjusted VE (Table 2). Pooling of unadjusted estimates of VE ($N = 4$ studies) revealed a high level of heterogeneity ($I^2 = 81\%$); the random-effects model showed a VE of 42% (95% CI: 0.01–67%). The sensitivity analysis (Appendix, Table S2) revealed that, after excluding the study by Gasparini et al. [30], the unadjusted VE dropped to 32.4% (95% CI: −7.3 to 57.5%); in any case, heterogeneity was constantly high: at least 70%. By contrast, no heterogeneity was found ($I^2 = 0\%$) when adjusted VEs were

Table 2
MF59-TIV effectiveness in preventing laboratory-confirmed influenza and hospitalization for pneumonia/influenza in community-dwelling elderly.

Outcome	Study [Ref.]	VE (95% CI), %	aVE (95% CI), %
Laboratory-confirmed influenza	Puig-Barberà [27]	43.8 (−56.1 to 79.7)	43.2 (−111.2 to 84.7)[a]
	Van Buynder [29]	73 (14–92)	72 (2–93)[b]
Hospitalization for pneumonia/influenza	Puig-Barberà [24]	9 (−23 to 32)	48 (20–66)[c]
	Puig-Barberà [26]	27 (−35 to 60)	69 (29–86)[d]
	Gasparini [30]	95.2 (64.6–99.4)	87.8 (−39.4 to 98.9)[e]
	Spadea [32]	52 (36–63)	49 (30–60)[f]

[a] Adjusted for age, sex, underlying pathologies, smoking, epidemiological week and days from onset of symptoms to swab.
[b] Adjusted for age, gender, presence of chronic conditions, health authority, week of testing.
[c] Adjusted for presence of heart disease, COPD, asthma, Barthel Index score <60, smoking status, pneumococcal vaccination, attending outpatient clinics.
[d] Adjusted for age, presence of heart disease, COPD, diabetes mellitus, Barthel Index, smoking status, pneumococcal vaccination, number of home visits, influenza vaccination status of the caregive.
[e] Adjusted for age, presence of respiratory disease, smoking and drinking habits.
[f] Adjusted for age, sex, civil status, educational level, citizenship, number of comorbidities.

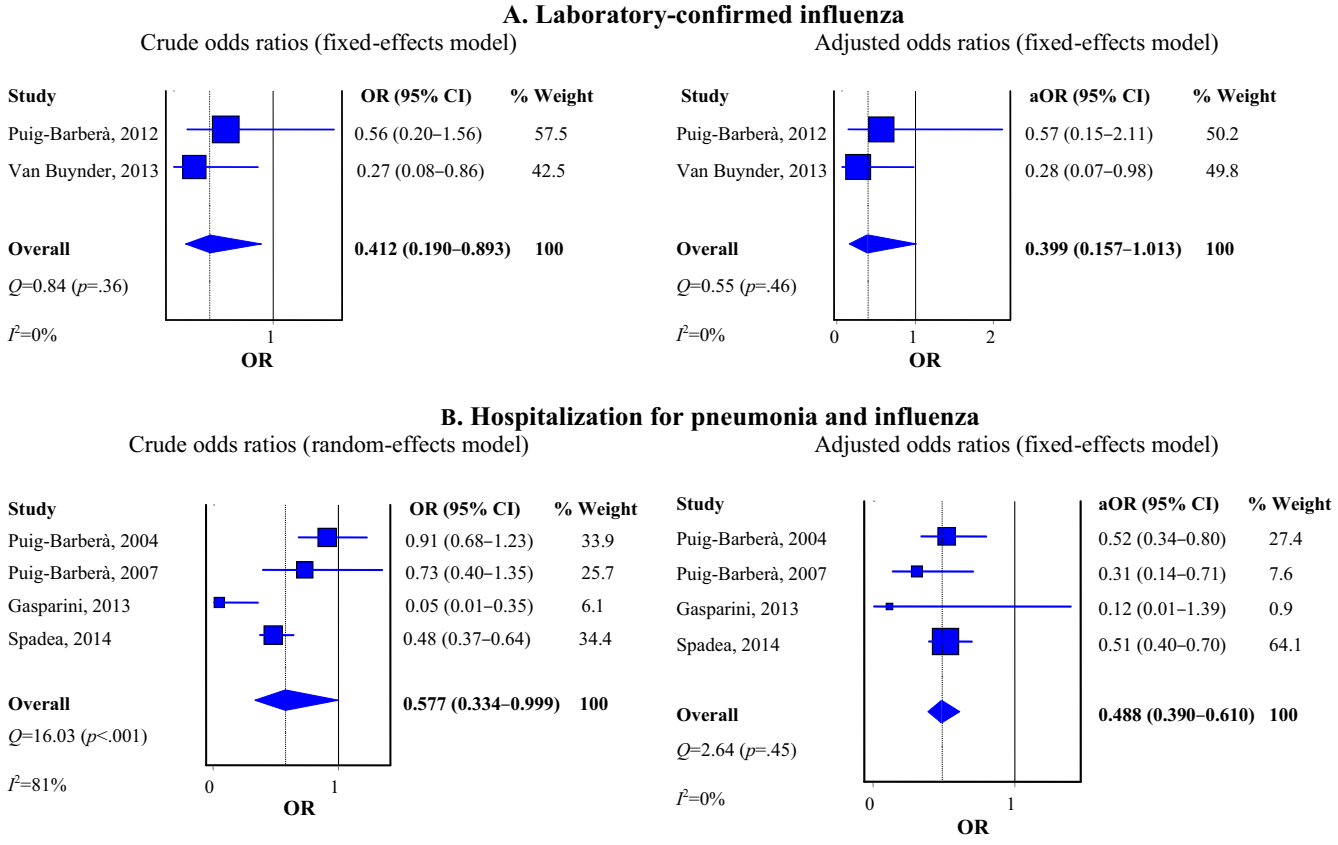

Fig. 2. Pooled estimates of unadjusted and adjusted vaccine effectiveness.

meta-analyzed ($N = 4$ studies), yielding a pooled estimate of 51% (95% CI: 39–61%) (Fig. 2B). The sensitivity analyses (Appendix, Table S2) showed consistently robust results, which signifies that the pooled estimate was not driven by a single study. Owing to the paucity of studies, neither publication bias or subgroup analyses could be performed.

Regarding other influenza-related outcomes, in the paper by Puig-Barberà et al. [26], MF59-TIV proved to be highly effective in reducing hospitalizations for acute coronary syndrome in the multivariable analysis [VE: 87% (95% CI: 35–97%)], but not in the unadjusted one [VE: 11% (95% CI: −108 to 63%)]. A similar pattern has been reported with regard to cerebrovascular accidents: VEs of 93% (95% CI: 52–99%) and 44% (95% CI: −40 to 69%) for adjusted and unadjusted estimates, respectively [26].

With regard to long-term care facilities, Iob et al. documented an unadjusted VE of MF59-TIV of 94% (95% CI: 47–100%) [25].

Table 3 summarizes available data on MF59-TIV VE.

3.3. Relative effectiveness of MF59-TIV

Table 4 reports ESs of the comparative VE of MF59-TIV versus other adjuvanted and non-adjuvanted vaccines [25,28–31]. The relative effectiveness of MF59-TIV tended to be significantly higher in comparison with intramuscular non-adjuvanted vaccines, but not virosomal (no longer commercially available) and intradermal TIVs. A meta-analysis was not feasible, owing to the different study designs, settings, comparators and influenza-related outcomes.

4. Discussion

Influenza vaccination is highly recommended in the elderly because these subjects are at high risk of developing severe complications due to influenza. Therefore, it is important to evaluate the effectiveness of influenza vaccines in this age-class. However, RCTs in this age-class are very uncommon, as ethics committees reject experimental placebo-controlled designs in most jurisdictions [33]; consequently, observational studies are a fundamental way of evaluating influenza VE among seniors. Since it was licensed, more than 20 years ago, MF59-TIV has been approved for human use in about 30 countries, and in most of these it is indicated only for immunization of the elderly [6]. To our knowledge, the present systematic review is the first that has specifically aimed to evaluate and quantify the effectiveness of MF59-TIV in the elderly.

Our results show that MF59-TIV is effective against a number of influenza-related outcomes in the elderly living in both communities and long-term care facilities. Specifically, the adjusted VE in preventing hospitalizations for pneumonia/influenza and acute coronary and cerebrovascular events exceeded 50%. Our pooled analysis revealed no heterogeneity among the studies included, suggesting that the vaccination effects were consistent in the four studies that evaluated these outcomes. Arguably, our meta-analysis included a limited number of papers; Q and I^2 statistics may therefore have had a low power. However, the data support consistency of the estimates, since the 95% CIs of the meta-analyzed studies overlapped.

With regard to laboratory-confirmed influenza, adjusted estimates of VE were around 60% in both community and mixed populations (communities and long-term care facilities). However, in the case of community-dwelling seniors, the lower confidence of the adjusted VE was −1.3% and the 95% CIs were fairly broad, suggesting a low precision of estimates. This observation can probably be attributed to the small sample sizes in both of the studies included.

Table 3
MF59-TIV effectiveness, by outcome, study design and setting.

Outcome	Study design	Setting									
		Community			Long-term care facilities			Mixed			
		N of studies	VE (95% CI), %	aVE (95% CI), %	N of studies	VE (95% CI), %	aVE (95% CI), %	N of studies	VE (95% CI), %	aVE (95% CI), %
Laboratory-confirmed influenza	Prospective case-control	2	**59 (11–81)**[a]	60 (−1 to 84)[a]	0	N/A	N/A	1	35 (−25 to 81)	**58 (5–82)**
Influenza-like illness	Cohort	0	N/A	N/A	1	**94 (47–100)**	N/A	0	N/A	N/A
Hospitalization for pneumonia and influenza	Case-control	4	**42 (0.01–67)**[a]	**51 (39–61)**[a]	0	N/A	N/A	0	N/A	N/A
Hospitalization for acute coronary syndrome	Case-control	1	11 (−108 to 63)	**87 (35–97)**	0	N/A	N/A	0	N/A	N/A
Hospitalization for cerebrovascular accidents	Case-control	1	44 (−40 to 69)	**93 (52–99)**	0	N/A	N/A	0	N/A	N/A

Statistically significant estimates are in bold.
[a] Pooled estimates.

Table 4
Relative effectiveness of MF59-TIV (MF59-TIV versus other vaccines).

Study [Ref.]	Design	Setting	Comparator	Outcome	ES (95% CI)	aES (95% CI)
Iob [25]	Prospective	Long-term care facility	IM-TIV	Influenza-like illness	**0.66 (0.53–0.82)**[a,b]	N/A
Mannino [28]	Prospective	Community	IM-TIV	Hospitalization for pneumonia and influenza	0.97 (0.74–1.25)[c]	**0.75 (0.57–0.98)**[c]
Puig-Barberà [31]	Retrospective	Community	Virosomal TIV	Influenza-related hospitalization	0.53 (0.53–1.30)[c]	0.85 (0.54–1.34)[c,d] 0.94 (0.37–2.38)[c,e]
Puig-Barberà [31]	Retrospective	Community	Virosomal TIV	Laboratory-confirmed influenza	0.72 (0.44–1.18)[c]	0.75 (0.46–1.24)[c,d] 0.84 (0.31–2.26)[c,e]
Gasparini [30]	Case-control	Community	ID-TIV	Hospitalization for pneumonia and influenza	**0.43 (0.20–0.91)**[a,f]	0.54 (0.22–1.29)[a,f]
Van Buynder [29]	Prospective case-control	Mixed	IM-TIV	Laboratory-confirmed influenza	0.58 (0.31–1.09)[a]	**0.37 (0.14–0.96)**[a]

[a] Odds ratio.
[b] Converted OR (in order to uniform effect sizes, i.e. MF59-TIV vs others); authors' reported OR was 2.16 (95% CI: 1.56–2.98).
[c] Risk ratio.
[d] Adjusted model.
[e] Multilevel model.
[f] Calculated from raw data provided by the corresponding author; statistically significant estimates are in bold.

The only study [25] that assessed MF59-TIV among institutionalized elderly subjects and had the outcome of ILI established a very high VE of 94%. However, in that study, the reported ES had not been adjusted.

It is worth comparing our results with those obtained from previously published systematic reviews and meta-analyses. Our results are in line with the paper by Gross et al. [34], which reported that influenza vaccination was effective in the elderly against some influenza-related outcomes. Specifically, our pooled estimate for hospitalization for pneumonia and influenza was very close to the pooled results of observational studies (53% and 50% in preventing pneumonia and hospitalization, respectively) reported in that meta-analysis [34]. On the other hand, both estimates from the studies included and our pooled results were higher than those of other meta-analyses [14,35]. This finding is, however, plausible, since both earlier analyses [16,35] mostly included studies on non-adjuvanted TIVs.

Concerning the relative VE, it appears that MF59-TIV is more effective that conventional non-adjuvanted TIVs. This finding is consistent with a pooled analysis of 13 immunogenicity RCTs [9], which found significantly higher antibody titers elicited by MF59-TIV than by non-adjuvanted TIVs. It should be acknowledged that quadrivalent inactivated vaccines (QIVs) that include both lineages of the type B virus have recently become available [36]; to the best of our knowledge, however, no study comparing MF59-TIV and non-adjuvanted QIVs has been published so far. Considering both a frequent B-type mismatch between trivalent vaccines and circulating B lineages and limited heterotypic activity between the two lineages, QIVs are presumed to provide additional benefits [36]. Indeed, a recent systematic review and meta-analysis by Moa et al. [37] reported that immunogenicity elicited by QIV was similar to that of TIV for the shared three strains, but superior to the non-TIV B lineage. However, it should be noted that, since several factors may impact VE (e.g. age, degree of mismatch, previous vaccination status, priming), the additional benefits of QIV could vary substantially among different populations. Given that children and young adults have relatively higher attack rates of type B virus, these age-classes would probably be major beneficiaries of QIV [38]. Moreover, Reed et al. [39] estimated that, in the United States population, using QIV instead of TIV would, on average, produce only a modest (about 1.4%) reduction in hospitalizations and mortality, although this estimate was highly dependent on season. Such a modest decrease may be partly attributed to the suboptimal efficacy of non-adjuvanted vaccines, especially in some age-classes [8]. A subsequent evaluation by Beyer et al. [40], which was based on an umbrella meta-analysis, indicated that the estimates made by Reed et al. [39] might be too optimistic and restricted to very young and unprimed subjects. Future research, including pharmacoeconomic evaluations, should consider these issues in comparing aTIV and non-adjuvanted QIVs.

Like all systematic reviews, the present one suffers from some limitations. In keeping with our aims and outcomes, only observational studies, the biases of which are well known, were comprehensively searched. However, most of the studies included implemented various measures to minimize biases in selection and information and confounders. Moreover, as mentioned above, some of our pooled estimates had large CIs, and therefore a relatively low precision of population-wide effect sizes. In the future, large well-designed observational (especially cohort) studies will undoubtedly help to establish more precise point estimates. At the review level, the paucity of studies included did not allow us to carry out the subgroup analysis and/or meta-regression that were planned *a priori*. For instance, it would have been useful to carry out a subgroup analysis by degree of matching between the strains included in vaccines and those circulating during single seasons. For the same reason, we were not able to check for publication bias. Finally, the inter-rater agreement in evaluating the methodological quality of the studies included may be interpreted only as poor to slight [41]. Although the NOS has been used in Cochrane reviews on influenza vaccines [17], previous research has found that the scale is difficult to use, has low inter-rater agreement [42] and low agreement between reviewers and authors [43].

To conclude, the available evidence suggests that MF59-TIV is effective in "real world" conditions, especially in preventing hospitalizations for various influenza complications, and is superior to conventional non-adjuvanted vaccines. In our opinion, well-designed and sufficiently powered future observational studies should investigate MF59-TIV VE against laboratory-confirmed influenza. In particular, considering that we identified only one study in which the population was composed of institutionalized elderly subjects, future research should target this vulnerable population group. Indeed, these subjects are particularly at risk of contracting influenza and developing severe complications, owing to their multiple underlying chronic conditions [44].

Conflict of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.12.011.

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