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Vaccines for preventing influenza in the elderly (Review)

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Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A.
Vaccines for preventing influenza in the elderly.
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD004876.
DOI: 10.1002/14651858.CD004876.pub4.

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[Intervention Review]

Vaccines for preventing influenza in the elderly

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), published in Issue 10, 2021.

Citation: Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub4.

ABSTRACT

Background

The consequences of influenza in the elderly (those age 65 years or older) are complications, hospitalisations, and death. The primary goal of influenza vaccination in the elderly is to reduce the risk of death among people who are most vulnerable. This is an update of a review published in 2010. Future updates of this review will be made only when new trials or vaccines become available. Observational data included in previous versions of the review have been retained for historical reasons but have not been updated because of their lack of influence on the review conclusions.

Objectives

To assess the effects (efficacy, effectiveness, and harm) of vaccines against influenza in the elderly.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 11), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to 31 December 2016); Embase (1974 to 31 December 2016); Web of Science (1974 to 31 December 2016); CINAHL (1981 to 31 December 2016); LILACS (1982 to 31 December 2016); WHO International Clinical Trials Registry Platform (ICTRP; 1 July 2017); and ClinicalTrials.gov (1 July 2017).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs assessing efficacy against influenza (laboratory-confirmed cases) or effectiveness against influenza-like illness (ILI) or safety. We considered any influenza vaccine given independently, in any dose, preparation, or time schedule, compared with placebo or with no intervention. Previous versions of this review included 67 cohort and case-control studies. The searches for these trial designs are no longer updated.

Data collection and analysis

Review authors independently assessed risk of bias and extracted data. We rated the certainty of evidence with GRADE for the key outcomes of influenza, ILI, complications (hospitalisation, pneumonia), and adverse events. We have presented aggregate control group risks to illustrate the effect in absolute terms. We used them as the basis for calculating the number needed to vaccinate to prevent one case of each event for influenza and ILI outcomes.

Main results

We identified eight RCTs (over 5000 participants), of which four assessed harms. The studies were conducted in community and residential care settings in Europe and the USA between 1965 and 2000. Risk of bias reduced our certainty in the findings for influenza and ILI, but not for other outcomes.

Older adults receiving the influenza vaccine may experience less influenza over a single season compared with placebo, from 6% to 2.4% (risk ratio (RR) 0.42, 95% confidence interval (CI) 0.27 to 0.66; low-certainty evidence). We rated the evidence as low certainty due to uncertainty over how influenza was diagnosed. Older adults probably experience less ILI compared with those who do not receive a vaccination over the course of a single influenza season (3.5% versus 6%; RR 0.59, 95% CI 0.47 to 0.73; moderate-certainty evidence). These results indicate that 30 people would need to be vaccinated to prevent one person experiencing influenza, and 42 would need to be vaccinated to prevent one person having an ILI.

The study providing data for mortality and pneumonia was underpowered to detect differences in these outcomes. There were 3 deaths from 522 participants in the vaccination arm and 1 death from 177 participants in the placebo arm, providing very low-certainty evidence for the effect on mortality (RR 1.02, 95% CI 0.11 to 9.72). No cases of pneumonia occurred in one study that reported this outcome (very low-certainty evidence). No data on hospitalisations were reported. Confidence intervals around the effect of vaccines on fever and nausea were wide, and we do not have enough information about these harms in older people (fever: 1.6% with placebo compared with 2.5% after vaccination (RR 1.57, 0.92 to 2.71; moderate-certainty evidence)); nausea (2.4% with placebo compared with 4.2% after vaccination (RR 1.75, 95% CI 0.74 to 4.12; low-certainty evidence)).

Authors' conclusions

Older adults receiving the influenza vaccine may have a lower risk of influenza (from 6% to 2.4%), and probably have a lower risk of ILI compared with those who do not receive a vaccination over the course of a single influenza season (from 6% to 3.5%). We are uncertain how big a difference these vaccines will make across different seasons. Very few deaths occurred, and no data on hospitalisation were reported. No cases of pneumonia occurred in one study that reported this outcome. We do not have enough information to assess harms relating to fever and nausea in this population.

The evidence for a lower risk of influenza and ILI with vaccination is limited by biases in the design or conduct of the studies. Lack of detail regarding the methods used to confirm the diagnosis of influenza limits the applicability of this result. The available evidence relating to complications is of poor quality, insufficient, or old and provides no clear guidance for public health regarding the safety, efficacy, or effectiveness of influenza vaccines for people aged 65 years or older. Society should invest in research on a new generation of influenza vaccines for the elderly.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing seasonal influenza and its complications in people aged 65 or older

Review aim

The aim of this Cochrane Review, first published in 2006, was to summarise research that looks at the effects of immunising the elderly (those aged 65 years or older) with influenza vaccine during influenza seasons. We used information from randomised trials comparing influenza vaccine with dummy vaccine or with nothing. The influenza vaccines were prepared by treating influenza viruses with a chemical that kills the virus (inactivated virus), and the vaccination was given by injection through the skin. We were interested in showing the effects of vaccines on reducing the number of elderly with confirmed influenza, the number who had influenza-like symptoms such as headache, high temperature, cough, and muscle pain (influenza-like illness, of ILI), and harms from vaccination. We looked for evidence of the impact of influenza or ILI such as hospital admission, complications, and death. We will update this review in the future only when new trials or vaccines become available.

Observational data from 67 studies included in previous versions of the review have been retained for historical reasons but have not been updated because of their lack of influence on the review conclusions.

What was studied in this review?

Over 200 viruses cause ILI, producing the same symptoms (fever, headache, aches, pains, cough, and runny nose). Without laboratory tests, doctors cannot distinguish between viruses, as they last for days and rarely lead to serious illness. At best, vaccines are only effective against influenza A and B, which represent about 5% of all circulating viruses. Inactivated vaccine is prepared by treating influenza viruses with a specific chemical agent that 'kills' the virus. Final preparations may contain either the complete viruses (whole-virion vaccine) or the active part of them (split or subunit vaccines). These vaccines are typically administered by injection through the skin. The virus strains contained in the vaccine are usually those that are expected to circulate in the following epidemic seasons (two type A and one or two B strains), which are recommended by the World Health Organization (seasonal vaccine). Pandemic vaccine contains only the virus strain that is responsible for the pandemic (e.g. the type A H1N1 for the 2009 to 2010 pandemic).

Key messages

Inactivated vaccines can reduce the proportion of elderly who have influenza and ILI. Data on deaths were sparse, and we found no data on hospitalisations due to complications. However, variation in the results of studies means we cannot be certain about how big a difference these vaccines will make across different seasons.

Main results

We found eight randomised controlled trials (over 5000 people), of which four assessed harms. The studies were conducted in community and residential care settings in Europe and the USA between 1965 and 2000.

Older adults receiving the influenza vaccine may experience less influenza over a single season, from 6% to 2.4%, meaning that 30 people would need to be vaccinated with inactivated influenza vaccines to avoid one case of influenza. Older adults also probably experience less ILI, from 6% to 3.5%, meaning that 42 people would need to be vaccinated to prevent one case of ILI. The amount of information on pneumonia and mortality was limited. Data were insufficient to be certain about the effect of vaccines on mortality. No cases of pneumonia occurred in one study that reported this outcome, and no data on hospitalisations were reported. We do not have enough information to assess harms relating to fever and nausea in this population.

The impact of influenza vaccines in older people is modest, irrespective of setting, outcome, population, and study design.

How up to date is this review?

The evidence is current to 31 December 2016.

Summary of findings 1. Influenza vaccine compared to placebo for preventing influenza in the elderly

Influenza vaccine compared to placebo for preventing influenza in the elderly

Patient or population: people aged over 65 years
Setting: community and residential care institutions in the USA and Europe during influenza seasons between 1965 and 2000
Intervention: influenza vaccine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with influenza vaccine				
Influenza assessed with: laboratory confirmation Follow-up was conducted over an influenza season.	Study population[1] 57 per 1000	24 per 1000 (15 to 38)	RR 0.42 (0.27 to 0.66)	2217 (3 RCTs)	⊕⊕⊖⊖ LOW [2 3]	
Influenza-like illness assessed with: subjective report Follow-up was conducted over an influenza season.	Study population[1] 59 per 1000	35 per 1000 (28 to 43)	RR 0.59 (0.47 to 0.73)	6894 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
Pneumonia Follow-up was conducted over an influenza season.	No events occurred in 1 study of 699 people.		-	699 (1 RCT)	⊕⊖⊖⊖ VERY LOW [4 5]	
Hospitalisations - not reported	-	-	-	-	-	
All deaths Follow-up was conducted over an influenza season.	Study population[1] 6 per 1000	6 per 1000 (1 to 55)	RR 1.02 (0.11 to 9.72)	699 (1 RCT)	⊕⊖⊖⊖ VERY LOW [4 5]	
Fever Follow-up was conducted over an influenza season.	Study population[1] 16 per 1000	25 per 1000 (15 to 43)	RR 1.57 (0.92 to 2.71)	2519 (3 RCTs)	⊕⊕⊕⊖ MODERATE [6]	

Nausea Follow-up was conducted over an influenza season.	Study population[1]		RR 1.75 (0.74 to 4.12)	672 (1 RCT)	⊕⊕⊝⊝ LOW [6 7]
	24 per 1000	42 per 1000 (18 to 98)			

*__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; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Control group risk taken as aggregate of the study control group risks.
[2]Downgraded one level due to serious risk of bias. Most of the evidence summarised in the meta-analysis comes from studies with high or unclear risk of bias for more than one 'Risk of bias' domain.
[3]Downgraded due to indirectness. Uncertainty over the definition, testing, and surveillance of influenza in older trials.
[4]Downgraded two levels due to very serious imprecision. No events occurred in one study of nearly 700 people. The study was likely underpowered to detect effects on either pneumonia or mortality.
[5]Downgraded one level due to serious risk of bias. One study contributing data to this outcome had high risk of selection bias.
[6]Downgraded one level due to serious imprecision. Confidence intervals for nausea and fever were wide and include reduction and increase in risk of adverse events.
[7]Downgraded one level due to serious risk of bias. One study contributing data to this outcome had unclear risk of selection bias.

BACKGROUND

Description of the condition

Viral respiratory disease imposes a heavy burden on society. The majority of viral respiratory disease (influenza-like illness (ILI)) is caused by many different agents that are not clinically distinguishable from one another. A variable proportion of ILI (7% to 15% on average) is caused by influenza viruses and is known as influenza (Jefferson 2009a).

Influenza is an acute respiratory infection caused by a virus of the *Orthomyxoviridae* family. Three serotypes are known (A, B, and C). Influenza causes an acute febrile illness with muscle ache, headache, and cough. Although the median duration of the acute illness is three days, cough and malaise can persist for weeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease, and bronchiolitis in children. Additionally, influenza can cause a range of non-respiratory complications including febrile convulsions, Reye's syndrome, and myocarditis (Treanor 2016; Wiselka 1994). Efforts to prevent or minimise the impact of seasonal influenza in the second part of the 20th century centred on the use of vaccines. Due to the yearly changes in viral antigenic configuration and the lack of carry-over protection from year to year, a new vaccination campaign needs to be organised annually, with a huge scientific and logistic effort to ensure production and delivery of the vaccines.

Description of the intervention

Currently there are three types of influenza vaccines:

1. whole-virion vaccines, which consist of complete viruses that have been 'killed' or inactivated, so that they are not infectious but retain their strain-specific antigenic properties;
2. subunit virion vaccines, which are made of surface antigens (H and N) only; and
3. split-virion vaccines, in which the viral structure is broken up by a disrupting agent.

These vaccines contain both surface and internal antigens. In addition, a variety of non-European manufacturers produce live attenuated vaccines. Traditionally, whole-virion vaccines are thought to be less well tolerated due to the presence of a lipid stratum on the surface of the viral particles (a remnant of the host cell membrane coating the virion, when budding from the host cell).

Influenza vaccines are produced worldwide. Periodic antigenic drifts and shifts pose problems for vaccine production and procurement, as a new vaccine closely matching the circulating antigenic configuration must be produced and procured for the beginning of each new influenza 'season'. To achieve this, the World Health Organization (WHO) has established a worldwide surveillance system, allowing for the identification and isolation of viral strains circulating the different parts of the globe. Sentinel practices (designated primary care points) recover viral particles from the nasopharynx of people with influenza-like symptoms, and the samples are swiftly sent to the laboratories of the national influenza centres (110 laboratories in 79 countries). When new strains are detected, the samples are sent to one of the four WHO reference centres (London, Atlanta, Tokyo, and Melbourne) for antigenic analysis. Information on the circulating strain is then sent to the WHO, which in February of each year recommends, through a committee, the strains to be included in the vaccine for the forthcoming 'season'. Individual governments may or may not follow the WHO recommendations. Surveillance and early identification thus play a central part in the composition of the vaccine.

The global influenza spread and burden can be assessed by consulting the WHO Global Influenza Surveillance and Response System (GISRS) web page, which provides an overview and country comparison options (www.who.int/influenza/resources/charts/en/).

How the intervention might work

Vaccines work by simulating an infection and stimulating the body to produce antibodies against the threat and activate other defence mechanisms.

Vaccines have been the main global weapon to minimise the impact of influenza in the elderly for the last four decades, as people aged 65 and older are at higher risk of complications, hospitalisations, and death from influenza. According to the Centers for Disease Control and Prevention, the primary goal of influenza vaccination in the elderly is to reduce the risk of complications among people who are most vulnerable (ACIP 2005; CDC 2004). Vaccines containing yearly WHO recommended influenza strains are used worldwide (Grohskopf 2016; Treanor 2016; WHO 2016).

The European Medicines Agency (EMA) recently made changes to the registration of seasonal, pre-pandemic, and pandemic influenza vaccines (EMA 2014; Wijnans 2016). Changes were introduced in 2014, triggered by the realisation that antibody responses are not sufficient predictors of field protection, as our reviews have consistently shown over the years. Most of the data for influenza vaccines included in our reviews are from registered vaccines, and yet the field protection afforded is modest or negligible. In addition, the methods of standardisation of antibody titres were lacking. The new rules for adults and elderly require demonstration of non-inferiority of antibody response (immunogenicity) by a candidate seasonal influenza vaccine compared to an established one. In addition, whenever a demonstration of clinical efficacy is necessary, EMA encourages minimal use of placebo and encourages the use of active controls (such as non-influenza vaccines) with ILI (and relevant polymerase chain reaction (PCR) results) as a primary endpoint. Clinical effectiveness should be tested by carrying out (preferably prospective) cohort studies or nested so-called test negative case-control studies following the European Centre for Disease Prevention and Control protocol (ECDC 2009a; ECDC 2009b).

Harms surveillance is now required with a follow-up of at least 6 months' duration and in the general elderly population a database of at least 3000 people exposed to the vaccine. Enhanced vaccine vigilance data should be collected as soon as possible at the beginning of the vaccination campaign each year.

Why it is important to do this review

Due to the unique production cycle of influenza vaccines (they are tested using surrogate outcomes - antibody stimulation - ahead of each influenza 'season'), past performance is probably the only reliable way to predict future performance.

An accurate assessment of the effects (efficacy, effectiveness, and safety profile) of influenza vaccines is essential to allow for rational choice between alternative strategies. This review, with its two companion reviews (Demicheli 2014; Jefferson 2012), are long-running reviews. They are among the most consistently accessed in the whole *Cochrane Database of Systematic Reviews*, confirming the importance of the topic and interest in it. Periodic updates, some stretching back almost two decades, have allowed us to include an increasing number of studies on the effects of influenza vaccines and monitor their impact on our reviews (Table 1).

The reviews are not methodologically homogeneous, as their methods reflect the history and development of Cochrane Reviews. In particular, the inclusion of observational studies, which was initially favoured for the assessment of harms, has been a source of discussion. In the elderly, randomised evidence represents 11% of included studies because no eligible trials have been completed in the past three decades, while numerous observational studies are completed each year.

Historically, observational studies have been of poor methodological quality, often reporting conflicting or paradoxical results, preventing the drawing of firm conclusions. However, inclusion of particular study types and increasing size of the data sets has not led to a change in the conclusion of the reviews, while leading to a greatly increased workload. This is the main reason why the authors, the review group, and the Cochrane editors have decided to stabilise all three reviews, that is to not carry out routine updates of the observational data set and to update the randomised data set if certain conditions are fulfilled in the future.

For the same reason, the observational content of this review and its companions have been retained as historical evidence of the life cycle of the reviews.

We plan to update the randomised evidence in this review if any or all of the following conditions are fulfilled in the future:

- a trial assessing the clinical effects of the evolution of current technologies becomes available;
- a new type of vaccine is developed; or
- a new credible causal paradigm for influenza is put forward.

For an overview of the three reviews, see the covering editorial at https://community.cochrane.org/news/why-have-three-long-running-cochrane-reviews-influenza-vaccines-been-stabilised.

OBJECTIVES

To assess the effects (efficacy, effectiveness, and harm) of vaccines against influenza in the elderly.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) or quasi-RCTs. We have not sought new cohort and case-control studies for the update of this review, but we have retained the data from previous versions for historical reasons. For study design definitions, see Appendix 1.

Types of participants

Elderly participants aged 65 years or older, irrespective of setting. We excluded studies assessing efficacy in selected groups affected by a specific chronic pathology (i.e. diabetes or cardiac disease), as we were interested in the whole population. The question of whether these vaccines are effective in specific at-risk populations is the topic of other reviews.

Types of interventions

1. Vaccination with any influenza vaccine given independently, in any dose, preparation, or time schedule, compared with placebo or with no intervention.
2. We also considered new, as yet unlicensed vaccine types (e.g. live attenuated and DNA vaccines).
3. Vaccination of staff in order to protect patients and residents admitted into hospitals, nursing homes, and long-term care facilities has been assessed by a separate review (Thomas 2010).
4. We excluded studies in which a vaccine was administered after the beginning of the epidemic period.
5. We excluded old oil adjuvant vaccine or vaccines with a content greater than 15 µg of haemagglutinin/strain/dose from the safety assessment.

Types of outcome measures

Primary outcomes

For treatment efficacy and effectiveness

We included outcomes occurring within the epidemic period (the six-month winter period, if not better specified). When trial authors presented data according to different levels of viral circulation, we only included data restricted to higher viral circulation.

1. Cases of influenza, laboratory-confirmed (by means of viral isolation, serological supporting evidence), or both.
2. Cases of influenza, clinically defined from a list of likely respiratory and systemic signs and symptoms. We accepted the trial authors' definition of clinical illness because some countries have their own official definition.
3. Cases of influenza (as defined above) admitted to hospital.
4. Deaths (total).
5. Deaths due to influenza (as defined above) or to its complications.
6. Other direct or indirect indicator of disease impact: pneumonia; hospitalisation due to any respiratory disease, and hospitalisation due to heart disease.

We excluded studies with generic outcomes (e.g. deaths from all causes) and long-term (one-year) follow-up, as most illnesses were most likely due to causes other than influenza. We excluded studies reporting only serological outcomes.

Secondary outcomes

For adverse events

1. Local events for aerosol vaccines (upper respiratory tract infection symptoms such as cough, coryza, sore throat, and hoarseness) within seven days of vaccination.

2. Local events for parenteral vaccines (tenderness/soreness, erythema, induration, and arm stiffness) within seven days from vaccination.
3. Systemic events (myalgia, fever, headache, fatigue, indisposition, rash, angioedema, and asthma) within seven days from vaccination.
4. Rare events (thrombocytopenia, neurological disorders, and Guillain-Barré syndrome.

Search methods for identification of studies

Electronic searches

For this 2016 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 11, searched 31 December 2016 via the Cochrane Library), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (Ovid) (1966 to 31 December 2016); Embase (Elsevier) (1974 to 31 December 2016); Web of Science (Thomson Reuters) (1974 to 31 December 2016); Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) (1981 to 31 December 2016); Latin American and Caribbean Health Sciences Information Database (LILACS) (Bireme) (1982 to 31 December 2016); World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en, 1 July 2017); and ClinicalTrials.gov (www.clinicaltrials.gov, 1 July 2017).

The MEDLINE search (Appendix 2) was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008) revision; Ovid format (Lefebvre 2011), and these search terms were adapted to search Embase (Appendix 3), Web of Science (Appendix 4), CINAHL (Appendix 5), LILACS (Appendix 6), WHO ICTRP (Appendix 7), and ClinicalTrials.gov (Appendix 7).

There were no language or publication restrictions.

Searching other resources

The 2016 update included searches of the databases just listed to identify trials only. For details of other resources searched for previous versions of the review, see Appendix 8.

Data collection and analysis

Selection of studies

Two review authors (TOJ, EF) independently applied inclusion criteria to all identified and retrieved articles.

Data extraction and management

Two review authors (EF and LAA) independently performed data extraction using a data extraction form (Appendix 9). Two review authors (TOJ, CDP) checked data and entered the data into Review Manager 5 (RevMan 2014).

We extracted data on the following.

1. Methodological quality of studies
2. Study design (Appendix 1)
3. Description of setting
4. Characteristics of participants
5. Description of vaccines (content and antigenic match)
6. Description of viral circulation degree
7. Description of outcomes
8. Length of follow-up
9. Publication status
10. Date of study
11. Location of study

Assessment of risk of bias in included studies

Experimental studies

All review authors independently assessed the methodological quality of the included studies using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and results were introduced into the sensitivity analysis.

We classified studies according to the following criteria.

Randomisation

A = individual participants allocated to vaccine or control group.
B = groups of participants allocated to vaccine or control group.

Generation of the allocation sequence

A = adequate, e.g. table of random numbers or computer-generated random numbers.
B = inadequate, e.g. alternation, date of birth, day of the week, or case record number.
C = not described.

Allocation concealment

A = adequate, e.g. numbered or coded identical containers administered sequentially, on-site computer system that can only be accessed after entering the characteristics of an enrolled participant, or serially numbered, opaque, sealed envelopes.
B = possibly adequate, e.g. sealed envelopes that are not sequentially numbered or opaque.
C = inadequate, e.g. open table of random numbers.
D = not described.

Blinding

A = adequate double-blinding, e.g. placebo vaccine.
B = single-blind, e.g. blinded outcome assessment.
C = no blinding.

Follow-up

Average duration of follow-up and number of losses to follow-up.

Non-experimental studies

In previous versions of this review we carried out quality assessment of non-RCTs in relation to the presence of potential confounders that could make interpretation of the results difficult. We evaluated the quality of case-control and cohort studies (prospective and retrospective) using the appropriate Newcastle-Ottawa Scales (NOS) (Appendix 10). Due to the lack of empirical evidence on the impact that the methodological quality has on the results of non-RCTs, this evaluation was only used at the analysis stage as a mean of interpretation of the results, and a set of sensitivity analyses was performed for this scope. We classified studies as at low risk of bias (up to one inadequate item in the NOS), medium risk of bias (up to three inadequate items), high risk of bias (more than three inadequate items), and very high risk of bias (when there was no description of methods).

In case of disagreement between the review authors, TOJ arbitrated.

Measures of treatment effect

We summarised efficacy (against influenza) and effectiveness (against influenza-like illness) estimates as risk ratio (RR) (using a 95% confidence interval (CI)) or odds ratio (OR) (using a 95% CI). Absolute vaccine efficacy (VE) is expressed as a proportion, using the formula VE = 1 - RR or VE = 1 - OR whenever significant. When not significant, we reported the relevant RR or OR.

We have calculated the number needed to vaccinate (NNV) as the reciprocal of the risk difference. Rather than use the pooled risk difference, we have multiplied an illustrative control group risk by the RR to generate a difference in risk.

Unit of analysis issues

We identified no studies with a cluster design, and no studies contributed more than one treatment comparison to the analyses.

Dealing with missing data

In earlier versions of the review, we considered contacting the first or corresponding author of the study to request missing data whenever we identified non-reporting or partial reporting of data. This proved to be a major task with few returns. It was not carried out for this update as we are stabilising this review, that is we will update the randomised data set if certain conditions are fulfilled in the future.

Assessment of heterogeneity

We calculated the I^2 statistic for every pooled estimate to assess the effect on statistical heterogeneity. The I^2 statistic can be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than sampling error, and it is intrinsically independent of the number of studies. When the I^2 statistic is less than 30%, there is little concern about statistical heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

Prior to the 2010 update, we carried out a complete re-extraction of all studies and reassessed their methodological quality. We also assessed concordance between data presented and conclusions and direction of conclusions (in favour or not of the performance of influenza vaccines). We also looked at the relationship between these variables and study funding and journal of publication (see 'Potential biases in the review process' in the Discussion and Jefferson 2009b).

Data synthesis

Aggregation of data was dependent on the sensitivity and homogeneity of definitions of exposure, populations, and outcomes used. Where we found studies to be homogenous, we carried out a meta-analysis of these studies within each design category. We pooled whole, split, and subunit vaccines, as in community studies this information was not reported. When a study reported data for more than one influenza season or for more than one setting, we considered these separately, creating separate data sets. Within the data sets, we used the term 'observation' to describe an occurrence (i.e. a particular outcome such as fever) and not number of participants, as multiple outcomes were sometimes recorded for the same participant. We used random-effects models throughout to take account of the between-study variance in our findings (DerSimonian 1986).

We analysed non-RCT separately from RCT evidence.

We grouped reports first according to the setting of the study (community or long-term care facilities) and then by level of viral circulation and vaccine matching (when trial authors presented data according to different levels of viral circulation, we included only data relating to higher viral circulation). We considered a period 'epidemic' when the weekly incidence rate exceeded the seasonal threshold. A vaccine was defined as 'matching' when the vaccine strains were antigenically similar to the wild circulating strains. We further stratified by co-administration of pneumococcal polysaccharide vaccine (PPV) and by different types of influenza vaccines (live, inactivated, with adjuvant).

Wherever possible, we performed a quantitative analysis adjusted for confounders if the cohort or case-control studies used the same methods of adjustment (logistic regression) for the same confounders (sex, age, smoking, and comorbidities). We constructed a comparison with effect sizes adjusted for the effects of possible known confounders and their standard error, which we derived from the reported confidence intervals (Greenland 1987), and performed quantitative analysis with the inverse of the variance (Higgins 2011).

We included the findings of one case-control study reporting data stratified by risk factors for influenza by use of the inverse variance combining stratum-specific effect size and overall effect size (Mullooly 1994).

Subgroup analysis and investigation of heterogeneity

We did a further analysis to investigate the causes of heterogeneity. To assess the effect of viral circulation and vaccine matching on overall heterogeneity, we calculated heterogeneity within each grouping and compared its sum with the overall heterogeneity (Greenland 1987).

Sensitivity analysis

We performed a subanalysis of studies describing a better defined epidemic period for most significant comparisons. We then tested effect size from cohort studies conducted in long-term care facilities (where data are more plentiful), stratified by methodological quality of the studies.

Summary of findings and assessment of the certainty of the evidence

We created a Summary of findings 1 using the following outcomes: influenza, ILI, pneumonia, hospitalisation, all deaths, fever, and nausea. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid readers' understanding of the review where necessary. We have restricted

our focus in the 'Summary of findings' table to evidence from randomised studies comparing influenza vaccine with placebo, which was the most commonly adopted strategy.

RESULTS

Description of studies

Results of the search

In the first publication of this review (Rivetti 2006), we identified 4400 titles of reports of potentially relevant studies and screened these for retrieval. We excluded 4088 reports by screening titles and abstracts and retrieved 312 reports for detailed assessment; 241 reports did not fulfil our inclusion criteria.

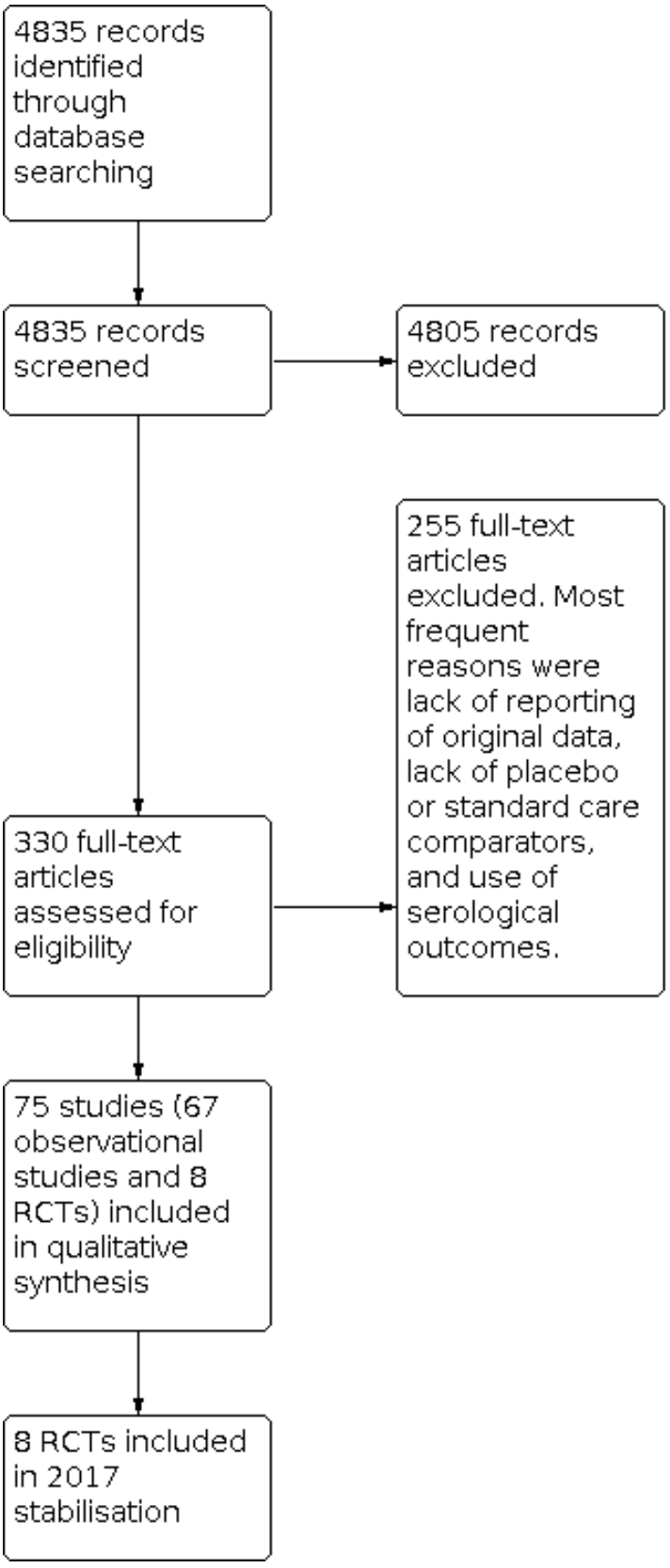
In the 2010 review update (Rivetti 2010), we identified 1435 reports of potentially relevant studies. We retrieved 18 studies for further evaluation; we included four and excluded 14 for various reasons. We identified two case-control studies, Jordan 2007 and Puig-Barbera 2007, and two cohort studies, Hara 2006 and Leung 2007, fulfilling the inclusion criteria.

For this 2016 update we did not identify new randomised evidence.

Included studies

We included 75 studies in previous versions of the review: 68 studies were used to assess efficacy/effectiveness, and 8 were included in the safety assessment (one RCT was included in both assessments). See Figure 1 for study flow.

Figure 1. Study flow. We identified no new randomised controlled trials for the 2016 update and stabilisation.



The 65 studies included in the efficacy/effectiveness assessment were split into subsets by influenza season or setting or vaccine type, resulting in 100 data sets.

We identified eight published RCTs published over four decades involving just over 5000 participants (Allsup 2004; Edmondson 1971; Govaert 1993; Govaert 1994a; Keitel 1996; Margolis 1990a; Rudenko 2001; Stuart 1969; Treanor 1994). Four of these RCTs only reported safety outcomes (Govaert 1993; Keitel 1996; Margolis 1990a; Treanor 1994).

Fifty-one cohort studies resulted in 80 data sets (Arden 1988; Arroyo 1984; Aymard 1979a; Aymard 1979b; Caminiti 1994; Cartter 1990a; Cartter 1990b; Cartter 1990c; Christenson 2001a; Christenson 2001b; Christenson 2004a; Christenson 2004b; Coles 1992; Comeri 1995; Consonni 2004a; Consonni 2004b; Cuneo Crovari 1980; Currier 1988; D'Alessio 1969; Davis 2001a; Davis 2001b; Deguchi 2001; Feery 1976; Fleming 1995; Fyson 1983a; Fyson 1983b; Gavira Iglesias 1987; Gené Badia 1991; Goodman 1982; Gross 1988; Hak 2002a; Hak 2002b; Hara 2006; Horman 1986; Howarth 1987a; Howarth 1987b; Howells 1975a; Howells 1975b; Howells 1975c; Isaacs 1997; Kawai 2003; Leung 2007; Lopez Hernandez 1994; Mangtani 2004b; Mangtani 2004c; Mangtani 2004d; Mangtani 2004e; Mangtani 2004f; Mangtani 2004g; Mangtani 2004h; Mangtani 2004i; Mangtani 2004j; Meiklejohn 1987; Monto 2001; Morens 1995; Mukerjee 1994; Murayama 1999; Nichol 1994a; Nichol 1994b; Nichol 1994c; Nichol 1998a; Nichol 1998b; Nichol 2003a; Nichol 2003b; Nicholson 1999; Nordin 2001a; Nordin 2001b; Patriarca 1985a; Patriarca 1985b; Pregliasco 2002; Ruben 1974; Saah 1986a; Saah 1986b; Saah 1986c; Saito 2002a; Saito 2002b; Shapiro 2003; Strassburg 1986; Taylor 1992; Voordouw 2003).

Twelve case-control studies resulted in 14 data sets (Ahmed 1995; Ahmed 1997; Crocetti 2001; Fedson 1993a; Fedson 1993b; Foster 1992; Jordan 2007; Mullooly 1994; Ohmit 1995a; Ohmit 1995b; Ohmit 1999; Puig-Barberà 1997; Puig-Barberà 2004; Puig-Barbera 2007).

Roughly half (n = 52) the data sets reported A/H3N2 virus circulating; 4% (n = 4) B viruses, 1% (n = 1) A/H1N1, 1% (n = 1) A/H2N2, and 7% (n = 7) reported A/H3N2 and A/H1N1 circulating at the same time. The remaining 37% (n = 35) of the data sets provided insufficient information on circulating subtypes.

Twenty-four studies resulting in 39 data sets collected information about the health conditions of vaccinated and unvaccinated people and reported stratified results or adjusted rates. Participants suffering from lung disease, heart disease, renal disease, diabetes and other endocrine disorders, immunodeficiency or immunosuppressive diseases, cancer, dementia or stroke, vasculitis, and rheumatic disease were considered as belonging to risk groups.

The included studies used the recommended and licenced vaccine formulation, even if some authors did not declare vaccine composition.

In the RCTs, the comparison was placebo. All cohort studies compared the effects of vaccination against no vaccination.

In our safety assessment, we included four RCTs (Govaert 1993; Keitel 1996; Margolis 1990a; Treanor 1994), and we commented on three surveillance studies with a non-comparative design assessing rare events (Guillain-Barré syndrome) in the text but did not include them in our meta-analysis (Kaplan 1982; Lasky 1998; Schonberger 1979). One RCT assessed a vaccine that has not been in production for decades (Stuart 1969); its harms data were not extracted.

Excluded studies

The most frequent reasons for study exclusion were lack of presentation of original data, lack of placebo or standard care comparator, and presence of antibody titres as outcomes. A complete list with reasons for exclusion is provided in the Characteristics of excluded studies table.

Risk of bias in included studies

The results of our 'Risk of bias' assessment were as follows.

Cohort/case-control studies (from previous versions of the review)

- Low risk of bias: 18
- Medium risk of bias: 31
- High risk of bias: 11
- Very high risk of bias: 3

Surveillance studies (from previous versions of the review)

For three surveillance studies assessing rare harms, we did not perform quality evaluation. All studies were population based with good case findings and case definitions.

Allocation

Experimental studies

- Allocation concealment: adequate 3
- Allocation concealment: unclear 1
- Allocation concealment: inadequate 0
- Allocation concealment: not described 5

Blinding

See 'Potential biases in the review process' in the Discussion.

Incomplete outcome data

The vast majority of evidence for our review stems from non-RCTs. In most of the trials, the quality of the text was such that we could not assess the impact of any incomplete outcome data (Jefferson 2009b).

Selective reporting

Selective reporting including major inconsistencies between different parts of the text was a common feature. See 'Potential biases in the review process' in the Discussion.

Other potential sources of bias

See 'Potential biases in the review process' in the Discussion.

Effects of interventions

See: **Summary of findings 1** Influenza vaccine compared to placebo for preventing influenza in the elderly

Randomised controlled trials

Given the heterogeneous nature of the vaccines tested (monovalent, trivalent, live, or inactivated aerosol vaccines), setting, follow-up, and outcome definition, we could draw no firm conclusions from this body of evidence. Only three trials specified follow-up (Govaert 1994a; Rudenko 2001; Stuart 1969), which ranged from 42 to 180 days.

We have presented the findings of the most important outcomes in Summary of findings 1.

Influenza vaccines may reduce the risk of influenza from 6% in unvaccinated people to 2.4% following vaccination (vaccine efficacy (VE) 58%, risk ratio (RR) 0.42, 95% confidence interval (CI) 0.27 to 0.66; low-certainty evidence) (Summary of findings 1). These results gave a number needed to vaccinate (NNV) of 30 (Analysis 1.1).

Based on a meta-analysis of four trials of inactivated vaccines (Allsup 2004; Edmondson 1971; Govaert 1994a; Stuart 1969), vaccines probably reduce the risk of ILI from 6% in unvaccinated people to 3.5% following vaccination (VE 41%, RR 0.59 95% CI 0.47 to 0.73; moderate-certainty evidence). These results gave a NNV of 42 (Analysis 1.2).

There was very limited information available regarding the effects of vaccines on risk of hospitalisation, pneumonia, and death. No study reported hospitalisations. One study of 699 participants reported no cases of pneumonia (very low-certainty evidence), and that 4 deaths occurred at comparable rates between the groups (RR 1.02, 95% CI 0.11 to 9.72; very low-certainty evidence).

Although small increases in fever (from 1.6% to 2.5%; RR 1.57, 95% CI 0.92 to 2.71; moderate-certainty evidence) and nausea (from 2.4% to 4.2%; RR 1.75, 95% CI 0.74 to 4.12; low-certainty evidence) occurred following influenza vaccination, CIs for these results are wide, and we downgraded the certainty of evidence in both cases for imprecision (Summary of findings 1).

Increased risks of general malaise, upper respiratory tract symptoms, and headache following vaccination ranged between 1.1 and 1.57, although the CIs are wide for all of these outcomes (see Analysis 2.1; Analysis 2.3; Analysis 2.4). Following vaccination there were increased risks of sore arm (RR 3.56, 95% CI 2.61 to 4.87) (Analysis 2.6) and swelling (RR 8.23, 95% CI 3.98 to 17.05) (Analysis 2.7) compared with placebo.

Three studies assessed the effects of inactivated aerosol vaccine (Edmondson 1971; Rudenko 2001; Treanor 1994). There was no evidence of lower risk of influenza or ILI following vaccination compared with placebo with vaccine matching in the presence of an outbreak (Analysis 3.1; Analysis 3.2), or with vaccine matching outside of an outbreak (influenza: Analysis 4.1). Effect sizes for harms (namely malaise, fever, upper and lower respiratory tract symptoms) were all higher with vaccines, but the size of the study contributing data to these outcomes was small, and the confidence interval includes there being no increase in these events with the vaccines (see Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4).

Cohort studies in long-term care facilities (from previous versions of the review)

Thirty cohort studies in long-term care facilities contributed data to 41 data sets and over 34,000 observations (Arden 1988; Arroyo 1984; Aymard 1979a; Aymard 1979b; Cartter 1990a; Cartter 1990b; Cartter 1990c; Coles 1992; Cuneo Crovari 1980; Currier 1988; Deguchi 2001; Feery 1976; Fyson 1983a; Fyson 1983b; Goodman 1982; Gross 1988; Horman 1986; Howarth 1987a; Howarth 1987b; Howells 1975a; Howells 1975b; Howells 1975c; Isaacs 1997; Leung 2007; Meiklejohn 1987; Monto 2001; Morens 1995; Mukerjee 1994; Murayama 1999; Patriarca 1985a; Patriarca 1985b; Ruben 1974; Saah 1986a; Saah 1986b; Saah 1986c; Saito 2002a; Saito 2002b; Strassburg 1986; Taylor 1992). These studies were very focused and were fairly well resourced: 35 data sets reported virologic surveillance that confirmed influenza virus circulation, and 22 data sets had short follow-up (less than three months). The studies assessed the effects of vaccines in residential communities. The resident population is described in about half of the included data sets as predominantly aged older than 75 years, with multiple chronic pathologies and a high dependency level. However, breakdown of potential confounding factors (such as age, sex, smoking status, and underlying chronic disease) is rarely reported by vaccine exposure, making correction of confounders impossible.

Studies recorded during outbreaks or periods of high viral circulation (from previous versions of the review)

Of the 41 data sets, 30 data sets with a total of 9879 observations were recorded during outbreaks or periods of high viral circulation (Arden 1988; Arroyo 1984; Aymard 1979a; Aymard 1979b; Cartter 1990a; Cartter 1990b; Cartter 1990c; Coles 1992; Cuneo Crovari 1980; Currier 1988; Feery 1976; Fyson 1983a; Fyson 1983b; Goodman 1982; Gross 1988; Horman 1986; Isaacs 1997; Leung 2007; Meiklejohn 1987; Monto 2001; Morens 1995; Mukerjee 1994; Murayama 1999; Patriarca 1985a; Ruben 1974; Saah 1986a; Saah 1986b; Strassburg 1986; Taylor 1992). The influenza virus subtype is positively identified in 28 data sets (A/H3N2 in 25 data sets). The focus of 22 data sets from 19 studies was on assessment of the effect of vaccination on single epidemic sources (Arden 1988; Arroyo 1984; Cartter 1990a; Cartter 1990b; Cartter 1990c; Coles 1992; Cuneo Crovari 1980; Currier 1988; Feery 1976; Fyson 1983a; Fyson 1983b; Goodman 1982; Horman 1986; Isaacs 1997; Meiklejohn 1987; Morens 1995; Murayama 1999; Ruben 1974; Saah 1986a; Saah 1986b; Strassburg 1986; Taylor 1992). Viral circulation was confirmed by isolates, increases in antibody titres, or observation of an epidemic of ILI in an institution at the same time as influenza A or B circulation in the surrounding community. A high proportion of cases classified as ILI were probably influenza cases. Twenty-two data sets from 18 studies provided information about vaccine content match with circulating influenza viruses (Arden 1988; Aymard 1979a; Cartter 1990a; Cartter 1990b; Cartter 1990c; Feery 1976; Fyson 1983a; Fyson 1983b; Goodman 1982; Gross 1988; Hara 2006; Horman 1986; Isaacs 1997; Meiklejohn 1987; Monto 2001; Morens 1995; Mukerjee 1994; Murayama 1999; Patriarca 1985a; Saah 1986b; Strassburg 1986; Taylor 1992). We thus grouped our analyses by viral circulation and vaccine match.

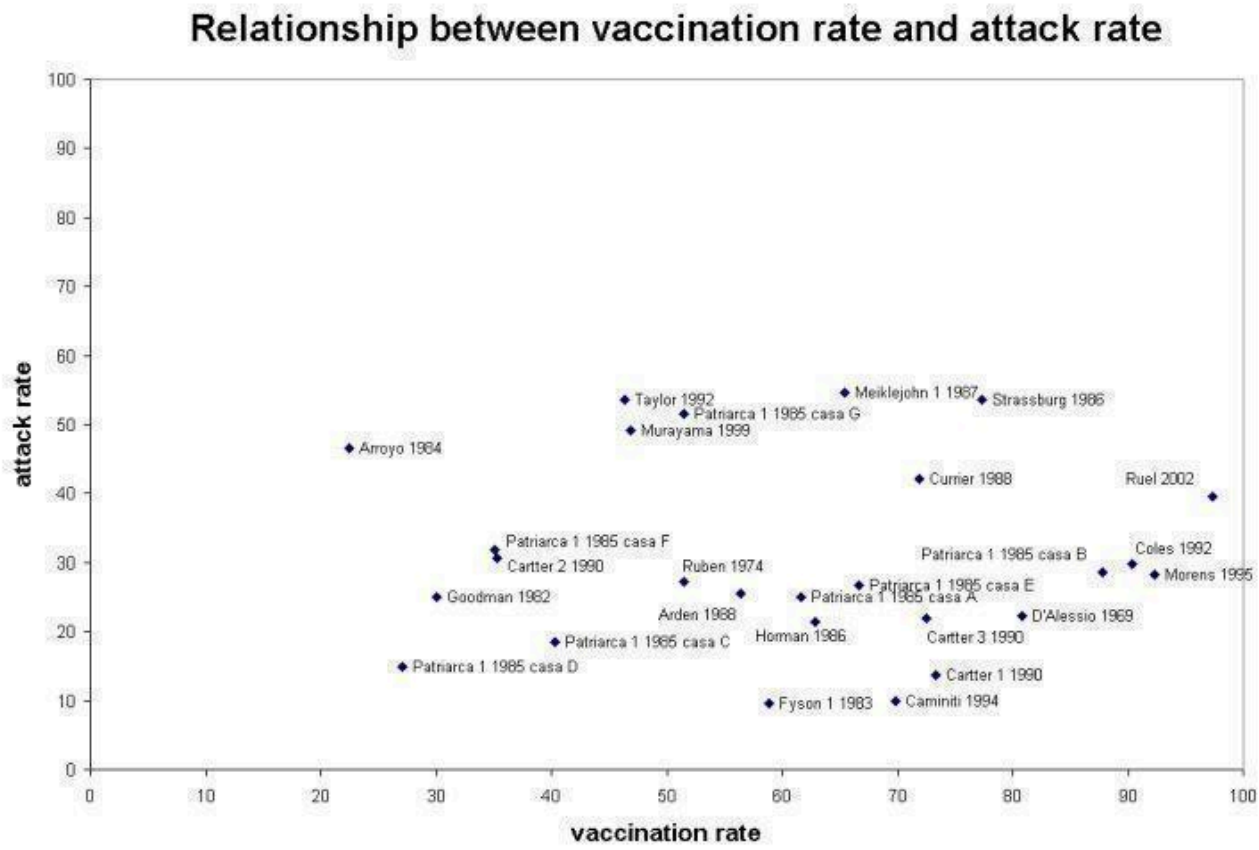
Efficacy of the vaccines against influenza was tested in only six data sets (1250 observations) (Cuneo Crovari 1980; Feery 1976; Gross 1988; Morens 1995; Ruben 1974; Taylor 1992), and was not significant both for vaccine matching (RR 1.04, 95% CI 0.43 to 2.51;

Analysis 6.1.1) and when matching was absent or unknown (RR 0.47, 95% CI 0.22 to 1.04; Analysis 6.1.2).

Twenty-two data sets assessed the effectiveness of influenza vaccines in preventing ILI (Analysis 6.1; Analysis 6.2). In these data sets, follow-up was restricted to an outbreak period, and the authors reported a virologic surveillance that confirmed influenza virus circulation.

The overall effectiveness of vaccines (VE) against ILI was 23% (6% to 36%; RR 0.77, 95% CI 0.64 to 0.94; Analysis 6.2.1) when vaccine matching was good and not significantly different from no vaccination (RR 0.80, 95% CI 0.60 to 1.05; Analysis 6.2.2) when matching was poor or unknown. Heterogeneity was high, even within the same influenza season and within the same institution when data from different accommodation blocks were analysed. We noted no association (correlation coefficient 0.09) between vaccine coverage and attack rate of ILI (Figure 2).

Figure 2. Relationship between vaccination rate and attack rate



The effectiveness of the vaccines in preventing pneumonia was assessed in 13 data sets (Analysis 6.3.1 and Analysis 6.3.2; 8446 observations). All of them reported virologic surveillance, and eight had follow-ups shorter than three months (Arroyo 1984; Coles 1992; Currier 1988; Horman 1986; Meiklejohn 1987; Morens 1995; Patriarca 1985a; Taylor 1992). Well-matched vaccines were 46% (30% to 58%; Analysis 6.3.1) effective in preventing pneumonia (Gross 1988; Horman 1986; Meiklejohn 1987; Monto 2001; Morens 1995; Patriarca 1985a; Saah 1986b; Taylor 1992). When matching was poor or unknown (Arroyo 1984; Coles 1992; Currier 1988; Leung 2007; Saah 1986a), vaccines had no effect (RR 0.68, 95% CI 0.39 to 1.21; Analysis 6.3.2). Excluding studies with the longest follow-up, that is six months, did not affect our conclusions (Gross 1988; Saah 1986a; Saah 1986b).

Eight data sets assessed the effectiveness of well-matched vaccines in preventing hospitalisation for influenza or pneumonia (Arden 1988; Cartter 1990a; Cartter 1990b; Cartter 1990c; Meiklejohn 1987; Murayama 1999; Patriarca 1985a; Taylor 1992). All of them had a brief and well-defined follow-up; effectiveness was 45% (16% to 64%; Analysis 6.4.1). Two studies reported a non-significant effect when the vaccine did not match the circulating strain or was not reported (Analysis 6.4.2) (Coles 1992; Leung 2007).

Vaccination had a significant effect on the prevention of deaths due to influenza or pneumonia, though this was in the presence of considerable heterogeneity between the 20 data sets (Analysis 6.5.1 and Analysis 6.5.2) (Arroyo 1984; Cartter 1990a; Cartter 1990b; Cartter 1990c; Coles 1992; Feery 1976; Fyson 1983a; Fyson 1983b; Goodman 1982; Horman 1986; Meiklejohn 1987; Monto 2001; Morens 1995; Murayama 1999; Patriarca 1985a; Ruben 1974; Saah 1986a; Saah 1986b; Strassburg 1986; Taylor 1992). Eighteen studies reported virologic surveillance to confirm influenza virus circulation; of these, 16 had a follow-up shorter than three months, and two had a four-month follow-up (Feery 1976; Monto 2001).

Two studies lacked virologic surveillance and had a follow-up of six months (Saah 1986a; Saah 1986b).

The vaccine was effective if it was a good match (VE 42%; 17% to 59%; Analysis 6.5.1), otherwise it was not effective (RR 0.34, 95% CI 0.11 to 1.02; Analysis 6.5.2).

Excluding two studies with a six-month follow-up and absence of viral surveillance affects the summary estimate more than the efficacy in the 'epidemic-matching' group, which drops from 42% to 39% (95% CI 12 to 58) (Saah 1986a; Saah 1986b).

Only one small study with a six-month follow-up assessed the effectiveness in reducing all-cause mortality (Gross 1988), which was found to be significant (60%; 23% to 79%; Analysis 6.6.1).

Studies carried out during low viral circulation (from previous versions of the review)

Eleven data sets (27,283 observations) assessed the effects of influenza vaccines in 350 institutional facilities during low viral circulation (Caminiti 1994; Deguchi 2001; Howarth 1987a; Howarth 1987b; Howells 1975a; Howells 1975b; Howells 1975c; Patriarca 1985b; Saah 1986c; Saito 2002a; Saito 2002b). Apart from Patriarca 1985, in this subgroup we found studies with the longest (five to six months) and most poorly defined follow-up. Two of these studies did not report virologic surveillance (Deguchi 2001; Saah 1986c).

The vaccines were 33% effective (2% to 54%; Analysis 6.2.3) in preventing ILI (Caminiti 1994; Patriarca 1985b; Saito 2002a; Saito 2002b), but had no significant effects in preventing influenza (RR 0.23, 95% CI 0.05 to 1.03; Analysis 6.1.3). This observations is based on two data sets from a single, relatively small study (691 observations) (Howarth 1987a; Howarth 1987b). Both comparisons are from well-matched vaccines.

We identified a few data sets that assessed the effectiveness of vaccines in preventing complications. Four briefly reported data sets from two studies carried out in situations of low viral circulation and poor vaccine matching reported a combined effectiveness of 65% (32% to 82%; Analysis 6.3.4) in preventing pneumonia (Howells 1975a; Howells 1975b; Howells 1975c; Saah 1986c).

During periods of low viral circulation, vaccines did prevent hospital admission for pneumonia or influenza (VE 68%; 24% to 86%; Analysis 6.4.3). However, one of the included studies was at high risk of bias, meaning that this outcome may not be accurate (Deguchi 2001). The study was set in 301 nursing homes comprising 22,462 elderly participants during the non-epidemic 1998 to 1999 season in Japan. The same study has a large weight in the analysis of effectiveness against deaths by influenza and pneumonia (VE 71%; 43% to 85%; Analysis 6.5.3 and Analysis 6.5.4) (Caminiti 1994; Deguchi 2001; Howells 1975a; Howells 1975b; Howells 1975c; Patriarca 1985b; Saah 1986c).

Cohort studies in community-dwelling elderly (from previous versions of the review)

We included 21 studies with 40 data sets in elderly participants living in open communities (Christenson 2001a; Christenson 2001b; Christenson 2004a; Christenson 2004b; Comeri 1995; Consonni 2004a; Consonni 2004b; Davis 2001a; Davis 2001b; Davis 2001c; Fleming 1995; Gavira Iglesias 1987; Gené Badia 1991; Hak 2002a; Hak 2002b; Hara 2006; Kawai 2003; Lopez Hernandez 1994; Mangtani 2004b; Mangtani 2004c; Mangtani 2004d; Mangtani 2004e; Mangtani 2004f; Mangtani 2004g; Mangtani 2004h; Mangtani 2004i; Mangtani 2004j; Nichol 1994a; Nichol 1994b; Nichol 1994c; Nichol 1998a; Nichol 1998b; Nichol 2003a; Nichol 2003b; Nicholson 1999; Nordin 2001a; Nordin 2001b; Pregliasco 2002; Shapiro 2003; Voordouw 2003). The studies contained over 3 million observations, mainly collected using data-linkage from insurance reimbursement, hospital, or primary care databases; 13 of these studies reported data stratified or adjusted by risk factors and other potential confounders. These studies had long follow-ups: 12 data sets had a follow-up =< 3 months; 13 data sets had a follow-up ranging from 4 to 5 months; 8 data sets had a follow-up ranging from 6 to 7 months; 4 data sets had a follow-up ranging from 8 to 12 months; and 2 data sets were without a well-defined follow-up. In nine data sets, follow-up was defined by relying on virologic surveillance, and three data sets had laboratory confirmation of cases. On the basis of this large body of evidence, we divided our analysis into six separate comparisons.

Inactivated influenza vaccines in all community-dwelling elderly (from previous versions of the review)

Our second comparison relied on 1 million observations in 20 data sets from 16 studies (Christenson 2001a; Christenson 2004a; Comeri 1995; Davis 2001c; Fleming 1995; Gavira Iglesias 1987; Gené Badia 1991; Hara 2006; Kawai 2003; Lopez Hernandez 1994; Mangtani 2004a; Nichol 1994a; Nichol 1994b; Nichol 1994c; Nichol 1998b; Nichol 2003a; Nichol 2003b; Nicholson 1999; Shapiro 2003; Voordouw 2003).

In elderly individuals living in the community, inactivated influenza vaccines were not effective against ILI, influenza, or pneumonia. No comparison provided enough data for stratification by viral circulation and vaccine matching.

Eight data sets (784,643 observations) with medium to long follow-up (135 to 365 days) addressed vaccine effectiveness against hospitalisations for influenza or pneumonia (Christenson 2001a; Christenson 2004a; Nichol 1994a; Nichol 1994b; Nichol 1994c; Nichol 1998b; Nichol 2003a; Nichol 2003b). Well-matched vaccines prevented hospital admissions for these illnesses (VE 26%; 12% to 38%; Analysis 8.4.1) but not for cardiac disease (RR 0.87, 95% CI 0.67 to 1.12; Analysis 8.9). Excluding the only study with a one-year follow-up (Christenson 2004a), effectiveness in preventing hospital admissions was increased to 29% (95% CI 14 to 42).

Inactivated influenza vaccines in all community-dwelling elderly (adjusted for confounders) (from previous versions of the review)

This is another data set with seven studies contributing 19 data sets with over a million observations from several consecutive influenza seasons (Davis 2001a; Davis 2001b; Davis 2001c; Fleming 1995; Mangtani 2004b; Mangtani 2004c; Mangtani 2004d; Mangtani 2004e; Mangtani 2004f; Mangtani 2004g; Mangtani 2004h; Mangtani 2004i; Mangtani 2004j; Nichol 1998a; Nichol 2003a; Nichol 2003b; Nordin 2001a; Nordin 2001b; Voordouw 2003). Most of the studies included in this analysis used data linkage and adjusted their odds ratio (OR) calculations to allow for the effect of confounding of several variables (sex, age, smoking, comorbidities). The effects of the vaccines were all significant.

Hospitalisations for influenza or pneumonia: eight data sets (based on 949,215 observations), all but one with a follow-up lasting 135 days (OR 0.73, 95% CI 0.67 to 0.79; Analysis 9.1) (Davis 2001a; Davis 2001b; Davis 2001c; Nichol 1998a; Nichol 2003a; Nichol 2003b; Nordin 2001b). Excluding the data set with the longest follow-up (eight months), Nordin 2001a, did not change the result.

Hospitalisations for respiratory diseases: OR 0.78, 95% CI 0.72 to 0.85 (Analysis 9.2). Data sets have a follow-up of 135 days or less, so a sensitivity analysis appears to be superfluous.

Hospitalisation for cardiac disease: OR 0.76, 95% CI 0.70 to 0.82 (Analysis 9.3). Data sets have a follow-up of 135 days or less, so a sensitivity analysis appears to be superfluous.

Mortality due to all causes: seven data sets with follow-up ranging from 75 to 240 days: OR 0.53, 95% CI 0.46 to 0.61 (Analysis 9.4) (Fleming 1995; Nichol 1998a; Nichol 2003a; Nichol 2003b; Nordin 2001a; Nordin 2001b; Voordouw 2003). Excluding data sets with a follow-up period equal to or longer than six months, Nordin 2001a and Voordouw 2003, did not change the final result.

Death from respiratory disease was not significantly affected. Seven data sets with a follow-up ranging from 75 to 210 days assessed the effect on mortality due to all causes (VE 42%; 24% to 55%; Analysis 8.8) (Fleming 1995; Gené Badia 1991; Lopez Hernandez 1994; Nichol 2003a; Nichol 2003b; Shapiro 2003; Voordouw 2003). Excluding four data sets with a follow-up equal to or longer than six months, Gené Badia 1991, Lopez Hernandez 1994, Voordouw 2003, or a non-defined follow-up (Shapiro 2003), the efficacy falls from 42% to 39% (95% CI 28 to 49).

Inactivated influenza vaccines in community-dwelling elderly at risk of influenza complications (from previous versions of the review)

In the third comparison, we assessed the effectiveness of inactivated influenza vaccines in elderly individuals living in the community and at risk of complications associated with influenza. People with any of the following underlying conditions were considered at risk of complications: lung disease, heart disease, renal disease, diabetes and other endocrine disorders, immunodeficiency or immunosuppressive diseases, cancer, dementia or stroke, vasculitis, or rheumatic disease. Seven data sets from six studies were relevant. The only significant effect was that for deaths from all causes (VE 61%; 3% to 84%; Analysis 10.6) from 68,032 observations with high heterogeneity ($I^2 = 94.1\%$) (Fleming 1995; Shapiro 2003; Voordouw 2003).

Inactivated influenza vaccines in community-dwelling elderly without risk of influenza complications (from previous versions of the review)

In this stratum, six studies with seven data sets contributed several hundred thousand observations (Fleming 1995; Hak 2002a; Hak 2002b; Mangtani 2004a; Nichol 1998a; Shapiro 2003; Voordouw 2003). However, most outcomes were only assessed by one study. The only notable results were the vaccines' effectiveness in preventing hospital admission for influenza or pneumonia (VE 50%; 37% to 60%; Analysis 11.3), although this observation was based on only one data set with 101,619 observations (Nichol 1998a), and there was a lack of effect on all-cause mortality (RR 0.65, 95% CI 0.33 to 1.29; 43,821 observations; Analysis 11.6) (Fleming 1995; Shapiro 2003; Voordouw 2003).

Inactivated influenza and polysaccharide vaccine (PPV) on community-dwelling elderly (from previous versions of the review)

Three studies assessed the impact of inactivated influenza and concomitant PPV on hospitalisations for influenza or pneumonia or respiratory diseases (VE 33%; 30% to 36%, based on 518,748 observations; Analysis 12.2) (Christenson 2001b; Christenson 2004b; Consonni 2004b), and two data sets assessed the effect on all-cause mortality (VE 56%; 54% to 59%; Analysis 12.4) (Christenson 2001b; Consonni 2004b).

The addition of PPV did not appear to improve the performance of influenza vaccines significantly.

Adjuvant influenza vaccines in all community-dwelling elderly (from previous versions of the review)

Two small studies with a combined denominator of 498 assessed the impact of vaccines containing a virosomal adjuvant in preventing ILI (VE 70%; 44% to 84%; Analysis 13.1) and hospitalisations (RR 0.17, 95% CI 0.02 to 1.28; Analysis 13.2.3) during a year of low viral circulation but with a vaccine with a good match (Consonni 2004a; Pregliasco 2002). The study by Consonni 2004a also assessed the impact on all-cause mortality and found no effect (RR 2.10, 95% CI 0.10 to 43.10; Analysis 13.3.3). This is not surprising given its population size of 129 people (too small for any significant effect to be evident).

Case-control studies (from previous versions of the review)

We included 12 studies contributing 14 data sets (Ahmed 1995; Ahmed 1997; Crocetti 2001; Fedson 1993a; Fedson 1993b; Foster 1992; Jordan 2007; Mullooly 1994; Ohmit 1995a; Ohmit 1995b; Ohmit 1999; Puig-Barberà 1997; Puig-Barberà 2004; Puig-Barbera 2007). Eight data sets from seven studies assessed the effects of inactivated influenza vaccines on community-dwelling elderly (Ahmed 1995; Ahmed 1997; Crocetti 2001; Fedson 1993a; Fedson 1993b; Jordan 2007; Puig-Barberà 1997; Puig-Barbera 2007); five looked at the co-administration of inactivated influenza with PPV on institutionalised elderly (Foster 1992; Mullooly 1994; Ohmit 1995a; Ohmit 1995b; Ohmit 1999); one study was of adjuvant influenza with PPV on community-dwelling elderly (Puig-Barberà 2004); and one was of adjuvanted influenza vaccines (MF59) alone (Puig-Barbera 2007). Only three of these studies, all of which assessed influenza and pneumococcal vaccines, had a long follow-up (six months). Since all data sets adjusted their ORs for likely confounding factors, we structured our analysis on five strata, further subdividing each analysis by viral circulation and vaccine matching whenever possible.

Inactivated influenza vaccines on community-dwelling elderly (from previous versions of the review)

Before adjustment, inactivated influenza vaccines were associated with an increased risk of admission for any respiratory disease (OR 1.08, 95% CI 0.92 to 1.26; 20,582 observations; Analysis 14.2.1) (Ahmed 1997; Fedson 1993a; Fedson 1993b), and did not prevent hospital admission for influenza and pneumonia in elderly individuals living in the community (OR 0.89, 95% CI 0.69 to 1.15; 1074 observations; Analysis 14.1) (Crocetti 2001; Puig-Barberà 1997), or affect hospitalisation for ILI (Analysis 14.2.2), Jordan 2007, or affect mortality from influenza and pneumonia, though this conclusion was based on a relatively small data set of 1092

observations (Analysis 14.3.1) (Ahmed 1995). The single study on adjuvanted vaccines showed no effect on pneumonia no better defined (Analysis 14.4.1) (Puig-Barbera 2007).

Inactivated influenza vaccines on community-dwelling elderly - adjusted analysis (from previous versions of the review)

After adjustment, however, the vaccines did reduce the risk of death from influenza and pneumonia (OR 0.74, 95% CI 0.60 to 0.92; Analysis 15.3) (Ahmed 1995; Mullooly 1994), and prevent admission for influenza and pneumonia (OR 0.59, 95% CI 0.47 to 0.74; Analysis 15.1), Crocetti 2001, Foster 1992, Mullooly 1994, Puig-Barberà 1997, Puig-Barberà 2004, and for all respiratory diseases (OR 0.71, 95% CI 0.56 to 0.90; Analysis 15.2) (Ahmed 1997; Fedson 1993a; Fedson 1993b).

Possible causes of observed heterogeneity - post hoc analysis

Of the 15 main comparisons with 61 outcome combinations, we noted in a subsequent analysis that seven comparisons with 20 outcome combinations had an I^2 statistic greater than 30% and that the heterogeneity of these studies could be explained by grouping by viral circulation and vaccine matching.

Safety

We included data on local and systemic harms. For local harms, we included tenderness, sore arm, swelling, erythema, and induration. Similar local symptoms were pooled in the analysis due to small data sets. Systemic symptoms were general malaise, fever, headache, nausea, and respiratory tract symptoms.

The only studies evaluating rare adverse events were three surveillance studies assessing Guillain-Barré syndrome with neither cohort nor case-control design (Table 2) (Kaplan 1982; Lasky 1998; Schonberger 1979). Case finding was carried out by interviewing neurologists or by searching discharge diagnoses databases. Vaccination rates in the relevant populations were estimated from specific survey or from national immunisation survey. All studies were conducted in the USA and assessed the entire population irrespective of age. Lasky 1998 and Schonberger 1979 reported outcome stratified by age, allowing data extraction for elderly people. We reported the results of these studies in Table 2. The strong and significant association between A/New Jersey/76 swine vaccine and Guillain-Barré syndrome during the 1976 to 1977 influenza season was not confirmed in subsequent seasons, when other vaccines not containing A/New Jersey/76 were used.

DISCUSSION

Summary of main results

Our findings show that according to randomised evidence, the effectiveness of trivalent inactivated influenza vaccines in elderly individuals, when considered in absolute terms, is modest irrespective of setting, outcome, population, and study design. The certainty of the evidence was low for influenza and moderate for ILI. Our estimates were consistently below those usually quoted for economic modelling or decision making. In view of the known variability of incidence and effect of influenza, we constructed a large number of comparisons and strata to minimise possible heterogeneity between studies and to aid comparability. We also performed subanalysis of studies describing better defined epidemic periods. Despite our attempts, we noted significant residual heterogeneity among studies that could be explained only in part by different study designs, methodological quality, settings, viral circulation, vaccine types and matching, age, population types, and risk factors. We think the residual heterogeneity could be the result of the unpredictable nature of the spread of influenza and ILI and the bias caused by the non-randomised nature of our evidence base. Our sensitivity analysis did not affect the final result.

Overall completeness and applicability of evidence

Whatever the causes of observed variability, we believe that the decision to vaccinate against influenza cannot be made based on the results of single studies, or reporting observations from a few seasons; rather, it should be taken on the basis of all available evidence. The conclusions drawn from studies done in individuals living in long-term care facilities differ from those drawn from studies in individuals living in the community. Studies done in residents of care homes often indicate the inevitably improvised nature of efforts to study the effect of vaccination during an epidemic. The resident population is usually more homogeneous than that in the community: older, with similar viral exposure and risk levels. Despite remaining heterogeneity and an overestimation of the effects as a result of study design, it is possible to detect a gradient of effectiveness, in which vaccines have little effect on cases of ILI. This finding suggests that control of influenza through vaccination is a possibility. However, the effectiveness of vaccines in the community is modest, irrespective of adjustment for systematic differences between vaccine recipients and non-recipients. The difficulties of achieving good coverage in those who need it most or the diluting effect on vaccines for influenza of other agents circulating in the community (causing ILI, clinically indistinguishable from influenza) might be to blame. We noted empirical proof of both these possibilities, with differential vaccine uptake among the same population (linked to age, sex, and health status) and a low effect on ILI throughout our data sets, even in periods of supposedly high influenza viral circulation, when the proportion of cases of ILI caused by influenza are highest and the possible benefits of vaccination should be greatest.

The impact of vaccines on pneumonia, mortality, and hospitalisations from the randomised evidence available is insufficient to draw conclusions. Very few studies have captured data on these outcomes, and where we have obtained data, the rate of events was too low to be able to determine the size of effect (Summary of findings 1).

Safety does not appear to be a particular problem: the public health safety profile of the vaccines is acceptable. However, relatively few studies assessed safety outcomes.

Quality of the evidence

We rated the quality of evidence to be moderate for ILI and fever, low for influenza and nausea, and very low for hospitalisations and death (Summary of findings 1). Most of the available evidence for these outcomes is from studies with unclear risk of bias across multiple domains. Fever was the only outcome where we did not consider bias to be influential due to consistency in direction and size of effect with the low risk of bias study (Govaert 1994a). The lack of detail regarding the diagnosis of influenza limits the applicability of our findings to laboratory-confirmed influenza and is a source of indirectness.

For other outcomes (e.g. nausea and fever), the method of ascertainment is less uncertain due to the expected mechanism of action of vaccines.

Imprecision arising from wide CIs or low event rates, or both, affects the evidence for adverse events, death, and pneumonia to varying degrees. The CIs for fever and nausea were wide (serious imprecision), but death and pneumonia were rare events in the studies, prompting us to downgrade two levels for very serious imprecision. The rating of very low quality for the latter two outcomes reflects the sparse nature of the data available for analysis.

The main problem with interpreting our substantial data set is caused by the relative scarcity of randomised controlled trials (RCTs). Only one trial assessed currently available vaccines and reached satisfactory completion (Govaert 1994a). The remainder of the data set consists of evidence from non-RCTs.

Our main concern was the quality of the non-RCTs, which likely affected the estimates of effect reported in our review. The findings of the included cohort studies are likely to have been affected to varying degrees by selection bias. Differential uptake of influenza vaccines is linked to several factors (anxiety over unwanted effects, disease threat perception, societal and economic conditions, education, health status) and hence to outcome. Confounding by indication (people with chronic illness or people who are perceived to be frailer than others are more likely to be vaccinated) might reduce the estimated vaccine efficacy. People with terminal illness or with socio-economic disadvantages are less likely to be vaccinated, and this fact might enhance vaccine efficacy. Both these interpretations are based on empirical evidence. For example, one cohort study had difficulty achieving high coverage in those most at need (Gené Badia 1991). Differential vaccine uptake and the resulting selection bias is the most likely explanation for the high effectiveness of influenza vaccines in preventing deaths from all causes. A good example of the potential effect of such confounders is the apparently counterintuitive effectiveness of the vaccines in elderly individuals living in the community. In this population, vaccine effectiveness shows an implausible sequence: the vaccines are apparently ineffective in the prevention of influenza, ILI, pneumonia, hospital admissions, or deaths from any respiratory disease, but are effective in the prevention of hospital admission for influenza and pneumonia and in the prevention of deaths from all causes.

Non-RCT evidence in this review is open to any alternative interpretation and consistently fails to give satisfactory answers. Since the publication of our 2006 review (Rivetti 2006), several empirical studies looking at the effect of selection bias in retrospective cohorts (variously called selection bias, confounding by indication, or healthy user effect) have been published. Some confirmed the presence and effect of confounders (Eurich 2008; Fukushima 2008; Glezen 2006; Hirota 2008; Jackson 2006a; Jackson 2006b; Jackson 2006c; Jackson 2006d; Jackson 2006e). Other studies, mainly carried out by the authors of cohort studies in question, failed to find any effect of confounding on mortality once adjustment had been carried out (Groenwold 2008; Groenwold 2009; Hak 2006; Nichol 2007). For example, proof of bias was provided by a study evaluating the risk of hospitalisation and death in vaccinated compared with unvaccinated seniors during influenza and non-influenza periods (Jackson 2006a). Consistent with other published studies, during influenza season, vaccination was associated with a 44% reduction in risk of all-cause mortality. However, in the period before the influenza season, vaccination was associated with a 61% reduction in risk of this outcome. The reduction in risk before the influenza season indicates the presence of bias due to preferential selection of vaccination by relatively healthy seniors, and the strength of that bias is sufficient to account entirely for the association found during the influenza season. In a second, nested case-control study, seniors with functional markers of frailty (such as dependence on washing) were found to be at a greatly increased risk of death and were less likely to have received influenza vaccine, indicating that these factors are important sources of bias in assessment of influenza vaccine effectiveness (Jackson 2006b).

Regardless of the results of empirical studies, the sheer implausibility of the effectiveness sequence which ends with high estimates of effect against mortality from all causes points to considerable confounding and calls into question the reliability of using such non-specific outcomes. Systematic differences between the intervention and control arms of cohort studies are likely to be the result of a baseline imbalance in health status and other known and unknown systematic differences in the two groups of participants. The rationale of the work starts from the observation that the 47% reduction in risk of all-cause mortality in elderly community dwellers observed in our review exceeds by far the estimated possible impact of influenza on winter-seasonal mortality of 5% in an average season (Glezen 2006). Until improvement of cohort study design is available, the use in non-RCTs of highly non-specific outcome indicators, such as all-cause mortality, is likely to lead to unrealistic estimates of the effects of the vaccines.

Evidence from RCTs, in which bias is reduced to a minimum, is scant and badly reported. Unfortunately, because of the global recommendations on influenza vaccination, placebo-controlled trials, which could clarify the effects of influenza vaccines in individuals, are no longer considered possible on ethical grounds.

Since publication of the first version of this review, we have noted increased reliance of the case test-negative study design to assess influenza vaccine effectiveness post hoc, that is after the influenza 'season'. The case test-negative design is described in detail elsewhere (Foppa 2013; Valenciano 2012).

The data included in a case test-negative design are sometimes harvested from an ongoing networked surveillance cohort. In this case, the case test-negative design is described as 'nested' within the cohort. The source cohort can include community and hospitalised cases and controls, allowing flexibility. In Europe, the surveillance programme has a formal structure and is known as Influenza - Monitoring Vaccine Effectiveness (I-MOVE). I-MOVE is partly funded and co-ordinated by the European Centre for Disease Prevention and Control (sites.google.com/site/epiflu/Home) (Kissling 2017).

Briefly, the study design, which is similar to a case-control design, consists of selecting influenza cases (e.g. cases of ILI who have tested positive for influenza) and controls (cases of ILI who have tested negative) and calculating the relevant odds ratio (OR). Cases and controls are subsequently stratified by vaccination status. An estimate of vaccines effectiveness (VE) is derived from the OR of influenza in vaccinated/unvaccinated participants using the standard formula VE = 1 - OR%. The practice of using the OR

estimate as an approximation of the risk ratio was first used in a 1980 study on pneumococcal vaccine (Broome 1980).

Despite their popularity, test-negative designs have limited public health significance.

The design does not test field effectiveness, but the capacity of the vaccines to generate a negative polymerase chain reaction result (what we would call laboratory efficacy). Both cases and controls are symptomatic, so any prevention is solely focused on the negativity of laboratory tests. In addition, no useful public health absolute measures of effect can be derived (such as absolute risk reduction and its reciprocal number needed to vaccinate) by such designs, as the background rates of infection and viral circulation are not part of the calculation of the estimates of effect. The mathematical method first used by Broome and colleagues is correct if three key assumptions are met:

1. the risk of non-influenza ILI is the same in vaccinated and non-vaccinated individuals (a factor called “k” by Broome and colleagues) (Broome 1980);
2. the attack rate in the vaccinated population is low; and
3. the circulating serotypes are similar to those in the selected population within the case-control studies based on test-negative design.

All assumptions are unlikely to be fulfilled at the same time, especially in multicentre/multi country surveillance cohorts with a non-random sampling frame. For example, Cowling and colleagues reported an increased risk of non-influenza respiratory virus infections associated with receipt of inactivated influenza vaccine. In addition, the OR will give falsely high VE if the attack rate in the vaccinated population is high (Cowling 2012; Orenstein 1985). Apart from these fundamental design problems, case test-negative studies are also affected by poor reporting. (See also Perencevich 2013a; Perencevich 2013b).

Potential biases in the review process

The publication of our 2006 review sparked a discussion that continues to this day (Rivetti 2006). Because we are conscious that (despite the inconclusive evidence) we could have introduced our own biases into the reviewing process, we re-extracted and reassessed all studies included in this and all other reviews of influenza vaccine studies (259 primary studies, reporting 274 data sets). We worked independently in two teams of two, extracting directly into pre-set forms with rigid criteria but using the same quality assessment scales used in the original version of the review. As well as assessing quality of study design, we assessed concordance between data presented and conclusions and direction of conclusions (in favour or not of the performance of influenza vaccines). We also looked at the relationship between these variables and study funding and journal of publication. We found that higher-quality studies were significantly more likely to show concordance between data presented and conclusions (OR 16.35, 95% CI 4.24 to 63.04) and less likely to favour effectiveness of vaccines (0.04, 0.02 to 0.09). Government-funded studies were less likely to have conclusions favouring the vaccines (0.45, 0.26 to 0.90). A higher mean journal impact factor was associated with complete or partial industry funding compared with government or private funding and no funding (differences between means 5.04). Study size was not associated with concordance, content of take-home message, funding, or study quality. Higher citation index factor was associated with partial or complete industry funding (Jefferson 2009b).

We concluded that the general quality of influenza vaccines studies is very low and that publication in prestigious journals is associated with partial or total industry funding. We could not explain this association with study quality, size or study status (registration trials using surrogate outcomes such as antibody titres were not included in the review).

Agreements and disagreements with other studies or reviews

Nichol provides a useful overview of reviews of influenza vaccines in all age groups (Nichol 2008). For the elderly, she identified our review and a review by Vu 2002. Although the point estimates appear approximately similar across the reviews, both Vu and Nichol fail to assess study quality and interpret results accordingly. We have summarised other main reviews identified below.

The review Belongia 2016 includes 56 case test-negative studies. The authors briefly list five methodological quality criteria which do not appear to have been validated. The authors do not list blinding of assessors to vaccination status, a very well-known source of bias in case-control studies. The authors report substantial variation in vaccine effectiveness, but mention none of the limitations of test-negative designs.

The review by Darvishian 2017 includes data from 4975 elderly who had been included in previous test-negative studies. The text refers to “individual participant data meta-analysis”, but the basic problems with test-negative designs are not addressed, and previous study authors were asked to extract their own study data on provided forms with no methodological quality assessment. The authors conclude that "Influenza vaccination is moderately effective against laboratory-confirmed influenza in elderly people during epidemic seasons".

The review by Osterholm 2012 included comparative studies with data from the USA and influenza diagnosed by polymerase chain reaction. The authors found variable effectiveness but a lack of evidence in the elderly.

AUTHORS' CONCLUSIONS

Implications for practice

Healthy older adults receiving the influenza vaccine may be at lower risk of influenza (from 6% to 2.4%, low-certainty evidence) and are probably at lower risk of influenza-like illness (ILI) (from 6% to 3.5%, moderate-certainty evidence) compared with those who do not receive a vaccination over the course of a single influenza season. Our uncertainty in the effect on influenza reflects a lack of information about how the diagnosis was confirmed in the studies and judgements of high or unclear risk of bias.

The findings of our review indicate that implementing vaccination programmes for elderly people may lead to reductions in influenza and ILI, but randomised studies to date have provided insufficient data on complications. Very few deaths occurred in the trials, and no data on hospitalisation were reported. No cases of pneumonia occurred in one study that reported this outcome. The sparse nature of the data overall may reflect the low risk of developing complications in the healthy population of interest and low rates

of ILI and influenza in the trials. Vaccination probably increases fever from 1.6% to 2.5% (moderate-certainty evidence) and may increase nausea from 2.4% to 4.2%, but for both of these harms the confidence interval is wide. Similar effects were observed for headache, general malaise, and upper respiratory tract symptoms. Sore arm and swelling occurred more frequently with vaccination.

Policymakers considering funding vaccine programmes and individuals contemplating vaccination should take into account the likely benefits in terms of the reductions in the risk of influenza and ILI (3.5% and 2.5%, respectively), uncertainty over complications, and possible increases in harms.

Implications for research

Investment in the development of better vaccines than are currently available should be linked to better knowledge of the causes and patterns of ILI in different communities. The additional effects of vaccinating carers in reducing transmission in nursing homes should be assessed. The effect of vaccination of high-risk groups should also be further assessed.

Until such time as the role of vaccines for preventing complications of influenza in the elderly is clarified, more comprehensive and effective strategies for the control of acute respiratory infections should be investigated. These should include several preventive interventions that take into account the multi-agent nature of ILI and its context (such as personal hygiene and adequate food, water, and sanitation).

When a new vaccination or preventive technology becomes available, an adequately powered, publicly funded, high-quality placebo-controlled trial run over several seasons should be undertaken. New insights on the role of viruses and other agents in the genesis of influenza and ILI are also needed.

ACKNOWLEDGEMENTS

The 2016 update was funded by the Cochrane Review Support Programme.

The review authors wish to acknowledge Daniela Rivetti, Melanie Rudin and Lubna Al-Ansary as previous authors.

The authors gratefully acknowledge the following people for commenting on previous drafts: Amy Zelmer, Laila Tata, Lohne Simonsen, Sree Nair Maryann Napoli, Anne Lyddiat, Wendy Keitel, Ludovic Reveiz, Mark Jones, Chris Del Mar and Geoff Spurling.

For this 2016 update, we acknowledge help and comments received from Liz Dooley, Toby Lasserson, David Honeyman, Janet Wale, Soumyadeep Bhaumik, Mark Jones, and Jenny Doust. We thank Lisa Winer for copy-editing this update.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmed 1995

Study characteristics	
Methods	Case-control study conducted in England, during the 1989 to 1990 influenza season, in the community. Data sources were: death certificates, general practitioner records. Follow-up period was 4 November 1989 to 23 February 1990. Cases died from influenza during the 1989 epidemic; controls died in the same period a year later and were matched for age, sex, and residence
Participants	1092 people 16 years or older; 412 cases and 1256 controls were identified; 315 and 777 were included in the analysis, respectively
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain
Outcomes	Certified influenza death
Notes	2 exposure definitions were used: current vaccinees and previous vaccinees (vaccinated between 1985 and 1989) the first was used; pneumococcal vaccination was very unlikely; circulating strain was A/England/308/89. The season was an epidemic one. The study controls for confounders in analysis: health status, previous vaccination. Quantitative analysis was also performed.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ahmed 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ahmed 1997

Study characteristics	
Methods	Case-control study conducted in England, during the 1989 to 1990 influenza season, in the community. Data sources were: hospital and general practitioner records. Follow-up period was 1 December 1989 to 31 January 1990. Cases were hospitalised and their discharge diagnosis or cause of death was pneumonia, influenza, emphysema, or bronchitis; community controls were matched for age and sex. Specific controls were matched for cases who died; controls died 6 to 12 months later.
Participants	445 patients admitted to hospital (303 cases were identified; 156 cases and 289 controls were included in the analysis, respectively), 16 years of age or older
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia, influenza, emphysema, or bronchitis (ICD 466, 480.9 to 482.9, 485 to 492.8)
Notes	2 exposure definitions were used: current vaccinees and previous vaccinees (vaccinated between 1985 and 1989): the first was used; pneumococcal vaccination was very unlikely; circulating strain was A/England/308/89. The season was an epidemic one. The study controls for confounders in analysis: health status, previous vaccination. Quantitative analysis was also performed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Allsup 2004

Study characteristics	
Methods	Experimental study conducted in Liverpool, UK during the 1999 to 2000 influenza season, randomised, single-blind, placebo controlled. Data sources were self administered questionnaire and medical records. Follow-up period was the entire winter season.
Participants	729 community-dwelling elderly without risk factors (552 treated and 177 controls, all included in the analysis), 65 to 74 years old
Interventions	Parenteral influenza vaccine: A/Beijing/262/95, A/Sydney/5/97, B/Beijing/184/93. All participants also received pneumococcal vaccine. Vaccine strains matched the circulating strains.
Outcomes	Clinically defined ILI (all of the following symptoms: sudden onset, fever, cough, prostration, weakness, myalgia, widespread aches), pneumonia, hospitalisation for any respiratory illness, death from all causes

Allsup 2004 *(Continued)*

Notes	Vaccine contained the WHO recommended strains. The study was supposed to run for 2 influenza seasons: 99-00 and 00-01. After the first season, the UK's Department of Health changed the coverage policy for influenza vaccine, and recruitment to the placebo arm dwindled, affecting the validity of the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number generation
Allocation concealment (selection bias)	Low risk	Opaque envelopes were sealed and serially numbered to assign participants to intervention.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as placebo controlled, but no further details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information available to reliably assess.

Arden 1988

Study characteristics

Methods	Authors investigated an outbreak in a nursing home, in Atlanta, USA, during the 1984 to 1985 influenza season; active surveillance; medical records were reviewed. Follow-up period was 26 January 1985 to 1 February 1985. Pharyngeal swab and paired sera were collected to confirm diagnosis.
Participants	55 nursing home residents (31 treated and 24 controls, all included in the analysis), mean age 85 years
Interventions	Parenteral influenza vaccine: A/Philippines/2/82, A/Chile/83, B/USSR/84. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever 38.7 °C or greater, cough, coryza, sore throat); hospitalisation from ILI; ILI severity (not extracted)
Notes	7 days after the outbreak started, all residents were given amantadine. Successive outcomes were not accounted for. The circulating strain was related to A/Philippines/2/82.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Arroyo 1984

Study characteristics

Arroyo 1984 *(Continued)*

Methods	Authors investigated an outbreak in a nursing home, in Columbia, UK, during the 1982 to 1983 influenza season; active surveillance by home staff. Follow-up period was 31 January 1983 to 25 February 1983. Pharyngeal swab and paired sera were collected to confirm diagnosis from 13 and 32 participants, respectively.
Participants	116 nursing home residents (26 treated and 90 controls, all included in the analysis) with underlying illnesses, 30 to 108 years old (mean age 71 years)
Interventions	Parenteral influenza vaccine: A/Brazil/11/78; A/Bangkok/1/79; B/Singapore/79. Vaccine strains did not match circulating strains.
Outcomes	ILI (any acute respiratory tract infection occurring during outbreak, with or without fever), pneumonia, death from respiratory disease
Notes	10 participants were given amantadine, not indicated if vaccinees or unvaccinated. The circulating strain was related to A/Philippines/2/82.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Aymard 1979a

Study characteristics

Methods	Authors investigated an outbreak in a geriatric hospital in France during the 1976 to 1977 influenza season.
Participants	100 nursing home residents (50 treated and 50 controls, all included in the analysis)
Interventions	Bivalent parenteral vaccine: A/Vic/3/75; B/HK/1/72. Vaccine strains matched circulating strains.
Outcomes	Disease and deaths without further specifications
Notes	Part of a surveillance study conducted in several communities; poor description of methods; circulating strains were mostly A/Vic/3/75 like

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Aymard 1979b

Study characteristics

Aymard 1979b *(Continued)*

Methods	Authors investigated an outbreak in a geriatric hospital in France during the 1977 to 1978 influenza season.
Participants	155 nursing home residents (85 treated and 70 controls, all included in the analysis)
Interventions	Bivalent parenteral vaccine: A/Vic/3/75; B/HK/1/73. Vaccine strains did not match circulating strains.
Outcomes	Disease and deaths without further specifications.
Notes	Part of a surveillance study conducted in several communities; poor description of methods; circulating strains were mostly A/Tex/1/77 like

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Caminiti 1994

Study characteristics

Methods	Prospective cohort study conducted in Italy during the 1990 to 1991 influenza season; medical charts, hospital records, and death certificate archives were reviewed. Follow-up period was 1 December 1990 to 30 April 1991. 110 participants were tested for serological follow-up. Throat swabs were obtained from ill residents.
Participants	242 nursing home residents (169 treated and 73 controls, all included in the analysis; 77 and 33 were tested for serological follow-up, respectively), 55 to 99 years old
Interventions	Parenteral influenza vaccine: A/Guizhou/54/89; A/Singapore/6/86; B/Yagamata/16/88. Vaccine strains matched the circulating strains.
Outcomes	Clinically defined ILI (fever + at least 2 of the following: cough, coryza, sore throat, myalgia, headache, shivering), hospitalisation for ILI, hospitalisation for all respiratory illness, deaths from respiratory illness
Notes	Circulating strain: B/Yagamata-like. Vaccinated and control groups were roughly comparable as underlying disease: vaccinated participants had more chronic respiratory diseases. The influenza season was relatively mild. Data were reported by health status.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Cartter 1990a

Study characteristics

Cartter 1990a *(Continued)*

Methods	Authors investigated an outbreak in a skilled care nursing home, in Connecticut, USA, during the 1984 to 1985 influenza season; medical records were reviewed. Follow-up period was 1 December 1984 to 15 January 1985. Paired sera specimens were obtained from some ill residents.
Participants	131 residents (96 treated and 48 controls, 96 and 35 included in the analysis respectively), 65 to 95 years old
Interventions	Parenteral influenza vaccine: A/Philippines/2/82; A/Chile/83; B/USSR/100/82. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater, cough, coryza, sore throat); hospitalisation from ILI; deaths occurring within 2 weeks of ILI with no other explanation
Notes	Amantadine was not used. There was serological evidence of A(H3N2) influenza infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cartter 1990b

Study characteristics

Methods	Authors investigated an outbreak in a skilled nursing home, in Connecticut, USA, during the 1984 to 1985 influenza season; medical records were reviewed. Follow-up period was 15 January 1985 to 15 February 1985. Throat swab and paired sera specimens were obtained from some ill residents.
Participants	85 residents (30 treated and 55 controls, all included in the analysis), 33 to 95 years old
Interventions	Parenteral influenza vaccine: A/Philippines/2/82; A/Chile/83; B/USSR/100/83. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater, cough, coryza, sore throat); hospitalisation from ILI; deaths occurring within 2 weeks of ILI with no other explanation
Notes	9 days after the outbreak started amantadine prophylaxis was given to most of the remaining well residents. Successive outcomes were not accounted for. The circulating strain was related to A/Philippines/2/82.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cartter 1990c

Study characteristics

Cartter 1990c *(Continued)*

Methods	Authors investigated an outbreak in a multiple-level care facility in Connecticut, USA, during the 1984 to 1985 influenza season; medical records were reviewed. Follow-up period was 1 February 1985 to 10 April 1985. Throat swab and paired sera specimens were obtained from some ill residents.
Participants	458 residents (332 treated and 151 controls, 332 and 126 included in the analysis respectively), 64 to 104 years old
Interventions	Parenteral influenza vaccine: A/Philippines/2/82; A/Chile/83; B/USSR/100/84. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater, cough, coryza, sore throat); hospitalisation from ILI; deaths occurring within 2 weeks of ILI with no other explanation
Notes	42 days after the outbreak started amantadine prophylaxis was given to most of the remaining well residents. Successive outcomes were not accounted for. The circulating strain was related to A/Philippines/2/82.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Christenson 2001a

Study characteristics

Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1998 to 1999 influenza season, in the community. Data sources were vaccination database and discharge diagnoses database. Follow-up period was 1 December 1998 to 31 May 1999. 23% of vaccinees received flu vaccine alone; 76% of vaccinated received flu and pneumococcal vaccine. 841 participants had only pneumococcal vaccine. Only flu vaccinated were included in analysis.
Participants	182,609 community-dwelling elderly (23,224 treated and 159,385 controls included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Harbin/7/94. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from influenza (ICD-X: J10.0, J10.1, J10.8, J11.0, J11.1, J11.8), hospitalisation from pneumonia (ICD-X: J12- J18, J69.0, A48.1); deaths from influenza and deaths from pneumonia were not available for this comparison
Notes	Vaccinated people had higher education, more underlying diseases, and smoked less. Circulating strain was A/Sydney (H3N2). The season was probably an epidemic one. 6% of the population lived in a nursing home. The study controls for age in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Christenson 2001b

Study characteristics	
Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1998 to 1999 influenza season in the community. Data sources were vaccination database and discharge diagnoses database. Follow-up period was 1 December 1998 to 31 May 1999. 23% of vaccinees received flu vaccine alone; 76% of vaccinated received flu and pneumococcal vaccine. 841 participants had only pneumococcal vaccine. All data were included in a separate analysis.
Participants	259,627 community-dwelling elderly (100,242 treated and 159,385 controls included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Harbin/7/94; pneumococcal vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from influenza (ICD-X: J10.0, J10.1, J10.8, J11.0, J11.1, J11.8), deaths from influenza, hospitalisation from pneumonia (ICD-X: J12- J18, J69.0, A48.1), deaths from pneumonia; all deaths
Notes	Vaccinated people had higher education, more underlying diseases, and smoked less. Circulating strain was A/Sydney (H3N2). The season was probably an epidemic one. 6% of the population lived in a nursing home. The study controls for age in analysis.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Christenson 2004a

Study characteristics	
Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1999 to 2000 influenza season, in the community. Data sources were vaccination database and discharge diagnoses database. Follow-up period was December 1999 to November 2000. 23% of vaccinated received flu vaccine alone; 58% of vaccinated received flu and pneumococcal vaccine. 19% of vaccinated participants received pneumococcal vaccine alone. Only flu vaccinated were included in analysis.
Participants	163,391 community-dwelling elderly (29,346 treated and 134,045 controls were included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Harbin/7/94. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from influenza (ICD-X: J10.0, J10.1, J10.8, J11.0, J11.1, J11.8), in-hospital deaths from influenza, hospitalisation from pneumonia (ICD-X: J12- J18, J69.0, A48.1), in-hospital deaths from pneumonia
Notes	Vaccinated people had higher education, more underlying diseases, and smoked less. Circulating strain was A/Sydney (H3N2). The season was probably an epidemic one. 6% of the population lived in a nursing home.

Risk of bias

Christenson 2004a *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Christenson 2004b

Study characteristics	
Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1999 to 2000 influenza season, in the community. Data sources were vaccination database and discharge diagnoses database. Follow-up period was December 1999 to May 2000. 23% of vaccinees received flu vaccine alone; 58% of vaccinated received flu and pneumococcal vaccine. 19% of vaccinated received pneumococcal vaccine alone. All data were included in a separate analysis.
Participants	258,747 community-dwelling elderly (124,702 treated and 134,045 controls were included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Harbin/7/94; pneumococcal vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from influenza (ICD-X: J10.0, J10.1, J10.8, J11.0, J11.1, J11.8), hospitalisation from pneumonia (ICD-X: J12- J18, J69.0, A48.1); in-hospital deaths from influenza and in-hospital deaths from pneumonia were not available for the 6-month period.
Notes	Vaccinated people had higher education, more underlying diseases, and smoked less. Circulating strain was A/Sydney (H3N2). The season was probably an epidemic one. 6% of the population lived in a nursing home.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Coles 1992

Study characteristics	
Methods	Authors investigated an outbreak in a skilled nursing home, in New York, USA during the 1987 to 1988 influenza season; individual charts were reviewed. Follow-up period was 26 December 1987 to 25 January 1988. Throat swab and paired sera specimens were obtained from some ill residents.
Participants	124 nursing home residents (112 treated and 12 controls, all included in the analysis), 20 to 100 years old (mean age 85 years). 105 participants had 1 or more underlying medical conditions.
Interventions	Parenteral influenza vaccine: A/Taiwan/1/86; A/Leningrad/360/86; B/Ann Arbor/1/86. Vaccine strains did not match the circulating strain.
Outcomes	Clinically defined ILI (fever 100 °F or greater, cough, coryza, sore throat, pneumonia); pneumonia; hospitalisation from ILI; flu-related deaths

Coles 1992 *(Continued)*

Notes	Vaccinated and not vaccinated participants were similar as underlying conditions. The circulating strain was Shanghai/11/87. Only 1 participant received amantadine prophylaxis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Comeri 1995

Study characteristics

Methods	Retrospective cohort study conducted in Italy during the 1991 to 1992 influenza season, in the community. Data sources were self administered questionnaire and vaccination registry. Follow-up period was 1 December 1991 to 29 February 1992. Random samples of vaccinated and control participants were extracted from vaccination and population registries.
Participants	213 community-dwelling elderly (150 treated and 63 controls; number of participants included in the analysis unknown), 65 years or older
Interventions	Parenteral influenza vaccine. Matching unknown, probably yes according to literature data.
Outcomes	Clinically defined ILI (fever, cough, sore throat, myalgia, headache, weakness)
Notes	Very poor description of methods, poor definitions, data extracted from percentages

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Consonni 2004a

Study characteristics

Methods	Prospective cohort study conducted in Italy during the 2002 to 2003 influenza season, in the community. Data sources were self administered questionnaire and phone interviews. Follow-up period went from enrolment to April 2003. Ambulatory patients were enrolled at random to undergo either adjuvant or subunit influenza vaccine plus antipneumococcal vaccine. A control group of unvaccinated patients was also enrolled. Only flu vaccinated were included in analysis.
Participants	235 ambulatory patients (166 vaccinated with adjuvant vaccine, 69 controls; all included in analysis), 65 years or older
Interventions	Adjuvant virosomal vaccine. Vaccine strains probably matched the circulating strain.
Outcomes	Clinically defined ILI (fever 38 °C or more + at least 1 systemic symptom: headache, discomfort, myalgia, chills or sweating, weakness + at least 1 respiratory symptom: cough, sore throat, nasal conges-

Consonni 2004a *(Continued)*

	tion), hospitalisation for all respiratory diseases, all deaths. Acute respiratory infection was also defined.
Notes	Vaccinated people had higher impairment. No information about flu activity; probably not epidemic year.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Consonni 2004b

Study characteristics

Methods	Prospective cohort study conducted in Italy during the 2002 to 2003 influenza season, in the community. Data sources were self administered questionnaire and phone interviews. Follow-up period went from enrolment to April 2004. Ambulatory patients were enrolled at random to undergo either adjuvant or subunit influenza vaccine plus antipneumococcal vaccine. A control group of unvaccinated patients was also enrolled. All data were included in a separate analysis.
Participants	374 ambulatory patients (166 vaccinated with adjuvant vaccine, 139 vaccinated with flu + pneumo vaccine; 69 controls; all included in analysis), 66 years or older
Interventions	Adjuvant virosomal vaccine; subunit influenza vaccine; antipneumococcal vaccine. Vaccine strains probably matched the circulating strain.
Outcomes	Clinically defined ILI (fever 38 °C or more + at least 1 systemic symptom: headache, discomfort, myalgia, chills or sweating, weakness + at least 1 respiratory symptom: cough, sore throat, nasal congestion), hospitalisation for all respiratory diseases, all deaths. Acute respiratory infection was also defined.
Notes	Vaccinated people had higher impairment. No information about flu activity; probably not epidemic year.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Crocetti 2001

Study characteristics

Methods	Case-control study conducted in Italy during the 1994 to 1995 influenza season, in the community. Data sources were database discharge diagnoses and mailed questionnaire. Follow-up period was 1 December 1994 to 31 March 1995. Cases were people discharged from hospital with pneumonia and influenza; community controls were matched for age, sex, and residence.

Crocetti 2001 *(Continued)*

Participants	825 residents of the province of Florence (275 cases and 550 controls were included in analysis; non-response rate was 15% in each group), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains did not match the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487)
Notes	Pneumococcal vaccination was very unlikely. The season was an epidemic one. The study controls for confounders in analysis: disability, socio-economic factors, and smoking habits. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cuneo Crovari 1980

Study characteristics

Methods	Prospective cohort study conducted in Italy during the 1978 to 1979 influenza season. Authors investigated an outbreak in a nursing home; individual cards were reviewed. Follow-up period was 1 November 1978 to 31 May 1979. Throat swab and paired sera specimens were obtained from residents.
Participants	196 nursing home residents (86 treated and 110 controls, all included in the analysis), 60 years or older
Interventions	Parenteral influenza vaccine: A/Texas/1/77; A/USSR/90/77; B/Hong Kong/8/73. Matching between vaccine and circulating strains is unknown.
Outcomes	Positive culture or 4-fold antibody titre increase with or without symptoms. Only symptomatic cases were included in the analysis.
Notes	Poor reporting of methods; no confounders control. The circulating strain was related to B/Hong Kong/5/72.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Currier 1988

Study characteristics

Methods	Authors investigated an outbreak in an intermediate and domiciliary care nursing home, in Maryland, USA during the 1987 to 1988 influenza season; medical records were reviewed. Follow-up period was 8 January 1988 to 26 January 1988. Throat swabs and acute sera specimens were obtained from some ill residents.

Currier 1988 *(Continued)*

Participants	126 nursing home residents (87 treated and 34 controls were included in the analysis; data on immunisation status for 5 residents were not available), mean age 87 years
Interventions	Parenteral influenza vaccine: A/Taiwan/1/86; A/Leningrad/360/86; B/Ann Arbor/1/86. Vaccine strains did not match the circulating strain.
Outcomes	Clinically defined ILI (fever 99.8 °F or greater + 1 of the following: cough, congestion, sore throat) or positive throat culture; pneumonia; deaths were also reported but not by immunisation status
Notes	Vaccinated and not vaccinated participants were similar as underlying conditions, only senile dementia was more frequent in vaccinees. The circulating strain was A/Leningrad-like.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

D'Alessio 1969

Study characteristics

Methods	Prospective outbreak investigation study conducted in the USA during the 1967 to 1968 influenza season. Authors investigated an outbreak in a nursing home. Follow-up period was December 1967 and January 1968. Throat swab and sera specimens were obtained from all ill residents and from an additional group of 27 residents with no illness.
Participants	176 nursing home residents (131 treated and 31 controls were included in the analysis, data on immunisation status for 14 residents were not available)
Interventions	Parenteral influenza vaccine: A2/Japan/170/62; A2/Taiwan/1/64; B/Massachusetts/3/66. Matching between vaccine and circulating strains is unknown.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater, headache, cough, sore throat, myalgia, and prostration)
Notes	Poor reporting; no confounders control. The circulating strain was A2/Wis/1/68.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Davis 2001a

Study characteristics

Methods	Prospective cohort study conducted in Hawaii during the 1994 to 1995 influenza season, in the community. Data source was insurance claim records. Follow-up period was 15 November 1994 to 31 March 1995. Only 10% of vaccinated participants and 3% of unvaccinated participants received pneumococcal vaccination.

Davis 2001a *(Continued)*

Participants	77,951 person periods members of a medical care program (44,271 treated and 33,680 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains probably did not match the circulating strain (literature data).
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460-462, 465-466, 480-487, 500-518), hospitalisation from congestive heart failure (ICD 428)
Notes	Odds ratios were adjusted by age and health status. Frequencies data were not available. To perform quantitative analysis, adjusted data were used. The season had low epidemic levels.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Davis 2001b

Study characteristics

Methods	Prospective cohort study conducted in Hawaii during the 1995 to 1996 influenza season, in the community. Data source was insurance claim records. Follow-up period was 15 November 1995 to 31 March 1996. Only 10% of vaccinated participants and 3% of unvaccinated participants received pneumococcal vaccination.
Participants	77,951 person periods members of a medical care programme (44,271 treated and 33,680 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains probably matched the circulating strain (literature data).
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460-462, 465-466, 480-487, 500-518), hospitalisation from congestive heart failure (ICD 428)
Notes	Odds ratios were adjusted by age and health status. Frequencies data were not available. To perform quantitative analysis, adjusted data were used. The season was probably an epidemic one.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Davis 2001c

Study characteristics

Methods	Prospective cohort study conducted in Hawaii during the 1996 to 1997 influenza season, in the community. Data source was insurance claim records. Follow-up period was 15 November 1996 to 31 March

Davis 2001c *(Continued)*

	1997. Only 10% of vaccinated participants and 3% of unvaccinated participants received pneumococcal vaccination.
Participants	77,951 person periods members of a medical care programme (44,271 treated and 33,680 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains probably matched the circulating strain (literature data).
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460-462, 465-466, 480-487, 500-518), hospitalisation from congestive heart failure (ICD 428)
Notes	Odds ratios were adjusted by age and health status. Frequencies data were not available. To perform quantitative analysis, adjusted data were used. The season was probably an epidemic one.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Deguchi 2001

Study characteristics

Methods	Prospective cohort study conducted in Japan during the 1998 to 1999 influenza season. Follow-up period was 1 November 1998 to 31 March 1999. 301 nursing homes were surveyed during an epidemic season; only a few residences had an outbreak of respiratory infections. Reports of illness were provided by study site staff.
Participants	22,462 residents in 301 nursing homes (10,739 treated and 11,723 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Mie/1/93. Vaccine strains probably matched circulating strains.
Outcomes	Clinical ILI (any of the following symptoms: fever, runny nose, sore throat, cough, headache, muscle aches, chills, vomiting, decreased activity, irritability, wheezing, pulmonary congestion), hospitalisation due to severe illness, deaths due to influenza
Notes	Poor description of methods, poor definitions; some cases were laboratory confirmed, but number of such cases was not indicated. Groups were comparable as age and gender. Health status was not investigated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Edmondson 1971

Study characteristics	
Methods	Experimental study conducted in Virginia, USA during the 1968 to 1969 influenza season. 4 arms: parenteral vaccine, aerosol vaccine, both, placebo. Methods are described in another article.
Participants	266 elderly psychiatric patients (90 in the parenteral arm, 89 in the aerosol arm, 88 in the arm with both administrations, 87 in the placebo arm)
Interventions	Monovalent inactivated A2 Hong Kong influenza vaccine. Vaccine strains probably matched the circulating strains.
Outcomes	Clinically defined ILI (fever + 1 or 2 respiratory symptoms or at least 2 systemic symptoms, lasting longer than 1 day; 3 respiratory symptoms or 2 respiratory symptoms + 2 systemic symptoms, lasting longer than 2 days); laboratory-confirmed influenza
Notes	The study year was an epidemic one; circulating strain was A2 HK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details provided.

Fedson 1993a

Study characteristics	
Methods	Case-control study conducted in Manitoba, Canada during the 1982 to 1983 influenza season, in the community. Data source was insurance claim records. Follow-up period was 1 December 1982 to 28 February 1983. Cases were admitted to the hospital with a lower respiratory tract condition as first diagnosis; community controls were matched for age, sex, and residence.
Participants	10,471 non-institutionalised people, 70% were older than 65 years (2619 cases and 7828 controls, all included in analysis)
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from a lower respiratory tract condition (ICD 466, 480-487, 490-496, 500-519), deaths from any respiratory condition, deaths from all causes. Data about deaths were not reported.
Notes	Circulating strain: A/Bangkok/1/79-like. The season was an epidemic one. The study controls for confounders in analysis: health status. Quantitative analysis was also performed.

Fedson 1993a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Fedson 1993b

Study characteristics

Methods	Case-control study conducted in Manitoba, Canada during the 1985 to 1986 influenza season, in the community. Data source was insurance claim records. Follow-up period was 1 December 1985 to 15 February 1986. Cases were admitted to the hospital with a lower respiratory tract condition as first diagnosis; community controls were matched for age, sex, and residence.
Participants	9666 non-institutionalised people, 70% were older than 65 years (2417 cases and 7249 controls, all included in analysis)
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from a lower respiratory tract condition (ICD 466, 480-487, 490-496, 500-519), deaths from any respiratory condition, deaths from all causes. Data about deaths were not reported.
Notes	Circulating strain: A/Philippines/2/82-like. The season was an epidemic one. The study controls for confounders in analysis: health status. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Feery 1976

Study characteristics

Methods	Prospective cohort study conducted in Melbourne, Australia during the 1976 influenza season. Authors investigated an outbreak in a nursing home. Follow-up period was from mid-April to mid-August. Throat swabs and paired sera specimens were obtained from residents.
Participants	222 nursing home residents (154 treated and 68 controls, all included in the analysis); elderly
Interventions	Parenteral influenza vaccine: A/Victoria/3/75; A/Scotland/840/74; B/Hong Kong/8/73. Vaccine strains matched circulating strains.
Outcomes	Laboratory-confirmed influenza, deaths from influenza
Notes	Poor reporting; no confounders control. The circulating strain was A/Victoria/3/75.

Risk of bias

Feery 1976 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Fleming 1995

Study characteristics	
Methods	Retrospective cohort study conducted in UK during the 1989 to 1990 influenza season, in the community. Data source was the general practitioner database. Follow-up period was 1 November 1989 to 15 January 1990. As vaccines used in 1988 and 1989 were antigenically closely related, 2 exposure definitions were used: recently vaccinated and previously vaccinated.
Participants	9391 people who had at least a general practitioner's consultation in previous months (599 treated and 8792 controls, all included in the analysis), 55 years or older
Interventions	Parenteral influenza vaccine: A/Shanghai/1197-like. Vaccine strains matched the circulating strain.
Outcomes	Death, death or severe respiratory illness, death or any respiratory illness without further specification
Notes	Important epidemic year. The study controls for confounders in analysis: age, gender, health status. Data were stratified by health status: people with minor underlying conditions are considered as healthy. People vaccinated during the previous year are considered as "non vaccinated". Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Foster 1992

Study characteristics	
Methods	Case-control study conducted in Michigan, USA during the 1989 to 1990 influenza season, in the community. Data sources were: discharge diagnoses, mailed questionnaire. Follow-up period was 1 November 1989 to 30 April 1990. Cases were admitted to the hospital with pneumonia or influenza; community controls were randomly selected.
Participants	1907 non-institutionalised people (1354 cases and 2389 controls were identified; 721 and 1786 were included in analysis, respectively), 65 years or older
Interventions	Parenteral influenza vaccine; 35% of cases and 28% of controls received pneumococcal vaccination. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480.8-483, 484.7-487.1)
Notes	Circulating strain: A/Shanghai/11/87. The season was an epidemic one. The study controls for confounders in analysis: health status, flu activity, pneumococcal vaccination, smoke. Peak data were used. Quantitative analysis was also performed.

Foster 1992 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fyson 1983a

Study characteristics

Methods	Authors investigated an outbreak in a nursing home in Canada during the 1982 to 1983 influenza season; active surveillance. Follow-up period was 3 November 1982 to 17 January 1983. Throat swab and paired sera specimens were obtained from some residents.
Participants	545 chronically ill nursing home residents (321 treated and 224 controls, all included in the analysis); 18 to 103 years old, mean age 80 years
Interventions	Parenteral influenza vaccine, whole and subvirion: A/Brazil/11/78; A/Bangkok/1/79; B/Singapore/222/79. Vaccine strains probably matched circulating strains.
Outcomes	Acute respiratory symptoms: fever, congestion, cough, sore throat, general malaise, without a clear definition; death from pneumonia
Notes	Poor reporting; no confounders control. Circulating strain: A/Bangkok/1/79-like; no other viruses were identified

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fyson 1983b

Study characteristics

Methods	Authors investigated an outbreak in a nursing home in Canada during the 1982 to 1983 influenza season; partial surveillance for delayed notification of outbreak. Follow-up period was 30 November 1982 to 9 January 1983. Throat swab and paired sera specimens were obtained from some residents.
Participants	171 female, chronically ill nursing home residents (53 treated and 118 controls, all included in the analysis); 19 to 105 years old
Interventions	Parenteral whole influenza vaccine: A/Brazil/11/78; A/Bangkok/1/79; B/Singapore/222/80. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI without further specification; death from pneumonia
Notes	Poor reporting; no confounders control. Circulating strain: A/Bangkok/1/79-like

Fyson 1983b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gavira Iglesias 1987

Study characteristics	
Methods	Prospective cohort study conducted in Spain during the 1984 to 1985 influenza season, in the community. Data source was a questionnaire retrospectively applied by investigators in June to July 1985 (door-to-door survey). The whole population of a rural village was investigated.
Participants	268 community-dwelling (188 treated and 80 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine: A/Philippines/2/82; A/Chile/1/83; B/USSR/100/83. Matching unknown.
Outcomes	Clinically defined ILI (fever 39 °C or more, chills, general malaise, myalgia, headache, arthralgia, conjunctivitis, lasting 3 days or more)
Notes	None of the observed deaths was due to flu-related illness. The season had low epidemic levels. Subgroup analysis was performed but only for the whole population.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Gené Badia 1991

Study characteristics	
Methods	Prospective cohort study conducted in Spain during the 1988 to 1989 influenza season, in the community. Data sources were the health centre register, death certificate archives, hospital records. Follow-up period was 1 November 1988 to 30 May 1989. In the first of the 4 health centres, all elderly people were enrolled; in the others only people approaching the centre for health reasons were enrolled.
Participants	4558 people enrolled at 4 health centres (1998 treated and 2560 controls, all included in the analysis), 65 years or older, mean age 74 years
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	All hospitalisations and hospitalisation from cardio-respiratory causes (ICD 401-414 and 460-519); deaths from all causes. Only deaths from all causes are included in analysis.
Notes	The season was an epidemic one.

Risk of bias

Gené Badia 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Goodman 1982

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home, in Atlanta, USA during the 1980 to 1981 influenza season; medical charts and hospital charts were reviewed. Follow-up period was 12 December 1980 to 21 January 1981. Throat swab and paired sera specimens were obtained from some residents.
Participants	120 nursing home residents (36 treated and 84 controls, all included in the analysis), 47 to 95 years old (median age 80 years). Participants required intermediate and skilled nursing care.
Interventions	Parenteral influenza vaccine: A/Bangkok/1/79; A/Brazil/11/78; B/Singapore/222/78. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.7 °C or greater or cough in the outbreak period (12 December 1980 to 21 January 1981)), death from ILI. Hospitalisation and pneumonia were also accounted for, but results were not presented by immunisation status.
Notes	No confounders control. The circulating strain was A/Bangkok/1/79-like. Serological tests were negative for other pathogens.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Govaert 1993

Study characteristics	
Methods	Experimental study conducted in the Netherlands during the 1991 to 1992 influenza season, randomised, double-blind, placebo controlled; randomisation scheme was stratified according to health status. Follow-up period was 48 hours after vaccination. Adverse reactions were self reported on postal questionnaire completed 4 weeks after vaccination
Participants	1838 not known as belonging to a high-risk group (927 treated and 911 controls; 23 and 9 dropped out, respectively), 60 years or older
Interventions	Parenteral influenza recommended vaccine: A/Singapore/6/86; A/Beijing/357/89; B/Beijing/1/97; B/Panama/45/90
Outcomes	Local: swelling, itching, warm feeling, pain when touched, constant pain, discomfort. Systemic: fever, headache, malaise, other complaints
Notes	Harms were reported for all participants and by risk condition. Data regarding all participants were included

Govaert 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate description
Allocation concealment (selection bias)	Low risk	Adequate description
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as placebo controlled, but no additional information was available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate description of follow up and attrition

Govaert 1994a

Study characteristics

Methods	Experimental study conducted in the Netherlands during the 1991 to 1992 influenza season, in the community. Follow-up period was 1 November 1991 to 30 April 1992. Randomised, double-blind, placebo controlled; randomisation scheme was stratified according to health status.
Participants	1838 people not known as belonging to a high-risk group (927 treated and 911 controls; 25 and 22 dropped out, respectively), 60 years or older
Interventions	Parenteral influenza recommended vaccine: A/Singapore/6/86; A/Beijing/357/89; B/Beijing/1/97; B/Panama/45/90. Vaccine strains matched the circulating strains.
Outcomes	Clinically defined ILI; laboratory-confirmed ILI. Several definitions for clinical and laboratory ILI were tested; the Dutch Sentinel Stations definition is used (fever 37.8 °C or greater + cough or coryza or sore throat or headache or myalgia).
Notes	The study year was an epidemic one; data were stratified by health status. Intention-to-treat analysis was performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate description
Allocation concealment (selection bias)	Low risk	Adequate description
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate description
Incomplete outcome data (attrition bias)	Low risk	Adequate description

Govaert 1994a *(Continued)*
All outcomes

Gross 1988

Study characteristics		
Methods	Prospective cohort study conducted in New York, USA during the 1982 to 1983 influenza season. Authors investigated an outbreak in a nursing home; independent blind assessment was conducted. Follow-up period was 1 November 1982 to 30 April 1983. 305 of the 525 residents volunteered to participate in study; diagnosis was made without knowledge of vaccination status	
Participants	305 nursing home residents, mostly ambulatory (181 treated and 124 controls; 138 and 94 had serological surveillance, respectively); groups were comparable for health status and drug use; mean age 85 years	
Interventions	Parenteral influenza vaccine: A/Bangkok/1/79; A/Brazil/11/78; B/Singapore/222/79. Vaccine strains matched circulating strains (slight drift)	
Outcomes	Laboratory-confirmed influenza (4-fold increase in antibody titre), X-ray-confirmed pneumonia, deaths from all causes	
Notes	Pneumococcal vaccine was rarely used. Amantadine was not used. The circulating strain was A/Arizona/80, closely related to A/Bangkok/1/79 Laboratory-confirmed cases were analysed by intention-to-treat	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Hak 2002a

Study characteristics	
Methods	Prospective cohort study conducted in the USA during the 1996 to 1997 influenza season, in the community. Data source was a managed care organisation database. Follow-up period was 5 October 1996 to 3 May 1997.
Participants	122,974 members of a medical care programme continuously enrolled for the 1-year period (71,005 treated and 51,969 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine matched the circulating strain.
Outcomes	Combined outcome: hospitalisation from influenza and pneumonia (ICD 480-487) or death from all causes
Notes	The study controls for confounders in analysis: age, gender, health status. Data were presented by health status. No information about pneumococcal vaccination. The season was an epidemic one.
Risk of bias	

Hak 2002a *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Hak 2002b

Study characteristics	
Methods	Prospective cohort study conducted in the USA during the 1997 to 1998 influenza season, in the community. Data source was a managed care organisation database. Follow-up period was 23 November 1997 to 4 April 1998.
Participants	158,454 members of a medical care programme continuously enrolled for the 1-year period (92,001 treated and 66,453 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine did not match the circulating strain.
Outcomes	Combined outcome: hospitalisation from influenza and pneumonia (ICD 480-487) or death from all causes
Notes	The study controls for confounders in analysis: age, gender, health status. Data were presented by health status. No information about pneumococcal vaccination. The season was an epidemic one; circulating strain: A/Sydney-like.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Hara 2006

Study characteristics	
Methods	Prospective cohort study conducted in Saga, Japan. 10,000 community-dwelling elderly were randomly selected from a population registry and were sent a letter explaining the study with a request for participation. Eligibility criteria were as follows: not being hospitalised, not being institutionalised, not having any long-term absence, not living alone, and able to contact by telephone at least once a month.
Participants	Among 10,000 elderly citizens, 7357 responded, and 4787 agreed to participate and matched our eligibility criteria. The vaccination status of the study participants was identified by self reporting verification and a list of recipients of partially funded vaccination; 3240 participants (3230 participants were self reported and 10 were known with verification) were vaccinated and 1547 non-vaccinated. The vaccination coverage was 67.7%.
Interventions	Influenza vaccination versus no vaccination
Outcomes	ILI, clinical influenza, hospitalisation for all causes, hospitalisation for influenza or pneumonia, and total deaths

Hara 2006 *(Continued)*

Notes	The author concludes that influenza vaccination was associated with decreased ILI during the epidemic period in community-dwelling elderly. The above risk reduction was greater under low-risk conditions. The results were inconclusive for preventing hospitalisation and death, due to an inadequate sample size. However, our findings support the finding that all elderly individuals substantially benefit from vaccination even in a season of mild influenza activity, and also when the antigenic match between the vaccine strains and the circulating strains is not closely matched.

Horman 1986

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home in Maryland, USA during the 1980 to 1981 influenza season; residents' medical records were reviewed. Follow-up period was 8 December 1980 to 13 January 1981. Throat swab and paired sera specimens were obtained from some residents.
Participants	159 nursing home residents, 62 to 100 years old (100 treated and 59 controls, all included in the analysis); most of the residents were chronically ill; risk status did not differ between vaccinees and unvaccinated.
Interventions	Parenteral influenza vaccine: A/Brazil; A/Bangkok; B/Singapore. Vaccine strains matched circulating strains.
Outcomes	Clinically defined ILI (2 case definitions; more specific definition was used: fever + cough or chest congestion), pneumonia without further specification, and case-fatality rate
Notes	Vaccination was not offered to staff. 36% of the observed deaths during the epidemic period occurred from causes other than flu. Circulating strains: A/Taiwan/1/79-like, very similar to the vaccine strain A/Bangkok. Isolation attempts for other pathogens were unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Howarth 1987a

Study characteristics	
Methods	Prospective cohort study conducted in Australia in 17 nursing homes during the 1983 influenza season. Follow-up period was autumn to spring; blinded assessment of illness was performed.
Participants	326 residents in 17 nursing homes (229 treated and 97 controls, all included in the analysis), 44 to 99 years old
Interventions	Parenteral influenza vaccine: A/Victoria/186/82; A/Philippines/2/82; B/Singapore/222/79. Vaccine strains matched circulating strains.
Outcomes	Laboratory-confirmed influenza (4-fold increase in antibody titre)
Notes	Poor description of methods; part of another study. The circulating strain was A/Philippines/2/82. No information about flu activity

Howarth 1987a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Howarth 1987b

Study characteristics	
Methods	Prospective cohort study conducted in Australia in 17 nursing homes during the 1984 influenza season. Follow-up period was autumn to spring; blinded assessment of illness was performed.
Participants	365 residents in 17 nursing homes (184 treated and 181 controls, all included in the analysis), 44 to 99 years old
Interventions	Parenteral influenza vaccine: A/Dunedin/27/83; A/Philippines/2/82; B/Singapore/222/80. Vaccine strains matched circulating strains.
Outcomes	Laboratory-confirmed influenza (4-fold increase in antibody titre)
Notes	Poor description of methods; part of another study. The circulating strain was A/Philippines/2/82. No information about flu activity

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Howells 1975a

Study characteristics	
Methods	Prospective cohort study conducted in the UK in several nursing homes during the 1971 to 1972 influenza season; all residents were under constant surveillance. Throat swab and paired sera specimens were obtained whenever possible.
Participants	490 nursing homes residents (134 treated and 356 controls, all included in the analysis), 60 years or older
Interventions	Parenteral influenza vaccine: A2/HK/68; B/Vic.98926/70. Matching between vaccine and circulating strains is unknown.
Outcomes	Respiratory illness and pneumonia without definition, deaths from pneumonia
Notes	Very poor description of methods; groups were roughly comparable as age and general health. No information about flu activity and laboratory confirmation

Risk of bias

Howells 1975a *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Howells 1975b

Study characteristics	
Methods	Prospective cohort study conducted in the UK in several nursing homes during the 1972 to 1973 influenza season; all residents were under constant surveillance. Throat swab and paired sera specimens were obtained whenever possible.
Participants	390 nursing homes residents (123 treated and 267 controls, all included in the analysis), 60 years or older
Interventions	Parenteral influenza vaccine: A2/HK/68; B/Vic.98926/71. Matching between vaccine and circulating strains is unknown.
Outcomes	Respiratory illness and pneumonia without definition, deaths from pneumonia
Notes	Very poor description of methods; groups were roughly comparable as age and general health. No information about flu activity and laboratory confirmation

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Howells 1975c

Study characteristics	
Methods	Prospective cohort study conducted in the UK in several nursing homes during the 1973 to 1974 influenza season; all residents were under constant surveillance. Throat swab and paired sera specimens were obtained whenever possible.
Participants	470 nursing homes residents (183 treated and 287 controls, all included in the analysis), 60 years or older
Interventions	Parenteral influenza vaccine: A/Eng/42/72; B/Vic.98926/71; B/Hong Kong/8/73. Matching between vaccine and circulating strains is unknown.
Outcomes	Respiratory illness and pneumonia without definition, deaths from pneumonia
Notes	Very poor description of methods; groups were roughly comparable as age and general health. No information about flu activity and laboratory confirmation

Risk of bias

Howells 1975c *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Isaacs 1997

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home in Ontario, Canada during the 1996 to 1997 influenza season. Follow-up period was 1 January 1997 to 11 January 1997. Nasal swabs were obtained from 3 ill residents.
Participants	172 nursing home residents (149 treated and 23 controls, all included in the analysis)
Interventions	Parenteral influenza vaccine. Vaccine strains probably matched circulating strains (other studies).
Outcomes	Clinically defined ILI (fever 38 °C or greater, cough, sore throat, nasal congestion, muscle ache, lethargy, lasting 2 days or more)
Notes	Amantadine was used in all residents. 1 positive result was obtained by rapid testing. Poor reporting

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Jordan 2007

Study characteristics	
Methods	Case-control study nested within a cohort of older people registered with 79 participating general practices in central England. People were included in the identified cohort if aged 65 to 89 years and if they consulted their general practitioner (or other emergency medical services) for an acute episode of respiratory infection or acute exacerbation of pre-existing respiratory disease, between 1 October 2003 and 31 March 2004. People with simple upper respiratory tract infections were excluded.
Participants	Cases were defined as all people admitted to hospital with acute respiratory disease. Only the first admission during the study period was included. Surviving cases were invited for interview. Controls were defined as people presenting with acute respiratory disease but who were managed in the community. 6 controls were invited per case to mitigate for a potential low uptake, in order to achieve 4 controls interviewed per case. Controls were matched to cases for age (within ± 5 years where possible), sex, and consultation date (within ± 7 days where possible). 3970 eligible participants were identified. 500 participants were admitted to hospital. Altogether 44.1% of invited cases and 54.5% of controls agreed to interview; 157 cases and 639 controls were finally interviewed. The proportion of cases vaccinated against influenza before entry to the study was 74.5% and in controls was 74.2%.
Interventions	Influenza vaccination and admissions to hospital for acute respiratory disease

Jordan 2007 *(Continued)*

Outcomes	—
Notes	The authors conclude that in a winter typical of the current levels of circulating influenza, they were unable to demonstrate that influenza vaccination had a specific effect on preventing hospitalisation among elderly people clinically ill with acute respiratory disease, although there was a possible effect during the peak weeks of influenza activity. Relying solely on the influenza vaccine to control the annual winter bed pressures in hospitals is unlikely to be a sufficiently effective yearly strategy, and continuing attention to other factors (e.g. the effective vaccination of healthcare workers, treatment of comorbidities, indoor housing conditions) is essential.

Kaplan 1982

Study characteristics		
Methods	Surveillance population-based study conducted in the USA during the 1979 to 1980 and 1980 to 1981 influenza seasons. Case report for each case was obtained from neurologists. All case reports were included. Follow-up period was 1 September 1979 to 31 March 1980 and 1 September 1980 to 31 March 1981.	
Participants	USA (minus Maryland) adult population, 18 years or older	
Interventions	Seasonal trivalent vaccine	
Outcomes	Cases of Guillain-Barré syndrome. Vaccine-associated cases were defined as those with onset within the 8-week period after influenza vaccination.	
Notes	Vaccination rates in population were obtained from national immunisation survey.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Kawai 2003

Study characteristics	
Methods	Prospective cohort study conducted in Japan during the 2001 to 2002 period in the community. Data sources were the general practitioner database and self administered questionnaire. Follow-up period was 31 December 2001 to 31 May 2002. Unvaccinated participants were matched as closely as possible for sex and age to the vaccinated participants. Laboratory confirmation was performed in 60% of cases.
Participants	4423 mostly community-dwelling (3520 treated and 903 controls were included in the analysis), 65 to 104 years old
Interventions	Parenteral influenza vaccine: A/New Caledonia/20/99; A/Panama/2007/99; B/Johannesburg/5/99. Vaccine strains matched the circulating strain.
Outcomes	Clinically defined ILI (all of the following symptoms: sudden onset, fever 38 °C or more, cough)
Notes	The influenza season was mild. The study controls for age, sex, and previous vaccinations in analysis.

Kawai 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Keitel 1996

Study characteristics	
Methods	Experimental study conducted in Texas, USA during the 1994 to 1995 influenza season, randomised, placebo-controlled trial; randomisation method and allocation concealment were not described. Participants were allocated to receive ascending doses (15 ug/45 ug/135 ug) of antigen. Only 15 ug vaccine was included in analysis. Follow-up period was 48 hours after vaccination.
Participants	21 ambulatory, medically stable people, 65 years or older
Interventions	Parenteral monovalent subvirion 15 ug (9 participants) and purified haemagglutinin 15 ug (12 participants) influenza vaccine: A/Singapore/6/86
Outcomes	Discomfort, erythema/induration, headache, malaise without further description
Notes	Different vaccines (haemagglutinin and subvirion) were analysed as a single "treatment group".

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Lasky 1998

Study characteristics	
Methods	Surveillance population-based study conducted in the USA (4 states: Illinois, Maryland, North Carolina, Washington) during the 1992 to 1993 and 1993 to 1994 influenza seasons. Discharge diagnoses database was used to identify cases. Hospital charts were reviewed to confirm diagnosis. Follow-up period was 1 September 1992 to 28 February 1993 and 1 September 1993 to 28 February 1994.
Participants	About 21 million people, 18 years or older
Interventions	Seasonal trivalent vaccine
Outcomes	Cases of Guillain-Barré syndrome. Vaccine-associated cases were defined a priori as those with onset within the 6-week period after influenza vaccination.
Notes	Results were stratified by age and adjusted by season and sex. Vaccination rates in population were estimated from a random-digit dialling telephone survey.

Risk of bias

Lasky 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Leung 2007

Study characteristics	
Methods	Retrospective cohort study conducted in 46 elderly homes in Hong Kong, China to assess the effectiveness of influenza vaccination on influenza, pneumonia, hospitalisation for influenza, and death. People were eligible if they were age 65 years or above. The exposed group comprised people who had not received influenza vaccination, while the control group comprised people who had received influenza vaccination from the Department of Health or other healthcare providers in 2004. Information regarding vaccination was based on its documentation in the elderly home records. A resident having unknown history of influenza vaccination in the preceding calendar year was regarded as not being vaccinated. A standardised questionnaire was used to collect data from the elderly homes once an influenza outbreak was defined in the elderly home. The occurrence of influenza was identified by the self administered questionnaires. The occurrence of pneumonia, hospitalisation, and death were identified from the hospital records.
Participants	3177 residents participated in the study. The mean age was 83 years; 2133 were females and 1044 males. There were 2943 vaccinated (92.6%) and 234 (7.4%) unvaccinated participants. More females were vaccinated (67.7%) than males (59.8%).
Interventions	Influenza vaccination versus no vaccination
Outcomes	Influenza, pneumonia, hospitalisation, and death
Notes	The authors conclude that this study failed to demonstrate a protective effect of influenza vaccine against influenza and its complications during outbreaks.

Lopez Hernandez 1994

Study characteristics	
Methods	Retrospective cohort study conducted in Spain during the 1991 to 1992 influenza season, in the community. Data sources were: the health centre register, death certificate archives, hospital records. Follow-up period was 7 months after vaccination. People were excluded if they did not approach the centre in the last 3 years.
Participants	1965 community-dwelling elderly enrolled in a health centre (779 treated and 1186 controls, all included in the analysis), 65 years or older, mean age 73.5 years
Interventions	Parenteral influenza vaccine. Vaccine strains probably matched the circulating strain.
Outcomes	Hospitalisation from cardio-respiratory causes, death from all causes. Only deaths from all causes are included in analysis.
Notes	The study controls for confounders in analysis (age, health status, home care). The season had low epidemic levels.
Risk of bias	

Lopez Hernandez 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mangtani 2004a

Study characteristics	
Methods	Retrospective cohort study conducted in the UK during the 1990 to 1998 influenza season, in the community. Data source was a managed care organisation database. Follow-up period was the epidemic period (period with consultation rate for ILI more than 50/100,000 person-weeks). People were identified and included in the study if they were registered on the first day of the week that included 1 September each year.
Participants	692,819 person-years in vaccine recipients and 1,534,280 person-years in vaccine non-recipients, 65 years or older
Interventions	Parenteral influenza vaccine
Outcomes	Hospitalisation for acute respiratory illness (ICD 466, 480-487), respiratory-related deaths
Notes	Most of the seasons were epidemic, with vaccine strains matching the circulating strains. Data were presented by health status; other strata: year, flu activity, age. Data by health status were extracted by rates reported in tables.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004b

Study characteristics	
Methods	See Mangtani 2004a. Influenza season 1990 to 1991
Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Epidemic year

Risk of bias

Bias	Authors' judgement	Support for judgement

Mangtani 2004b *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004c

Study characteristics		
Methods	See Mangtani 2004a. Influenza season 1991 to 1992	
Participants	See Mangtani 2004a	
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.	
Outcomes	See Mangtani 2004a	
Notes	See Mangtani 2004a. Epidemic year	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004d

Study characteristics		
Methods	See Mangtani 2004a. Influenza season 1992 to 1993	
Participants	See Mangtani 2004a	
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.	
Outcomes	See Mangtani 2004a	
Notes	See Mangtani 2004a. Non-epidemic year	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004e

Study characteristics	
Methods	See Mangtani 2004a. Influenza season 1993 to 1994

Mangtani 2004e *(Continued)*

Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Epidemic year

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004f

Study characteristics

Methods	See Mangtani 2004a. Influenza season 1994 to 1995
Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Non-epidemic year

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004g

Study characteristics

Methods	See Mangtani 2004a. Influenza season 1995 to 1996
Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Epidemic year

Risk of bias

Mangtani 2004g *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004h

Study characteristics	
Methods	See Mangtani 2004a. Influenza season 1996 to 1997
Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Epidemic year

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004i

Study characteristics	
Methods	See Mangtani 2004a. Influenza season 1997 to 1998
Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine did not match the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Non-epidemic year

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Mangtani 2004j

Study characteristics

Mangtani 2004j *(Continued)*

Methods	See Mangtani 2004a. Influenza season 1998 to 1999
Participants	See Mangtani 2004a
Interventions	See Mangtani 2004a. Vaccine matched the epidemic strain.
Outcomes	See Mangtani 2004a
Notes	See Mangtani 2004a. Epidemic year

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Margolis 1990a

Study characteristics

Methods	Experimental study conducted in Minneapolis, USA during the 1988 to 1989 influenza season, randomised, double-blind, placebo-controlled cross-over trial. Follow-up period was 7 days after vaccination. Symptoms were assessed by phone interview.
Participants	672 outpatients (336 treated and 336 controls were included in the analysis), 65 years or older
Interventions	Parenteral influenza recommended vaccine: A/Taiwan/1/86; A/Sichuan/2/87; B/Victoria/2/87
Outcomes	Cough, coryza, fatigue, malaise, myalgia, headache, nausea, sore arm, disability, feverish without further description
Notes	Placebo was saline injection.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Probably acceptable since placebo was a saline injection
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Short-term follow-up for most outcomes was by phone, but unclear how complete data were for longer-term outcomes.

Meiklejohn 1987

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home in Wyoming, USA during the 1984 to 1985 influenza season. Follow-up period was 2 January 1985 to 3 March 1985. Throat washing and convalescent sera were obtained from some residents.
Participants	55 nursing home residents (36 treated and 19 controls, all included in the analysis), 60 to 98 years old
Interventions	Parenteral influenza vaccine: A/Philippines/82; A/Chile/83; B/USSR/84. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined URI (upper respiratory illness: fever, chills, myalgia, respiratory symptoms), radiologically confirmed pneumonia, hospitalisation, and death without further specification
Notes	Amantadine was used in cases. The circulating strain that year was of A/Philippines type. No virus strain was isolated from participants, but serologic tests confirmed influenza A virus infections. Poor description of methods

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Monto 2001

Study characteristics	
Methods	Prospective cohort study conducted in Michigan, USA during the 1991 to 1992 influenza season. Authors investigated 26 skilled nursing homes with evidence of flu activity; nursing homes with high rates of immunisation (herd immunity) were excluded from the study; data on ILI or pneumonia were recorded prospectively under supervision of a nurse co-ordinator. Follow-up period was 1 November 1991 to 29 February 1992.
Participants	2351 residents in 26 nursing homes (1728 treated and 623 controls, all included in the analysis), 65 years or older, for whom vaccination status was known
Interventions	Parenteral influenza vaccine. Vaccine strains matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater + cough, sore throat, or nasal congestion), clinical pneumonia, deaths occurring within 3 months of the onset of respiratory illness. Influenza was considered to have been introduced into a nursing home when a least 2% of residents developed ILI within a 7-day period during community-documented virus circulation or when virus was isolated from cases.
Notes	Both influenza A (H3N2) and A (H1N1) co-circulated with influenza A (H3N2) predominantly. The circulating strains were closely related to the vaccine strain. Rate ratio estimates were adjusted by sex, age, home size and presented by "peak period". Groups were comparable as age and chronic conditions.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Morens 1995

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home in Honolulu, USA during the 1989 to 1990 influenza season; vaccination records, hospital records, resident records were reviewed. Follow-up period was 15 December 1989 to 28 January 1990. Specimens for virus isolation were obtained from 9 ill residents, and paired sera specimens were obtained from 34 case and non-case residents.
Participants	39 nursing home residents with multiple chronic conditions (36 treated and 3 controls, all included in the analysis), 36 to 102 years (mean age 80 years)
Interventions	Parenteral influenza vaccine; pneumococcal vaccine was also used. Vaccine strains matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater + cough, coryza, or sore throat), laboratory-confirmed influenza, pneumonia, deaths from ILI or pneumonia
Notes	Amantadine was administered to all participants over a 1-week period (January 4 to 12, 1990). The circulating strain was indistinguishable from the vaccine strain A/England/4/27/88. Lack of serologic evidence for other respiratory agents

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mukerjee 1994

Study characteristics	
Methods	Authors investigated outbreaks in 14 nursing homes in Wales, UK during the 1991 to 1992 influenza season. Follow-up period was 15 December 1991 to 28 February 1992. Paired sera specimens were collected from 7 cases in 2 homes.
Participants	466 residents in 14 nursing homes (104 treated and 362 controls, all included in the analysis)
Interventions	Parenteral influenza vaccine. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined URI (upper respiratory illness: fever, chills, myalgia, cough)
Notes	Very poor reporting. Vaccine strain was assumed to match the circulating strain according to literature data.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Mullooly 1994

Study characteristics	
Methods	Case-control study conducted in the USA during the 1981 to 1989 period, in the community. Data source was a managed care organisation database. Follow-up period was the epidemic period according to surveillance data. Cases were admitted to services with pneumonia or influenza or died in hospital from pneumonia or influenza; community controls were matched for high-risk status.
Participants	251,034 members of a medical care programme, 65 years or older
Interventions	Parenteral influenza vaccine; participants also received pneumococcal vaccination. Vaccine strains matched the circulating strain.
Outcomes	Pneumonia and influenza without hospitalisation, hospitalisation from pneumonia and influenza (ICD 480-487), hospitalised death
Notes	Most of the seasons were epidemic, and vaccine strains did not match the circulating strains. The study controls for confounders in analysis (age, sex, pneumococcal vaccination). Data are stratified by health status, but allow only quantitative analysis. The odds ratio adjusted by risk status was obtained by pooling the data reported in the paper using Wolf method.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Murayama 1999

Study characteristics	
Methods	Authors investigated 2 consecutive outbreaks in the same nursing home in Japan during the 1996 to 1997 influenza season; patients' records were reviewed. Follow-up period was 25 December 1996 to 14 January 1997 and 19 February 1997 to 26 February 1997. Throat swab and paired sera specimens were obtained from ill residents.
Participants	128 nursing home residents (60 treated and 68 controls, all included in the analysis), 70 years or older. None of the residents was previously vaccinated.
Interventions	2 doses of parenteral influenza vaccine: A/Yamagata/32/89; A/Wuhan/359/95; B/Mie/1/93. Vaccine strains matched circulating strains.
Outcomes	ICHPP-2 defined ILI (laboratory evidence or epidemiological criteria or 6 of the following symptoms: sudden onset, fever, cough, prostration, chills, weakness, myalgia, widespread aches), hospitalisations, and deaths without definition
Notes	Epidemic reoccurrence of influenza A outbreak was observed. Both outbreaks were investigated; vaccinated and control groups were comparable as age or risk status. The circulating strain was A/Wuhan/359/95. Amantadine was not used. Other respiratory viruses were not isolated.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Murayama 1999 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Nichol 1994a

Study characteristics	
Methods	Prospective cohort study conducted in Minneapolis, USA during the 1990 to 1991 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 1 October 1990 to 31 March 1991. The rate was adjusted for age, sex, health status, pneumococcal vaccination.
Participants	25,532 members of a medical care programme continuously enrolled for the 1-year period (11,483 treated and 14,049 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. 3% of vaccinees and 1% of unvaccinated received pneumococcal vaccination. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460, 462, 465-466, 480-487, 490-96, 500-518), hospitalisation from congestive heart failure (ICD 428), death from all causes (not reported)
Notes	The season was an epidemic one. Data were extracted by rates reported in tables. Quantitative analysis with adjusted rates was not performed because data reported and statistical model used were not homogeneous to those reported in the other studies.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nichol 1994b

Study characteristics	
Methods	Prospective cohort study conducted in Minneapolis, USA during the 1991 to 1992 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 1 October 1991 to 31 March 1992. The rate was adjusted for age, sex, health status, pneumococcal vaccination.
Participants	26,369 members of a medical care programme continuously enrolled for the 1-year period (15,288 treated and 11,081 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. 5% of vaccinees and 2% of unvaccinated received pneumococcal vaccination. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460, 462, 465-466, 480-487, 490-496, 500-518), hospitalisation from congestive heart failure (ICD 428), death from all causes (not reported)

Nichol 1994b *(Continued)*

Notes	The season was an epidemic one. Data were extracted by rates reported in tables. Quantitative analysis with adjusted rates was not performed because data reported and statistical model used were not homogeneous to those reported in the other studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nichol 1994c

Study characteristics

Methods	Prospective cohort study conducted in Minneapolis, USA during the 1992 to 1993 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 1 October 1992 to 31 March 1993. The rate was adjusted for age, sex, health status, pneumococcal vaccination.
Participants	26,626 members of a medical care programme continuously enrolled for the 1-year period (14,647 treated and 11,979 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. 6% of vaccinees and 3% of unvaccinated received pneumococcal vaccination. Vaccine strains did not match the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460, 462, 465-466, 480-487, 490-496, 500-518), hospitalisation from congestive heart failure (ICD 428), death from all causes (not reported)
Notes	The season was an epidemic one. Data were extracted by rates reported in tables. Quantitative analysis with adjusted rates was not performed because data reported and statistical model used were not homogeneous to those reported in the other studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nichol 1998a

Study characteristics

Methods	Prospective cohort study conducted in Minneapolis, USA during the 1990 to 1995 period, in the community. Data source was the managed care organisation database. Follow-up period was 15 November to 31 February. A subgroup analysis by health status was performed. The rate was adjusted for age, sex, health status, vaccination status.
Participants	147,551 members of a medical care programme continuously enrolled for the 1-year period (87,898 treated and 59,653 controls included in the analysis), 64 years or older

Nichol 1998a *(Continued)*

Interventions	Parenteral influenza vaccine. 11.3% of vaccinees and 4.5% of unvaccinated received pneumococcal vaccination, on average.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions, hospitalisation from congestive heart failure, death from all causes (deaths were not reported)
Notes	Most of the seasons were epidemic, with vaccine strains matching the circulating strains. Data were extracted by rates reported in tables. Only data stratified by health status were included in the analysis. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nichol 1998b

Study characteristics

Methods	Prospective cohort study conducted in Minneapolis, USA during the 1993 to 1995 period, in the community. Data source was the managed care organisation database. Follow-up period was 15 November to 31 March. The rate was adjusted for age, sex, health status, vaccination status.
Participants	69,024 members of a medical care programme continuously enrolled for the 1-year period (46,480 treated and 22,544 controls included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. 11.3% of vaccinees and 4.5% of unvaccinated received pneumococcal vaccination, on average.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions, hospitalisation from congestive heart failure, death from all causes (deaths were not reported)
Notes	All the seasons were epidemic, with vaccine strains matching the circulating strains. Data were extracted by rates reported in tables and calculated by difference with data reported in previous studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nichol 2003a

Study characteristics

Methods	Prospective cohort study conducted in the USA, during the 1998 to 1999 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 15 November to 31 February. The rate was adjusted for age, sex, health status.

Nichol 2003a *(Continued)*

Participants	140,055 members of a medical care programme continuously enrolled for the 1-year period (77,738 treated and 62,317 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from cerebrovascular disease (ICD 431-437), hospitalisation from heart disease (ICD 410-414, 428), death from all causes
Notes	The season probably was an epidemic one. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nichol 2003b

Study characteristics

Methods	Prospective cohort study conducted in the USA during the 1999 to 2000 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 15 November to 31 March. The rate was adjusted for age, sex, health status.
Participants	146,328 members of a medical care programme continuously enrolled for the 1-year period (87,357 treated and 58,971 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from cerebrovascular disease (ICD 431-437), hospitalisation from heart disease (ICD 410-414, 428), death from all causes
Notes	The season probably was an epidemic one. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nicholson 1999

Study characteristics

Methods	Prospective cohort study conducted in Leicester, UK during the 1993 to 1994 influenza season, in the community. Data source was weekly phone interviews. Follow-up period was 18 October 1993 to 19 December 1993. The sample was randomly selected. Symptomatic participants were checked for laboratory confirmation.

Nicholson 1999 *(Continued)*

Participants	427 community-dwelling elderly (223 treated and 216 controls; 218 and 209 included in the analysis, respectively), 63 to 89 years old
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Laboratory-confirmed influenza (4-fold increase in antibody titre)
Notes	The study was conducted throughout an outbreak of influenza. The study controls for age, health status, and smoking habits in analysis. Data are presented by smoking habits.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nordin 2001a

Study characteristics

Methods	Prospective cohort study conducted in the USA during the 1996 to 1997 influenza season, in the community. Data source was a 3 managed care organisation database. Follow-up period was 5 October 1996 to 3 May 1997.
Participants	122,974 members of a medical care programme continuously enrolled for the 1-year period (71,005 treated and 51,969 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine matched the circulating strain.
Outcomes	Hospitalisation from influenza and pneumonia (ICD 480-487), death from all causes
Notes	Identical to Hak 1. Odds ratios adjusted for age, sex, site, health status were presented. Frequencies data were not available. To perform quantitative analysis adjusted data were used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nordin 2001b

Study characteristics

Methods	Prospective cohort study conducted in the USA during the 1997 to 1998 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 23 November 1997 to 4 April 1998.
Participants	158,454 members of a medical care programme continuously enrolled for the 1-year period (92,001 treated and 66,453 controls, all included in the analysis), 65 years or older

Nordin 2001b *(Continued)*

Interventions	Parenteral influenza vaccine. Vaccine did not match the circulating strain.
Outcomes	Hospitalisation from influenza and pneumonia (ICD 480-487), death from all causes
Notes	Identical to Hak 2. Odds ratios adjusted for age, sex, site, health status were presented. Frequencies data were not available. To perform quantitative analysis adjusted data were used

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ohmit 1995a

Study characteristics

Methods	Case-control study conducted in Michigan, USA during the 1990 to 1991 influenza season, in the community. Data sources were: database discharge diagnoses, mailed questionnaire. Follow-up period was 1 November 1990 to 30 April 1991. Cases were people discharged from hospital with pneumonia or influenza; community controls were matched for age, sex, and residence.
Participants	2197 non-institutionalised elderly (860 cases and 1828 controls were identified; 667 and 1530 were included in analysis, respectively), 65 years or older
Interventions	Parenteral influenza vaccine, participants were also offered pneumococcal vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487)
Notes	41% of cases and 28% of controls received pneumococcal vaccination. The season probably had low epidemic levels. The study controls for confounders in analysis: influenza activity, health status, age, sex, region. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ohmit 1995b

Study characteristics

Methods	Case-control study conducted in Michigan, USA during the 1991 to 1992 influenza season, in the community. Data sources were: database discharge diagnoses, mailed questionnaire. Follow-up period was 1 November 1991 to 30 April 1992. Cases were people discharged from hospital with pneumonia or influenza; community controls were matched for age, sex, and residence.
Participants	2761 non-institutionalised elderly (1186 cases and 2345 controls were identified; 890 and 1871 were included in analysis, respectively), 65 years or older

Ohmit 1995b *(Continued)*

Interventions	Parenteral influenza vaccine, participants were also offered pneumococcal vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487)
Notes	44% of cases and 32% of controls received pneumococcal vaccination. The season was probably an epidemic one. The study controls for confounders in analysis: influenza activity, health status, age, sex, region. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ohmit 1999

Study characteristics

Methods	Case-control study conducted in Michigan, USA during the 1989 to 1990 influenza season, in 23 nursing homes. Data sources were: patients specific logs, vaccination records. Follow-up period was the epidemic period according to surveillance data. Cases developed ILI during the period of laboratory-confirmed community influenza activity; controls resided in the same facility and were matched for age.
Participants	1198 residents in 23 nursing homes that experienced outbreaks or with virus isolation (361 cases and 837 controls, all included in analysis), 65 years or older
Interventions	Parenteral influenza vaccine; 17% of cases and 17% of controls received pneumococcal vaccination. Vaccine strains matched the circulating strain.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater and 1 or more of the following: cough, sore throat, coryza)
Notes	Circulating strain: A/Shanghai/11/87. The season was an epidemic one. The study controls for confounders in analysis: home size, vaccination level, sex, and age. Quantitative analysis was not performed, as the logistic model used by the authors did not control by health status.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Patriarca 1985a

Study characteristics

Methods	Retrospective cohort study conducted in Michigan, USA during the 1982 to 1983 influenza season. Authors investigated 7 nursing homes with evidence of flu activity. Throat swab and paired sera specimens were obtained from some residents; medical records. Follow-up period was 10 December 1982 to 4 March 1983.

Patriarca 1985a *(Continued)*

Participants	1018 residents in 7 nursing homes with outbreak (548 treated and 470 controls, all included in the analysis)
Interventions	Parenteral influenza vaccine: A/Bangkok/79; A/Brazil/78; B/Singapore/79. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater + cough, coryza, or sore throat), X-ray-confirmed pneumonia, hospitalisation for ILI, deaths occurring within 2 weeks of onset of ILI. An outbreak was defined by a number of ILI per week that exceeded 10% of the residents.
Notes	Cohorts were comparable as age and level of nursing care. Amantadine was not used. The circulating strain was A/Bangkok/1/79-like. Laboratory confirmation of influenza A infection was obtained in 3 homes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Patriarca 1985b

Study characteristics

Methods	Retrospective cohort study conducted in Michigan, USA during the 1982 to 1983 influenza season, in 6 nursing homes. Throat swab and paired sera specimens were obtained from some residents; medical records were reviewed. Follow-up period was 10 December 1982 to 4 March 1983.
Participants	458 residents in 6 nursing homes without outbreak (339 treated and 119 controls, all included in the analysis)
Interventions	Parenteral influenza vaccine: A/Bangkok/79; A/Brazil/78; B/Singapore/79. Vaccine strains matched circulating strains.
Outcomes	Clinically defined ILI (fever 37.8 °C or greater + cough, coryza, or sore throat), deaths occurring within 2 weeks of onset of ILI
Notes	Cohorts were comparable as age and level of nursing care. Amantadine was not used. The circulating strain in the community was A/Bangkok/1/79-like, but laboratory confirmation was not available in the homes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Pregliasco 2002

Study characteristics

Pregliasco 2002 *(Continued)*

Methods	Prospective cohort study conducted in Milan, Italy during the 2000 to 2001 influenza season, in the community. Data sources were: monthly phone interviews and self administered questionnaires. Follow-up period was 30 November 2000 to 31 March 2001.
Participants	363 community-dwelling elderly (264 treated and 99 controls; 184 and 79 included in the analysis, respectively), mean age 75 years
Interventions	Adjuvant virosomal vaccine. Vaccine strains probably matched the circulating strain.
Outcomes	Clinically defined ILI (fever + at least 1 systemic symptom: headache, myalgia, chills, weakness + at least 1 respiratory symptom: cough, sore throat, congestion); acute respiratory infection (respiratory symptoms without immediate fever); hospitalisation for pulmonary infection
Notes	Low viral circulation. Cohorts were not significantly different as comorbidity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Puig-Barberà 1997

Study characteristics

Methods	Case-control study conducted in Spain during the 1994 to 1995 influenza season, in the community. Data sources were: hospital emergency logs and records; structured interview. Follow-up period was 15 November 1994 to 31 March 1995. Cases were people admitted to hospital for pneumonia; controls were admitted to hospital in the same week for acute abdominal surgical condition or trauma.
Participants	249 non-institutionalised people (94 cases and 166 controls were identified; 83 and 166 were included in analysis, respectively), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation for pneumonia; pneumonia was clinically defined and radiologically confirmed
Notes	The study controls for confounders in analysis: health status, age, socio-economic factors. The season probably had low epidemic levels. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Puig-Barberà 2004

Study characteristics

Puig-Barberà 2004 *(Continued)*

Methods	Case-control study conducted in Valencia, Spain during the 2002 to 2003 influenza season, in the community. Data sources were: hospital records; structured interview by trained field investigator. Follow-up period was 15 November 2002 to 31 March 2003. Cases were people admitted to hospital for pneumonia; controls were admitted to hospital in the same week for acute abdominal surgical condition or trauma.
Participants	815 non-institutionalised people (325 cases and 525 controls were identified; 290 and 525 were included in analysis, respectively), 65 years or older
Interventions	Parenteral influenza MF59 adjuvant vaccine. 42% of cases and 34% of controls received pneumococcal vaccination. Vaccine strains matched the circulating strain.
Outcomes	Hospitalisation for pneumonia (ICD-9 code 480-487); pneumonia was clinically defined and radiologically confirmed
Notes	The study controls for confounders in analysis: health status, smoking habits, pneumococcal vaccination. The season had low epidemic levels. Quantitative analysis was also performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Puig-Barbera 2007

Study characteristics

Methods	3 case-control studies were performed in the elderly population (> 64 years of age) of 3 health districts in the Valencia Autonomous Region, Spain (total number of elderly residents in these districts: n = 105,454 at 31 December 2004), where MF59-adjuvanted subunit influenza vaccine was used. The risk of hospitalisation for ACS, CVA, or pneumonia was evaluated for people who had received influenza vaccine and for those who had not received influenza vaccine.
Participants	**Description of cases** Incident cases for each disease were identified from all consecutive emergency hospitalisations following their admission between 15 November 2004 and 31 March 2005. Diagnoses were made according to the International Classification of Diseases, 9th version, Clinical Modification for ACS (410-411.89 and 413), CVA (431-436), or pneumonia (480-487). Only non-institutionalised patients who were > 64 years of age, had lived in the hospital catchment area for the previous 6 months, were able to give informed consent, and remained in hospital for at least 72 hours were included in the study. After consideration of the exclusion criteria, 144 cases admitted for ACS, 134 for CVA, and 198 for pneumonia were included in the study. **Description of controls** Each case was paired with 1 or 2 controls, matched for hospital and gender. Controls were recruited based on the same inclusion criteria as cases, following emergency hospitalisations for an acute surgical process or trauma. The admission date for controls was matched to the case admission date, preferably being the same day, and with a maximum interval of 10 days. 258 controls were admitted for ACS, 246 for CVA, and 321 for pneumonia. A total of 75.2% and 78.1% of vaccinated cases and controls, respectively (P = 0.314) were vaccinated and on the population register. Of these, all cases and 99.73% of controls had received MF59-adjuvanted subunit influenza vaccine.

Puig-Barbera 2007 *(Continued)*

Interventions	Influenza vaccination and hospitalisation for ACS, CVA, and pneumonia
Outcomes	—
Notes	The authors conclude that the results suggest that MF59-adjuvanted influenza vaccination is associated with a significant reduction in the risk of hospitalisation for ACS, CVA, and pneumonia during the period of influenza virus circulation.

Ruben 1974

Study characteristics		
Methods	Authors investigated an outbreak in a nursing home in California, USA during the 1972 to 1973 influenza season; independent blind assessment was conducted. Follow-up period was 20 December 1972 to 28 January 1973. Throat swabs were obtained from ill residents.	
Participants	392 nursing home residents (204 treated and 192 controls, all included in the analysis). Participants were both ambulatory and bedridden.	
Interventions	Parenteral influenza vaccine: A/Aichi/2/62; B/Mass/1/71. Vaccine strains did not match circulating strains.	
Outcomes	Clinically defined ILI (fever 37.7 °C + upper respiratory symptoms), laboratory-confirmed ILI (positive swab culture), deaths from outbreak-related respiratory illness	
Notes	Data stratified by nurse floor. The circulating strain was A/ENG/42/72.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rudenko 2001

Study characteristics	
Methods	Experimental study conducted in Russia during the 1996 to 1997 influenza season, randomised, double-blind, placebo controlled; random sample stratified by age and underlying health conditions. Follow-up period was 20 January 1997 to 2 March 1997
Participants	602 nursing home residents (93 vaccinated with parenteral vaccine, 111 vaccinated with aerosol vaccine, and 109 controls); severely debilitated and immunosuppressed people were excluded; 41 to 95 years, median 73 years
Interventions	Live cold-adapted vaccine aerosol administered: A/Leningrad/134/17/57; B/Ann Arbor/60/69 parenteral vaccine: A/Texas/36/91; A/Nanchang/933/95; B/Harbin/7/94. Vaccine strains matched the circulating strains
Outcomes	Laboratory-confirmed influenza: positive swab or 4-fold or greater increase in antibody titre

Rudenko 2001 *(Continued)*

Notes	No description of methods; 1 or 2 doses' efficacy was tested; data were extracted irrespective of the number of doses administered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random allocation sequence not described and the six groups have uneveven denominators
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Unexplained attrition both for efficacy and serological outcomes. Harms are not mentioned at all in the report. This is a particular problem in the use of live attenuated vaccines in elderly or infirm people

Saah 1986a

Study characteristics

Methods	Prospective cohort study conducted in New York, USA during the 1979 to 1980 influenza season. Authors investigated a nursing home with evidence of flu activity; medical records were reviewed. Comparability between cohorts was assessed by analysis of the underlying conditions of a sample of the population; 62 people with severe organic brain syndrome were excluded. Follow-up period was 1 November 1979 to 30 April 1980.
Participants	453 residents in nursing home for healthy and ill elderly (219 treated and 234 controls, all included in the analysis); most patients required skilled nursing home care
Interventions	Parenteral influenza vaccine: A/Brazil/78; A/Texas/77; B/Hong Kong/72. Matching between vaccine and circulating strains is unknown.
Outcomes	Symptoms defined and radiologically confirmed pneumonia; death from pneumonia within 60 days from the onset of pneumonia
Notes	Vaccinated participants had very slight excess of underlying conditions; smokers were rare; pneumococcal vaccine was rarely used. Specific viral diagnosis was not attempted, but the circulating strain in the community was B/Singapore/79-like.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Saah 1986b

Study characteristics	
Methods	Prospective cohort study conducted in New York, USA during the 1980 to 1981 influenza season. Authors investigated a nursing home with evidence of flu activity; medical records were reviewed. Comparability between cohorts was assessed by analysis of the underlying conditions of a sample of the population; 62 people with severe organic brain syndrome were excluded. Follow-up period was 1 November 1980 to 30 April 1981.
Participants	458 residents in nursing home for healthy and ill elderly (244 treated and 214 controls, all included in the analysis); most patients required skilled nursing home care
Interventions	Parenteral influenza vaccine: A/Brazil/78; A/Bangkok/79; B/Singapore/79. Vaccine strains matched circulating strains.
Outcomes	Symptoms defined and radiologically confirmed pneumonia; death from pneumonia within 60 days from the onset of pneumonia
Notes	Vaccinated participants had very slight excess of underlying conditions; smokers were rare; pneumococcal vaccine was rarely used. Specific viral diagnosis was not attempted, but the circulating strain in the community was A/Bangkok/79-like.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Saah 1986c

Study characteristics	
Methods	Prospective cohort study conducted in New York, USA during the 1981 to 1982 influenza season in 26 nursing homes. Comparability between cohorts was assessed by analysis of the underlying conditions of a sample of the population; 62 people with severe organic brain syndrome were excluded; medical records were reviewed. Follow-up period was 1 November 1981 to 30 April 1982.
Participants	451 residents in nursing home for healthy and ill elderly (225 treated and 226 controls, all included in the analysis); most patients required skilled nursing home care
Interventions	Parenteral influenza vaccine: A/Brazil/78; A/Bangkok/79; B/Singapore/80. Matching between vaccine and circulating strains is unknown.
Outcomes	Symptoms defined and radiologically confirmed pneumonia; death from pneumonia within 60 days from the onset of pneumonia
Notes	Vaccinated participants had very slight excess of underlying conditions; smokers were rare; pneumococcal vaccine was rarely used. The circulating strain was not identified.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Saito 2002a

Study characteristics	
Methods	Prospective cohort study conducted in Japan during the 1998 to 1999 influenza season in 9 nursing homes. Follow-up period was the epidemic period. Efficacy assessment was also performed by vaccination rate in residents and HCWs, physical impairment, sex, age, and health status of residents. Throat swabs were obtained from ill individuals; medical charts were reviewed.
Participants	699 residents in 9 nursing homes (331 treated and 368 controls, all included in the analysis). The vaccinated group had more underlying diseases.
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Mie/1/93. Vaccine strains matched circulating strains (good match).
Outcomes	Clinically defined ILI (fever + cough or coryza or sore throat) occurring during the epidemic period
Notes	The circulating strain was A/Sydney. Influenza virus exposure was confirmed in all 9 facilities. Outbreaks were demonstrated in only 4 homes. No other respiratory viruses were isolated. Data were extracted by RRs reported in tables.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Saito 2002b

Study characteristics	
Methods	Prospective cohort study conducted in Japan during the 1999 to 2000 influenza season in 11 nursing homes. Follow-up period was the epidemic period. Efficacy assessment was also performed by vaccination rate in residents and HCWs, physical impairment, sex, age, and health status of residents. Throat swabs were obtained from ill individuals; medical charts were reviewed.
Participants	930 residents in 11 nursing homes (743 treated and 187 controls, all included in the analysis). The vaccinated group had more physical impairment of daily living.
Interventions	Parenteral influenza vaccine: A/Beijing/262/95; A/Sydney/5/97; B/Shandon/7/97. Vaccine strains matched circulating strains (good match).
Outcomes	Clinically defined ILI (fever + cough or coryza or sore throat) occurring during the epidemic period
Notes	The circulating strain was A/Sydney. Influenza virus exposure was confirmed in only 4/11 facilities. No outbreaks were detected. No other respiratory viruses were isolated. Data were extracted by RRs reported in tables.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Schonberger 1979

Study characteristics	
Methods	Surveillance population-based study conducted in the USA during the 1976 to 1977 influenza season. Neurologists were directly contacted; physician and hospital records were reviewed. Suspected cases reported to the Centers for Disease Control and Prevention directly by patients or medical personnel were included only if accepted by a state health department. Follow-up period was 1 October 1976 to 31 January 1977.
Participants	USA population
Interventions	Monovalent A/New Jersey/76 or bivalent A/New Jersey/76 and A/Victoria/75 parenteral vaccine
Outcomes	Cases of Guillain-Barré syndrome
Notes	Results were stratified by age group and vaccine type. Vaccination rates in population were obtained from national immunisation survey.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Shapiro 2003

Study characteristics	
Methods	Retrospective cohort study conducted in Israel during the 2000 to 2001 influenza season, in the community. Data source was managed care organisation database. Follow-up period was the entire influenza season.
Participants	84,640 community-dwelling elderly (36,596 treated and 48,044 controls included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strain probably matched the circulating strain (literature).
Outcomes	Hospitalisation for any reason; deaths from all causes
Notes	Very poor description of methods; no information about flu activity: probably not epidemic year. Data were presented by health status. Only deaths were included in the analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Strassburg 1986

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home in Los Angeles, USA during the 1982 to 1983 influenza season; patients records were reviewed. Follow-up period was 1 February 1983 to 31 March 1983. Virus circulation was confirmed with throat swab from ill people.
Participants	87 nursing home residents, 59 to 94 years old, most of them suffering from dementia (65 treated and 19 controls were included in the analysis; vaccination status could not be determined for 3 residents)
Interventions	Parenteral influenza vaccine: A/Bangkok/79; A/Brazil/78; B/Singapore/79. Vaccine strains probably matched circulating strains.
Outcomes	Clinically defined ILI (fever or fever + respiratory symptoms) occurring during the epidemic period, deaths from ILI
Notes	Age, sex ratio, and health status were similar in vaccinated and unvaccinated people. The circulating strain was A/Bangkok/79-like. No other positive laboratory findings were found. Amantadine was not used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Stuart 1969

Study characteristics	
Methods	Experimental study conducted in California, USA during the 1965 to 1966 influenza season; the control group received influenza B vaccine, placebo, or no vaccine; laboratory samples were obtained from ill people to confirm the infection active surveillance. Follow-up period was 1 February 1966 to 30 April 1966.
Participants	4180 residents in the nursing home, healthy (1561 treated and 2619 controls were included in the analysis), 52 years or older
Interventions	Monovalent A2 parenteral influenza vaccine: A2/Taiwan/1/64. Vaccine strains matched the circulating strains
Outcomes	Clinically defined febrile illness (fever + cough or malaise or coryza or myalgia or headache), clinically defined afebrile illness, hospitalisation and deaths without definition. Harms were reported, but they were excluded from analysis, as they refer to an old oil adjuvant vaccine
Notes	Participants randomised the previous year but not vaccinated (reason not explained) in the current year were added in the control group; the study year was an epidemic one

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details available to permit judgement

Stuart 1969 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient details available to permit judgement
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data available for most participants in the study

Taylor 1992

Study characteristics	
Methods	Authors investigated an outbreak in a nursing home in Washington, USA during the 1988 to 1989 influenza season; residents' records and hospital charts were reviewed. Follow-up period was 29 January 1989 to 1 March 1989. Throat swabs were obtained from a sample of acutely ill residents; paired sera were obtained from 63% of both ill and well residents.
Participants	109 nursing home residents (48 treated and 61 controls; 45 and 52 included in the analysis, respectively), 58 to 105 years old. Groups were similar in age, gender, and level of care required.
Interventions	Parenteral influenza vaccine: A/Taiwan; A/Sichuan; B/Victoria. Vaccine strains probably matched circulating strains.
Outcomes	Outbreak-associated cases: clinically defined ILI (fever + cough) or laboratory-confirmed influenza (4-fold increase in antibody titre), pneumonia, hospitalisation from ILI or pneumonia, deaths from ILI or pneumonia
Notes	Vaccination was not offered to staff. Positive specimens showed a diagnostic titre rise to A/Sichuan, but no virus was isolated; matching was only hypothetic. Amantadine was not used. Laboratory-confirmed cases were analysed by intention-to-treat.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Treanor 1994

Study characteristics	
Methods	Experimental study conducted in New York, USA during the 1990 to 1991 influenza season, randomised, double-blind, placebo-controlled study. 34 participants received live vaccine; 30 participants received trivalent vaccine; 11 participants received placebo. Follow-up period was for 7 days after vaccination. Participants filled self administered diary card.
Participants	75 outpatients with chronic disease or elderly, mostly 65 years or older

Treanor 1994 *(Continued)*

Interventions	Live cold-adapted influenza B virus vaccine, aerosol administered; parenteral trivalent influenza vaccine
Outcomes	Upper respiratory symptoms (coryza or sore throat), lower respiratory symptoms (cough, hoarseness, or dyspnoea), systemic symptoms (malaise and myalgia), sore arm, fever
Notes	Participants experiencing symptoms within 1 week of vaccination were considered.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as placebo controlled, but no further details available
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition

Voordouw 2003

Study characteristics

Methods	Retrospective cohort study conducted in the Netherlands during the 1996 to 1997 influenza season, in the community. Data source was the managed care organisation database. Follow-up period was 1 September 1996 to 1 June 1997. For every individual who had received an influenza vaccination, 1 age-sex matched unvaccinated control participant was randomly selected.
Participants	17,822 community-dwelling elderly with a permanent status in 1 of the practices (8911 treated and 8911 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strain matched the circulating strain.
Outcomes	Influenza as defined by International Classification of Primary Care (R80: proven influenza without pneumonia), pneumonia, deaths from all causes
Notes	The influenza season was relatively mild. Data were stratified by age and health status. Quantitative analysis was also performed only for the outcome 'deaths from all causes'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

ACS = acute coronary syndromes
CAP = community-acquired pneumonia

CVA = cerebrovascular accident
HCWs = healthcare workers
ICD = International Classification of Diseases
ILI = influenza-like illness
NI = neuroaminidase inhibitor
OR = odds ratio
RR = risk ratio
URI = upper respiratory infection
WHO = World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allsup 2001	Elderly denominator 19 and no breakdown of cases by age groups is given
Allsup 2003	See Allsup 2004
Anonymous 1995	Comment
Anonymous 2004b	No data presented.
Ansaldi 2002	Cross-sectional study
Arden 1986	Review
Armstrong 2004	Data presented cannot be used in the analysis; the statistical model is not comparable with that used in the other studies.
Arroyo 1988	Description of epidemic
Arya 2003	No data presented.
Ayala-Montiel 2004	No placebo/do nothing comparator: influenza + pneumococcus versus influenza vaccine
Baldo 1999	Lack of a control group
Barker 1980	Cross-sectional study
Bektimirov 1993	No original data presented.
Belshe 2004	Children and adults
Ben-Yehuda 2003	No placebo/do nothing comparator
Berg 2004	The study does not investigate the vaccine efficacy.
Buxton 2001	Lack of a control group
Carman 2000	Data are not presented by vaccine condition.
Castilla 2006	Retrospective paper looking at vaccination cover in > 65 and relations with effectiveness claimed as efficacy. Only 60 influenza-like illness cases were tested out of a total of 2300.
Chen 2004	The study does not investigate the vaccine efficacy.
Chlibek 2002	This could be a cohort study to be considered for the adults review.

Study	Reason for exclusion
Christenson 2002	Same cohorts of Christenson 2001
Chumakov 1992	High-risk groups
Cohen 2004	Does not present original data
Conne 1997	Lack of a control group
Cruijff 1999	Same cohorts of Govaert 1994a
D'Alessandro 2004	Both arms administered influenza vaccine, no placebo/do nothing comparator.
de Bernardi 2002	Healthy adults; lack of a control group
de Bruijn 2004	Serological outcome only
Deguchi 2000a	Same cohorts of Deguchi 2001
Deguchi 2000b	Same cohorts of Deguchi 2001
Deguchi 2000c	Same cohorts of Deguchi 2001
Deibel 1970	The study does not investigate the vaccine efficacy.
De Serres 2004	Same data set as Skowronski - high-risk group
Elder 1996	Healthy adults
Ender 2001	Assessment of vitamins before vaccination as immunomodulators
Erofeeva 2001	Frequency data are not reported; outcome is not clearly defined.
Fedson 1992	The study does not investigate the vaccine efficacy.
Fedson 1993	Comment
Fitzner 2001	Economic study without original data
Fukumi 1969	The study does not investigate the vaccine efficacy.
Fukushima 1999	Serological outcome only
Galanti 1976	Data presented cannot be estimated for the analysis.
Galasso 1977	Healthy adults
Garcia-Doval 2001	Case report
Garcia-Garcia 2009	Only 16% of participants are over the age of 60.
Gasparini 2002	Economic study; data source not described
Gavira 1990	Economic evaluation
Gendon 1988	No original data presented.

Study	Reason for exclusion
Giglio 1994	Unclear study design; probably retrospective cohort based only on individual recall of disease
Glass 1978	The study does not investigate the vaccine efficacy.
Glezen 1987	The study does not investigate the vaccine efficacy.
Gomez de Caso 1996	The study does not investigate the vaccine efficacy.
Govaert 1994b	Antibody outcomes only
Gowda 1979	The study does not investigate the vaccine efficacy.
Grigor'eva 1994	Study population is children.
Grigor'eva 2002	Study population is children.
Gross 1977	Study population is children.
Gross 1995	Review
Guarino 1977	Serological survey
Guillevin 1983	The study does not investigate the vaccine efficacy.
Gutierrez 2001	Unclear study design; probably retrospective cohort based only on individual recall of disease; 1-year follow-up
Hak 1998	High-risk groups
Hall 1981	The study does not investigate the vaccine efficacy.
Hampson 1997	Economic review
Hara 2008	Redundant publication of Hara 2006
Harling 2004	NI used
Harper 1985	Comment
Hedlund 2003	Same cohorts of Christenson 2001
Helliwell 1988	Economic evaluation
Hennessen 1978	Cross-sectional study
Herzog 2003	The study does not investigate the vaccine efficacy.
Heymann 2004	Same cohorts of Shapiro 2003
Hirota 1997	Healthy adults
Hoberman 2003	Study population is children.
Hope-Simpson 1970	The study does not investigate the vaccine efficacy.

Study	Reason for exclusion
Howell 1967	Not elderly
Hurwitz 1983	Non-comparative data
Icardi 2002	Unclear study design; probably cross-sectional
Ikematsu 1998	Poorly described study. Influenza-like illness was defined only as "fever". Deaths from all causes referred to too long a period (from January to September).
Ikematsu 2000	Poorly described study. Influenza-like illness was defined only as "fever". Asymptomatic infections were indistinguishable from symptomatic ones.
Isahak 2007	Inadequate comparator
Jackson 1999	High-risk groups
Jackson 2002	High-risk groups
Jahnz-Rozyk 2003	Economic evaluation
Jani 1994	Case report
Jarstrand 1974	The study does not investigate the vaccine efficacy.
Jovanovic 1977	Lack of a control group; high-risk groups
Kaplan 1983	Non-comparative design
Keavey 1999	No data
King 1997	Comment
Knight 1984	Case report
Knottnerus 1996	Cost-of-illness study
Kurland 1984	Non-comparative study
Landi 2003	1-year follow-up in a population with important diseases
Landi 2006	Same data set as Landi 2003
Lavergne 1980	No placebo/do nothing comparator, serological responses and age group?
Lawson 2000	Frequency data not reported.
Lindahl 1999	Case report
Lohse 1999	Case report
Luce 2001	Economic evaluation
Mair 1974	Lack of a control group
Mandal 1973	Descriptive

Study	Reason for exclusion
Manzano 2000	Case report
Manzoli 2007	Feasibility study of general practice reporting method to assess vaccine effectiveness
Margolis 1990b	No placebo/do nothing comparator
Marine 1973	Serological outcome only
Marinich 1997	Serological outcome only
Martin 1997	Lack of a control group
Marwick 1995	Comment
Masurel 1979	Antibody only
Maxim 1998	No data presented.
Mayon-White 1994	No data presented.
McCall 1996	No data presented.
McCarthy 1978	No data presented.
McElhaney 2002	No data presented.
McGuffey 1993	No data presented.
Meiklejohn 1989	Interruption study
Mendelman 2001	Study population is children and adults.
Meynaar 1991	Comment
Mignogna 2000	Case report
Miller 1975	Lack of a control group
Modlin 1977	Children
Monto 1994	No data presented.
Moreno 2009	Non-systematic review and meta-analysis with metaviews back to front
Mostow 1969	Lack of a control group
Mostow 1988	No data presented.
Nguyen-van-Tam 1992	Unclear study design
Nichol 1996	Same cohorts of Nichol 1994
Nichol 1999a	No original effectiveness data presented.
Nichol 1999b	Same cohorts of Nichol 1994

Study	Reason for exclusion
Nichol 1999c	High-risk groups
Nichol 1999d	Adult population
Nichol 2002	Same cohorts of Nichol 1998
Nichol 2007	Data already included in review from other publication by the same author
Nicholson 1979	No placebo/do nothing comparator
Nicholson 1983	Lack of a control group
Nicholson 1990a	Unclear study design; symptomatic participants only
Nicholson 1990b	No data presented.
Nicholson 1992	Unclear study design; symptomatic participants only
Nielsen 1996	No data presented.
Nygaard 1999	No data presented.
Odelin 1993	Lack of a control group
Odelin 2003	Lack of a control group
Ohmit 1995	Same population as Ohmit 1995
Ortqvist 2007	Data already included in the 2005 review; re-analysis of the same data set
Oshitani 2000	Ecological study
Parkin 1978	Case series
Parsons 1997	No data
Patel 1988	Case report
Patriarca 1985	The study does not investigate the vaccine efficacy.
Patriarca 1994	Comment
Pena-Rey 2003	The study does not investigate the vaccine efficacy.
Perez 2000	Case report
Perez-Tirse 1992	Review of economic evaluations
Perucchini 2004	Lack of a control group
Peters 1988	Serological outcomes
Philip 1969	Data are not presented by age.
Phillips 1970	Lack of a control group

Study	Reason for exclusion
Phillips 1971	Comment
Piedra 2002	Study population is children.
Poe 1977	Not about vaccine effectiveness
Poland 2002	Review
Potter 1997	Data are not presented by vaccine condition.
Powers 1991	Serological outcome only
Pregliasco 1997	Not about vaccine effectiveness
Pregliasco 1999	The study does not investigate the vaccine efficacy.
Profeta 1987	Serological outcome only
Provinciali 1994	Unclear study design
Puig Barberà 1995	Review
Puretz 1979	Review
Pyhala 1997	Guideline
Quinlisk 1990	Not about vaccines
Quinnan 1983	Does not report safety outcomes by age group
Rao 1982	Not about vaccines
Read 2000	No outcome data by vaccine status, uncertain denominators
Reedy 2000	Review
Ruben 1973	Serological outcome only
Rubin 1973	No data
Rudenko 1981	Review
Rudenko 1993	Children
Ruel 2002	Only 1 participant was unvaccinated.
Ruf 2004	Antibody titres and no placebo/do nothing comparator
Runehagen 2002	Not about vaccines
Russell 2001	Not about vaccines
Ryan 1984	No placebo/do nothing comparator
Sadler 2000	Not about vaccines

Study	Reason for exclusion
Sandrini 1997	Data only in graphs
Saslaw 1966	Antibody responses
Satsuta 1985	Not about vaccines
Schoenbaum 1969	Poor description; data do not fit the comparison of this review
Schwartz 1995	Comment
Selvaraj 1998	Case report
Serie 1977	Very poor description; absence of definitions, incoherence between data reported in text and data reported in tables
Sethi 2002	Not about vaccines
Sharbaugh 1997	Descriptive study
Shinkawa 2002	No data
Shoji 2003	Comment
Siewert 1988	The study does not investigate the vaccine efficacy.
Simonsen 2005	Ecological study
Skowronski 2003	High-risk groups
Skull 2009	Study assessing risk factors for community-acquired pneumonia. Insufficient data presented for evaluation of influenza vaccine effectiveness.
Slepuskin 1967	Ecological study
Sloan 1993	Comment
Socan 2004	Lack of a control group
Solomon 1984	Case report
Solomon 1996	Case report
Solomon 1999	Case report
Spencer 1979	Healthy adults
Sprenger 1990	The study does not investigate the vaccine efficacy.
Squarcione 2003	No placebo/do nothing comparator
Stamboulian 1999	Unclear study design
Stott 2001	Letter with no data
Tamblyn 1997	Comment

Study	Reason for exclusion
Thompson 1988	Review
Treanor 1992	Lack of a control group
Treanor 1998	Lack of a control group
Tsai 2007	Model based on aspecific outcomes
Upshur 2000	Descriptive study
Urquhart 1974	Antibody titres
Uyeki 2003	The study does not investigate the vaccine efficacy.
Vallee 2000	No data presented.
Van Horren 1976	Not about effectiveness
van Vuuren 2009	Insufficient data
Verde 1973	Serological outcomes
Verweij 2002	Ethical study
Vila-Corcoles 2005	Insufficient data reported.
Visconti 1973	Serological outcomes
Voordouw 2004	Lack of a control group
Voordouw 2006	Insufficient data reported (denominators are not reported).
Vu 2002	Review
Wagner 1993	Lacks controls
Wagner 1994	Comment
Wakefield 1990	The study does not investigate the vaccine efficacy.
Wang 1986	Comment
Wang 2002	1-year follow-up
Warburton 1972	Ecological study
Wareing 2001	Review
Watson 1997	Review
Weaver 2001	The study does not investigate the vaccine efficacy.
Wiehl 2001	Comment
Williams 1980	Comment

Study	Reason for exclusion
Wilson 1994	Comment
Winer 1984	Survey of cases
Wise 1977	Healthy adults
Wood 2000	Review
Woratz 1984	Methodological paper
Yassi 1993	Vaccine and amantadine were used to control outbreak: amantadine acts as confounder.
Zambon 2001	The study does not investigate the vaccine efficacy.
Zimmerman 2004	Not about vaccine effectiveness
Zoffmann 1977	Not about vaccine effectiveness
Zourbas 1973	Serological outcome only
Zuckerman 1990	Serological outcome only
Zuckerman 1992	Serological outcome only
Zuckerman 1993	Serological outcome only

NI: neuoraminidase inhibitors

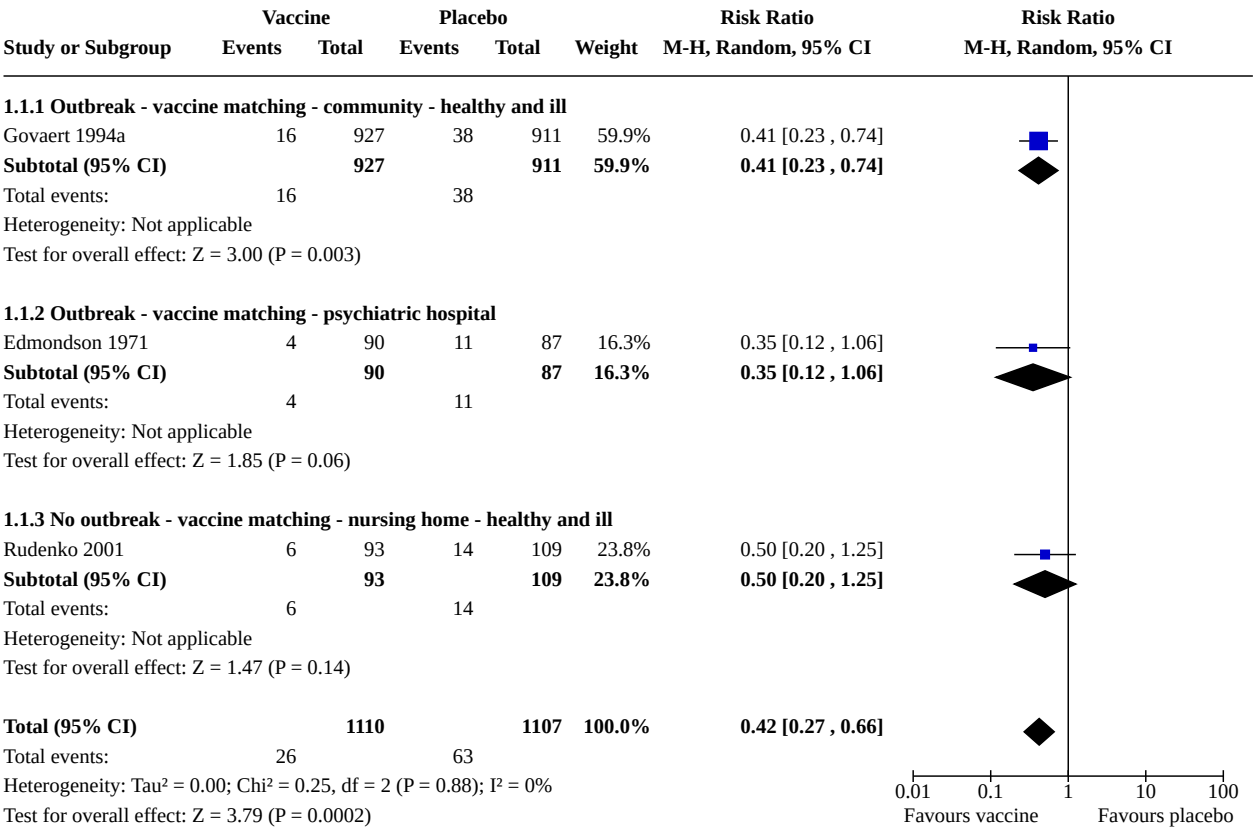
DATA AND ANALYSES

Comparison 1. Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Influenza	3	2217	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.27, 0.66]
1.1.1 Outbreak - vaccine matching - community - healthy and ill	1	1838	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.74]
1.1.2 Outbreak - vaccine matching - psychiatric hospital	1	177	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.12, 1.06]
1.1.3 No outbreak - vaccine matching - nursing home - healthy and ill	1	202	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.25]
1.2 Influenza-like illness	4	6894	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.47, 0.73]
1.2.1 Outbreak - vaccine matching (circulating strains) - community - healthy	2	2047	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.79]

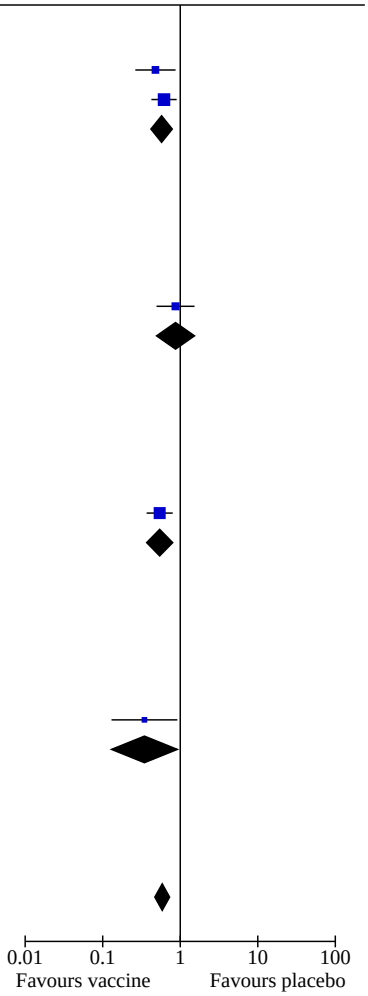
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Outbreak - vaccine matching - community - risk groups	1	490	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.49, 1.53]
1.2.3 Outbreak - vaccine matching - nursing home - healthy	1	4180	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.37, 0.80]
1.2.4 Outbreak - vaccine matching - psychiatric hospital	1	177	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.92]
1.3 Pneumonia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3.1 Outbreak - vaccine matching - community - healthy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.4 All deaths	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.4.1 Outbreak - vaccine matching - community - healthy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine, Outcome 1: Influenza



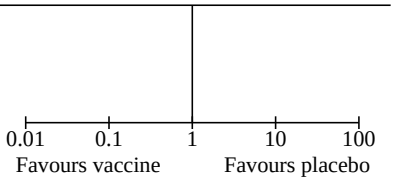
Analysis 1.2. Comparison 1: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine, Outcome 2: Influenza-like illness

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Outbreak - vaccine matching (circulating strains) - community - healthy						
Allsup 2004	24	522	17	177	13.5%	0.48 [0.26 , 0.87]
Govaert 1994a	41	676	66	672	34.3%	0.62 [0.42 , 0.90]
Subtotal (95% CI)		**1198**		**849**	**47.8%**	**0.57 [0.42 , 0.79]**
Total events:	65		83			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
1.2.2 Outbreak - vaccine matching - community - risk groups						
Govaert 1994a	21	251	23	239	15.1%	0.87 [0.49 , 1.53]
Subtotal (95% CI)		**251**		**239**	**15.1%**	**0.87 [0.49 , 1.53]**
Total events:	21		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
1.2.3 Outbreak - vaccine matching - nursing home - healthy						
Stuart 1969	33	1561	102	2619	32.1%	0.54 [0.37 , 0.80]
Subtotal (95% CI)		**1561**		**2619**	**32.1%**	**0.54 [0.37 , 0.80]**
Total events:	33		102			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
1.2.4 Outbreak - vaccine matching - psychiatric hospital						
Edmondson 1971	5	90	14	87	5.0%	0.35 [0.13 , 0.92]
Subtotal (95% CI)		**90**		**87**	**5.0%**	**0.35 [0.13 , 0.92]**
Total events:	5		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.13 (P = 0.03)						
Total (95% CI)		**3100**		**3794**	**100.0%**	**0.59 [0.47 , 0.73]**
Total events:	124		222			
Heterogeneity: Tau² = 0.00; Chi² = 3.67, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 4.78 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.17, df = 3 (P = 0.37), I² = 5.2%						



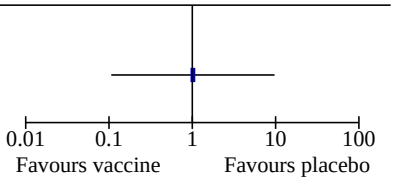
Analysis 1.3. Comparison 1: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine, Outcome 3: Pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.3.1 Outbreak - vaccine matching - community - healthy					
Allsup 2004	0	522	0	177	Not estimable



Analysis 1.4. Comparison 1: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine, Outcome 4: All deaths

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.4.1 Outbreak - vaccine matching - community - healthy					
Allsup 2004	3	522	1	177	1.02 [0.11 , 9.72]



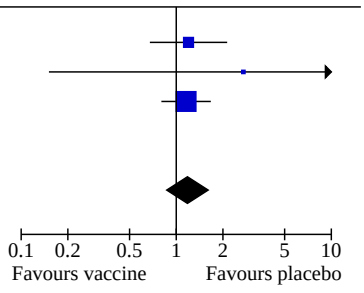
Comparison 2. Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 General malaise	4	2560	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.87, 1.61]
2.2 Nausea	1	672	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.74, 4.12]
2.3 Upper respiratory tract symptoms	2	713	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.90, 2.01]
2.4 Headache	3	2519	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.76, 1.58]
2.5 Fever	3	2519	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.92, 2.71]
2.6 Local tenderness/sore arm	4	2560	Risk Ratio (M-H, Random, 95% CI)	3.56 [2.61, 4.87]
2.7 Swelling - erythema - induration	2	1847	Risk Ratio (M-H, Random, 95% CI)	8.23 [3.98, 17.05]

Analysis 2.1. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 1: General malaise

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Margolis 1990a	24	336	20	336	28.7%	1.20 [0.68 , 2.13]
Treanor 1994	3	30	0	11	1.1%	2.71 [0.15 , 48.62]
Govaert 1993	58	904	50	902	70.2%	1.16 [0.80 , 1.67]
Keitel 1996	0	21	0	20		Not estimable
Total (95% CI)		**1291**		**1269**	**100.0%**	**1.18 [0.87 , 1.61]**
Total events:	85		70			

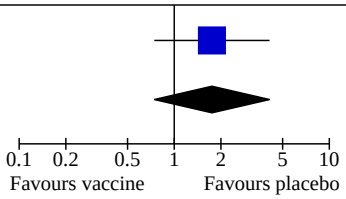
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 2: Nausea

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Margolis 1990a	14	336	8	336	100.0%	1.75 [0.74 , 4.12]
Total (95% CI)		**336**		**336**	**100.0%**	**1.75 [0.74 , 4.12]**
Total events:	14		8			

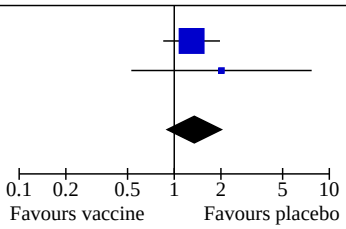
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 3: Upper respiratory tract symptoms

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Margolis 1990a	44	336	34	336	91.0%	1.29 [0.85 , 1.97]
Treanor 1994	11	30	2	11	9.0%	2.02 [0.53 , 7.69]
Total (95% CI)		**366**		**347**	**100.0%**	**1.35 [0.90 , 2.01]**
Total events:	55		36			

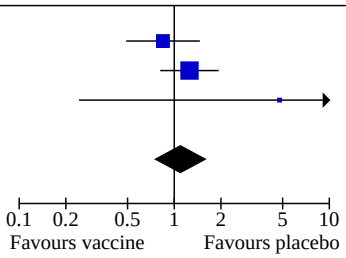
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 4: Headache

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Margolis 1990a	22	336	26	336	39.6%	0.85 [0.49 , 1.46]
Govaert 1993	44	904	35	902	58.8%	1.25 [0.81 , 1.94]
Keitel 1996	2	21	0	20	1.5%	4.77 [0.24 , 93.67]
Total (95% CI)		**1261**		**1258**	**100.0%**	**1.10 [0.76 , 1.58]**
Total events:	68		61			

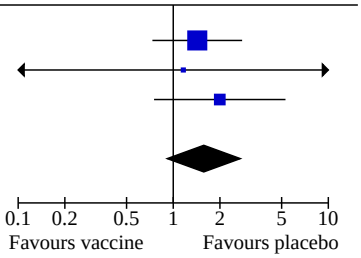
Heterogeneity: Tau² = 0.01; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 5: Fever

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Margolis 1990a	20	336	14	336	66.2%	1.43 [0.73 , 2.78]
Treanor 1994	1	30	0	11	3.0%	1.16 [0.05 , 26.58]
Govaert 1993	12	904	6	902	30.8%	2.00 [0.75 , 5.29]
Total (95% CI)		**1270**		**1249**	**100.0%**	**1.57 [0.92 , 2.71]**
Total events:	33		20			

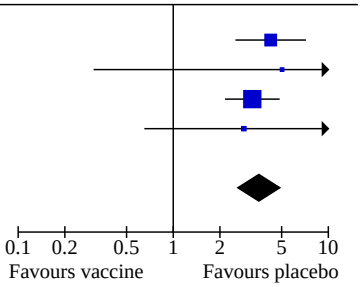
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 6: Local tenderness/sore arm

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Margolis 1990a	68	336	16	336	35.5%	4.25 [2.52 , 7.17]
Treanor 1994	6	30	0	11	1.2%	5.03 [0.31 , 82.60]
Govaert 1993	94	904	29	902	58.9%	3.23 [2.16 , 4.85]
Keitel 1996	6	21	2	20	4.4%	2.86 [0.65 , 12.53]
Total (95% CI)		**1291**		**1269**	**100.0%**	**3.56 [2.61 , 4.87]**
Total events:	174		47			

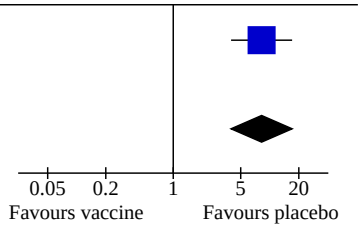
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 7.99 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Influenza vaccines versus placebo: randomised controlled trials - parenteral vaccine - adverse events, Outcome 7: Swelling - erythema - induration

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Govaert 1993	66	904	8	902	100.0%	8.23 [3.98 , 17.05]
Keitel 1996	0	21	0	20		Not estimable
Total (95% CI)		**925**		**922**	**100.0%**	**8.23 [3.98 , 17.05]**
Total events:	66		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.68 (P < 0.00001)
Test for subgroup differences: Not applicable

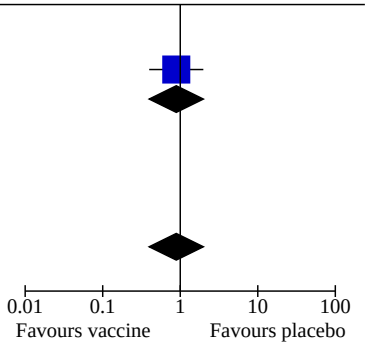


Comparison 3. Influenza vaccines versus placebo: randomised controlled trials - inactivated aerosol vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Influenza	1	176	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.40, 1.99]
3.1.1 Outbreak - vaccine matching - psychiatric hospital	1	176	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.40, 1.99]
3.2 Influenza-like illness	1	176	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.71]
3.2.1 Outbreak - vaccine matching - psychiatric hospital	1	176	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.71]

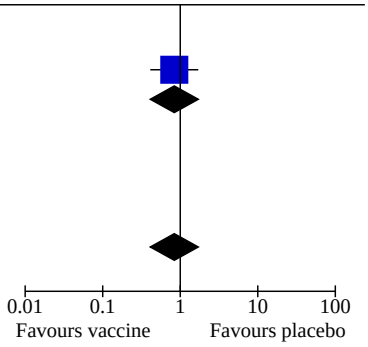
Analysis 3.1. Comparison 3: Influenza vaccines versus placebo: randomised controlled trials - inactivated aerosol vaccine, Outcome 1: Influenza

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Outbreak - vaccine matching - psychiatric hospital						
Edmondson 1971	10	89	11	87	100.0%	0.89 [0.40 , 1.99]
Subtotal (95% CI)		**89**		**87**	**100.0%**	**0.89 [0.40 , 1.99]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**89**		**87**	**100.0%**	**0.89 [0.40 , 1.99]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Not applicable						



Analysis 3.2. Comparison 3: Influenza vaccines versus placebo: randomised controlled trials - inactivated aerosol vaccine, Outcome 2: Influenza-like illness

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Outbreak - vaccine matching - psychiatric hospital						
Edmondson 1971	12	89	14	87	100.0%	0.84 [0.41 , 1.71]
Subtotal (95% CI)		**89**		**87**	**100.0%**	**0.84 [0.41 , 1.71]**
Total events:	12		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
Total (95% CI)		**89**		**87**	**100.0%**	**0.84 [0.41 , 1.71]**
Total events:	12		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
Test for subgroup differences: Not applicable						

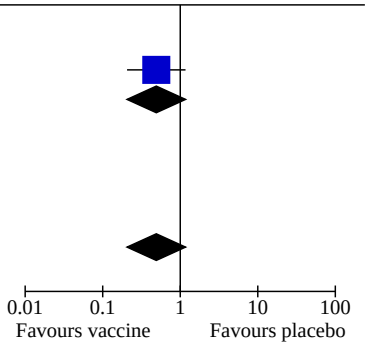


Comparison 4. Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Influenza	1	220	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.17]
4.1.1 No outbreak - vaccine matching - nursing home - healthy and ill	1	220	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.17]

Analysis 4.1. Comparison 4: Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine, Outcome 1: Influenza

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 No outbreak - vaccine matching - nursing home - healthy and ill						
Rudenko 2001	7	111	14	109	100.0%	0.49 [0.21 , 1.17]
Subtotal (95% CI)		**111**		**109**	**100.0%**	**0.49 [0.21 , 1.17]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
Total (95% CI)		**111**		**109**	**100.0%**	**0.49 [0.21 , 1.17]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
Test for subgroup differences: Not applicable						



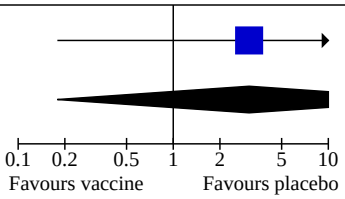
Comparison 5. Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine - adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 General malaise	1	45	Risk Ratio (M-H, Random, 95% CI)	3.09 [0.18, 53.20]
5.2 Fever	1	45	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.09, 33.24]
5.3 Upper respiratory tract symptoms	1	45	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.42, 6.29]
5.4 Lower respiratory tract symptoms	1	45	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.41, 20.48]

Analysis 5.1. Comparison 5: Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine - adverse events, Outcome 1: General malaise

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Treanor 1994	4	34	0	11	100.0%	3.09 [0.18 , 53.20]
Total (95% CI)		**34**		**11**	**100.0%**	**3.09 [0.18 , 53.20]**
Total events:	4		0			

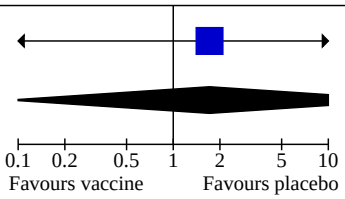
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine - adverse events, Outcome 2: Fever

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Treanor 1994	2	34	0	11	100.0%	1.71 [0.09 , 33.24]
Total (95% CI)		**34**		**11**	**100.0%**	**1.71 [0.09 , 33.24]**
Total events:	2		0			

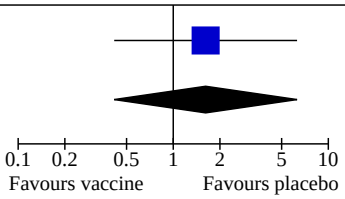
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine - adverse events, Outcome 3: Upper respiratory tract symptoms

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Treanor 1994	10	34	2	11	100.0%	1.62 [0.42 , 6.29]
Total (95% CI)		**34**		**11**	**100.0%**	**1.62 [0.42 , 6.29]**
Total events:	10		2			

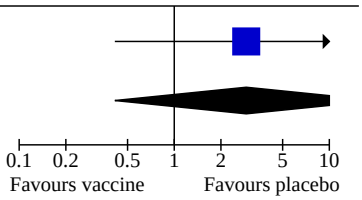
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Influenza vaccines versus placebo: randomised controlled trials - live aerosol vaccine - adverse events, Outcome 4: Lower respiratory tract symptoms

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Treanor 1994	9	34	1	11	100.0%	2.91 [0.41 , 20.48]
Total (95% CI)		**34**		**11**	**100.0%**	**2.91 [0.41 , 20.48]**
Total events:	9		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable



Comparison 6. Influenza vaccines versus no vaccination: cohort studies in nursing homes

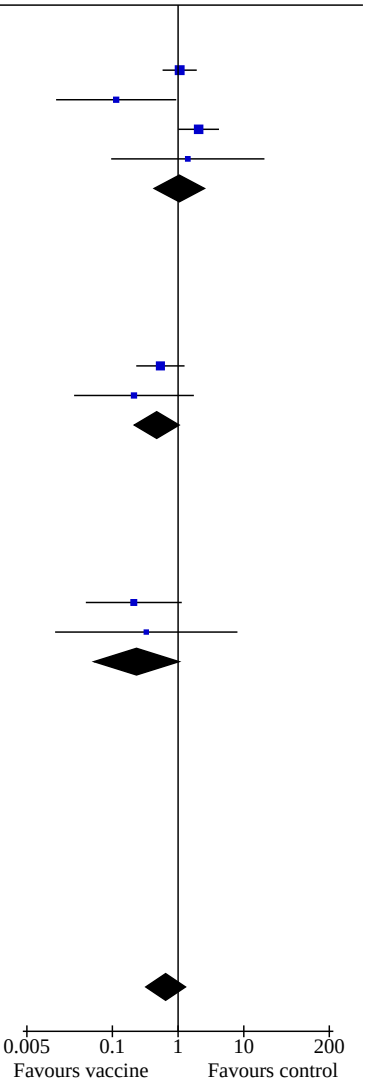
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Influenza	8	1941	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.32, 1.29]
6.1.1 Outbreak - vaccine matching	4	658	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.43, 2.51]
6.1.2 Outbreak - vaccine matching absent or unknown	2	592	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 1.04]
6.1.3 No outbreak - vaccine matching	2	691	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.03]
6.1.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 Influenza-like illness	26	12388	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.66, 0.88]
6.2.1 Outbreak - vaccine matching (circulating strains)	16	5963	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.94]
6.2.2 Outbreak - vaccine matching absent or unknown	6	4096	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.60, 1.05]
6.2.3 No outbreak - vaccine matching	4	2329	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
6.2.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Pneumonia	17	10274	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.43, 0.66]
6.3.1 Outbreak - vaccine matching	8	4482	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.42, 0.70]
6.3.2 Outbreak - vaccine matching absent or unknown	5	3991	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3.3 No outbreak - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3.4 No outbreak - matching absent or unknown	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.18, 0.68]
6.4 Hospitalisation for influenza-like illness or pneumonia	12	28032	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.32, 0.81]
6.4.1 Outbreak - vaccine matching	8	2027	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.36, 0.84]
6.4.2 Outbreak - vaccine matching absent or unknown	2	3301	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.43, 1.58]
6.4.3 No outbreak - vaccine matching	2	22704	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.14, 0.76]
6.4.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.5 Deaths from flu or pneumonia	27	32179	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.63]
6.5.1 Outbreak - vaccine matching	16	6127	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.41, 0.83]
6.5.2 Outbreak - vaccine matching absent or unknown	4	1089	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.11, 1.02]
6.5.3 No outbreak - vaccine matching	3	23162	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.09, 0.87]
6.5.4 No outbreak - vaccine matching absent or unknown	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.14, 0.67]
6.6 All deaths	1	305	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.77]
6.6.1 Outbreak - vaccine matching	1	305	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.77]
6.6.2 Outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.6.3 No outbreak - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.6.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.7 Influenza cases (clinically defined without clear definition)	7	24238	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 1.02]

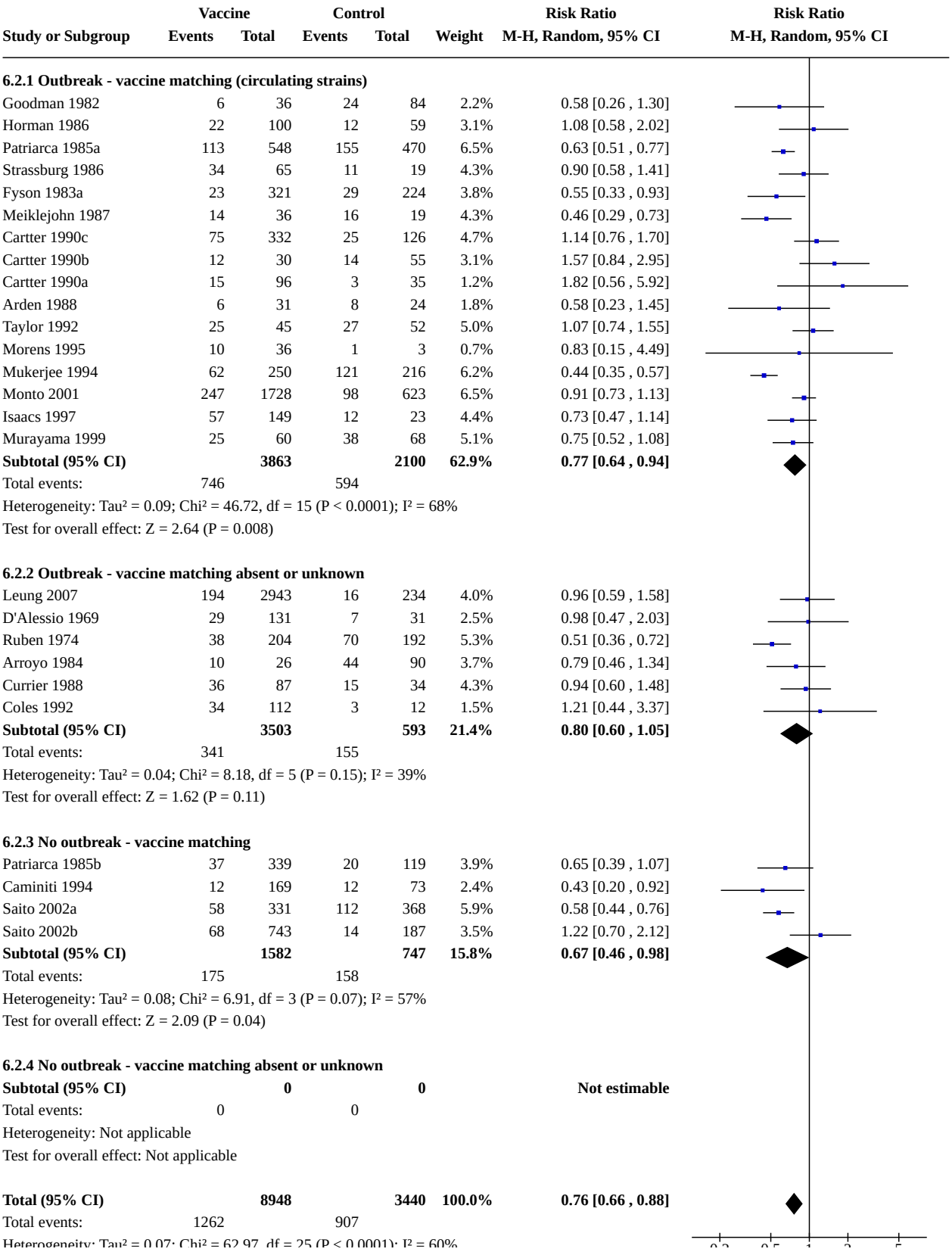
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.1 Outbreak - vaccine matching	2	271	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.11, 4.56]
6.7.2 Outbreak - vaccine matching absent or unknown	1	155	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.09, 0.59]
6.7.3 No outbreak - vaccine matching	1	22462	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.35, 0.46]
6.7.4 No outbreak - vaccine matching absent or unknown	3	1350	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.41, 1.28]

Analysis 6.1. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 1: Influenza

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Outbreak - vaccine matching						
Feery 1976	31	154	12	63	23.1%	1.06 [0.58 , 1.92]
Gross 1988	1	181	6	124	7.8%	0.11 [0.01 , 0.94]
Taylor 1992	16	45	9	52	21.5%	2.05 [1.01 , 4.19]
Morens 1995	6	36	0	3	5.4%	1.41 [0.10 , 20.60]
Subtotal (95% CI)		**416**		**242**	**57.8%**	**1.04 [0.43 , 2.51]**
Total events:	54		27			
Heterogeneity: Tau² = 0.40; Chi² = 7.39, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 0.09 (P = 0.92)						
6.1.2 Outbreak - vaccine matching absent or unknown						
Ruben 1974	8	204	14	192	19.7%	0.54 [0.23 , 1.25]
Cuneo Crovari 1980	1	86	6	110	7.9%	0.21 [0.03 , 1.74]
Subtotal (95% CI)		**290**		**302**	**27.6%**	**0.47 [0.22 , 1.04]**
Total events:	9		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
6.1.3 No outbreak - vaccine matching						
Howarth 1987a	2	229	4	97	10.6%	0.21 [0.04 , 1.14]
Howarth 1987b	0	184	1	181	4.0%	0.33 [0.01 , 8.00]
Subtotal (95% CI)		**413**		**278**	**14.6%**	**0.23 [0.05 , 1.03]**
Total events:	2		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.05)						
6.1.4 No outbreak - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1119**		**822**	**100.0%**	**0.65 [0.32 , 1.29]**
Total events:	65		52			
Heterogeneity: Tau² = 0.45; Chi² = 16.15, df = 7 (P = 0.02); I² = 57%						
Test for overall effect: Z = 1.23 (P = 0.22)						
Test for subgroup differences: Chi² = 3.42, df = 2 (P = 0.18), I² = 41.5%						



Analysis 6.2. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 2: Influenza-like illness



Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Outbreak - vaccine matching (circulating strains)						
Goodman 1982	6	36	24	84	2.2%	0.58 [0.26 , 1.30]
Horman 1986	22	100	12	59	3.1%	1.08 [0.58 , 2.02]
Patriarca 1985a	113	548	155	470	6.5%	0.63 [0.51 , 0.77]
Strassburg 1986	34	65	11	19	4.3%	0.90 [0.58 , 1.41]
Fyson 1983a	23	321	29	224	3.8%	0.55 [0.33 , 0.93]
Meiklejohn 1987	14	36	16	19	4.3%	0.46 [0.29 , 0.73]
Cartter 1990c	75	332	25	126	4.7%	1.14 [0.76 , 1.70]
Cartter 1990b	12	30	14	55	3.1%	1.57 [0.84 , 2.95]
Cartter 1990a	15	96	3	35	1.2%	1.82 [0.56 , 5.92]
Arden 1988	6	31	8	24	1.8%	0.58 [0.23 , 1.45]
Taylor 1992	25	45	27	52	5.0%	1.07 [0.74 , 1.55]
Morens 1995	10	36	1	3	0.7%	0.83 [0.15 , 4.49]
Mukerjee 1994	62	250	121	216	6.2%	0.44 [0.35 , 0.57]
Monto 2001	247	1728	98	623	6.5%	0.91 [0.73 , 1.13]
Isaacs 1997	57	149	12	23	4.4%	0.73 [0.47 , 1.14]
Murayama 1999	25	60	38	68	5.1%	0.75 [0.52 , 1.08]
Subtotal (95% CI)		**3863**		**2100**	**62.9%**	**0.77 [0.64 , 0.94]**
Total events:	746		594			
Heterogeneity: Tau² = 0.09; Chi² = 46.72, df = 15 (P < 0.0001); I² = 68%						
Test for overall effect: Z = 2.64 (P = 0.008)						
6.2.2 Outbreak - vaccine matching absent or unknown						
Leung 2007	194	2943	16	234	4.0%	0.96 [0.59 , 1.58]
D'Alessio 1969	29	131	7	31	2.5%	0.98 [0.47 , 2.03]
Ruben 1974	38	204	70	192	5.3%	0.51 [0.36 , 0.72]
Arroyo 1984	10	26	44	90	3.7%	0.79 [0.46 , 1.34]
Currier 1988	36	87	15	34	4.3%	0.94 [0.60 , 1.48]
Coles 1992	34	112	3	12	1.5%	1.21 [0.44 , 3.37]
Subtotal (95% CI)		**3503**		**593**	**21.4%**	**0.80 [0.60 , 1.05]**
Total events:	341		155			
Heterogeneity: Tau² = 0.04; Chi² = 8.18, df = 5 (P = 0.15); I² = 39%						
Test for overall effect: Z = 1.62 (P = 0.11)						
6.2.3 No outbreak - vaccine matching						
Patriarca 1985b	37	339	20	119	3.9%	0.65 [0.39 , 1.07]
Caminiti 1994	12	169	12	73	2.4%	0.43 [0.20 , 0.92]
Saito 2002a	58	331	112	368	5.9%	0.58 [0.44 , 0.76]
Saito 2002b	68	743	14	187	3.5%	1.22 [0.70 , 2.12]
Subtotal (95% CI)		**1582**		**747**	**15.8%**	**0.67 [0.46 , 0.98]**
Total events:	175		158			
Heterogeneity: Tau² = 0.08; Chi² = 6.91, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 2.09 (P = 0.04)						
6.2.4 No outbreak - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**8948**		**3440**	**100.0%**	**0.76 [0.66 , 0.88]**
Total events:	1262		907			
Heterogeneity: Tau² = 0.07; Chi² = 62.97, df = 25 (P < 0.0001); I² = 60%						

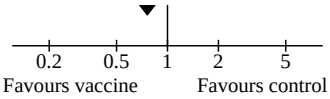
Analysis 6.2. (Continued)

Total events:	1262	907

Heterogeneity: Tau² = 0.07; Chi² = 62.97, df = 25 (P < 0.0001); I² = 60%

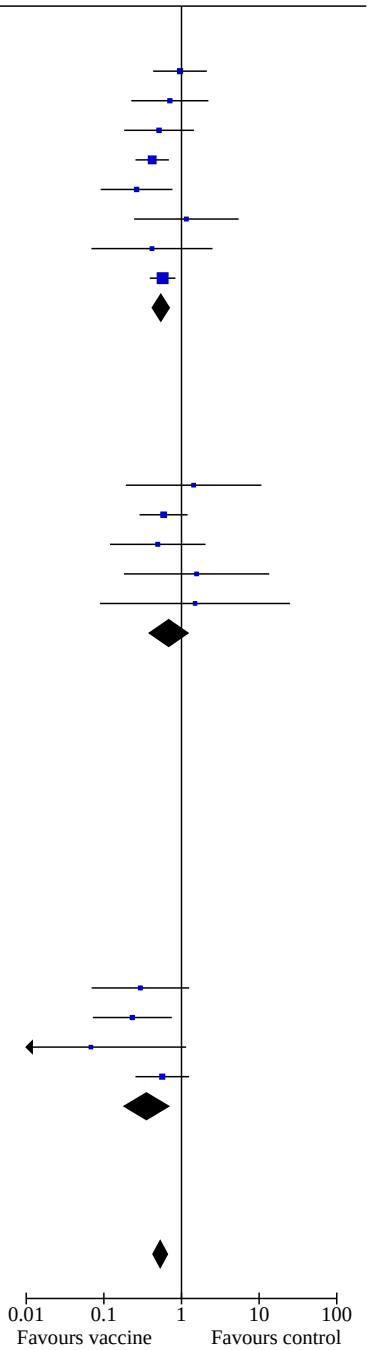
Test for overall effect: Z = 3.79 (P = 0.0002)

Test for subgroup differences: Chi² = 0.54, df = 2 (P = 0.76), I² = 0%



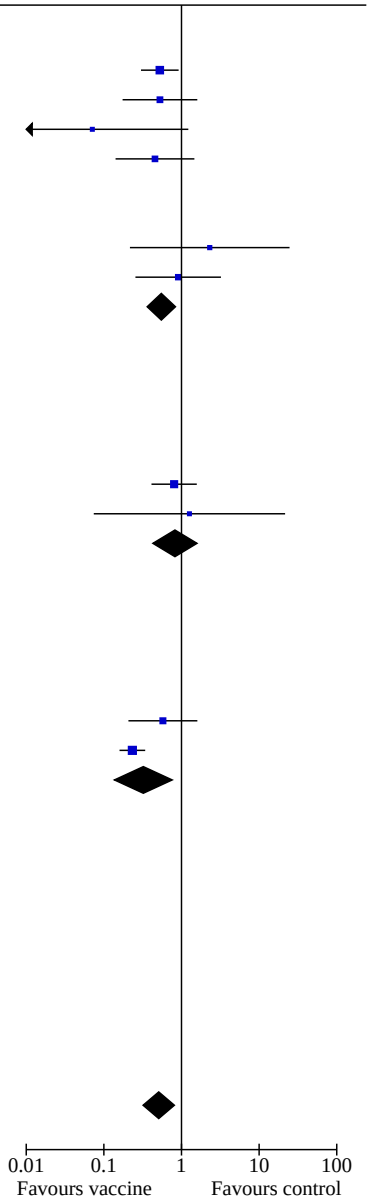
Analysis 6.3. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 3: Pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Outbreak - vaccine matching						
Saah 1986b	12	244	11	214	7.2%	0.96 [0.43 , 2.12]
Horman 1986	6	100	5	59	3.5%	0.71 [0.23 , 2.22]
Gross 1988	6	181	8	124	4.3%	0.51 [0.18 , 1.44]
Patriarca 1985a	22	548	45	470	18.7%	0.42 [0.26 , 0.69]
Meiklejohn 1987	4	36	8	19	4.0%	0.26 [0.09 , 0.76]
Taylor 1992	3	45	3	52	1.9%	1.16 [0.25 , 5.44]
Morens 1995	5	36	1	3	1.4%	0.42 [0.07 , 2.51]
Monto 2001	65	1728	41	623	31.7%	0.57 [0.39 , 0.84]
Subtotal (95% CI)		**2918**		**1564**	**72.7%**	**0.54 [0.42 , 0.70]**
Total events:	123		122			
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 4.80 (P < 0.00001)						
6.3.2 Outbreak - vaccine matching absent or unknown						
Leung 2007	18	2943	1	234	1.1%	1.43 [0.19 , 10.67]
Saah 1986a	11	219	20	234	9.0%	0.59 [0.29 , 1.20]
Arroyo 1984	2	26	14	90	2.3%	0.49 [0.12 , 2.04]
Currier 1988	4	87	1	34	1.0%	1.56 [0.18 , 13.49]
Coles 1992	6	112	0	12	0.6%	1.50 [0.09 , 25.06]
Subtotal (95% CI)		**3387**		**604**	**14.0%**	**0.68 [0.39 , 1.21]**
Total events:	41		36			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 4 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
6.3.3 No outbreak - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.3.4 No outbreak - matching absent or unknown						
Howells 1975a	2	134	18	356	2.2%	0.30 [0.07 , 1.26]
Howells 1975b	3	123	28	267	3.3%	0.23 [0.07 , 0.75]
Howells 1975c	0	183	11	287	0.6%	0.07 [0.00 , 1.15]
Saah 1986c	9	225	16	226	7.2%	0.56 [0.26 , 1.25]
Subtotal (95% CI)		**665**		**1136**	**13.3%**	**0.35 [0.18 , 0.68]**
Total events:	14		73			
Heterogeneity: Tau² = 0.06; Chi² = 3.44, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**6970**		**3304**	**100.0%**	**0.53 [0.43 , 0.66]**
Total events:	178		231			
Heterogeneity: Tau² = 0.00; Chi² = 13.29, df = 16 (P = 0.65); I² = 0%						
Test for overall effect: Z = 5.79 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.24, df = 2 (P = 0.33), I² = 10.7%						

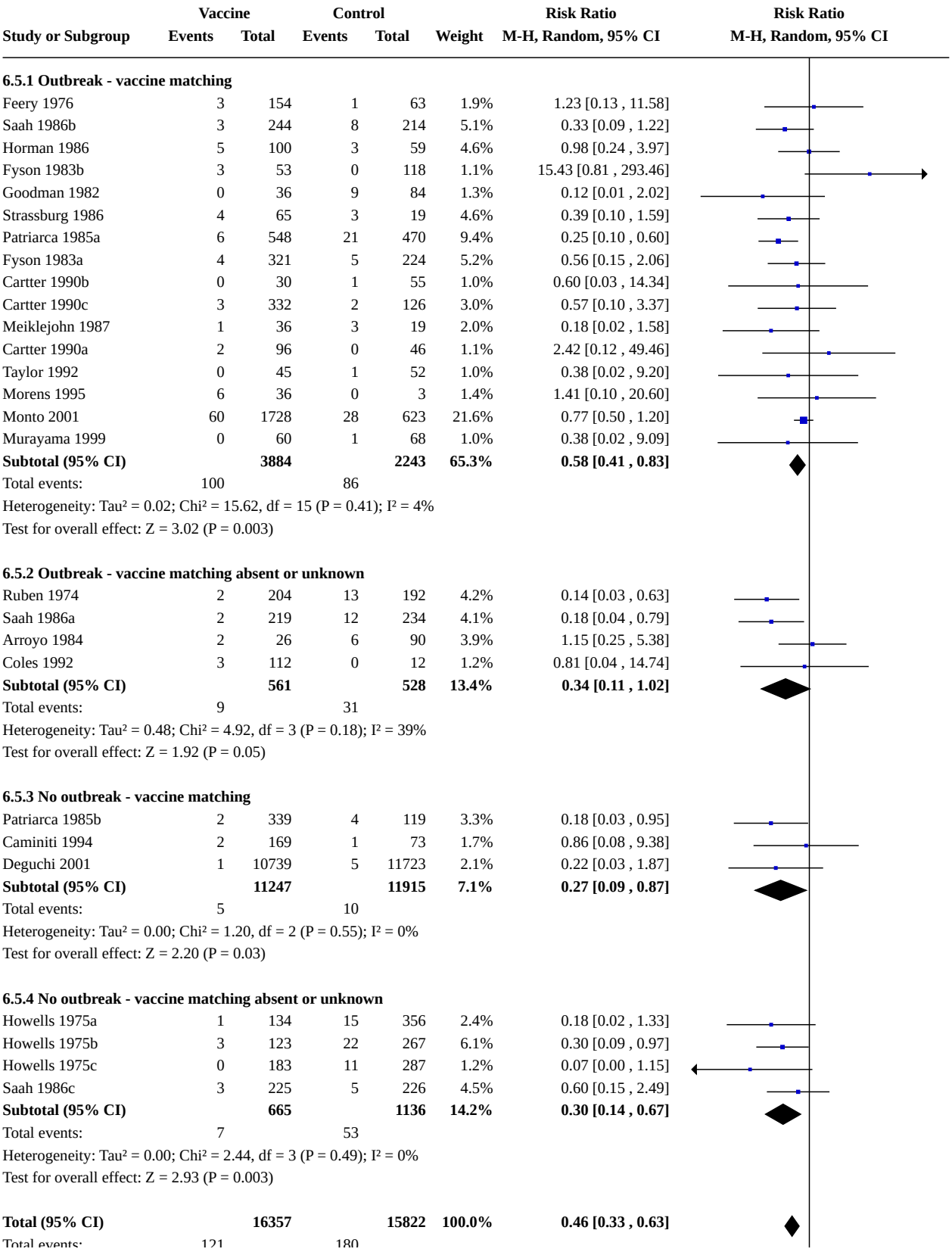


Analysis 6.4. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 4: Hospitalisation for influenza-like illness or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 Outbreak - vaccine matching						
Patriarca 1985a	19	548	31	470	17.4%	0.53 [0.30 , 0.92]
Meiklejohn 1987	5	36	5	19	10.0%	0.53 [0.17 , 1.60]
Arden 1988	0	31	5	24	2.4%	0.07 [0.00 , 1.22]
Cartter 1990c	6	332	5	126	9.4%	0.46 [0.14 , 1.47]
Cartter 1990a	0	96	0	35		Not estimable
Cartter 1990b	0	30	0	55		Not estimable
Taylor 1992	2	45	1	52	3.3%	2.31 [0.22 , 24.65]
Murayama 1999	4	60	5	68	8.5%	0.91 [0.26 , 3.22]
Subtotal (95% CI)		**1178**		**849**	**50.9%**	**0.55 [0.36 , 0.84]**
Total events:	36		52			
Heterogeneity: Tau² = 0.00; Chi² = 4.16, df = 5 (P = 0.53); I² = 0%						
Test for overall effect: Z = 2.80 (P = 0.005)						
6.4.2 Outbreak - vaccine matching absent or unknown						
Leung 2007	91	2943	9	234	15.6%	0.80 [0.41 , 1.57]
Coles 1992	5	112	0	12	2.4%	1.27 [0.07 , 21.61]
Subtotal (95% CI)		**3055**		**246**	**18.0%**	**0.82 [0.43 , 1.58]**
Total events:	96		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
6.4.3 No outbreak - vaccine matching						
Caminiti 1994	8	169	6	73	10.9%	0.58 [0.21 , 1.60]
Deguchi 2001	32	10739	150	11723	20.1%	0.23 [0.16 , 0.34]
Subtotal (95% CI)		**10908**		**11796**	**31.0%**	**0.32 [0.14 , 0.76]**
Total events:	40		156			
Heterogeneity: Tau² = 0.26; Chi² = 2.68, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 2.59 (P = 0.010)						
6.4.4 No outbreak - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**15141**		**12891**	**100.0%**	**0.51 [0.32 , 0.81]**
Total events:	172		217			
Heterogeneity: Tau² = 0.24; Chi² = 19.87, df = 9 (P = 0.02); I² = 55%						
Test for overall effect: Z = 2.85 (P = 0.004)						
Test for subgroup differences: Chi² = 2.94, df = 2 (P = 0.23), I² = 32.1%						



Analysis 6.5. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 5: Deaths from flu or pneumonia

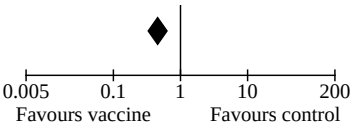


Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Outbreak - vaccine matching						
Feery 1976	3	154	1	63	1.9%	1.23 [0.13 , 11.58]
Saah 1986b	3	244	8	214	5.1%	0.33 [0.09 , 1.22]
Horman 1986	5	100	3	59	4.6%	0.98 [0.24 , 3.97]
Fyson 1983b	3	53	0	118	1.1%	15.43 [0.81 , 293.46]
Goodman 1982	0	36	9	84	1.3%	0.12 [0.01 , 2.02]
Strassburg 1986	4	65	3	19	4.6%	0.39 [0.10 , 1.59]
Patriarca 1985a	6	548	21	470	9.4%	0.25 [0.10 , 0.60]
Fyson 1983a	4	321	5	224	5.2%	0.56 [0.15 , 2.06]
Cartter 1990b	0	30	1	55	1.0%	0.60 [0.03 , 14.34]
Cartter 1990c	3	332	2	126	3.0%	0.57 [0.10 , 3.37]
Meiklejohn 1987	1	36	3	19	2.0%	0.18 [0.02 , 1.58]
Cartter 1990a	2	96	0	46	1.1%	2.42 [0.12 , 49.46]
Taylor 1992	0	45	1	52	1.0%	0.38 [0.02 , 9.20]
Morens 1995	6	36	0	3	1.4%	1.41 [0.10 , 20.60]
Monto 2001	60	1728	28	623	21.6%	0.77 [0.50 , 1.20]
Murayama 1999	0	60	1	68	1.0%	0.38 [0.02 , 9.09]
Subtotal (95% CI)		**3884**		**2243**	**65.3%**	**0.58 [0.41 , 0.83]**
Total events:	100		86			
Heterogeneity: Tau² = 0.02; Chi² = 15.62, df = 15 (P = 0.41); I² = 4%						
Test for overall effect: Z = 3.02 (P = 0.003)						
6.5.2 Outbreak - vaccine matching absent or unknown						
Ruben 1974	2	204	13	192	4.2%	0.14 [0.03 , 0.63]
Saah 1986a	2	219	12	234	4.1%	0.18 [0.04 , 0.79]
Arroyo 1984	2	26	6	90	3.9%	1.15 [0.25 , 5.38]
Coles 1992	3	112	0	12	1.2%	0.81 [0.04 , 14.74]
Subtotal (95% CI)		**561**		**528**	**13.4%**	**0.34 [0.11 , 1.02]**
Total events:	9		31			
Heterogeneity: Tau² = 0.48; Chi² = 4.92, df = 3 (P = 0.18); I² = 39%						
Test for overall effect: Z = 1.92 (P = 0.05)						
6.5.3 No outbreak - vaccine matching						
Patriarca 1985b	2	339	4	119	3.3%	0.18 [0.03 , 0.95]
Caminiti 1994	2	169	1	73	1.7%	0.86 [0.08 , 9.38]
Deguchi 2001	1	10739	5	11723	2.1%	0.22 [0.03 , 1.87]
Subtotal (95% CI)		**11247**		**11915**	**7.1%**	**0.27 [0.09 , 0.87]**
Total events:	5		10			
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
6.5.4 No outbreak - vaccine matching absent or unknown						
Howells 1975a	1	134	15	356	2.4%	0.18 [0.02 , 1.33]
Howells 1975b	3	123	22	267	6.1%	0.30 [0.09 , 0.97]
Howells 1975c	0	183	11	287	1.2%	0.07 [0.00 , 1.15]
Saah 1986c	3	225	5	226	4.5%	0.60 [0.15 , 2.49]
Subtotal (95% CI)		**665**		**1136**	**14.2%**	**0.30 [0.14 , 0.67]**
Total events:	7		53			
Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.93 (P = 0.003)						
Total (95% CI)		**16357**		**15822**	**100.0%**	**0.46 [0.33 , 0.63]**
Total events:	121		180			

Analysis 6.5. (Continued)

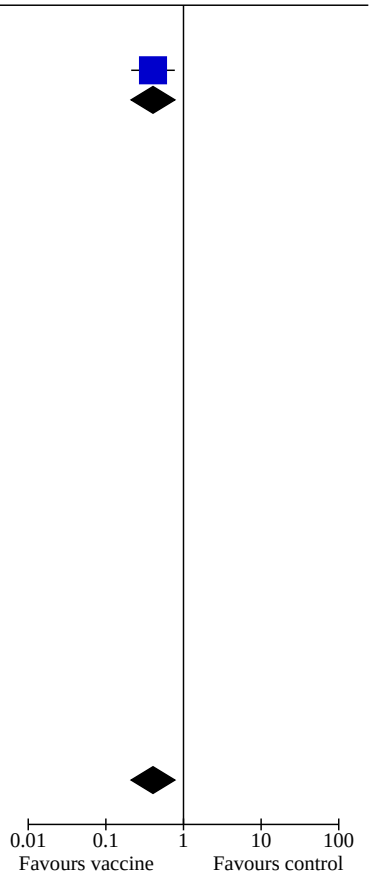
Total (95% CI)	**16357**	**15822**	**100.0%**	**0.46 [0.33 , 0.63]**	
Total events:	121	180			

Heterogeneity: Tau² = 0.07; Chi² = 29.31, df = 26 (P = 0.30); I² = 11%
Test for overall effect: Z = 4.79 (P < 0.00001)
Test for subgroup differences: Chi² = 3.78, df = 3 (P = 0.29), I² = 20.6%

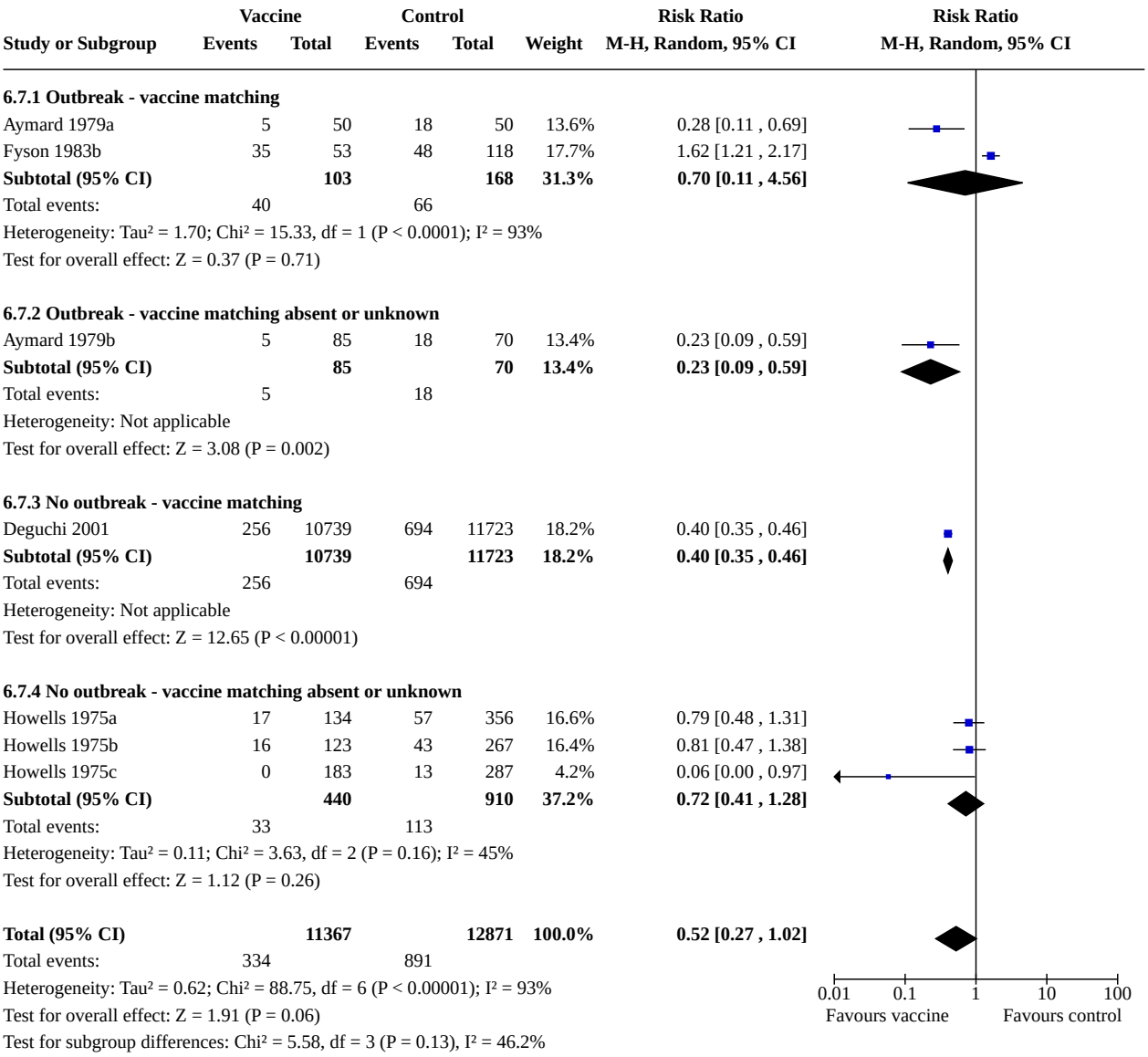


Analysis 6.6. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 6: All deaths

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.6.1 Outbreak - vaccine matching						
Gross 1988	13	181	22	124	100.0%	0.40 [0.21 , 0.77]
Subtotal (95% CI)		**181**		**124**	**100.0%**	**0.40 [0.21 , 0.77]**
Total events:	13		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.74 (P = 0.006)						
6.6.2 Outbreak - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.6.3 No outbreak - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.6.4 No outbreak - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**181**		**124**	**100.0%**	**0.40 [0.21 , 0.77]**
Total events:	13		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.74 (P = 0.006)						
Test for subgroup differences: Not applicable						



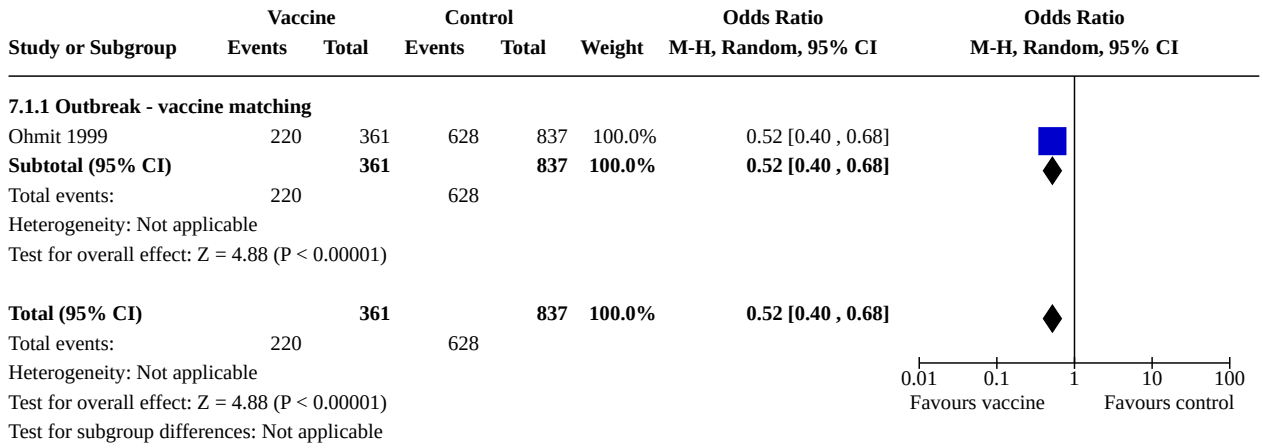
Analysis 6.7. Comparison 6: Influenza vaccines versus no vaccination: cohort studies in nursing homes, Outcome 7: Influenza cases (clinically defined without clear definition)



Comparison 7. Influenza and pneumococcal vaccines versus no vaccination: case-control studies in nursing homes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Influenza-like illness	1	1198	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.68]
7.1.1 Outbreak - vaccine matching	1	1198	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.68]

Analysis 7.1. Comparison 7: Influenza and pneumococcal vaccines versus no vaccination: case-control studies in nursing homes, Outcome 1: Influenza-like illness



Comparison 8. Influenza vaccines versus no vaccination: cohort studies in community-dwellers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Influenza	2	18249	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 2.01]
8.1.1 Epidemic year - vaccine matching	1	427	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.37]
8.1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.1.3 Non-epidemic year - vaccine matching	1	17822	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.27, 0.91]
8.1.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.2 Influenza-like illness	4	9613	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.42, 1.33]
8.2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.2.3 Non-epidemic year - vaccine matching	2	4636	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.58, 2.03]
8.2.4 Non-epidemic year - vaccine matching absent or unknown	1	268	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.16, 4.55]
8.2.5 Epidemic year - vaccine not matching	1	4709	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.24, 0.81]

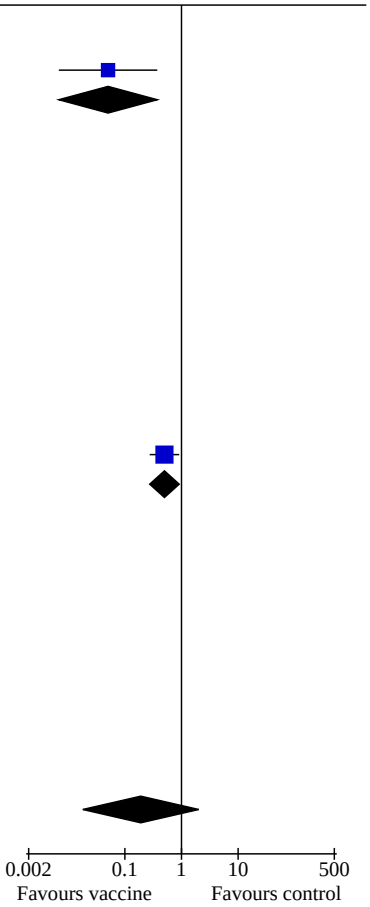
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 Pneumonia	2	18090	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]
8.3.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.3.3 Non-epidemic year - vaccine matching	1	17822	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.19]
8.3.4 Non-epidemic year - vaccine matching absent or unknown	1	268	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.16, 57.42]
8.4 Hospitalisation for flu or pneumonia	9	784643	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.85]
8.4.1 Epidemic year - vaccine matching	6	727776	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
8.4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.4.3 Non-epidemic year - vaccine matching	1	25532	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.83]
8.4.4 Non-epidemic year - vaccine matching absent or unknown	1	26626	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.54, 0.99]
8.4.5 Epidemic year - vaccine not matching	1	4709	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.40]
8.5 Hospitalisation for any respiratory disease	5	567299	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.54, 1.43]
8.5.1 Epidemic year - vaccine matching	3	515141	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.64]
8.5.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.5.3 Non-epidemic year - vaccine matching	1	25532	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.12]
8.5.4 Non-epidemic year - vaccine matching absent or unknown	1	26626	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.01, 1.34]
8.6 Deaths from flu or pneumonia	1	163391	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.09]
8.6.1 Epidemic year - vaccine matching	1	163391	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.6.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.6.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.7 Deaths from respiratory disease	1	426668	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.25, 1.39]
8.7.1 Epidemic year - vaccine matching	1	426668	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.25, 1.39]
8.8 All deaths	8	409468	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.47, 0.80]
8.8.1 Epidemic year - vaccine matching	4	300332	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.50, 0.70]
8.8.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.8.3 Non-epidemic year - vaccine matching	3	104427	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.30, 1.39]
8.8.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.8.5 Epidemic year - vaccine not matching	1	4709	Risk Ratio (M-H, Random, 95% CI)	3.89 [0.90, 16.89]
8.9 Hospitalisation for heart disease	6	433934	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.12]
8.9.1 Epidemic year - vaccine matching	4	381776	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.56, 0.97]
8.9.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.9.3 Non-epidemic year - vaccine matching	1	25532	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.81, 1.38]
8.9.4 Non-epidemic year - vaccine matching absent or unknown	1	26626	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.07, 2.36]
8.10 Combined outcome: all deaths or severe respiratory illness	3	290819	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.85]
8.10.1 Epidemic year - vaccine matching	2	132365	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.10.2 Epidemic year - vaccine matching absent or unknown	1	158454	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.69, 0.80]

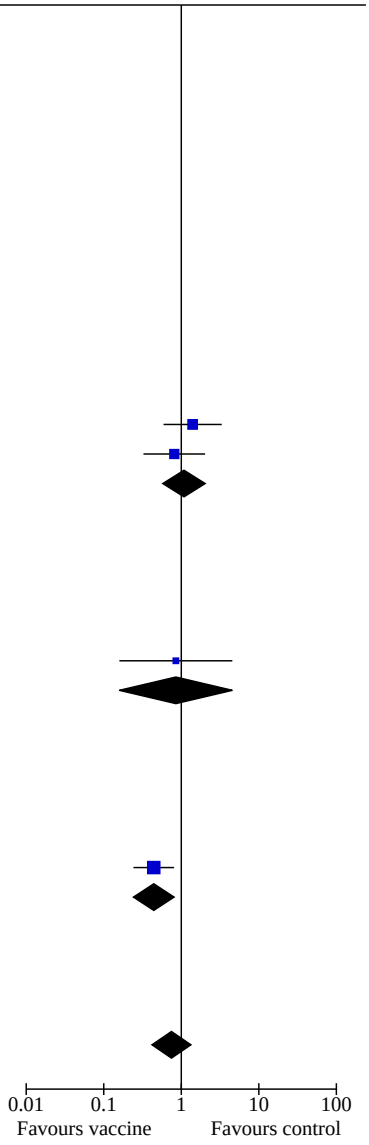
Analysis 8.1. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 1: Influenza

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Epidemic year - vaccine matching						
Nicholson 1999	1	218	19	209	42.0%	0.05 [0.01 , 0.37]
Subtotal (95% CI)		**218**		**209**	**42.0%**	**0.05 [0.01 , 0.37]**
Total events:	1		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.92 (P = 0.003)						
8.1.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.1.3 Non-epidemic year - vaccine matching						
Voordouw 2003	16	8911	32	8911	58.0%	0.50 [0.27 , 0.91]
Subtotal (95% CI)		**8911**		**8911**	**58.0%**	**0.50 [0.27 , 0.91]**
Total events:	16		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.27 (P = 0.02)						
8.1.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**9129**		**9120**	**100.0%**	**0.19 [0.02 , 2.01]**
Total events:	17		51			
Heterogeneity: Tau² = 2.40; Chi² = 5.22, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Test for subgroup differences: Chi² = 4.63, df = 1 (P = 0.03), I² = 78.4%						



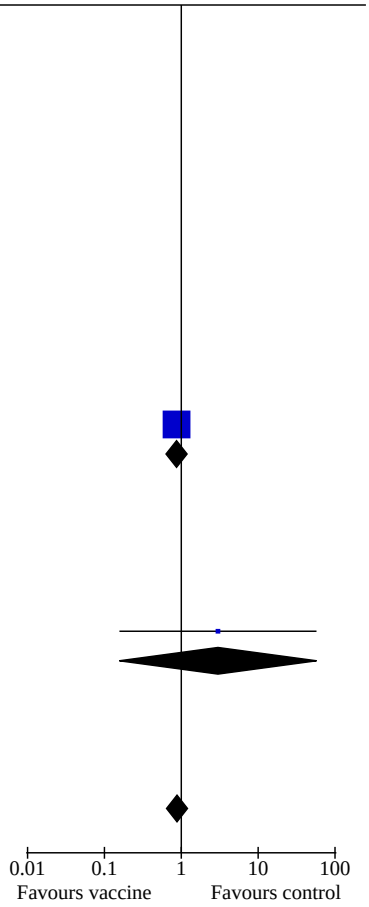
Analysis 8.2. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 2: Influenza-like illness

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.3 Non-epidemic year - vaccine matching						
Comeri 1995	20	150	6	63	26.7%	1.40 [0.59 , 3.32]
Kawai 2003	19	3520	6	903	24.8%	0.81 [0.33 , 2.03]
Subtotal (95% CI)		**3670**		**966**	**51.5%**	**1.08 [0.58 , 2.03]**
Total events:	39		12			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.72$, df = 1 (P = 0.40); $I^2 = 0\%$						
Test for overall effect: Z = 0.25 (P = 0.80)						
8.2.4 Non-epidemic year - vaccine matching absent or unknown						
Gavira Iglesias 1987	4	188	2	80	10.0%	0.85 [0.16 , 4.55]
Subtotal (95% CI)		**188**		**80**	**10.0%**	**0.85 [0.16 , 4.55]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
8.2.5 Epidemic year - vaccine not matching						
Hara 2006	20	3169	22	1540	38.4%	0.44 [0.24 , 0.81]
Subtotal (95% CI)		**3169**		**1540**	**38.4%**	**0.44 [0.24 , 0.81]**
Total events:	20		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.66 (P = 0.008)						
Total (95% CI)		**7027**		**2586**	**100.0%**	**0.75 [0.42 , 1.33]**
Total events:	63		36			
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 4.87$, df = 3 (P = 0.18); $I^2 = 38\%$						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: $Chi^2 = 4.15$, df = 2 (P = 0.13), $I^2 = 51.8\%$						



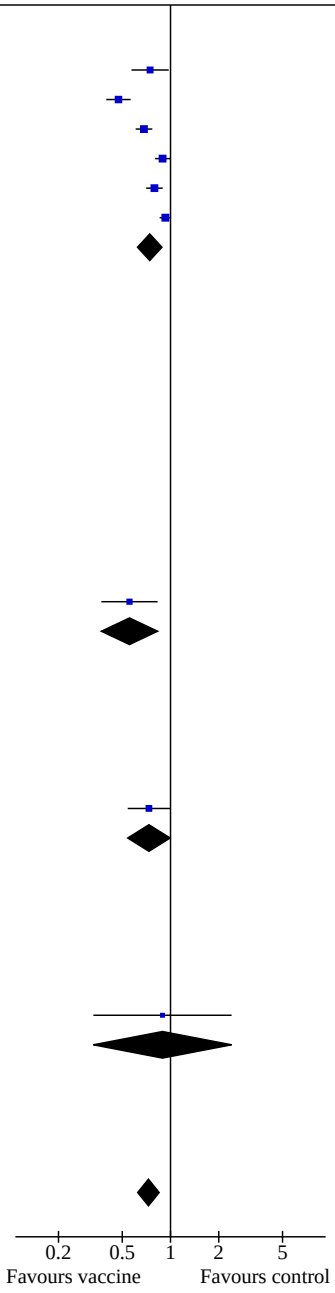
Analysis 8.3. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 3: Pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.3.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.3.3 Non-epidemic year - vaccine matching						
Voordouw 2003	72	8911	83	8911	98.9%	0.87 [0.63 , 1.19]
Subtotal (95% CI)		**8911**		**8911**	**98.9%**	**0.87 [0.63 , 1.19]**
Total events:	72		83			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.38)						
8.3.4 Non-epidemic year - vaccine matching absent or unknown						
Gavira Iglesias 1987	3	188	0	80	1.1%	3.00 [0.16 , 57.42]
Subtotal (95% CI)		**188**		**80**	**1.1%**	**3.00 [0.16 , 57.42]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**9099**		**8991**	**100.0%**	**0.88 [0.64 , 1.20]**
Total events:	75		83			
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%						



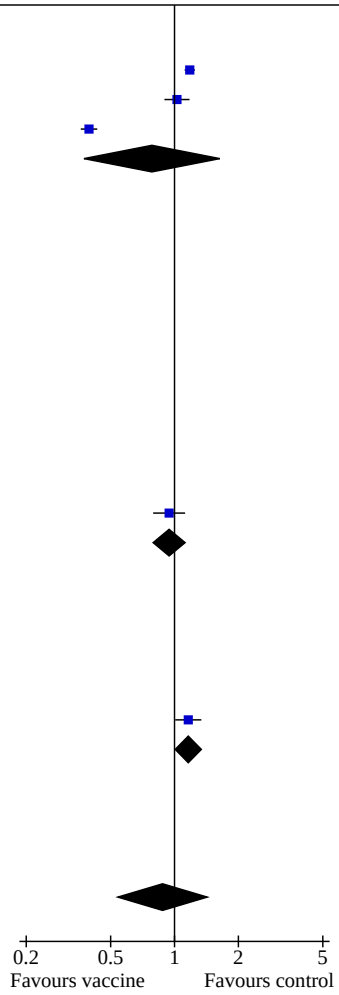
Analysis 8.4. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 4: Hospitalisation for flu or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.4.1 Epidemic year - vaccine matching						
Nichol 1994b	108	15288	105	11081	10.5%	0.75 [0.57 , 0.97]
Nichol 1998b	246	46480	252	22544	12.9%	0.47 [0.40 , 0.56]
Nichol 2003a	495	77738	581	62317	14.1%	0.68 [0.61 , 0.77]
Christenson 2001a	371	23224	2854	159385	14.4%	0.89 [0.80 , 0.99]
Nichol 2003b	589	87357	501	58971	14.1%	0.79 [0.70 , 0.89]
Christenson 2004a	672	29346	3305	134045	14.8%	0.93 [0.86 , 1.01]
Subtotal (95% CI)		**279433**		**448343**	**80.8%**	**0.74 [0.62 , 0.88]**
Total events:	2481		7598			
Heterogeneity: Tau² = 0.04; Chi² = 58.24, df = 5 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
8.4.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.4.3 Non-epidemic year - vaccine matching						
Nichol 1994a	34	11483	75	14049	7.5%	0.55 [0.37 , 0.83]
Subtotal (95% CI)		**11483**		**14049**	**7.5%**	**0.55 [0.37 , 0.83]**
Total events:	34		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
8.4.4 Non-epidemic year - vaccine matching absent or unknown						
Nichol 1994c	78	14647	87	11979	9.6%	0.73 [0.54 , 0.99]
Subtotal (95% CI)		**14647**		**11979**	**9.6%**	**0.73 [0.54 , 0.99]**
Total events:	78		87			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						
8.4.5 Epidemic year - vaccine not matching						
Hara 2006	11	3169	6	1540	2.1%	0.89 [0.33 , 2.40]
Subtotal (95% CI)		**3169**		**1540**	**2.1%**	**0.89 [0.33 , 2.40]**
Total events:	11		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**308732**		**475911**	**100.0%**	**0.73 [0.62 , 0.85]**
Total events:	2604		7766			
Heterogeneity: Tau² = 0.04; Chi² = 61.76, df = 8 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.90, df = 3 (P = 0.59), I² = 0%						



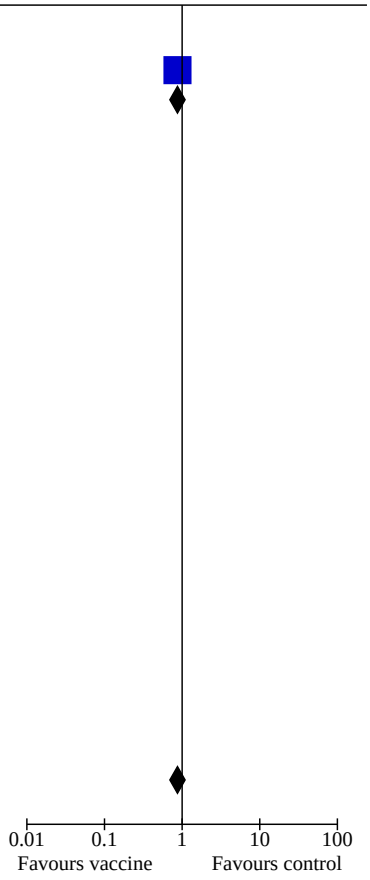
Analysis 8.5. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 5: Hospitalisation for any respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 Epidemic year - vaccine matching						
Mangtani 2004a	1993	145706	3177	274042	20.2%	1.18 [1.12 , 1.25]
Nichol 1994b	486	15288	343	11081	20.0%	1.03 [0.90 , 1.18]
Nichol 1998b	846	46480	1038	22544	20.1%	0.40 [0.36 , 0.43]
Subtotal (95% CI)		**207474**		**307667**	**60.3%**	**0.78 [0.37 , 1.64]**
Total events:	3325		4558			
Heterogeneity: Tau² = 0.42; Chi² = 419.59, df = 2 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 0.65 (P = 0.51)						
8.5.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.5.3 Non-epidemic year - vaccine matching						
Nichol 1994a	222	11483	288	14049	19.8%	0.94 [0.79 , 1.12]
Subtotal (95% CI)		**11483**		**14049**	**19.8%**	**0.94 [0.79 , 1.12]**
Total events:	222		288			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
8.5.4 Non-epidemic year - vaccine matching absent or unknown						
Nichol 1994c	450	14647	317	11979	19.9%	1.16 [1.01 , 1.34]
Subtotal (95% CI)		**14647**		**11979**	**19.9%**	**1.16 [1.01 , 1.34]**
Total events:	450		317			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						
Total (95% CI)		**233604**		**333695**	**100.0%**	**0.88 [0.54 , 1.43]**
Total events:	3997		5163			
Heterogeneity: Tau² = 0.30; Chi² = 432.59, df = 4 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 0.52 (P = 0.60)						
Test for subgroup differences: Chi² = 3.98, df = 2 (P = 0.14), I² = 49.8%						



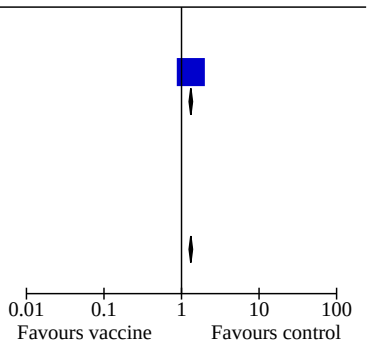
Analysis 8.6. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 6: Deaths from flu or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.6.1 Epidemic year - vaccine matching						
Christenson 2004a	90	29346	472	134045	100.0%	0.87 [0.70 , 1.09]
Subtotal (95% CI)		**29346**		**134045**	**100.0%**	**0.87 [0.70 , 1.09]**
Total events:	90		472			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
8.6.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.6.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.6.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**29346**		**134045**	**100.0%**	**0.87 [0.70 , 1.09]**
Total events:	90		472			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
Test for subgroup differences: Not applicable						



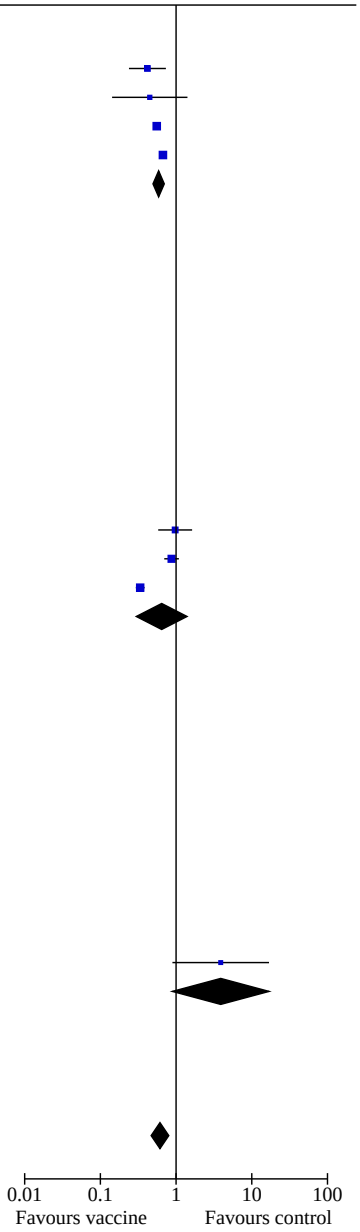
Analysis 8.7. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 7: Deaths from respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.7.1 Epidemic year - vaccine matching						
Mangtani 2004a	2585	147294	3720	279374	100.0%	1.32 [1.25 , 1.39]
Subtotal (95% CI)		**147294**		**279374**	**100.0%**	**1.32 [1.25 , 1.39]**
Total events:	2585		3720			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.87 (P < 0.00001)						
Total (95% CI)		**147294**		**279374**	**100.0%**	**1.32 [1.25 , 1.39]**
Total events:	2585		3720			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.87 (P < 0.00001)						
Test for subgroup differences: Not applicable						



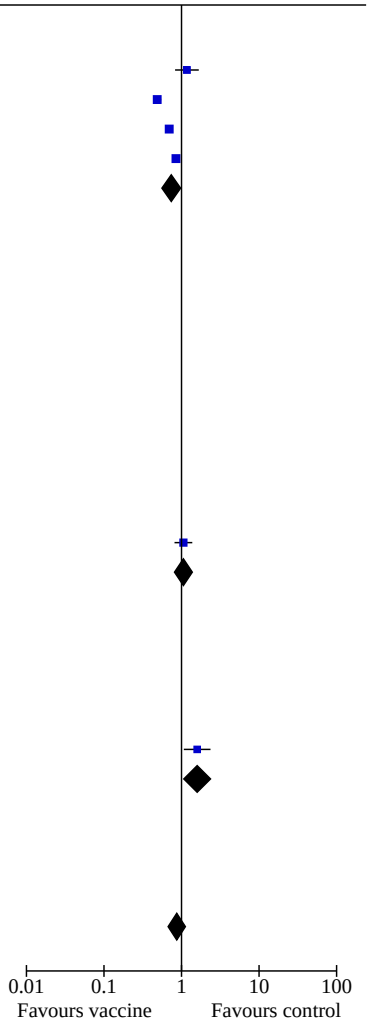
Analysis 8.8. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 8: All deaths

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.8.1 Epidemic year - vaccine matching						
Gené Badia 1991	16	1998	49	2560	10.3%	0.42 [0.24 , 0.73]
Fleming 1995	3	599	98	8792	4.2%	0.45 [0.14 , 1.41]
Nichol 2003a	943	77738	1361	62317	18.5%	0.56 [0.51 , 0.60]
Nichol 2003b	1019	87357	1026	58971	18.5%	0.67 [0.62 , 0.73]
Subtotal (95% CI)		**167692**		**132640**	**51.5%**	**0.59 [0.50 , 0.70]**
Total events:	1981		2534			
Heterogeneity: Tau² = 0.02; Chi² = 11.54, df = 3 (P = 0.009); I² = 74%						
Test for overall effect: Z = 6.07 (P < 0.00001)						
8.8.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.8.3 Non-epidemic year - vaccine matching						
Lopez Hernandez 1994	23	779	36	1186	11.1%	0.97 [0.58 , 1.63]
Voordouw 2003	143	8911	164	8911	16.7%	0.87 [0.70 , 1.09]
Shapiro 2003	269	36596	1052	48044	18.0%	0.34 [0.29 , 0.38]
Subtotal (95% CI)		**46286**		**58141**	**45.7%**	**0.65 [0.30 , 1.39]**
Total events:	435		1252			
Heterogeneity: Tau² = 0.44; Chi² = 61.64, df = 2 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 1.11 (P = 0.27)						
8.8.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.8.5 Epidemic year - vaccine not matching						
Hara 2006	16	3169	2	1540	2.8%	3.89 [0.90 , 16.89]
Subtotal (95% CI)		**3169**		**1540**	**2.8%**	**3.89 [0.90 , 16.89]**
Total events:	16		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
Total (95% CI)		**217147**		**192321**	**100.0%**	**0.61 [0.47 , 0.80]**
Total events:	2432		3788			
Heterogeneity: Tau² = 0.10; Chi² = 101.29, df = 7 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 3.59 (P = 0.0003)						
Test for subgroup differences: Chi² = 6.29, df = 2 (P = 0.04), I² = 68.2%						

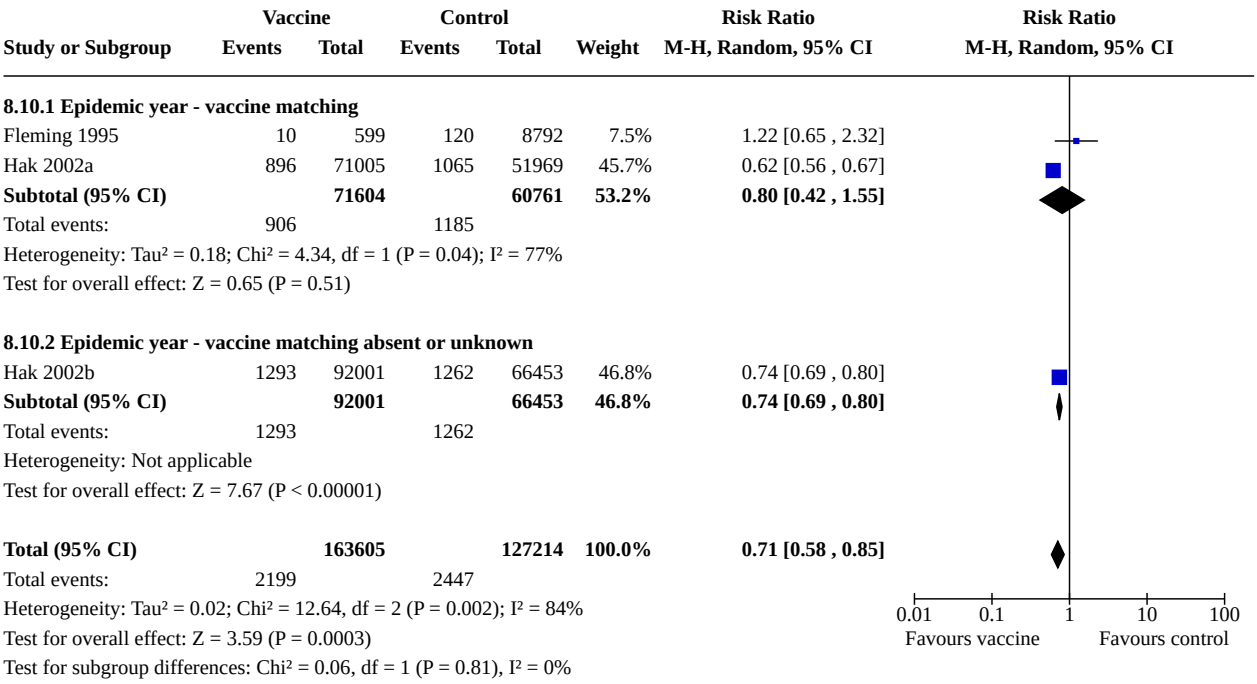


Analysis 8.9. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 9: Hospitalisation for heart disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.9.1 Epidemic year - vaccine matching						
Nichol 1994b	81	15288	50	11081	14.2%	1.17 [0.83 , 1.67]
Nichol 1998b	554	46480	553	22544	18.6%	0.49 [0.43 , 0.55]
Nichol 2003a	888	77738	1026	62317	18.9%	0.69 [0.63 , 0.76]
Nichol 2003b	1029	87357	819	58971	18.9%	0.85 [0.77 , 0.93]
Subtotal (95% CI)		**226863**		**154913**	**70.7%**	**0.74 [0.56 , 0.97]**
Total events:	2552		2448			
Heterogeneity: Tau² = 0.07; Chi² = 62.97, df = 3 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 2.16 (P = 0.03)						
8.9.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.9.3 Non-epidemic year - vaccine matching						
Nichol 1994a	102	11483	118	14049	16.1%	1.06 [0.81 , 1.38]
Subtotal (95% CI)		**11483**		**14049**	**16.1%**	**1.06 [0.81 , 1.38]**
Total events:	102		118			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
8.9.4 Non-epidemic year - vaccine matching absent or unknown						
Nichol 1994c	72	14647	37	11979	13.2%	1.59 [1.07 , 2.36]
Subtotal (95% CI)		**14647**		**11979**	**13.2%**	**1.59 [1.07 , 2.36]**
Total events:	72		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
Total (95% CI)		**252993**		**180941**	**100.0%**	**0.87 [0.67 , 1.12]**
Total events:	2726		2603			
Heterogeneity: Tau² = 0.09; Chi² = 87.72, df = 5 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Chi² = 10.12, df = 2 (P = 0.006), I² = 80.2%						



Analysis 8.10. Comparison 8: Influenza vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 10: Combined outcome: all deaths or severe respiratory illness



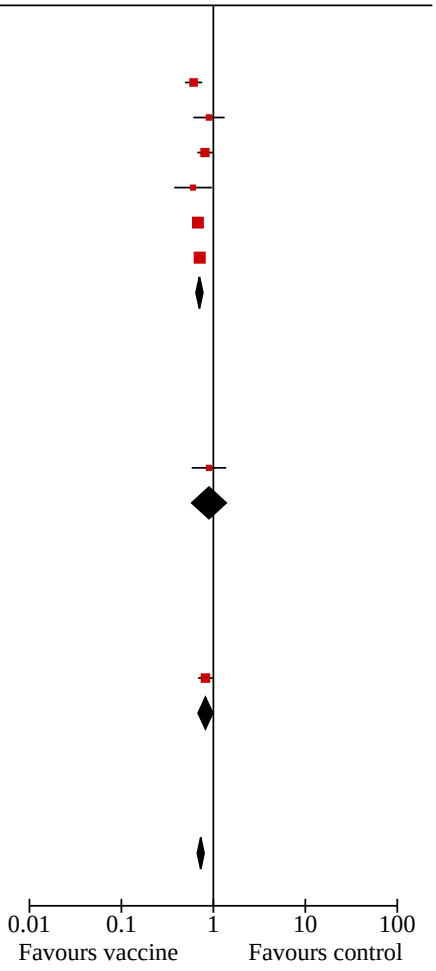
Comparison 9. Influenza vaccines versus no vaccination: cohort studies in community - adjusted rates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Hospitalisation for influenza or pneumonia	8		Odds Ratio (IV, Random, 95% CI)	0.73 [0.67, 0.79]
9.1.1 Epidemic - vaccine matching	6		Odds Ratio (IV, Random, 95% CI)	0.71 [0.65, 0.77]
9.1.2 Non-epidemic - vaccine not matching	1		Odds Ratio (IV, Random, 95% CI)	0.90 [0.58, 1.38]
9.1.3 Epidemic year - vaccine matching absent or unknown	1		Odds Ratio (IV, Random, 95% CI)	0.82 [0.68, 0.98]
9.2 Hospitalisation for any respiratory disease	13		Odds Ratio (IV, Random, 95% CI)	0.78 [0.72, 0.85]
9.2.1 Epidemic - vaccine matching	9		Odds Ratio (IV, Random, 95% CI)	0.71 [0.67, 0.74]
9.2.2 Non-epidemic - vaccine not matching	2		Odds Ratio (IV, Random, 95% CI)	0.91 [0.76, 1.08]
9.2.3 Non-epidemic year - vaccine matching	2		Odds Ratio (IV, Random, 95% CI)	0.94 [0.84, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Hospitalisation for heart disease	6		Odds Ratio (IV, Random, 95% CI)	0.76 [0.70, 0.82]
9.3.1 Epidemic year - vaccine matching	5		Odds Ratio (IV, Random, 95% CI)	0.75 [0.70, 0.82]
9.3.2 Non-epidemic - vaccine not matching	1		Odds Ratio (IV, Random, 95% CI)	0.80 [0.55, 1.16]
9.4 All deaths	7		Odds Ratio (IV, Random, 95% CI)	0.53 [0.46, 0.61]
9.4.1 Epidemic year - vaccine matching	5		Odds Ratio (IV, Random, 95% CI)	0.47 [0.42, 0.53]
9.4.2 Epidemic year - vaccine matching absent or unknown	1		Odds Ratio (IV, Random, 95% CI)	0.65 [0.57, 0.75]
9.4.3 Non-epidemic year - vaccine matching	1		Odds Ratio (IV, Random, 95% CI)	0.76 [0.60, 0.97]
9.5 Combined outcome: all deaths or severe respiratory illness	1		Odds Ratio (IV, Random, 95% CI)	0.70 [0.37, 1.34]
9.5.1 Epidemic year - vaccine matching	1		Odds Ratio (IV, Random, 95% CI)	0.70 [0.37, 1.34]

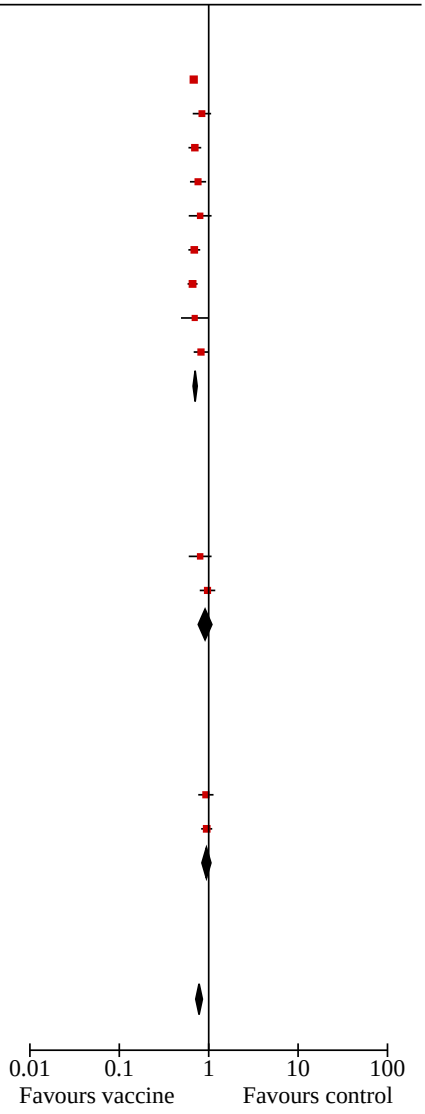
Analysis 9.1. Comparison 9: Influenza vaccines versus no vaccination: cohort studies in community - adjusted rates, Outcome 1: Hospitalisation for influenza or pneumonia

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
9.1.1 Epidemic - vaccine matching				
Nichol 1998a	-0.4943	0.1104	11.8%	0.61 [0.49 , 0.76]
Davis 2001b	-0.11	0.2	4.2%	0.90 [0.61 , 1.33]
Nordin 2001a	-0.2107	0.097	14.4%	0.81 [0.67 , 0.98]
Davis 2001c	-0.51	0.24	3.0%	0.60 [0.38 , 0.96]
Nichol 2003a	-0.3857	0.0669	23.5%	0.68 [0.60 , 0.78]
Nichol 2003b	-0.3425	0.065	24.3%	0.71 [0.63 , 0.81]
Subtotal (95% CI)			**81.2%**	**0.71 [0.65 , 0.77]**
Heterogeneity: Tau² = 0.00; Chi² = 5.95, df = 5 (P = 0.31); I² = 16%				
Test for overall effect: Z = 7.97 (P < 0.00001)				
9.1.2 Non-epidemic - vaccine not matching				
Davis 2001a	-0.11	0.22	3.5%	0.90 [0.58 , 1.38]
Subtotal (95% CI)			**3.5%**	**0.90 [0.58 , 1.38]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				
9.1.3 Epidemic year - vaccine matching absent or unknown				
Nordin 2001b	-0.1985	0.0932	15.3%	0.82 [0.68 , 0.98]
Subtotal (95% CI)			**15.3%**	**0.82 [0.68 , 0.98]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.13 (P = 0.03)				
Total (95% CI)			**100.0%**	**0.73 [0.67 , 0.79]**
Heterogeneity: Tau² = 0.00; Chi² = 9.18, df = 7 (P = 0.24); I² = 24%				
Test for overall effect: Z = 7.40 (P < 0.00001)				
Test for subgroup differences: Chi² = 3.02, df = 2 (P = 0.22), I² = 33.8%				



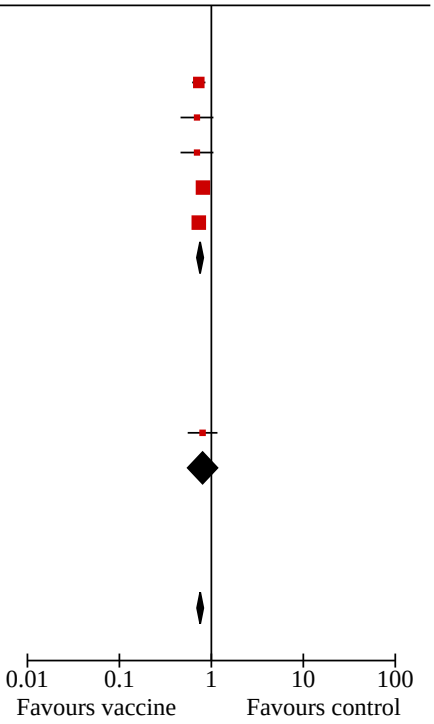
Analysis 9.2. Comparison 9: Influenza vaccines versus no vaccination: cohort studies in community - adjusted rates, Outcome 2: Hospitalisation for any respiratory disease

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
9.2.1 Epidemic - vaccine matching				
Nichol 1998a	-0.3857	0.0429	11.6%	0.68 [0.63 , 0.74]
Mangtani 2004b	-0.1744	0.1209	6.4%	0.84 [0.66 , 1.06]
Mangtani 2004c	-0.3567	0.084	8.7%	0.70 [0.59 , 0.83]
Mangtani 2004e	-0.2744	0.1062	7.3%	0.76 [0.62 , 0.94]
Davis 2001b	-0.22	0.15	5.1%	0.80 [0.60 , 1.08]
Mangtani 2004g	-0.3711	0.0777	9.2%	0.69 [0.59 , 0.80]
Mangtani 2004h	-0.4155	0.0656	10.0%	0.66 [0.58 , 0.75]
Davis 2001c	-0.36	0.18	4.0%	0.70 [0.49 , 0.99]
Mangtani 2004j	-0.1985	0.0958	7.9%	0.82 [0.68 , 0.99]
Subtotal (95% CI)			**70.2%**	**0.71 [0.67 , 0.74]**
Heterogeneity: Tau² = 0.00; Chi² = 7.64, df = 8 (P = 0.47); I² = 0%				
Test for overall effect: Z = 13.17 (P < 0.00001)				
9.2.2 Non-epidemic - vaccine not matching				
Davis 2001a	-0.22	0.15	5.1%	0.80 [0.60 , 1.08]
Mangtani 2004i	-0.0305	0.1018	7.6%	0.97 [0.79 , 1.18]
Subtotal (95% CI)			**12.6%**	**0.91 [0.76 , 1.08]**
Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%				
Test for overall effect: Z = 1.05 (P = 0.30)				
9.2.3 Non-epidemic year - vaccine matching				
Mangtani 2004d	-0.0726	0.1003	7.7%	0.93 [0.76 , 1.13]
Mangtani 2004f	-0.0513	0.0726	9.5%	0.95 [0.82 , 1.10]
Subtotal (95% CI)			**17.2%**	**0.94 [0.84 , 1.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
Total (95% CI)			**100.0%**	**0.78 [0.72 , 0.85]**
Heterogeneity: Tau² = 0.01; Chi² = 34.73, df = 12 (P = 0.0005); I² = 65%				
Test for overall effect: Z = 5.74 (P < 0.00001)				
Test for subgroup differences: Chi² = 25.25, df = 2 (P < 0.00001), I² = 92.1%				

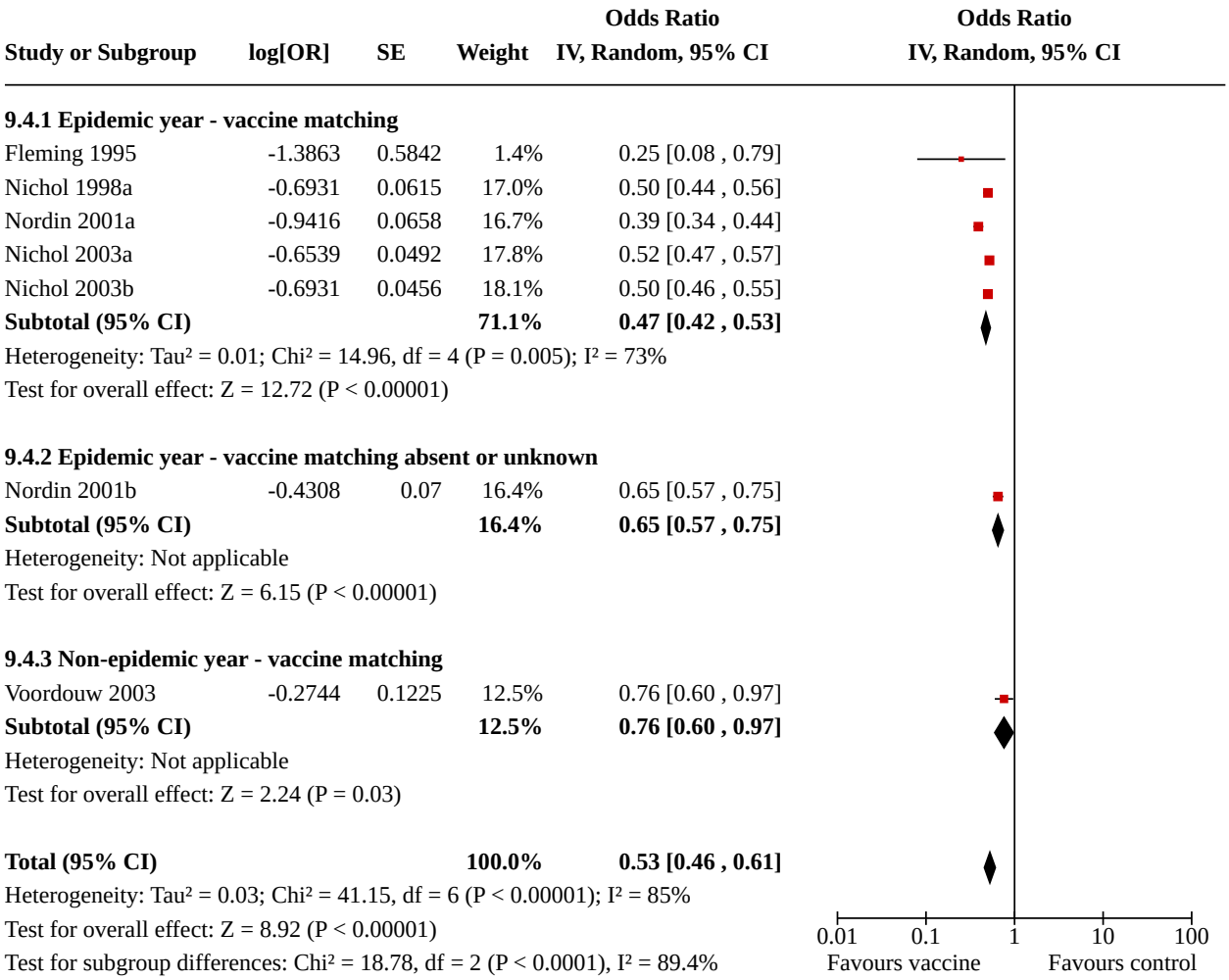


Analysis 9.3. Comparison 9: Influenza vaccines versus no vaccination: cohort studies in community - adjusted rates, Outcome 3: Hospitalisation for heart disease

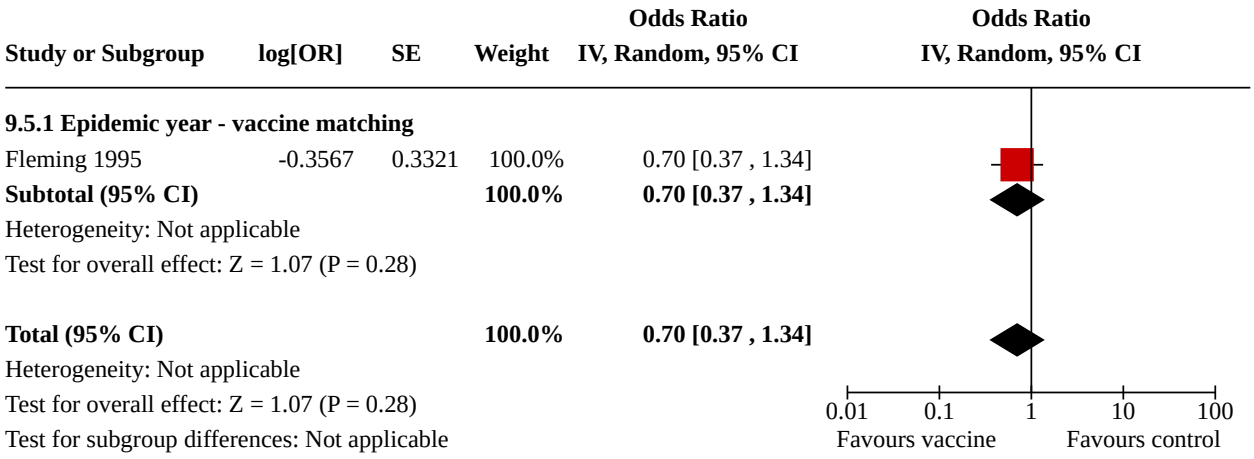
Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
9.3.1 Epidemic year - vaccine matching				
Nichol 1998a	-0.3147	0.0846	22.3%	0.73 [0.62 , 0.86]
Davis 2001b	-0.36	0.21	3.6%	0.70 [0.46 , 1.05]
Davis 2001c	-0.36	0.21	3.6%	0.70 [0.46 , 1.05]
Nichol 2003a	-0.2107	0.0697	32.9%	0.81 [0.71 , 0.93]
Nichol 2003b	-0.3147	0.0694	33.2%	0.73 [0.64 , 0.84]
Subtotal (95% CI)			**95.6%**	**0.75 [0.70 , 0.82]**
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 4 (P = 0.79); I² = 0%				
Test for overall effect: Z = 6.91 (P < 0.00001)				
9.3.2 Non-epidemic - vaccine not matching				
Davis 2001a	-0.22	0.19	4.4%	0.80 [0.55 , 1.16]
Subtotal (95% CI)			**4.4%**	**0.80 [0.55 , 1.16]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.16 (P = 0.25)				
Total (95% CI)			**100.0%**	**0.76 [0.70 , 0.82]**
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 5 (P = 0.88); I² = 0%				
Test for overall effect: Z = 7.00 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%				



Analysis 9.4. Comparison 9: Influenza vaccines versus no vaccination: cohort studies in community - adjusted rates, Outcome 4: All deaths



Analysis 9.5. Comparison 9: Influenza vaccines versus no vaccination: cohort studies in community - adjusted rates, Outcome 5: Combined outcome: all deaths or severe respiratory illness



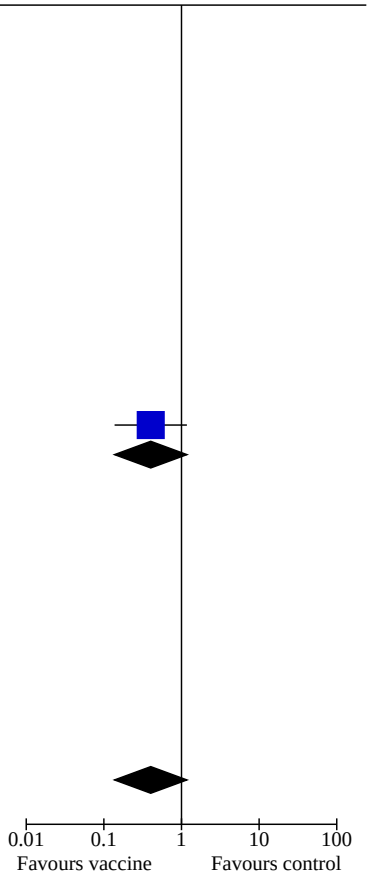
Comparison 10. Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Influenza	1	6423	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.17]
10.1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.1.3 Non-epidemic year - vaccine matching	1	6423	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.17]
10.1.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.2 Pneumonia	1	6423	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
10.2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.2.3 Non-epidemic year - vaccine matching	1	6423	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
10.2.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.3 Hospitalisation for influenza or pneumonia	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.86]
10.3.1 Epidemic year - vaccine matching	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.86]
10.3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.3.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.3.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.4 Hospitalisation for any respiratory disease	2	189004	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.80, 0.92]
10.4.1 Epidemic year - vaccine matching	2	189004	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.80, 0.92]
10.4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.4.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.4.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.5 Deaths from respiratory disease	1	142464	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
10.5.1 Epidemic year - vaccine matching	1	142464	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
10.6 All deaths	3	68032	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.16, 0.97]
10.6.1 Epidemic year - vaccine matching	1	2344	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.92]
10.6.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.6.3 Non-epidemic year - vaccine matching	2	65688	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.17, 1.28]
10.6.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.7 Hospitalisation for heart disease	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.03]
10.7.1 Epidemic year - vaccine matching	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.03]
10.7.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.7.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.7.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.8 Combined outcome: all deaths or severe respiratory illness	2	146248	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.74]
10.8.1 Epidemic year - vaccine matching	1	54438	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.49, 0.60]
10.8.2 Epidemic year - vaccine matching absent or unknown	1	91810	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.61, 0.72]

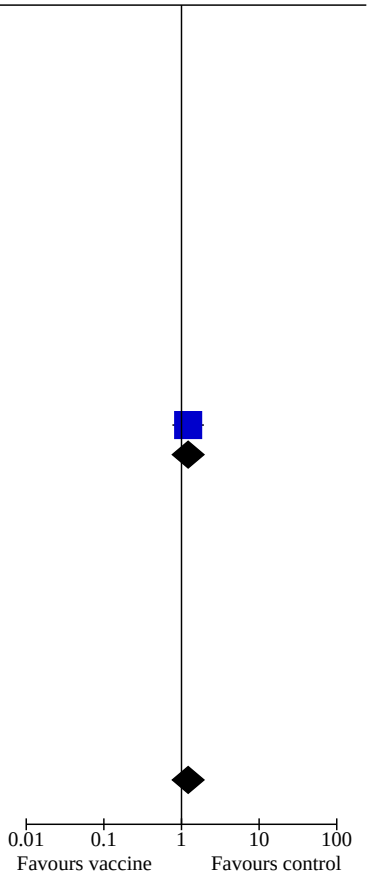
Analysis 10.1. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 1: Influenza

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.1.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.1.3 Non-epidemic year - vaccine matching						
Voordouw 2003	5	3562	10	2861	100.0%	0.40 [0.14 , 1.17]
Subtotal (95% CI)		**3562**		**2861**	**100.0%**	**0.40 [0.14 , 1.17]**
Total events:	5		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
10.1.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**3562**		**2861**	**100.0%**	**0.40 [0.14 , 1.17]**
Total events:	5		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Not applicable						



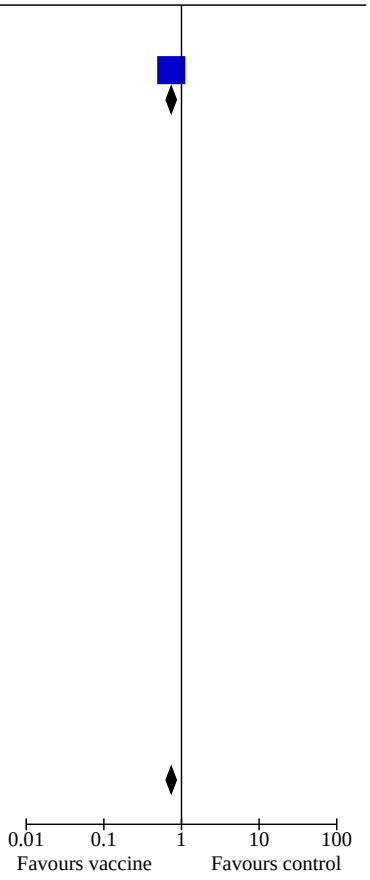
Analysis 10.2. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 2: Pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.2.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.2.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.2.3 Non-epidemic year - vaccine matching						
Voordouw 2003	44	3562	29	2861	100.0%	1.22 [0.76 , 1.94]
Subtotal (95% CI)		**3562**		**2861**	**100.0%**	**1.22 [0.76 , 1.94]**
Total events:	44		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
10.2.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**3562**		**2861**	**100.0%**	**1.22 [0.76 , 1.94]**
Total events:	44		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Not applicable						



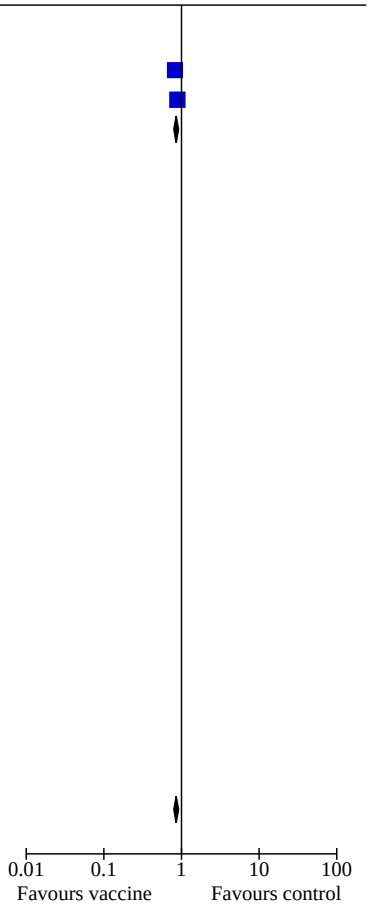
Analysis 10.3. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 3: Hospitalisation for influenza or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 Epidemic year - vaccine matching						
Nichol 1998a	419	30840	278	15092	100.0%	0.74 [0.63 , 0.86]
Subtotal (95% CI)		**30840**		**15092**	**100.0%**	**0.74 [0.63 , 0.86]**
Total events:	419		278			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.97 (P < 0.0001)						
10.3.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.3.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.3.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**30840**		**15092**	**100.0%**	**0.74 [0.63 , 0.86]**
Total events:	419		278			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.97 (P < 0.0001)						
Test for subgroup differences: Not applicable						



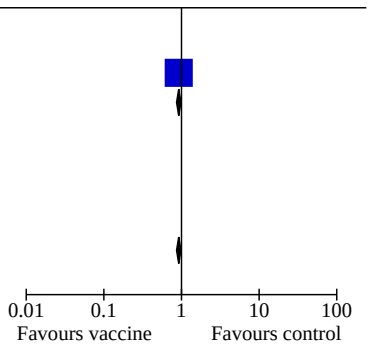
Analysis 10.4. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 4: Hospitalisation for any respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.4.1 Epidemic year - vaccine matching						
Nichol 1998a	1937	30840	1150	15092	49.5%	0.82 [0.77 , 0.88]
Mangtani 2004a	1426	67877	1785	75195	50.5%	0.89 [0.83 , 0.95]
Subtotal (95% CI)		**98717**		**90287**	**100.0%**	**0.85 [0.80 , 0.92]**
Total events:	3363		2935			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
10.4.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.4.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.4.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**98717**		**90287**	**100.0%**	**0.85 [0.80 , 0.92]**
Total events:	3363		2935			
Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
Test for subgroup differences: Not applicable						

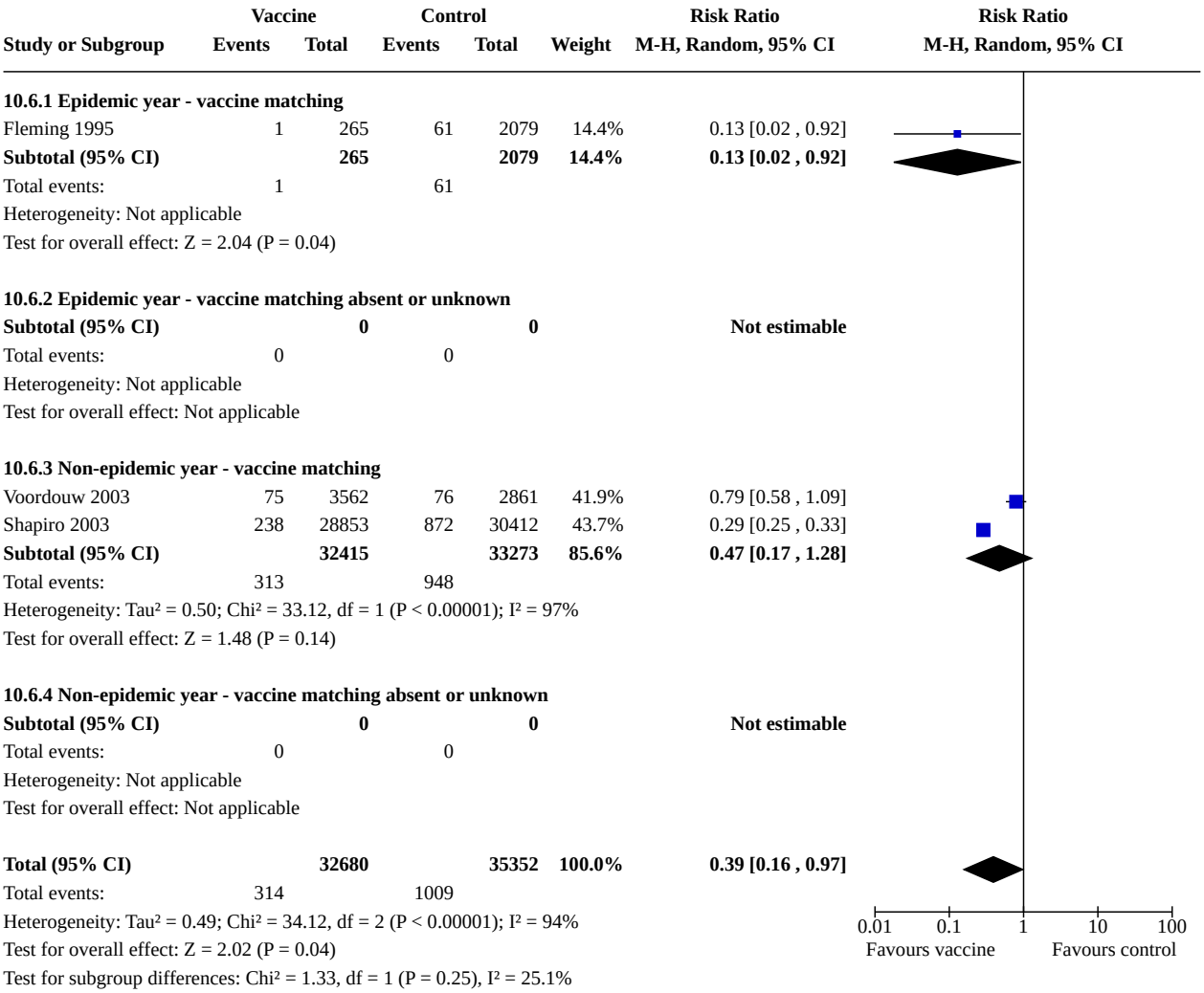


Analysis 10.5. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 5: Deaths from respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.5.1 Epidemic year - vaccine matching						
Mangtani 2004a	1653	66850	2029	75614	100.0%	0.92 [0.86 , 0.98]
Subtotal (95% CI)		**66850**		**75614**	**100.0%**	**0.92 [0.86 , 0.98]**
Total events:	1653		2029			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)		**66850**		**75614**	**100.0%**	**0.92 [0.86 , 0.98]**
Total events:	1653		2029			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
Test for subgroup differences: Not applicable						

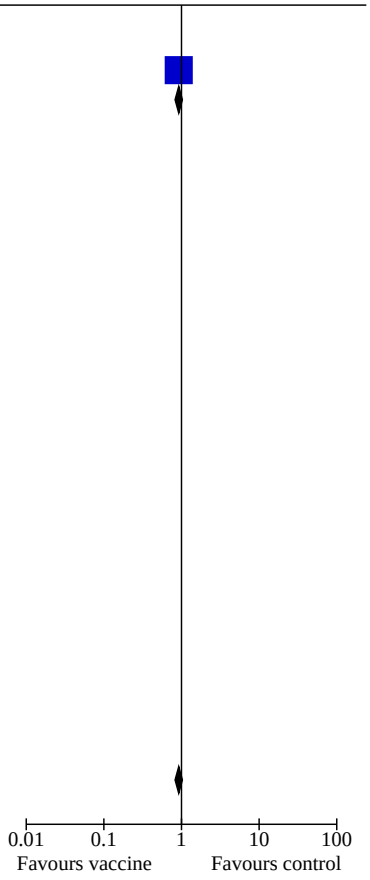


Analysis 10.6. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 6: All deaths



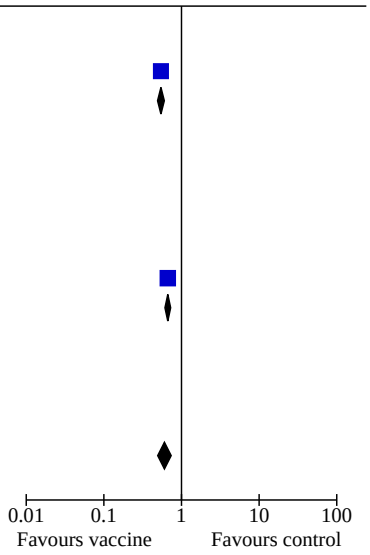
Analysis 10.7. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 7: Hospitalisation for heart disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.7.1 Epidemic year - vaccine matching						
Nichol 1998a	917	30840	487	15092	100.0%	0.92 [0.83 , 1.03]
Subtotal (95% CI)		**30840**		**15092**	**100.0%**	**0.92 [0.83 , 1.03]**
Total events:	917		487			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
10.7.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.7.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.7.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**30840**		**15092**	**100.0%**	**0.92 [0.83 , 1.03]**
Total events:	917		487			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Not applicable						



Analysis 10.8. Comparison 10: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - risk groups, Outcome 8: Combined outcome: all deaths or severe respiratory illness

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.8.1 Epidemic year - vaccine matching						
Hak 2002a	695	33312	811	21126	49.1%	0.54 [0.49 , 0.60]
Subtotal (95% CI)		**33312**		**21126**	**49.1%**	**0.54 [0.49 , 0.60]**
Total events:	695		811			
Heterogeneity: Not applicable						
Test for overall effect: Z = 11.97 (P < 0.00001)						
10.8.2 Epidemic year - vaccine matching absent or unknown						
Hak 2002b	1129	57846	995	33964	50.9%	0.67 [0.61 , 0.72]
Subtotal (95% CI)		**57846**		**33964**	**50.9%**	**0.67 [0.61 , 0.72]**
Total events:	1129		995			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.46 (P < 0.00001)						
Total (95% CI)		**91158**		**55090**	**100.0%**	**0.60 [0.49 , 0.74]**
Total events:	1824		1806			
Heterogeneity: Tau² = 0.02; Chi² = 9.34, df = 1 (P = 0.002); I² = 89%						
Test for overall effect: Z = 4.97 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.34, df = 1 (P = 0.002), I² = 89.3%						



Comparison 11. Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups

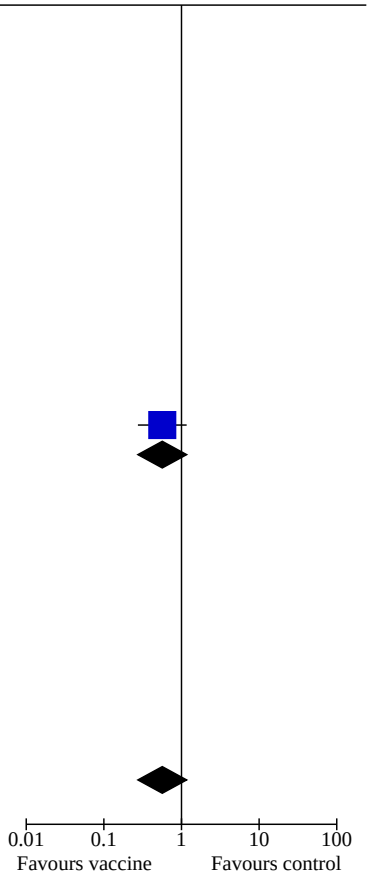
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Influenza	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.17]
11.1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.1.3 Non-epidemic year - vaccine matching	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.17]
11.1.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.2 Pneumonia	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.92]
11.2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.2.3 Non-epidemic year - vaccine matching	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.3 Hospitalisation for influenza or pneumonia	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.40, 0.63]
11.3.1 Epidemic year - vaccine matching	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.40, 0.63]
11.3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.3.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.3.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.4 Hospitalisation for any respiratory disease	2	376324	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.55, 1.27]
11.4.1 Epidemic year - vaccine matching	2	376324	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.55, 1.27]
11.4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.4.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.4.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.5 Deaths from respiratory disease	1	281424	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.31, 1.53]
11.5.1 Epidemic year - vaccine matching	1	281424	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.31, 1.53]
11.6 All deaths	3	43821	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.33, 1.29]
11.6.1 Epidemic year - vaccine matching	1	7047	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.26, 4.49]
11.6.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.6.3 Non-epidemic year - vaccine matching	2	36774	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.30]
11.6.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.7 Hospitalisation for heart disease	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.01]
11.7.1 Epidemic year - vaccine matching	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.01]
11.7.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.7.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.7.4 Non-epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.8 Combined outcome: all deaths or severe respiratory illness	2	135180	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.54, 0.70]
11.8.1 Epidemic year - vaccine matching	1	68536	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.54, 0.78]
11.8.2 Epidemic year - vaccine matching absent or unknown	1	66644	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.48, 0.71]

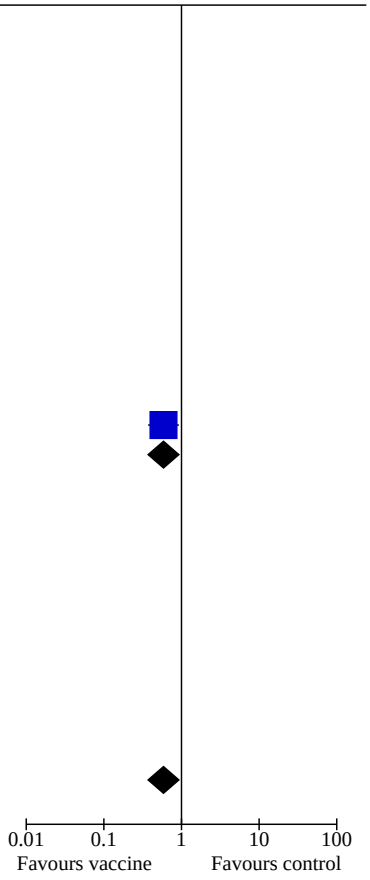
Analysis 11.1. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 1: Influenza

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.1.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.1.3 Non-epidemic year - vaccine matching						
Voordouw 2003	11	5349	22	6050	100.0%	0.57 [0.27 , 1.17]
Subtotal (95% CI)		**5349**		**6050**	**100.0%**	**0.57 [0.27 , 1.17]**
Total events:	11		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
11.1.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**5349**		**6050**	**100.0%**	**0.57 [0.27 , 1.17]**
Total events:	11		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Not applicable						



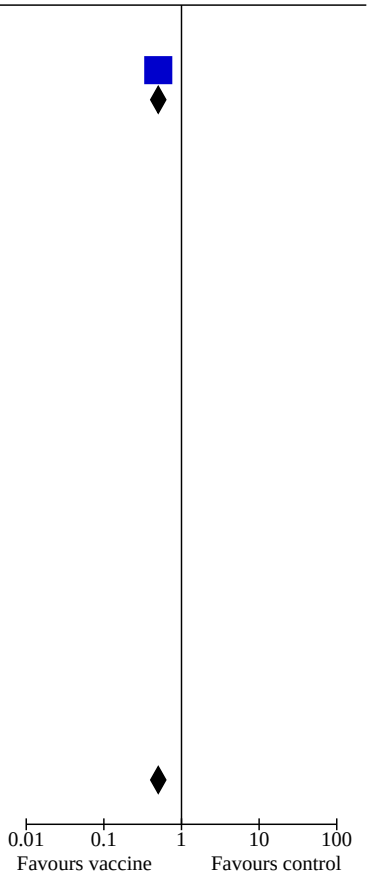
Analysis 11.2. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 2: Pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.2.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.2.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.2.3 Non-epidemic year - vaccine matching						
Voordouw 2003	28	5349	54	6050	100.0%	0.59 [0.37 , 0.92]
Subtotal (95% CI)		**5349**		**6050**	**100.0%**	**0.59 [0.37 , 0.92]**
Total events:	28		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
11.2.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**5349**		**6050**	**100.0%**	**0.59 [0.37 , 0.92]**
Total events:	28		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
Test for subgroup differences: Not applicable						



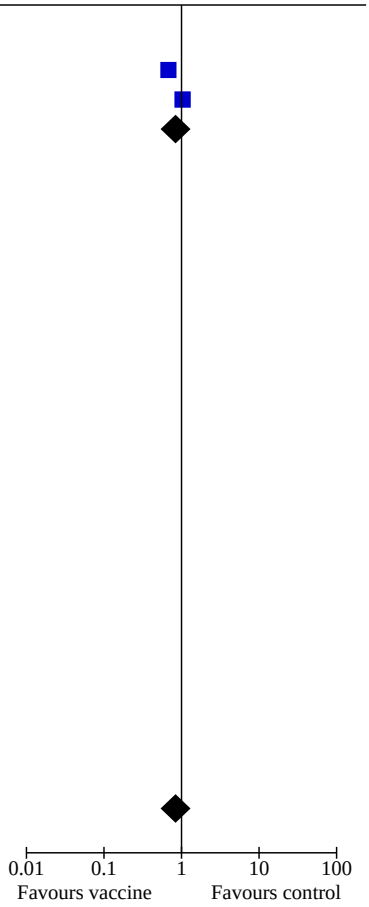
Analysis 11.3. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 3: Hospitalisation for influenza or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.3.1 Epidemic year - vaccine matching						
Nichol 1998a	126	57058	196	44561	100.0%	0.50 [0.40 , 0.63]
Subtotal (95% CI)		**57058**		**44561**	**100.0%**	**0.50 [0.40 , 0.63]**
Total events:	126		196			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.04 (P < 0.00001)						
11.3.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.3.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.3.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**57058**		**44561**	**100.0%**	**0.50 [0.40 , 0.63]**
Total events:	126		196			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.04 (P < 0.00001)						
Test for subgroup differences: Not applicable						



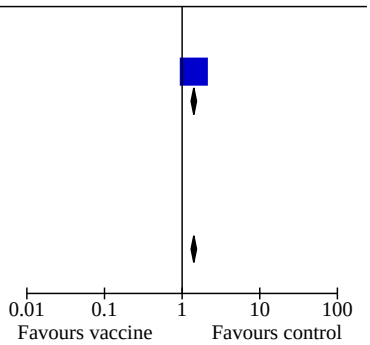
Analysis 11.4. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 4: Hospitalisation for any respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.4.1 Epidemic year - vaccine matching						
Nichol 1998a	491	57058	566	44561	49.6%	0.68 [0.60 , 0.76]
Mangtani 2004a	567	77722	1392	196983	50.4%	1.03 [0.94 , 1.14]
Subtotal (95% CI)		**134780**		**241544**	**100.0%**	**0.84 [0.55 , 1.27]**
Total events:	1058		1958			
Heterogeneity: Tau² = 0.09; Chi² = 28.49, df = 1 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.84 (P = 0.40)						
11.4.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.4.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.4.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**134780**		**241544**	**100.0%**	**0.84 [0.55 , 1.27]**
Total events:	1058		1958			
Heterogeneity: Tau² = 0.09; Chi² = 28.49, df = 1 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Not applicable						



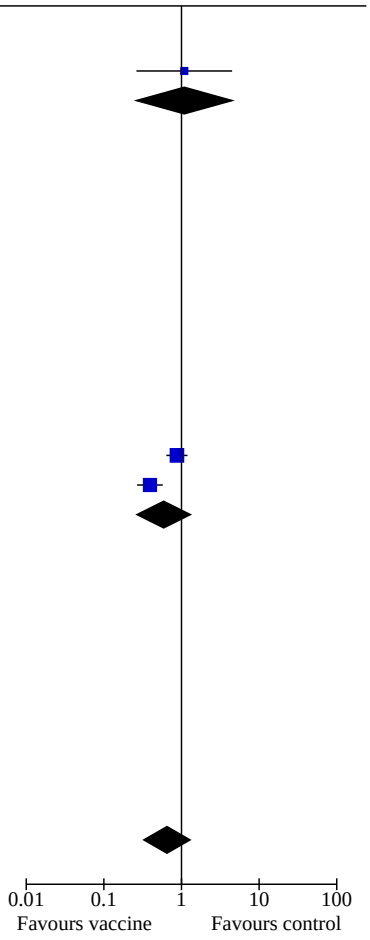
Analysis 11.5. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 5: Deaths from respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.5.1 Epidemic year - vaccine matching						
Mangtani 2004a	932	78912	1691	202512	100.0%	1.41 [1.31 , 1.53]
Subtotal (95% CI)		**78912**		**202512**	**100.0%**	**1.41 [1.31 , 1.53]**
Total events:	932		1691			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.54 (P < 0.00001)						
Total (95% CI)		**78912**		**202512**	**100.0%**	**1.41 [1.31 , 1.53]**
Total events:	932		1691			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.54 (P < 0.00001)						
Test for subgroup differences: Not applicable						



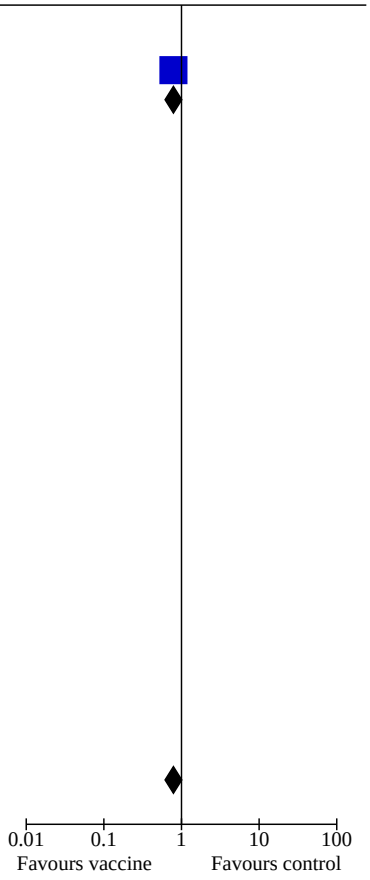
Analysis 11.6. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 6: All deaths

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.6.1 Epidemic year - vaccine matching						
Fleming 1995	2	334	37	6713	15.6%	1.09 [0.26 , 4.49]
Subtotal (95% CI)		**334**		**6713**	**15.6%**	**1.09 [0.26 , 4.49]**
Total events:	2		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
11.6.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.6.3 Non-epidemic year - vaccine matching						
Voordouw 2003	68	5349	88	6050	43.1%	0.87 [0.64 , 1.20]
Shapiro 2003	31	7743	180	17632	41.3%	0.39 [0.27 , 0.57]
Subtotal (95% CI)		**13092**		**23682**	**84.4%**	**0.59 [0.27 , 1.30]**
Total events:	99		268			
Heterogeneity: Tau² = 0.30; Chi² = 10.32, df = 1 (P = 0.001); I² = 90%						
Test for overall effect: Z = 1.31 (P = 0.19)						
11.6.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**13426**		**30395**	**100.0%**	**0.65 [0.33 , 1.29]**
Total events:	101		305			
Heterogeneity: Tau² = 0.26; Chi² = 10.88, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 1.24 (P = 0.22)						
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%						

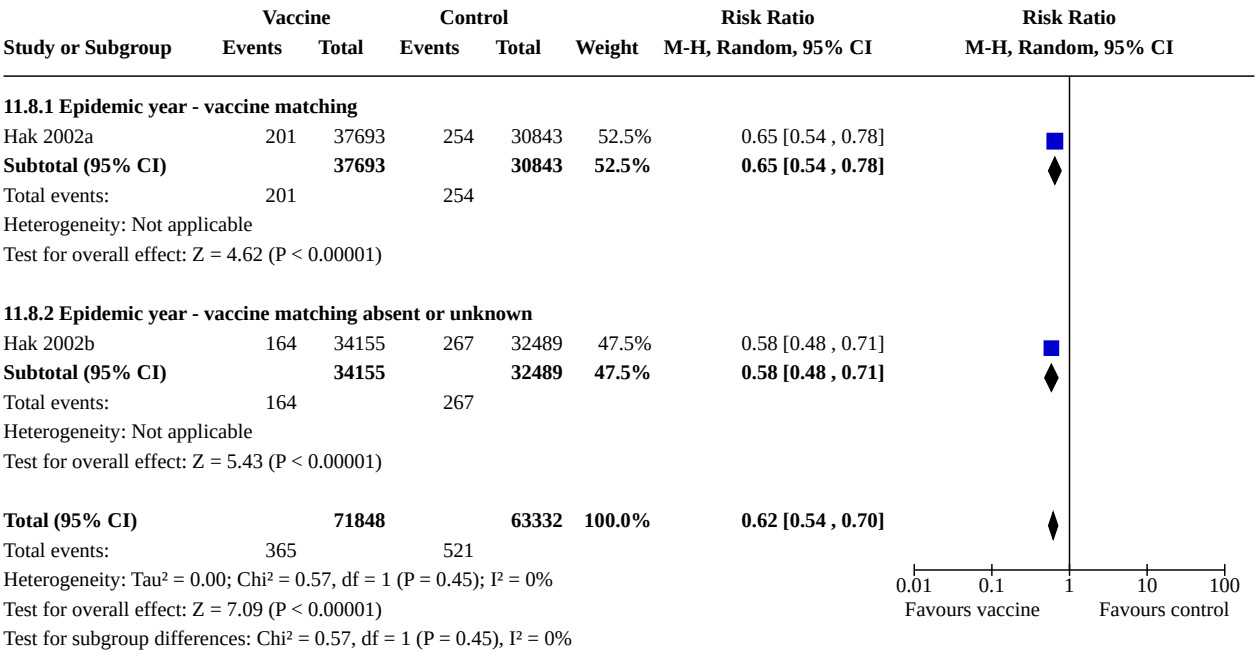


Analysis 11.7. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 7: Hospitalisation for heart disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.7.1 Epidemic year - vaccine matching						
Nichol 1998a	126	57058	125	44561	100.0%	0.79 [0.61 , 1.01]
Subtotal (95% CI)		**57058**		**44561**	**100.0%**	**0.79 [0.61 , 1.01]**
Total events:	126		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						
11.7.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.7.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.7.4 Non-epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**57058**		**44561**	**100.0%**	**0.79 [0.61 , 1.01]**
Total events:	126		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						
Test for subgroup differences: Not applicable						



Analysis 11.8. Comparison 11: Influenza vaccines versus no vaccination: cohort studies in community-dwellers - no risk groups, Outcome 8: Combined outcome: all deaths or severe respiratory illness



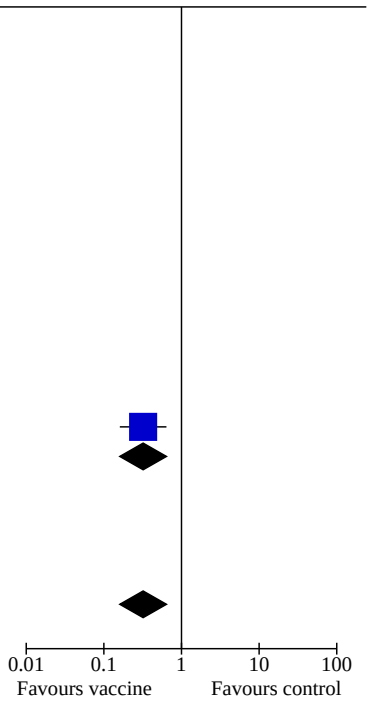
Comparison 12. Influenza and pneumococcal vaccines versus no vaccination: cohort studies in community-dwellers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Influenza-like illness	1	374	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.64]
12.1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.1.3 Non-epidemic year - vaccine matching	1	374	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.64]
12.2 Hospitalisation for influenza or pneumonia or respiratory disease	3	518748	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.64, 0.70]
12.2.1 Epidemic year - vaccine matching	2	518374	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.63, 0.71]
12.2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.2.3 Non-epidemic year - vaccine matching	1	374	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.10, 7.97]
12.3 Deaths from influenza or pneumonia	1	259627	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3.1 Epidemic year - vaccine matching	1	259627	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.57]
12.3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.3.3 Non-epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.4 All deaths	2	260001	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.41, 0.46]
12.4.1 Epidemic year - vaccine matching	1	259627	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.41, 0.46]
12.4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
12.4.3 Non-epidemic year - vaccine matching	1	374	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.08, 30.65]

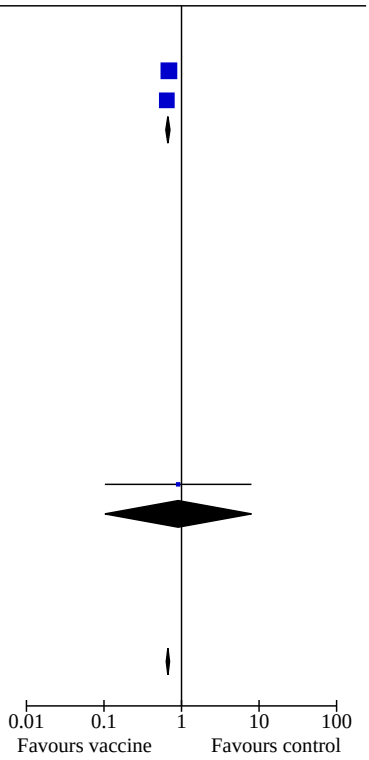
Analysis 12.1. Comparison 12: Influenza and pneumococcal vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 1: Influenza-like illness

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.1.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.1.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.1.3 Non-epidemic year - vaccine matching						
Consonni 2004b	17	305	12	69	100.0%	0.32 [0.16 , 0.64]
Subtotal (95% CI)		**305**		**69**	**100.0%**	**0.32 [0.16 , 0.64]**
Total events:	17		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.23 (P = 0.001)						
Total (95% CI)		**305**		**69**	**100.0%**	**0.32 [0.16 , 0.64]**
Total events:	17		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.23 (P = 0.001)						
Test for subgroup differences: Not applicable						



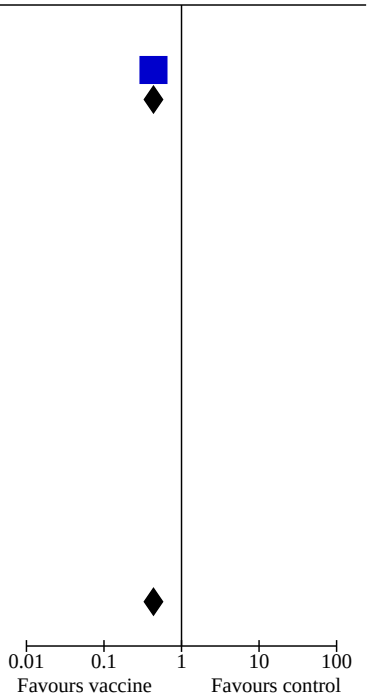
Analysis 12.2. Comparison 12: Influenza and pneumococcal vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 2: Hospitalisation for influenza or pneumonia or respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.2.1 Epidemic year - vaccine matching						
Christenson 2001b	1234	100242	2854	159385	52.2%	0.69 [0.64 , 0.73]
Christenson 2004b	1266	124702	2106	134045	47.8%	0.65 [0.60 , 0.69]
Subtotal (95% CI)		**224944**		**293430**	**100.0%**	**0.67 [0.63 , 0.71]**
Total events:	2500		4960			
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 1 (P = 0.21); I² = 38%						
Test for overall effect: Z = 13.07 (P < 0.00001)						
12.2.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.2.3 Non-epidemic year - vaccine matching						
Consonni 2004b	4	305	1	69	0.0%	0.90 [0.10 , 7.97]
Subtotal (95% CI)		**305**		**69**	**0.0%**	**0.90 [0.10 , 7.97]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**225249**		**293499**	**100.0%**	**0.67 [0.64 , 0.70]**
Total events:	2504		4961			
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 16.54 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

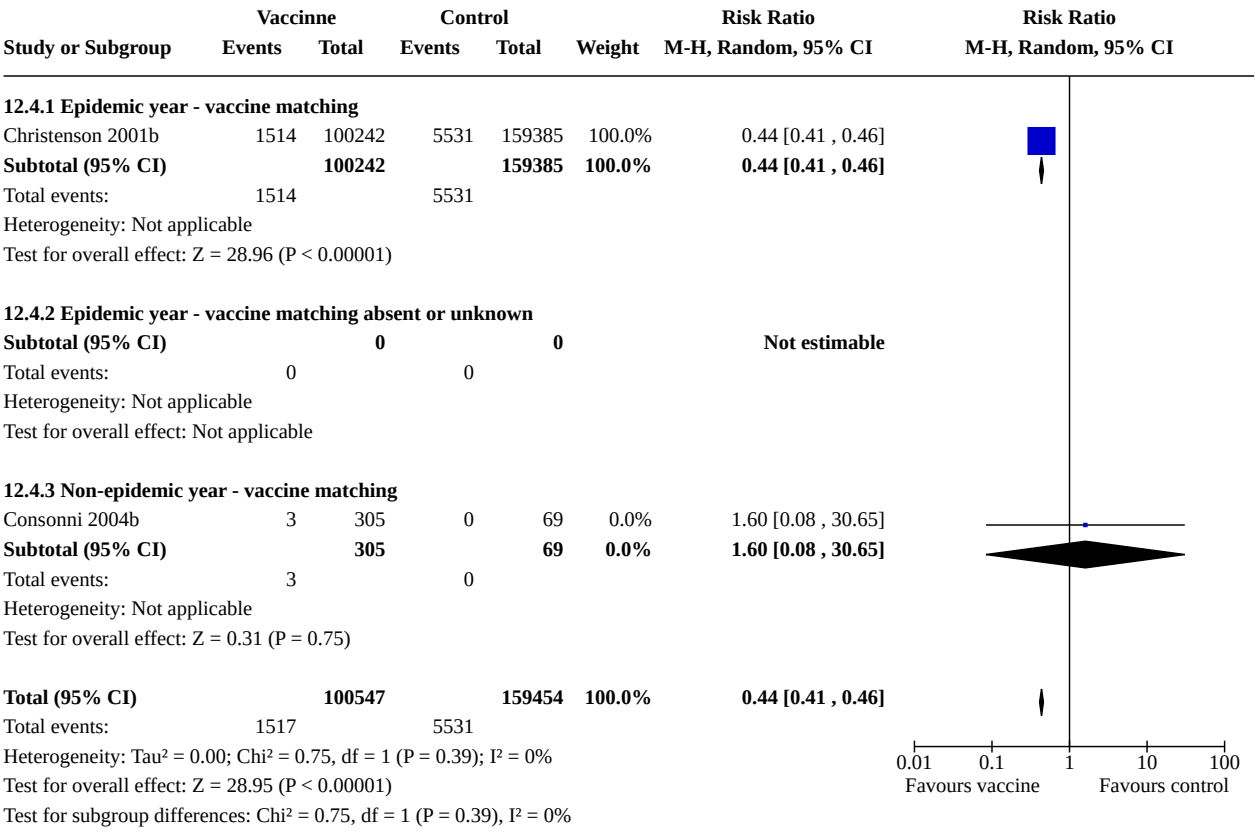


Analysis 12.3. Comparison 12: Influenza and pneumococcal vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 3: Deaths from influenza or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 Epidemic year - vaccine matching						
Christenson 2001b	67	100242	245	159385	100.0%	0.43 [0.33 , 0.57]
Subtotal (95% CI)		**100242**		**159385**	**100.0%**	**0.43 [0.33 , 0.57]**
Total events:	67		245			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.04 (P < 0.00001)						
12.3.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.3.3 Non-epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**100242**		**159385**	**100.0%**	**0.43 [0.33 , 0.57]**
Total events:	67		245			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.04 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 12.4. Comparison 12: Influenza and pneumococcal vaccines versus no vaccination: cohort studies in community-dwellers, Outcome 4: All deaths

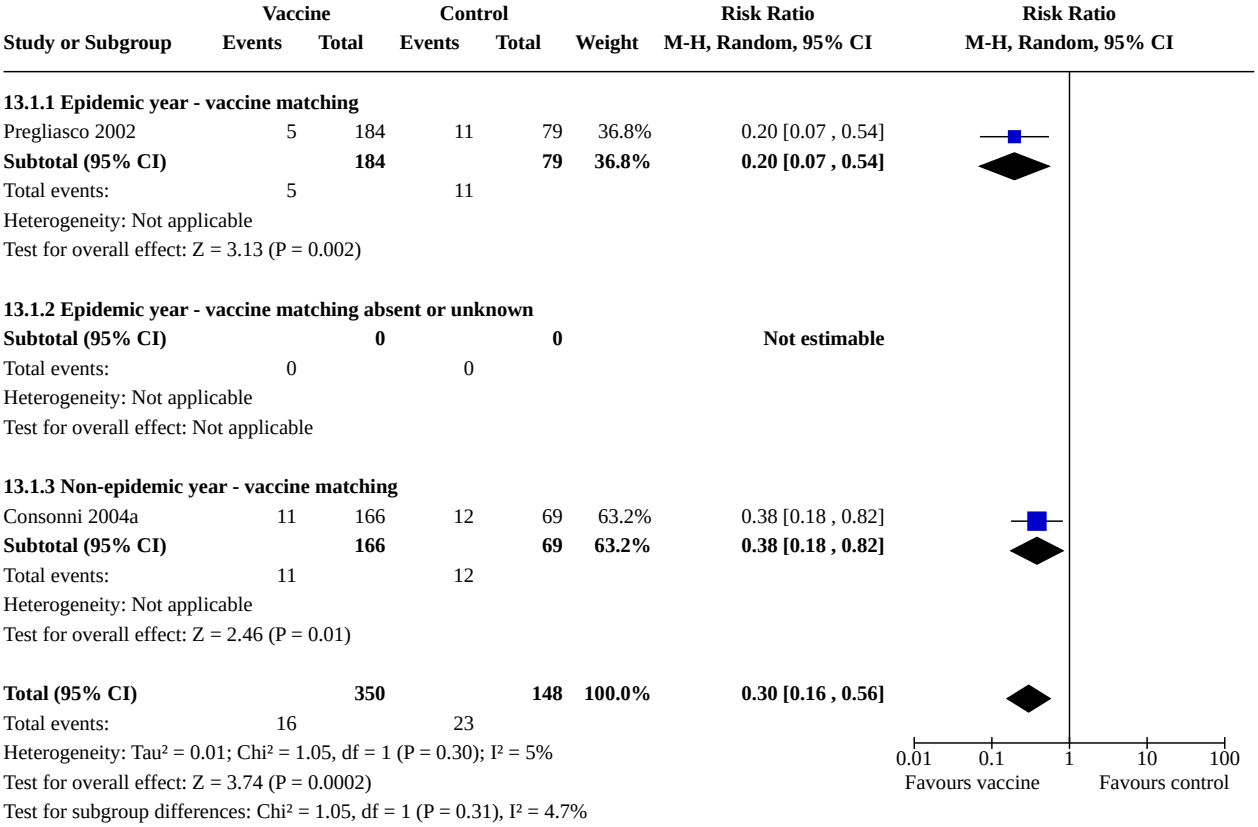


Comparison 13. Influenza vaccines with adjuvant versus no vaccination: cohort studies in community-dwellers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Influenza-like illness	2	498	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.56]
13.1.1 Epidemic year - vaccine matching	1	263	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.54]
13.1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
13.1.3 Non-epidemic year - vaccine matching	1	235	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.18, 0.82]
13.2 Hospitalisation for influenza or pneumonia or respiratory disease	2	498	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.28]
13.2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
13.2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

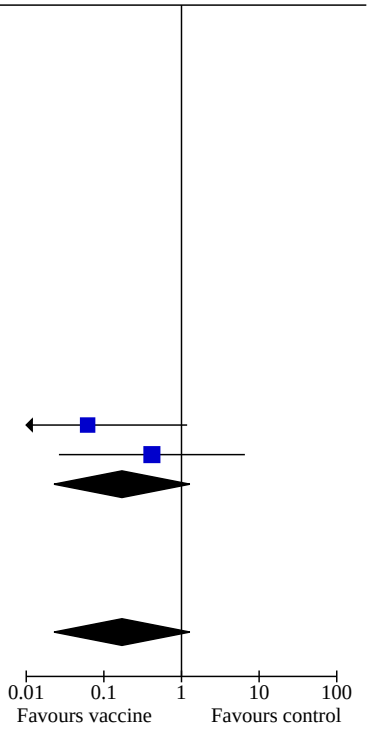
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2.3 Non-epidemic year - vaccine matching	2	498	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.28]
13.3 All deaths	1	235	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.10, 43.10]
13.3.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
13.3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
13.3.3 Non-epidemic year - vaccine matching	1	235	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.10, 43.10]

Analysis 13.1. Comparison 13: Influenza vaccines with adjuvant versus no vaccination: cohort studies in community-dwellers, Outcome 1: Influenza-like illness

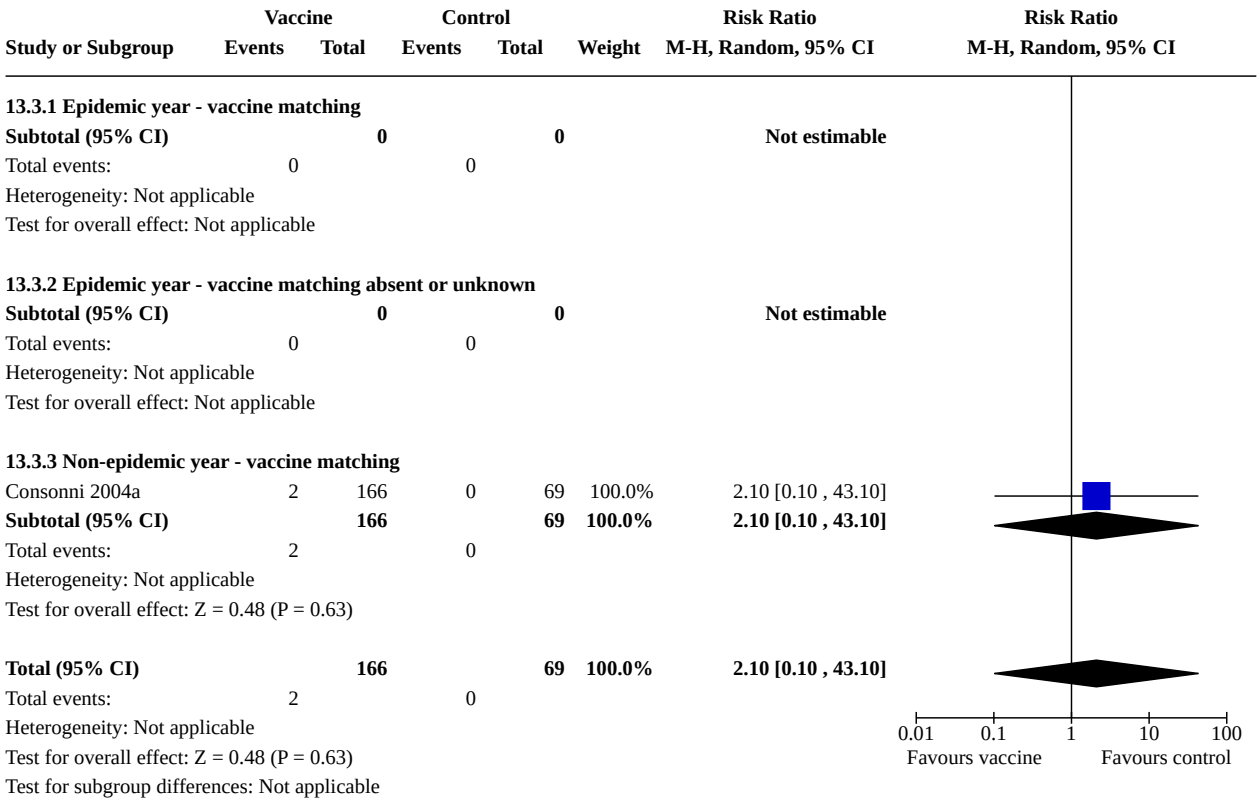


Analysis 13.2. Comparison 13: Influenza vaccines with adjuvant versus no vaccination: cohort studies in community-dwellers, Outcome 2: Hospitalisation for influenza or pneumonia or respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.2.1 Epidemic year - vaccine matching						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.2.2 Epidemic year - vaccine matching absent or unknown						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.2.3 Non-epidemic year - vaccine matching						
Pregliasco 2002	0	184	3	79	46.6%	0.06 [0.00 , 1.18]
Consonni 2004a	1	166	1	69	53.4%	0.42 [0.03 , 6.55]
Subtotal (95% CI)		**350**		**148**	**100.0%**	**0.17 [0.02 , 1.28]**
Total events:	1		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**350**		**148**	**100.0%**	**0.17 [0.02 , 1.28]**
Total events:	1		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Not applicable						



Analysis 13.3. Comparison 13: Influenza vaccines with adjuvant versus no vaccination: cohort studies in community-dwellers, Outcome 3: All deaths



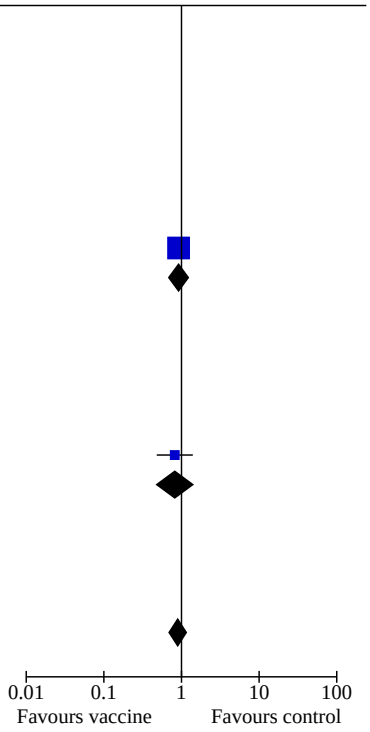
Comparison 14. Influenza vaccines versus no vaccination: case-control studies in community

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Hospitalisations for influenza or pneumonia	2	1074	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
14.1.1 Outbreak - vaccine matching (circulating strains)	0	0	Odds Ratio (M-H, Random, 95% CI)	Not estimable
14.1.2 Outbreak - vaccine matching absent or unknown	1	825	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.22]
14.1.3 No outbreak - vaccine matching	1	249	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.48, 1.40]
14.2 Hospitalisations for any respiratory disease	4	21378	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.95, 1.23]
14.2.1 Outbreak - vaccine matching	3	20582	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.26]
14.2.2 No outbreak - not matching	1	796	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.68, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3 Deaths from influenza or pneumonia	1	1092	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.04]
14.3.1 Outbreak - vaccine matching	1	1092	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.04]
14.4 Pneumonia (no better defined)	1	519	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.33]
14.4.1 Outbreak - partially matching	1	519	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.33]

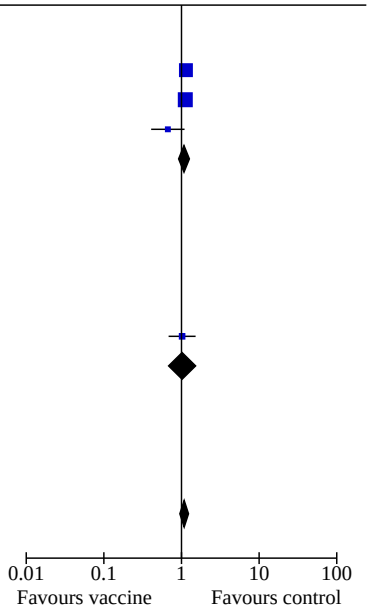
Analysis 14.1. Comparison 14: Influenza vaccines versus no vaccination: case-control studies in community, Outcome 1: Hospitalisations for influenza or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
14.1.1 Outbreak - vaccine matching (circulating strains)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
14.1.2 Outbreak - vaccine matching absent or unknown						
Crocetti 2001	133	275	278	550	77.3%	0.92 [0.69 , 1.22]
Subtotal (95% CI)		**275**		**550**	**77.3%**	**0.92 [0.69 , 1.22]**
Total events:	133		278			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
14.1.3 No outbreak - vaccine matching						
Puig-Barberà 1997	47	83	102	166	22.7%	0.82 [0.48 , 1.40]
Subtotal (95% CI)		**83**		**166**	**22.7%**	**0.82 [0.48 , 1.40]**
Total events:	47		102			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Total (95% CI)		**358**		**716**	**100.0%**	**0.89 [0.69 , 1.15]**
Total events:	180		380			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.39)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						



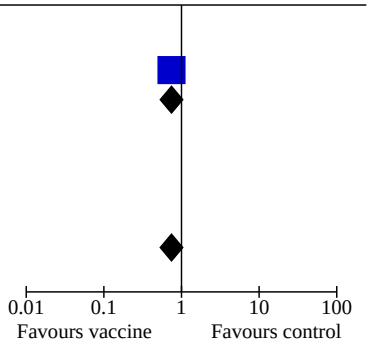
Analysis 14.2. Comparison 14: Influenza vaccines versus no vaccination: case-control studies in community, Outcome 2: Hospitalisations for any respiratory disease

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
14.2.1 Outbreak - vaccine matching						
Fedson 1993a	283	2619	754	7852	40.1%	1.14 [0.99 , 1.32]
Fedson 1993b	370	2417	1008	7249	44.6%	1.12 [0.98 , 1.27]
Ahmed 1997	27	156	69	289	6.2%	0.67 [0.41 , 1.09]
Subtotal (95% CI)		**5192**		**15390**	**90.9%**	**1.08 [0.92 , 1.26]**
Total events:	680		1831			
Heterogeneity: Tau² = 0.01; Chi² = 4.20, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 0.91 (P = 0.36)						
14.2.2 No outbreak - not matching						
Jordan 2007	117	157	474	639	9.1%	1.02 [0.68 , 1.52]
Subtotal (95% CI)		**157**		**639**	**9.1%**	**1.02 [0.68 , 1.52]**
Total events:	117		474			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**5349**		**16029**	**100.0%**	**1.08 [0.95 , 1.23]**
Total events:	797		2305			
Heterogeneity: Tau² = 0.01; Chi² = 4.36, df = 3 (P = 0.22); I² = 31%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.80), I² = 0%						

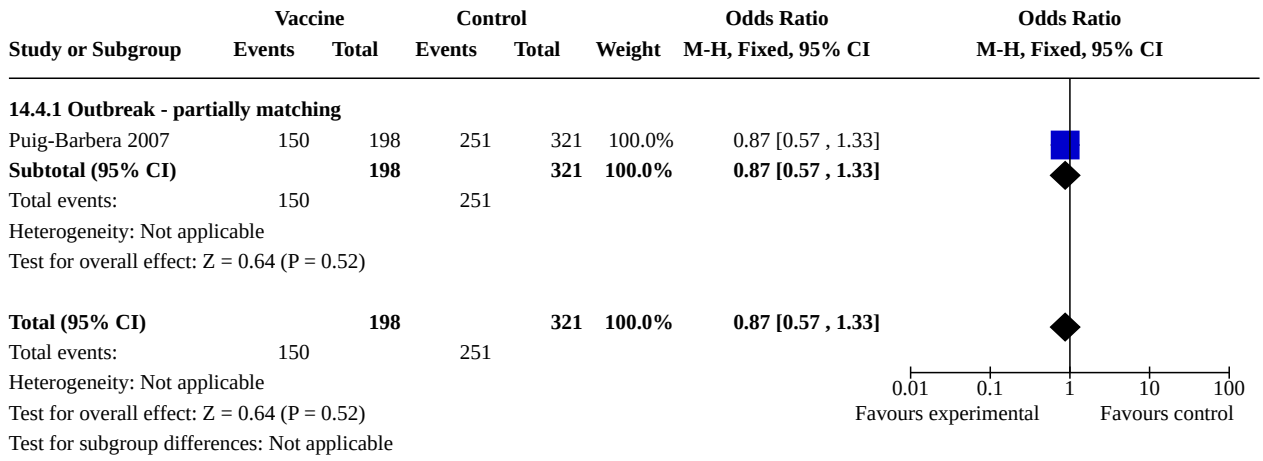


Analysis 14.3. Comparison 14: Influenza vaccines versus no vaccination: case-control studies in community, Outcome 3: Deaths from influenza or pneumonia

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
14.3.1 Outbreak - vaccine matching						
Ahmed 1995	57	315	178	777	100.0%	0.74 [0.53 , 1.04]
Subtotal (95% CI)		**315**		**777**	**100.0%**	**0.74 [0.53 , 1.04]**
Total events:	57		178			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**315**		**777**	**100.0%**	**0.74 [0.53 , 1.04]**
Total events:	57		178			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Not applicable						



Analysis 14.4. Comparison 14: Influenza vaccines versus no vaccination: case-control studies in community, Outcome 4: Pneumonia (no better defined)



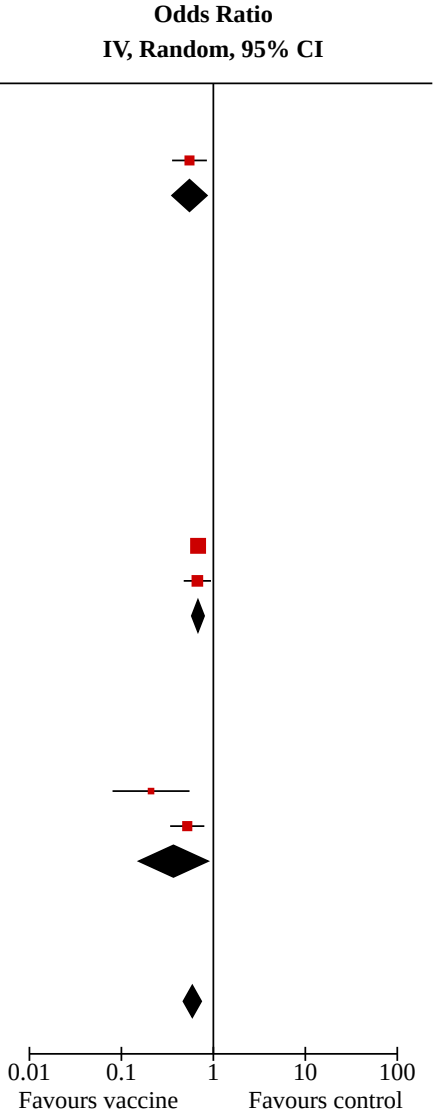
Comparison 15. Influenza vaccines versus no vaccination: case-control studies in community - adjusted rates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Hospitalisations for influenza or pneumonia	5		Odds Ratio (IV, Random, 95% CI)	0.59 [0.47, 0.74]
15.1.1 Epidemic - vaccine matching	1		Odds Ratio (IV, Random, 95% CI)	0.55 [0.36, 0.85]
15.1.2 Non-epidemic - vaccine not matching	0		Odds Ratio (IV, Random, 95% CI)	Not estimable
15.1.3 Epidemic year - vaccine matching absent or unknown	2		Odds Ratio (IV, Random, 95% CI)	0.68 [0.58, 0.79]
15.1.4 Non-epidemic - vaccine matching	2		Odds Ratio (IV, Random, 95% CI)	0.37 [0.16, 0.87]
15.2 Hospitalisations for any respiratory disease	3		Odds Ratio (IV, Random, 95% CI)	0.71 [0.56, 0.90]
15.2.1 Epidemic - vaccine matching	3		Odds Ratio (IV, Random, 95% CI)	0.71 [0.56, 0.90]
15.2.2 Non-epidemic - vaccine matching	0		Odds Ratio (IV, Random, 95% CI)	Not estimable
15.2.3 Non-epidemic year - vaccine matching	0		Odds Ratio (IV, Random, 95% CI)	Not estimable
15.3 Deaths from pneumonia or influenza	2		Odds Ratio (IV, Random, 95% CI)	0.74 [0.60, 0.92]
15.3.1 Epidemic year - vaccine matching	1		Odds Ratio (IV, Random, 95% CI)	0.76 [0.60, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.3.2 Epidemic year - vaccine matching absent or unknown	1		Odds Ratio (IV, Random, 95% CI)	0.67 [0.42, 1.07]

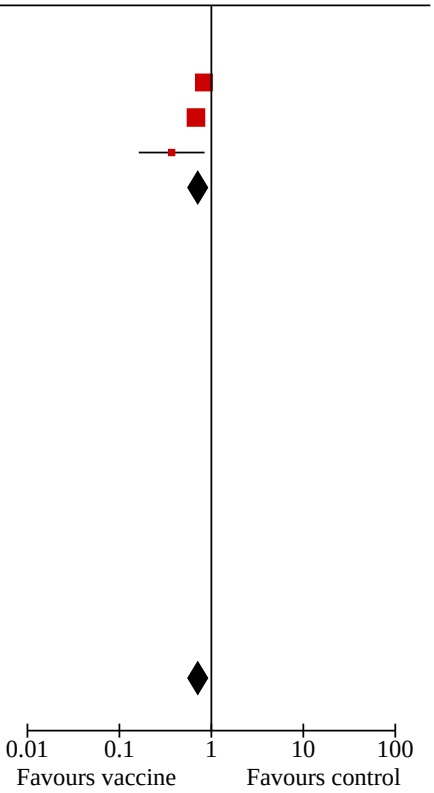
Analysis 15.1. Comparison 15: Influenza vaccines versus no vaccination: case-control studies in community - adjusted rates, Outcome 1: Hospitalisations for influenza or pneumonia

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
15.1.1 Epidemic - vaccine matching				
Foster 1992	-0.5978	0.2222	17.0%	0.55 [0.36 , 0.85]
Subtotal (95% CI)			**17.0%**	**0.55 [0.36 , 0.85]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.69 (P = 0.007)				
15.1.2 Non-epidemic - vaccine not matching				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
15.1.3 Epidemic year - vaccine matching absent or unknown				
Mullooly 1994	-0.3823	0.0878	38.0%	0.68 [0.57 , 0.81]
Crocetti 2001	-0.4005	0.1742	22.8%	0.67 [0.48 , 0.94]
Subtotal (95% CI)			**60.7%**	**0.68 [0.58 , 0.79]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%				
Test for overall effect: Z = 4.92 (P < 0.00001)				
15.1.4 Non-epidemic - vaccine matching				
Puig-Barberà 1997	-1.5606	0.4918	4.8%	0.21 [0.08 , 0.55]
Puig-Barberà 2004	-0.6539	0.2183	17.4%	0.52 [0.34 , 0.80]
Subtotal (95% CI)			**22.2%**	**0.37 [0.16 , 0.87]**
Heterogeneity: Tau² = 0.27; Chi² = 2.84, df = 1 (P = 0.09); I² = 65%				
Test for overall effect: Z = 2.27 (P = 0.02)				
Total (95% CI)			**100.0%**	**0.59 [0.47 , 0.74]**
Heterogeneity: Tau² = 0.03; Chi² = 7.08, df = 4 (P = 0.13); I² = 44%				
Test for overall effect: Z = 4.65 (P < 0.00001)				
Test for subgroup differences: Chi² = 2.56, df = 2 (P = 0.28), I² = 21.8%				

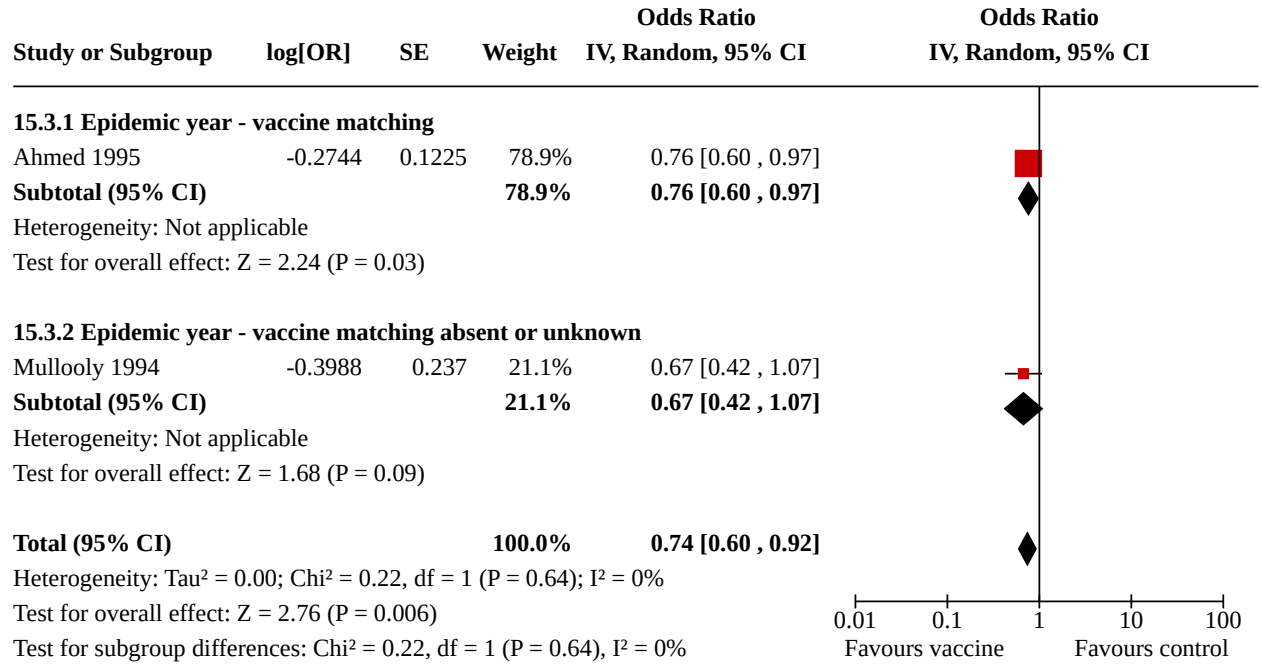


Analysis 15.2. Comparison 15: Influenza vaccines versus no vaccination: case-control studies in community - adjusted rates, Outcome 2: Hospitalisations for any respiratory disease

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Random, 95% CI
15.2.1 Epidemic - vaccine matching				
Fedson 1993a	-0.1863	0.0958	45.1%	0.83 [0.69 , 1.00]
Fedson 1993b	-0.3857	0.0865	47.5%	0.68 [0.57 , 0.81]
Ahmed 1997	-0.9943	0.42	7.5%	0.37 [0.16 , 0.84]
Subtotal (95% CI)			**100.0%**	**0.71 [0.56 , 0.90]**
Heterogeneity: Tau² = 0.02; Chi² = 5.09, df = 2 (P = 0.08); I² = 61%				
Test for overall effect: Z = 2.79 (P = 0.005)				
15.2.2 Non-epidemic - vaccine matching				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
15.2.3 Non-epidemic year - vaccine matching				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
Total (95% CI)			**100.0%**	**0.71 [0.56 , 0.90]**
Heterogeneity: Tau² = 0.02; Chi² = 5.09, df = 2 (P = 0.08); I² = 61%				
Test for overall effect: Z = 2.79 (P = 0.005)				
Test for subgroup differences: Not applicable				



Analysis 15.3. Comparison 15: Influenza vaccines versus no vaccination: case-control studies in community - adjusted rates, Outcome 3: Deaths from pneumonia or influenza

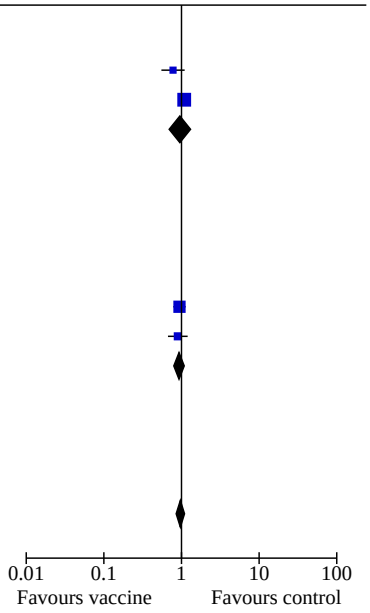


Comparison 16. Influenza and pneumococcal vaccines versus no vaccination: case-control studies in community

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Hospitalisations for influenza or pneumonia	4	6629	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.09]
16.1.1 Outbreak - vaccine matching	2	3617	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.31]
16.1.2 No outbreak - vaccine matching	2	3012	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.08]

Analysis 16.1. Comparison 16: Influenza and pneumococcal vaccines versus no vaccination: case-control studies in community, Outcome 1: Hospitalisations for influenza or pneumonia

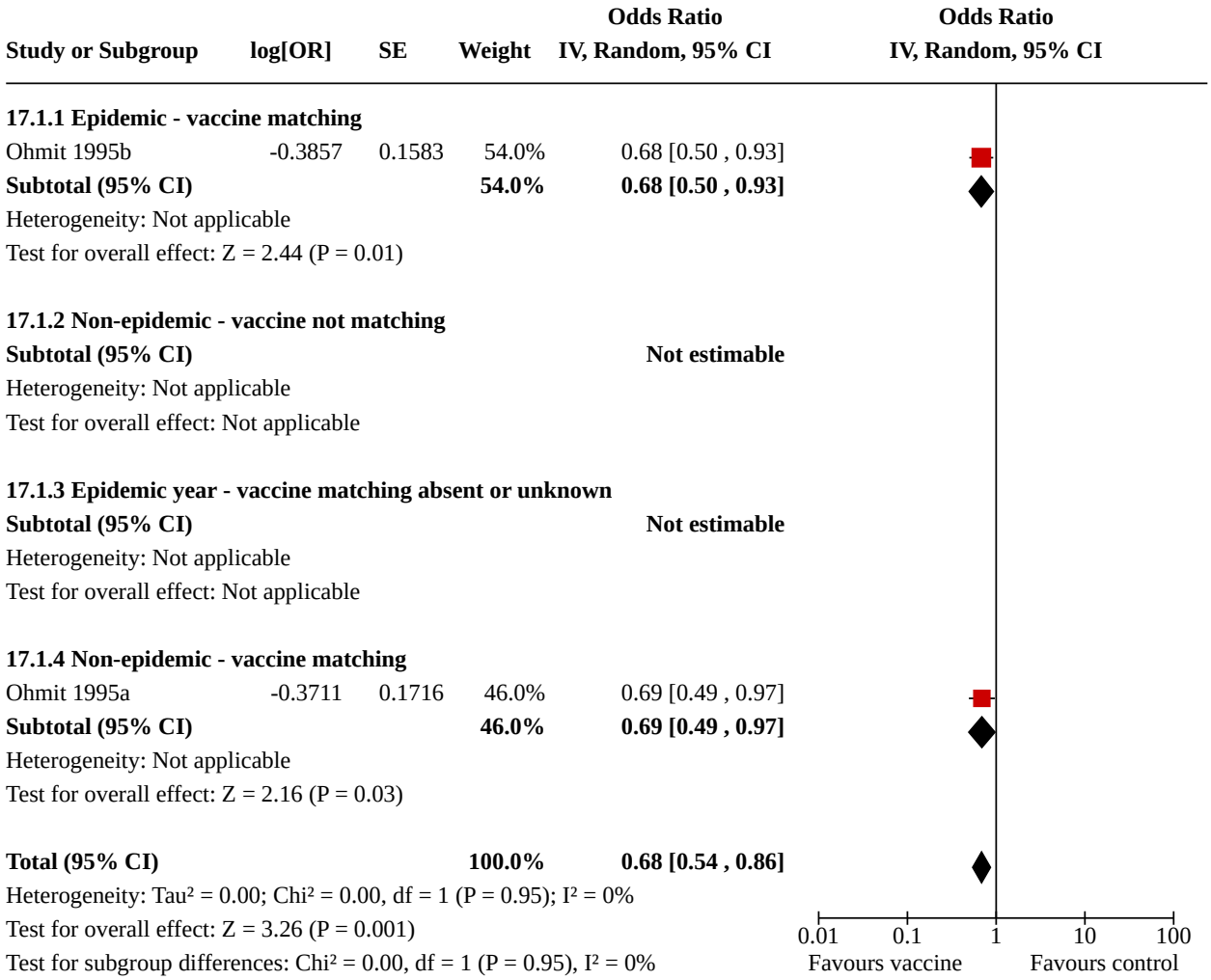
Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
16.1.1 Outbreak - vaccine matching						
Foster 1992	60	185	256	671	11.6%	0.78 [0.55 , 1.10]
Ohmit 1995b	484	890	980	1871	39.6%	1.08 [0.92 , 1.27]
Subtotal (95% CI)		**1075**		**2542**	**51.2%**	**0.95 [0.69 , 1.31]**
Total events:	544		1236			
Heterogeneity: Tau² = 0.04; Chi² = 2.92, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 0.30 (P = 0.76)						
16.1.2 No outbreak - vaccine matching						
Ohmit 1995a	314	667	743	1530	33.2%	0.94 [0.79 , 1.13]
Puig-Barberà 2004	168	290	318	525	15.6%	0.90 [0.67 , 1.20]
Subtotal (95% CI)		**957**		**2055**	**48.8%**	**0.93 [0.80 , 1.08]**
Total events:	482		1061			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**2032**		**4597**	**100.0%**	**0.97 [0.85 , 1.09]**
Total events:	1026		2297			
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 3 (P = 0.29); I² = 21%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						



Comparison 17. Influenza and pneumococcal vaccines versus no vaccination: case-control studies in community - adjusted rates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Hospitalisations for influenza or pneumonia	2		Odds Ratio (IV, Random, 95% CI)	0.68 [0.54, 0.86]
17.1.1 Epidemic - vaccine matching	1		Odds Ratio (IV, Random, 95% CI)	0.68 [0.50, 0.93]
17.1.2 Non-epidemic - vaccine not matching	0		Odds Ratio (IV, Random, 95% CI)	Not estimable
17.1.3 Epidemic year - vaccine matching absent or unknown	0		Odds Ratio (IV, Random, 95% CI)	Not estimable
17.1.4 Non-epidemic - vaccine matching	1		Odds Ratio (IV, Random, 95% CI)	0.69 [0.49, 0.97]

Analysis 17.1. Comparison 17: Influenza and pneumococcal vaccines versus no vaccination: case-control studies in community - adjusted rates, Outcome 1: Hospitalisations for influenza or pneumonia

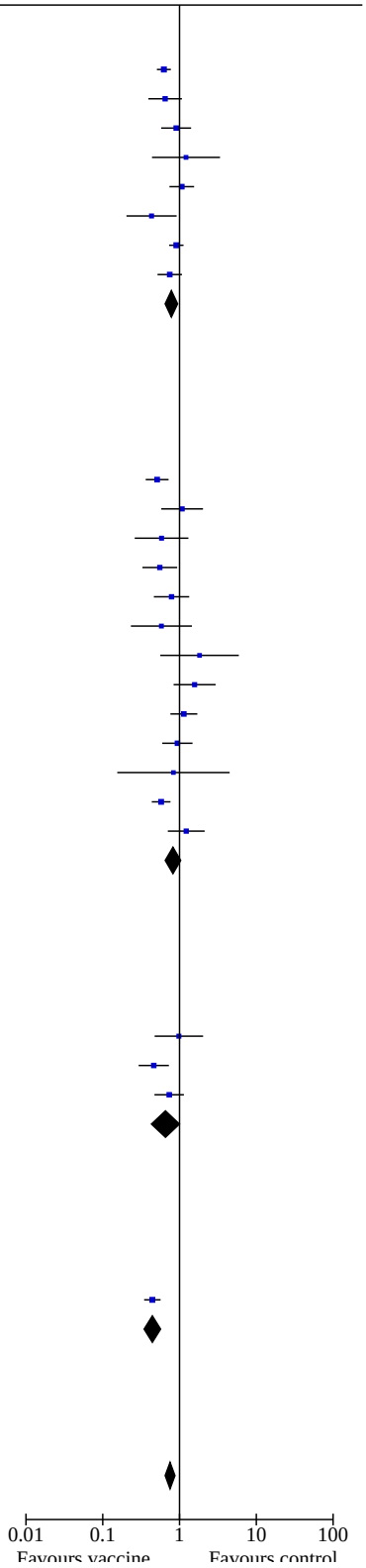


Comparison 18. Sensitivity analysis: comparison 01: subgroup analysis by study quality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Influenza-like illness	25	9211	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.65, 0.87]
18.1.1 Quality A	8	4502	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.94]
18.1.2 Quality B	13	3854	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.03]
18.1.3 Quality C	3	389	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.00]
18.1.4 Quality D	1	466	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.35, 0.57]

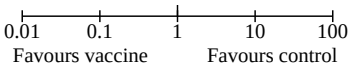
Analysis 18.1. Comparison 18: Sensitivity analysis: comparison 01: subgroup analysis by study quality, Outcome 1: Influenza-like illness

Study or Subgroup	Vaccine Events	Vaccine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.1.1 Quality A						
Patriarca 1985a	113	548	155	470	6.8%	0.63 [0.51 , 0.77]
Patriarca 1985b	37	339	20	119	4.1%	0.65 [0.39 , 1.07]
Strassburg 1986	34	65	11	19	4.5%	0.90 [0.58 , 1.41]
Coles 1992	34	112	3	12	1.6%	1.21 [0.44 , 3.37]
Taylor 1992	25	45	27	52	5.2%	1.07 [0.74 , 1.55]
Caminiti 1994	12	169	12	73	2.5%	0.43 [0.20 , 0.92]
Monto 2001	247	1728	98	623	6.7%	0.91 [0.73 , 1.13]
Murayama 1999	25	60	38	68	5.3%	0.75 [0.52 , 1.08]
Subtotal (95% CI)		**3066**		**1436**	**36.8%**	**0.78 [0.65 , 0.94]**
Total events:	527		364			
Heterogeneity: Tau² = 0.03; Chi² = 13.17, df = 7 (P = 0.07); I² = 47%						
Test for overall effect: Z = 2.58 (P = 0.010)						
18.1.2 Quality B						
Ruben 1974	38	204	70	192	5.5%	0.51 [0.36 , 0.72]
Horman 1986	22	100	12	59	3.2%	1.08 [0.58 , 2.02]
Goodman 1982	6	36	24	84	2.3%	0.58 [0.26 , 1.30]
Fyson 1983a	23	321	29	224	3.9%	0.55 [0.33 , 0.93]
Arroyo 1984	10	26	44	90	3.9%	0.79 [0.46 , 1.34]
Arden 1988	6	31	8	24	1.9%	0.58 [0.23 , 1.45]
Cartter 1990a	15	96	3	35	1.3%	1.82 [0.56 , 5.92]
Cartter 1990b	12	30	14	55	3.2%	1.57 [0.84 , 2.95]
Cartter 1990c	75	332	25	126	4.9%	1.14 [0.76 , 1.70]
Currier 1988	36	87	15	34	4.5%	0.94 [0.60 , 1.48]
Morens 1995	10	36	1	3	0.7%	0.83 [0.15 , 4.49]
Saito 2002a	58	331	112	368	6.1%	0.58 [0.44 , 0.76]
Saito 2002b	68	743	14	187	3.7%	1.22 [0.70 , 2.12]
Subtotal (95% CI)		**2373**		**1481**	**45.1%**	**0.82 [0.65 , 1.03]**
Total events:	379		371			
Heterogeneity: Tau² = 0.09; Chi² = 27.13, df = 12 (P = 0.007); I² = 56%						
Test for overall effect: Z = 1.68 (P = 0.09)						
18.1.3 Quality C						
D'Alessio 1969	29	131	7	31	2.7%	0.98 [0.47 , 2.03]
Meiklejohn 1987	14	36	16	19	4.5%	0.46 [0.29 , 0.73]
Isaacs 1997	57	149	12	23	4.6%	0.73 [0.47 , 1.14]
Subtotal (95% CI)		**316**		**73**	**11.7%**	**0.66 [0.43 , 1.00]**
Total events:	100		35			
Heterogeneity: Tau² = 0.07; Chi² = 3.87, df = 2 (P = 0.14); I² = 48%						
Test for overall effect: Z = 1.97 (P = 0.05)						
18.1.4 Quality D						
Mukerjee 1994	62	250	121	216	6.4%	0.44 [0.35 , 0.57]
Subtotal (95% CI)		**250**		**216**	**6.4%**	**0.44 [0.35 , 0.57]**
Total events:	62		121			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.49 (P < 0.00001)						
Total (95% CI)		**6005**		**3206**	**100.0%**	**0.75 [0.65 , 0.87]**
Total events:	1068		891			
Heterogeneity: Tau² = 0.07; Chi² = 61.54, df = 24 (P < 0.0001); I² = 61%						
Test for overall effect: Z = 3.82 (P = 0.0001)						



Analysis 18.1. (Continued)

Heterogeneity: Tau² = 0.07; Chi² = 61.54, df = 24 (P < 0.0001); I² = 61%
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Chi² = 16.47, df = 3 (P = 0.0009), I² = 81.8%



ADDITIONAL TABLES

Table 1. Studies included in the various versions of this review and their impact on our conclusions

Review version (searches date)	Number of included trials (RCTs/CCTs)	Number of included observational studies	Estimates of effect (RCTs/CCTs only)	Conclusions (1 to 2 lines from abstract)
Version 1 (24 May 2006)	9	62[1]	**Influenza-like illness** LAIV = no data TIV = 41% (95% CI 27% to 53%) IAV = n.s. **Influenza** LAIV = n.s. TIV = 58% (95% CI 34% to 73%) IAV = n.s.	In long-term care facilities, where vaccination is most effective against complications, the aims of the vaccination campaign are fulfilled, at least in part. However, according to reliable evidence the usefulness of vaccines in the community is modest. The apparent high effectiveness of the vaccines in preventing death from all causes may reflect a baseline imbalance in health status and other systematic differences in the 2 groups of participants.
Version 2 (20 January 2010)	9	66[2]	**Influenza-like illness** LAIV = no data TIV = 41% (95% CI 27% to 53%) IAV = n.s. **Influenza** LAIV = n.s. TIV = 58% (95% CI 34% to 73%) IAV = n.s.	The available evidence is of poor quality and provides no guidance regarding the safety, efficacy, or effectiveness of influenza vaccines for people aged 65 years or older. To resolve the uncertainty, an adequately powered publicly-funded randomised, placebo-controlled trial run over several seasons should be undertaken.

[1]These include 49 cohort studies for efficacy/effectiveness (79 data sets); 10 case-control studies for efficacy/effectiveness (12 data sets); 3 studies (cohorts) for Guillain-Barré syndrome.
[2]For this update, two cohort studies and two case-control studies were added to the review (all assessing efficacy/effectiveness).
Key: CCT = controlled clinical trial; CI = confidence interval; IAV = inactivated aerosol vaccines; LAIV = live attenuated vaccines; n.s. = not significant; RCT = randomised controlled trial; TIV = trivalent inactivated vaccines

Table 2. Guillain-Barré syndrome

Study	Influenza season	Vaccine	Population	Age	RR (95% CI)
Schonberger 1979	1976 to 1977	A/New Jersey/76 or A/New Jersey/76 and A/Victoria/75 swine vaccine	All the USA population	> 64 years	5.2 (3.9 to 7.0)
Kaplan 1982	1979 to 1980	Inactivated trivalent	All the USA population	> 18 years	0.6 (0.45 to 1.32)
Kaplan 1982	1980 to 1981	Inactivated trivalent	All the USA population	> 18 years	1.4 (0.80 to 1.76)
Lasky 1998	1992 to 1994	Inactivated trivalent	21 million	> 64 years	1.5 (0.7 to 3.3)

Key: CI = confidence interval; RR = risk ratio

APPENDICES

Appendix 1. Included studies design

Case-control study: a retrospective epidemiological study usually used to investigate the association between two variables (e.g. hospitalisation for pneumonia and influenza vaccination). Study participants who have experienced an event (adverse or disease-related) are compared with participants who have not. Any differences in the presence or absence of hypothesised risk or protective variables are observed.

Cohort study: an epidemiological study where groups of individuals are identified who vary in their exposure to an intervention or hazard, and who are then followed to assess outcomes. Association between exposure and outcome are then estimated. Cohort studies are best performed prospectively, but can also be undertaken retrospectively if suitable data records are available.

Randomised controlled trial: any study on humans in which the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation.

Quasi-randomised clinical trial: any study on humans in which the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth, or case record number).

Appendix 2. MEDLINE (Ovid) and CENTRAL search strategy

1 Influenza Vaccines/
2 Influenza, Human/tm, pc, im, mo, ep [Transmission, Prevention & Control, Immunology, Mortality, Epidemiology]
3 Influenza, Human/
4 exp Influenzavirus A/
5 exp Influenzavirus B/
6 (flu or influenza*).tw.
7 or/3-6
8 Vaccines/
9 vaccines, attenuated/ or vaccines, inactivated/ or exp vaccines, subunit/ or exp vaccines, synthetic/ or viral vaccines/
10 exp Immunization/
11 (vaccin* or immuni* or inocul*).tw.
12 exp Adjuvants, Immunologic/
13 (vaccin* adj5 adjuvant*).tw.
14 Squalene/
15 (aluminium or squalene or MF59 or virosom*).tw,nm.
16 or/8-15
17 7 and 16
18 1 or 2 or 17
19 exp Adult/

20 Men/
21 Women/
22 Retirement/
23 ((old* or age*) adj3 (people* or person* or adult* or women* or men* or citizen* or residen*)).tw.
24 (pension* or retire* or adult* or aged or elderly or senior* or geriatric*).tw.
25 long-term care/ or nursing care/ or palliative care/
26 homes for the aged/ or nursing homes/
27 nursing home*.tw.
28 or/19-27
29 28 and 18

Appendix 3. Embase (Elsevier) search strategy

26. #23 AND #26
25. #24 OR #25
24. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti
23. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
22. #15 AND #22
21. #16 OR #17 OR #18 OR #19 OR #20
20. 'aged care':ab,ti OR 'nursing home':ab,ti OR 'nursing homes':ab,ti
19. 'nursing home'/exp OR 'hospice'/de OR 'residential home'/de
18. pension*:ab,ti OR retire*:ab,ti OR adult*:ab,ti OR aged:ab,ti OR elderly:ab,ti OR senior*:ab,ti OR geriatric*:ab,ti
17. ((old* OR age*) NEAR/3 (people* OR person* OR adult* OR women OR men OR citizen* OR residen*)):ab,ti
16. 'adult'/de OR 'aged'/exp OR 'pensioner'/exp
15. #1 OR #14
14. #5 AND #13
13. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
12. aluminium:ab,ti OR squalene:ab,ti OR mf59:ab,ti OR virosom*:ab,ti
11. 'squalene'/de
10. (vaccin* NEAR/5 adjuvant*):ab,ti
9. 'immunological adjuvant'/de
8. vaccin*:ab,ti OR immuni*:ab,ti OR inocul*:ab,ti
7. 'immunization'/de OR 'vaccination'/de OR 'active immunization'/de OR 'immunoprophylaxis'/de OR 'mass immunization'/de
6. 'vaccine'/de OR 'acellular vaccine'/de OR 'dna vaccine'/de OR 'inactivated vaccine'/de OR 'live vaccine'/de OR 'subunit vaccine'/de OR 'virus vaccine'/de OR 'virosome vaccine'/de OR 'recombinant vaccine'/de
5. #2 OR #3 OR #4
4. flu:ab,ti OR influenza*:ab,ti
3. 'influenza virus a'/exp OR 'influenza virus b'/exp
2. 'influenza'/exp
1. 'influenza vaccine'/de

Appendix 4. Web of Science search strategy

Topic=(influenza or flu or influenzavirus) AND Topic=(vaccine* or immuni* or inocul* or adjuvant* or squalene or aluminium or MF59 or virosom*) AND Topic=(aged or elderly or senior* or geriatric* or retire* or pension* or old* people or old* person* or old* adult* or old* men or old* women or old* citizen* or old* residen* or nursing home*)

Refined by: Topic=(random* or placebo* or rct or single blind* or double blind*)

Timespan = 2006 to 2009.

Appendix 5. CINAHL (EBSCO) search strategy

S1	(MH "Influenza Vaccine")
S2	(MH "Influenza, Human+/TM/PC/IM/MO/EP")

(Continued)

S3	(MH "Influenza, Human") OR (MH "Influenza A H5N1") OR (MH "Influenza, Pandemic (H1N1) 2009") OR (MH "Influenza, Seasonal")
S4	(MH "Influenza A Virus+")
S5	(MH "Influenzavirus B+")
S6	TI (influenza* or flu) OR AB (influenza* or flu)
S7	S3 or S4 or S5 or S6
S8	(MH "Vaccines+")
S9	(MH "Immunization+")
S10	(MH "Immunization Programs")
S11	TI (vaccin* or immuni* or inocul*) OR AB (vaccin* or immuni* or inocul*)
S12	TI (aluminium or squalene or mf59 or virosom*) OR AB (aluminium or squalene or mf59 or virosom*)
S13	S8 or S9 or S10 or S11 or S12
S14	S7 and S13
S15	S1 or S2 or S14
S16	(MH "Aged+")
S17	(MH "Gerontologic Care")
S18	(MH "Nursing Homes") OR (MH "Residential Facilities")
S19	(MH "Nursing Home Patients")
S20	(MH "Long Term Care")
S21	(MH "Adult")
S22	(MH "Men") OR (MH "Aged, Hospitalized") OR (MH "Women")
S23	TI (pension* or retire* or adult* or aged or elderly or senior* or geriatric*) OR AB (pension* or retire* or adult* or aged or elderly or senior* or geriatric*)
S24	TI ((old* or age*) N3 (people* or person* or adult* or women* or men* or citizen* or residen*)) OR AB ((old* or age*) N3 (people* or pension* or adult* or women* or men* or citizen* or residen*))
S25	TI ("aged care" or "nursing home" or "nursing homes") OR AB ("aged care" or "nursing home" or "nursing homes")
S26	S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S27	S15 and S26
S28	(MH "Clinical Trials+")

(Continued)

S29	PT clinical trial
S30	TI clinic* trial* OR AB clinic* trial*
S31	TI ((singl* or doubl* or trebl* or tripl*) N1 (blind* or mask*)) OR AB ((singl* or doubl* or trebl* or tripl*) N1 (blind* or mask*))
S32	(MH "Random Assignment")
S33	(MH "Placebos")
S34	(MH "Quantitative Studies")
S35	TI (random* or placebo*) OR AB (random* or placebo*)
S36	S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35
S37	S27 and S36

Appendix 6. LILACS (Bireme) search strategy

(mh:"Influenza Vaccines" OR "Vacunas contra la Influenza" OR "Vacinas contra Influenza" OR "Vacunas contra Gripe" OR "Vacunas Antigripales" OR "Vacinas contra Gripe" OR "Vacinas Antigripais" OR ((mh:"Influenza,Human" OR "Gripe Humana" OR "Influenza Humana" OR grippe OR influenza* OR flu OR gripe OR "Influenza en Humanos" OR "Influenza em Humanos") AND (mh:"vaccines" OR vacunas OR vacinas OR mh:d20.215.894* OR mh:"Immunization" OR inmunización OR imunização OR vaccin* OR immuni* OR inocul*))) AND (mh:"Aged" OR anciano* OR idoso* OR elderly OR mh:m01.060.116.100* OR mh:"adult" OR adulto OR idosa OR mh:"Retirement" OR retire* OR jubilación OR aposentadoria OR jubilado OR aposentado OR geriatric* OR geriátrica OR geriátricos OR pension* OR "old age" OR mh:"Homes for the Aged" OR "Hogares para Ancianos" OR "Instituição de Longa Permanência para Idosos" OR "Asilos de Ancianos" OR "Casas para Ancianos" OR "Instituição Asilar" OR "Asilos para Idosos" OR ancianatos OR mh:"nursing homes" OR "Casas de Salud" OR "Casas de Saúde") AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix 7. Trials registers search strategies

WHO ICTRP (http://www.who.int/ictrp/en/)

vaccine* AND influenza

immuni* AND influenza

inocul* AND influenza

vaccine* AND flu

immuni* AND flu

inocul* AND flu

ClinicalTrials.gov (www.clinicaltrials.gov)

(vaccine OR vaccines OR vaccinate OR vaccination OR vaccinated OR vaccinating OR immunise OR immunised OR immunising OR immunisation OR immunize OR immunized OR immunizing OR immunization) AND (influenza OR influenza OR flu)

(inoculate OR inoculated OR inoculating OR inoculation) AND (influenza OR influenza OR flu)

Appendix 8. Previous search details

For the 2009 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects (The Cochrane Library 2009, Issue 4); MEDLINE (January 1966 to October Week 1 2009); EMBASE (1974 to October 2009) and Web of Science (1974 to October 2009).

We used the search in Appendix 2 to search MEDLINE and CENTRAL. The search terms were combined with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity- and precision-maximising version (2008) revision; Ovid format (Lefebvre 2011). This search was adapted for Embase (Appendix 3) and Web of Science (Appendix 4). The search terms were also combined with the SIGN (SIGN 2009) search strategy for identifying observational studies (see Appendix 11) and MEDLINE, Embase and Web of Science were searched for observational studies.

There were no language or publication restrictions. The search of CENTRAL included trial reports identified by the systematic search by hand of the journal *Vaccine*.

In order to identify additional published and unpublished studies:

1. We used the Science Citation Index to identify articles that cite the relevant studies;
2. We keyed the relevant studies into PubMed and used the Related Articles feature;
3. We searched the bibliographies of all relevant articles obtained, any published reviews and proceedings from relevant conferences for additional studies;
4. We explored Internet sources: NHS National Research Register (www.update-software.com/national/), the *meta*Register of Clinical Trials (www.controlled-trials.com/) and the digital dissertations web site (wwwlib.umi.com/dissertations);
5. We searched the Vaccine Adverse Event Reporting System web site (www.vaers.org); and
6. We contacted vaccine manufacturers listed at the WHO web site.

For the 2006 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness (*The Cochrane Library* 2006, issue 1); MEDLINE (January 1966 to March Week 3 2006); EMBASE (Dialog 1974 to 1979; SilverPlatter 1980 to December 2005); Biological Abstracts (SilverPlatter 1969 to December 2004); and Science Citation Index (Web of Science 1974 to December 2004). The following MEDLINE search terms were combined with a methodological search filter for high sensitivity in identifying randomised controlled trials in MEDLINE (Dickersin 1994) and adapted to search the other above mentioned electronic databases.

MEDLINE (Ovid) (2006 update)

1 exp Influenza Vaccines/
2 Influenza, Human/ep [Epidemiology]
3 Influenza, Human/im [Immunology]
4 Influenza, Human/mo [Mortality]
5 Influenza, Human/pc [Prevention & Control]
6 Influenza, Human/tm [Transmission]
7 influenza vaccin$.ti,ab.
8 (influenza or flu).ti,ab.
9 (vaccin$ or immuni$ or inocul$ or efficacy or effectiveness).ti,ab.
10 and/8-9
11 or/1-7,10
12 RANDOMIZED CONTROLLED TRIAL.pt.
13 CONTROLLED CLINICAL TRIAL.pt.
14 RANDOMIZED CONTROLLED TRIALS.sh.
15 RANDOM ALLOCATION.sh.
16 DOUBLE BLIND METHOD.sh.
17 SINGLE-BLIND METHOD.sh.
18 or/12-17
19 Animals/
20 Humans/
21 19 not 20
22 18 not 21
23 CLINICAL TRIAL.pt.
24 exp Clinical Trials/
25 (clin$ adj25 trial$).ti,ab.
26 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
27 PLACEBOS.sh.
28 placebo$.ti,ab.
29 random$.ti,ab.
30 or/23-29
31 30 not 21
32 exp Research Design/

33 exp Comparative Study/
34 exp Evaluation Studies/
35 exp Follow-Up Studies/
36 exp Prospective Studies/
37 prospectiv$.ti,ab.
38 volunteer$.ti,ab.
39 exp Case-Control Studies/
40 (cases and controls).ti,ab.
41 case control stud$.ti,ab.
42 exp Cohort Studies/
43 cohort stud$.ti,ab.
44 observational.ti,ab.
45 or/32-44
46 45 not 21
47 or/22,31,46
48 11 and 47

Appendix 9. Data extraction form

PART 1

Background Information and Description of study
Reviewer:
Study unique identifier:
Published: Y/N
Journal: (if applicable)
Year of publication:
Period study conducted:
Abstract/full paper:
Country or countries of study:
Number of studies included in this paper:
Funding source (delete non applicable items):
Government, Pharmaceutical, Private, Unfunded, Unclear:
Paper/abstract numbers of other studies with which these data are linked:
Reviewer's assessment of study design (delete non applicable items):

Study Category - Study Design
Experimental - RCT/CCT; HCT ; X cross-over RCT
Non-randomised analytical (specifically designed to assess association) - Prospective/
Retrospective Cohort ; Case Control ; X sectional
Non-randomised comparative (not specifically designed to assess association) - Case X Over/Time series ;
Ecological study; Indirect comparison (before and after)
Non-comparative EXCLUDE

Does the study present data distributed by age group/occupation/health status? (Yes/No)
Sub group distribution:
Age group Y/N
Occupation Y/N
Health status Y/N
Gender Y/N
Risk group Y/N

Description of study
Methods
Participants
Interventions/exposure
Outcomes
Notes

PART 2a

Methodological Quality Assessment RCT and CCT only
Randomisation:
A = individual participants allocated to vaccine or control group.

B = groups of participants allocated to vaccine or control group.

Generation of the allocation sequence:
A = adequate, e.g. table of random numbers or computer-generated random numbers.
B = inadequate, e.g. alternation, date of birth, day of the week, or case record number.
C = not described.

Allocation concealment:
A = adequate, e.g. numbered or coded identical containers administered sequentially, on-site computer system that can only be accessed after entering the characteristics of an enrolled participant, or serially numbered, opaque, sealed envelopes.
B = possibly adequate, e.g. sealed envelopes that are not sequentially numbered or opaque.
C = inadequate, e.g. open table of random numbers.
D = not described.

Blinding:
A = adequate double-blinding, e.g. placebo vaccine.
B = single-blind, i.e. blinded outcome assessment.
C = no blinding.

Follow up:

Average duration of follow up and number of losses to follow up.

PART 2b

Description of interventions and outcomes RCT and CCT only
Vaccines used
Vaccines and composition | Product and manufacturer | Schedule & dosage and status | Route of administration
Arm 1
Arm 2
Arm 3
Arm 4
Placebo
Rule: index vaccine goes in the Arm 1 line, placebo in the last line

Status: primary, secondary or tertiary immunisation.

Vaccine Batch Numbers

Details of Participants
Enrolled | Missing | Reasons | Inclusion in analysis | Notes
Active arm 1
Active arm 2
Active arm 3
Active arm 4
Controls

Outcomes List - Efficacy and Effectiveness
Outcome | How defined | Description/Follow up/Notes

Outcomes List - Safety
Outcome | How defined | Description/Follow up/Notes

Investigators to be contacted for more information? Yes/No

Contact details (principal investigator, fill in only if further contact is necessary):

PART 2c

Data extraction and manipulation (to be used for dichotomous or continuous outcomes) RCT and CCT only
Comparison
Outcomes | n/N Index Arm | n/N Comparator
Outcomes | n/N Index Arm | n/N Comparator
Outcomes | n/N Index Arm | n/N Comparator

Notes (for statistical use only)

PART 3a

Methodological Quality Assessment. Non-randomised studies only

Newcastle - Ottawa quality assessment scale (case-control and cohort studies ; see Appendix 10)

PART 3b

Description of interventions and outcomes. Non-randomised longitudinal studies only
Vaccines used
Vaccines and composition | Product and manufacturer | Schedule & dosage and status | Route of administration
Group 1
Group 2
Group 3
Group 4
Comparator

Rule: index vaccine goes in the Group 1 line, placebo in the last line

Vaccine Batch Numbers

Details of Participants
Enrolled | Missing | Reasons | Inclusion in analysis | Notes
Group 1
Group 2
Group 3
Group 4
Comparator

Outcomes List - Effectiveness
Outcome | How defined (including length of follow up) | Description/Follow up/Notes

Outcomes List - Safety
Outcome | How defined (including length of follow up) | Description/Follow up/Notes

Investigators to be contacted for more information? Yes/No

Contact details (principal investigator, fill in only if further contact is necessary):

PART 3c

Data extraction and manipulation (to be used for dichotomous outcomes). Non-randomised longitudinal studies only

Comparison
Outcomes | n/N Index Group | n/N Comparator

Notes (for statistical use only)

PART 3d

Description of studies. Case-control studies only

Event 1
How defined | Enrolled | Missing | Reasons | Inclusion in analysis
Cases n =
Controls n =

Exposure
How defined | How ascertained | Notes
Vaccine Exposure 1
Vaccine Exposure 2

Event 2
How defined | Enrolled | Missing | Reasons | Inclusion in analysis
Cases n =
Controls n =

Exposure
How defined | How ascertained | Notes
Vaccine Exposure 1
Vaccine Exposure 2

Notes (for statistical use only)

Part 3e

Data extraction and manipulation. Case-control studies only

Status | Numerator | Denominator
Cases
Control

Notes (for statistical use only)

Appendix 10. Methodological quality of non-randomised studies

Newcastle-Ottawa Quality Assessment Scale

Case-control studies

Selection

1. Is the case definition adequate?
   a. yes, with independent validation
   b. yes, e.g. record linkage or based on self reports
   c. no description
2. Representation of the cases
   a. consecutive or obviously representative series of cases
   b. potential for selection biases or not stated
3. Selection of controls
   a. community controls
   b. hospital controls
   c. no description
4. Definition of controls
   a. no history of disease (endpoint)
   b. no description of source

Comparability

1. Comparability of cases and controls on the basis of the design or analysis
   a. study controls for _____ (select the most important factor)
   b. study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)

Exposure

1. Ascertainment of exposure
   a. secure record (e.g. surgical records)
   b. structured interview where blind to case/control status
   c. interview not blinded to case/control status
   d. written self report or medical record only
   e. no description
2. Same method of ascertainment for cases and controls
   a. yes
   b. no
3. Non-response rate
   a. same rate for both groups
   b. non-respondents described
   c. rate different and no designation

Newcastle-Ottawa Quality Assessment Scale

Cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the 'Selection' and 'Outcome' categories. A maximum of two stars can be given for 'Comparability'.

Selection

1. Representation of the exposed cohort
   a. truly representative of the average _____ (describe) in the community
   b. somewhat representative of the average _____ in the community
   c. selected group of users (e.g. nurses, volunteers)
   d. no description of the derivation of the cohort
2. Selection of the non-exposed cohort
   a. drawn from the same community as the exposed cohort
   b. drawn from a different source
   c. no description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
   a. secure record (e.g. surgical records)
   b. structured interview
   c. written self report
   d. no description
4. Demonstration that outcome of interest was not present at start of study
   a. yes
   b. no

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   a. study controls for _____ (select the most important factor)
   b. study controls for any additional factor* (this criteria could be modified to indicate specific control for a second important factor)

Outcome

1. Assessment of outcome
   a. independent blind assessment
   b. record linkage
   c. self report
   d. no description
2. Was follow-up long enough for outcomes to occur?
   a. yes (select an adequate follow-up period for outcome of interest)
   b. no
3. Adequacy of follow-up of cohorts
   a. complete follow up - all participants accounted for
   b. participants lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow-up, or description provided of those lost*
   c. follow-up rate < ____% (select an adequate %) and no description of those lost
   d. no statement

Appendix 11. SIGN filter for observational studies

SIGN Scottish Intercollegiate Guidelines Network [Internet]. Edinburgh: c2001-2009; [Last modified 03 August 2009; accessed 02 October 2009]. Available from www.sign.ac.uk/methodology/filters.html on 02 October 2009 (SIGN 2009)

The Observational Studies search filter used by SIGN has been developed in-house to retrieve studies most likely to meet SIGN's methodological criteria.

MEDLINE

1	Epidemiologic studies/
2	Exp case control studies/
3	Exp cohort studies/
4	Case control.tw.
5	(cohort adj (study or studies)).tw.
6	Cohort analy$.tw.
7	(Follow up adj (study or studies)).tw.
8	(observational adj (study or studies)).tw.
9	Longitudinal.tw.
10	Retrospective.tw.
11	Cross sectional.tw.
12	Cross-sectional studies/
13	Or/1-12

EMBASE

1	Clinical study/
2	Case control study
3	Family study/
4	Longitudinal study/
5	Retrospective study/
6	Prospective study/
7	Randomised controlled trials/
8	6 not 7
9	Cohort analysis/
10	(Cohort adj (study or studies)).mp.
11	(Case control adj (study or studies)).tw.
12	(follow up adj (study or studies)).tw.

(Continued)

13	(observational adj (study or studies)).tw.
14	(epidemiologic$ adj (study or studies)).tw.
15	(cross sectional adj (study or studies)).tw.
16	Or/1-5,8-15

FEEDBACK

Vaccines for preventing influenza in the elderly,

Summary

Dear Dr Rivetti,

We have several questions about the review 'Vaccines for preventing influenza in the elderly'.

Although the authors recognized that "The findings of the cohort studies that we included are likely to have been affected to a varying degree by selection bias.", the reviewers drew conclusions that "in long-term care facilities, where vaccination is most effective against complications," based on the results of cohort studies that is not compatible with the strict prospective study method of RCT.

However they argued that RCT can minimize the bias, they concluded that extracted RCTs can offer no definitive evidence due to their scant and bad reports. If so, they should suggest a well-designed placebo controlled RCT of influenza vaccination for preventing influenza in the elderly.

Moreover they insist that placebo-controlled RCT is no longer possible on ethical ground, because the influenza vaccinations are globally recommended.
The statement is very surprising. If it is true, RCTs are no longer possible after the recommendations or medical interventions have been globally implemented, even though they are clearly erroneous. We think the idea is against Cochrane Collaboration's principle.

On the contrary, we cannot ethically accept the scant and bad situation itself of RCTs on the vaccine, because flu vaccinations have been awkwardly recommended all over the world without high level evidence.

The reviewers discussed that "Consistent with other published studies, during influenza season, vaccination was associated with a 44% reduction in risk of all-cause mortality during influenza season. However, in the period before influenza vaccination was associated with a 61% reduction in risk of this outcome."

In fact, Japanese cohort studies which evaluated the influenza vaccine have also large selection bias favourable to the vaccinated group in various outcomes including mortality, fever and absence from school.

For examples, in the cohort study of over 65 years old at Geriatric Health Service Facility
1) vaccination associated with a 51.9% relative risk reduction in all-cause mortality during influenza season; but the mortality in the vaccinated group was 61.5% lower during extra-influenza season. This study also showed a 37.8% relative risk reduction in fever during influenza season, but fever rate in the vaccinated group was 37.3% lower during extra-influenza season.

In Japanese cohort studies which evaluated the effectiveness of the influenza vaccine for children
2) the vaccination was associated with a 12.2% relative risk reduction in fever during influenza season, but it also showed a 17.3% reduction prior to influenza season.

Moreover Takahashi K et al. reported the absence rate of vaccinated and unvaccinated students in Mie prefecture during influenza season and during prior to influenza season.
3) In the study of elementary school vaccination was associated with a 26.1% relative risk reduction in absence during influenza season, but it associated with a 23.7% reduction prior to influenza season. In the study of junior high school it associated with a 29.1% relative risk reduction during influenza season but it also associated a 31% reduction during prior to influenza season.

According to these cohort studies, the vaccinated groups revealed more increase of mortality, fever rate, or absence rate during influenza season relative to the extra-influenza season.

In conclusion, "no firm conclusions can be drawn from" the cohort studies, because of its large bias as the review authors suggest. However the cohort studies may become more reliable after the outcomes during influenza season corrected at least with the outcomes during non-influenza season, their results cannot replace evidences from well-designed placebo controlled RCT.

References
1) Hitoshi Kamiya. Summary and Group Report 1998-1999 'Study of the effectiveness of the influenza vaccine' (Koseik Kagaku Kenkyuhi Hozyokin Zigyou Zisseki Houkokusyo) [The study was supported by federal funds from the Japanese Ministry of Health, Labor and Welfare]

2) Hitoshi Kamiya 'Study of the effectiveness of influenza vaccine in infants and young children.' 2001 (Heisei 12, (Koseik Kagaku Kenkyuhi Hozyokin Zigyou Zisseki Houkokusyo) [The study was supported by federal funds from the Japanese Ministry of Health, Labor and Welfare]

3) Kosei Takahashi et al. Evaluation of the effectiveness of influenza vaccine by the absence rates of the elementary and junior high school students. Kusurino Hiroba 1988:96;2

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Thank you for the comments. For the review we identified few RCTs and with small Ns. We stated that we needed to base our conclusions mostly on the large number of observational studies, and recommended that large well-designed and well-executed RCTs should be undertaken.

Daniela Rivetti
Alessandro Rivetti
Vittorio Demichelli
Tom Jefferson
Roger Thomas
Carlo Di Pietrantonj
Melanie Rudin

Contributors

Keiji Hayashi
Feedback comment and reply added 25 July 2007.

WHAT'S NEW

Date	Event	Description
6 October 2021	Amended	Correction made to the risk of bias assessment for Govaert 1994a. In the 'Characteristics of included studies' for Govaert 1994a, the authors' judgement for each bias in the Risk of Bias table was marked as "low" for each bias, but the description in the justification for the judgment did not correlate. This has now been corrected.

HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 3, 2006

Date	Event	Description
6 November 2019	Amended	Correction made to the risk of bias assessment for Govaert 1994a. In the 'Characteristics of included studies' for Govaert 1994a, the authors' judgement for each bias in the risk of bias table was marked as "unclear" in error. This error

Date	Event	Description
		was introduced in the 2018 version of the review (https://doi.org/10.1002/14651858.CD004876.pub4) and has now been corrected to "low" for each bias, as in earlier versions of this review.
31 December 2016	New citation required but conclusions have not changed	Our conclusions remain unchanged.
31 December 2016	New search has been performed	We updated our searches for randomised trials conducted. We did not identify any new trials for inclusion or exclusion.
20 January 2010	New search has been performed	Searches conducted. We identified 18 potential trials. We included four new trials, two case-control studies (Jordan 2007; Puig-Barbera 2007), and two cohort studies (Hara 2006; Leung 2007). We excluded 13 new trials (Castilla 2006; Garcia-Garcia 2009; Hara 2008; Isahak 2007; Landi 2006; Manzoli 2007; Moreno 2009; Nichol 2007; Ortqvist 2007; Skull 2009; Tsai 2007; van Vuuren 2009; Voordouw 2006). One excluded trial was formerly awaiting classification (Vila-Corcoles 2005).
20 January 2010	New citation required and conclusions have changed	Three new authors (EF, LAA, ST) joined the review team, while previous authors no longer contributed to this update. Our conclusion changed in part. This was due both to a re-evaluation of the whole topic and to ambiguity in the previous text which readers found confusing.
8 May 2008	Amended	Converted to new review format
25 July 2007	Feedback has been incorporated	Feedback comment and reply added to review.
24 May 2006	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Alessandro Rivetti conducted the original searches.
Tom Jefferson, Daniela Rivetti, and Vittorio Demicheli applied inclusion criteria.
Tom Jefferson, Daniela Rivetti, and Melanie Rudin extracted the original data.
Vittorio Demicheli arbitrated and checked the data extraction.
Carlo Di Pietrantonj undertook the meta-analysis and performed statistical testing.
Tom Jefferson wrote the first review and the updates.
Eliana Ferroni extracted the data.
For the 2016 update, Sarah Thorning conducted the updated searches, Tom Jefferson and Alessandro Rivetti wrote the review, Vittorio Demicheli checked the data, and all authors contributed to the final updated review.

DECLARATIONS OF INTEREST

Vittorio Demicheli: none known.

Tom Jefferson (TJ) was a recipient of a UK National Institute for Health Research grant for a Cochrane Review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products (remunerated). In 2011-13, TJ acted as an expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage, and in a labour case on influenza vaccines in healthcare workers in Canada (remunerated). He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013) (remunerated). In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir (remunerated). TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boerhinger Ingelheim (remunerated). TJ is holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane Reviews. TJ was a member of an independent data monitoring committee for a Sanofi

Pasteur clinical trial on an influenza vaccine (remunerated). Between 1994 and 2013, TJ was the co-ordinator of the Cochrane Vaccines Field. TJ is a cosignatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of human papillomavirus vaccines and consequent complaints to the European Ombudsman. TJ is coholder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017-20) and Jean Monnet Network Grant, 2017-20 for The Jean Monnet Health Law and Policy Network.

Carlo Di Pietrantonj: none known.

Eliana Ferroni: none known.

Sarah Thorning: none known.

Roger E Thomas: none known.

Alessandro Rivetti: none known.

SOURCES OF SUPPORT

Internal sources

- ASL 20 (Alessandria), ASL 19 (Asti), Regione Piemonte, Italy

External sources

- National Health and Medical Research Council (NHMRC), Australia

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Prior to starting the 2016 update of this review, we decided that evidence from observational studies should no longer be updated, given its inherent biases and our intention to focus the main synthesis, 'Summary of findings' tables, conclusions, and summary versions on randomised evidence. For historical purposes we have retained data from non-randomised evidence in the review.

In previous versions of this review, we computed the reciprocal of the pooled risk difference as the basis for calculating numbers needed to vaccinate (NNV). Given expected variation in control group risks, we decided to revise this approach and have calculated NNVs based on the difference between the assumed and corresponding risks based on the Summary of findings 1.

INDEX TERMS

Medical Subject Headings (MeSH)

Influenza Vaccines [*administration & dosage] [adverse effects]; Influenza, Human [*prevention & control]; Randomized Controlled Trials as Topic; Vaccines, Inactivated [administration & dosage]

MeSH check words

Aged; Humans