Vaccines for preventing influenza in the elderly (Review)

Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 2

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Vaccines for preventing influenza in the elderly

Tom Jefferson[1], Carlo Di Pietrantonj[2], Lubna A Al-Ansary[3], Eliana Ferroni[4], Sarah Thorning[5], Roger E Thomas[6]

[1]Vaccines Field, The Cochrane Collaboration, Roma, Italy. [2]Servizio Regionale di Riferimento per l'Epidemiologia, SSEpi-SeREMI - Cochrane Vaccines Field, Azienda Sanitaria Locale ASL AL, Alessandria, Italy. [3]Department of Family & Community Medicine, Holder of "Shaikh Abdullah S. Bahamdan" Research Chair for Evidence-Based Health Care and Knowledge Translation, College of Medicine, King Saud University, Riyadh, Saudi Arabia. [4]Infectious Diseases Unit, Public Health Agency of Lazio Region, Rome, Italy. [5]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia. [6]Department of Medicine, University of Calgary, Calgary, Canada

Contact address: Tom Jefferson, Vaccines Field, The Cochrane Collaboration, Via Adige 28a, Anguillara Sabazia, Roma, 00061, Italy. jefferson.tom@gmail.com. jefferson@assr.it.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 2, 2010.
Review content assessed as up-to-date: 6 October 2009.

Citation: Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub3.

ABSTRACT

Background

Vaccines have been the main global weapon to minimise the impact of influenza in the elderly for the last four decades and are recommended worldwide for individuals aged 65 years or older. The primary goal of influenza vaccination in the elderly is to reduce the risk of complications among persons who are most vulnerable.

Objectives

To assess the effectiveness of vaccines in preventing influenza, influenza-like illness (ILI), hospital admissions, complications and mortality in the elderly.

To identify and appraise comparative studies evaluating the effects of influenza vaccines in the elderly.

To document types and frequency of adverse effects associated with influenza vaccines in the elderly.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register (*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).

Selection criteria

Randomised controlled trials (RCTs), quasi-RCTs, cohort and case-control studies assessing efficacy against influenza (laboratory-confirmed cases) or effectiveness against influenza-like illness (ILI) or safety. Any influenza vaccine given independently, in any dose, preparation or time schedule, compared with placebo or with no intervention was considered.

Data collection and analysis

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. We further stratified by co-administration of pneumococcal polysaccharide vaccine (PPV) and by different types of influenza vaccines. We analysed the following outcomes: influenza, influenza-like illness, hospital admissions, complications and deaths.

Main results

We included 75 studies. Overall we identified 100 data sets. We identified one RCT assessing efficacy and effectiveness. Although this seemed to show an effect against influenza symptoms it was underpowered to detect any effect on complications (1348 participants). The remainder of our evidence base included non-RCTs. Due to the general low quality of non-RCTs and the likely presence of biases, which make interpretation of these data difficult and any firm conclusions potentially misleading, we were unable to reach clear conclusions about the effects of the vaccines in the elderly.

Authors' conclusions

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.

PLAIN LANGUAGE SUMMARY

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

Influenza vaccination of elderly individuals is recommended worldwide as people aged 65 and older are at a higher risk of complications, hospitalisations and deaths from influenza. This review looked at evidence from experimental and non-experimental studies carried out over 40 years of influenza vaccination. We included 75 studies. These were grouped first according to study design and then the setting (community or long-term care facilities). The results are mostly based on non-experimental (observational) studies, which are at greater risk of bias, as not many good quality trials were available. Trivalent inactivated vaccines are the most commonly used influenza vaccines. Due to the poor quality of the available evidence, any conclusions regarding the effects of influenza vaccines for people aged 65 years or older cannot be drawn. The public health safety profile of the vaccines appears to be acceptable.

BACKGROUND

Description of the condition

Influenza vaccination of elderly individuals is recommended worldwide as people aged 65 and older are at higher risk of complications, hospitalisations and deaths from influenza.

Description of the intervention

Vaccines have been the main global weapon to minimise the impact of influenza in the elderly for the last four decades. In the year 2000, 40 out of 51 high-income or middle-income countries recommended vaccination for all persons aged 60 or 65 or older (van Essen 2003). Up to 290 million doses of vaccine were distributed worldwide in 2003 (WHO 2005). According to the Centres for Disease Control (CDC), the primary goal of influenza vaccination in the elderly is to reduce the risk of complications among persons who are most vulnerable (ACIP 2005; CDC 2004). To achieve this goal, CDC defined two higher priority groups: adults aged 65 years or older and residents of nursing homes and long-term care facilities. We present an up-to-date, comprehensive assessment of the effects of influenza vaccines in the elderly. The current pandemic has caused a heightened interest in influenza vaccines and

their performance.

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.

Why it is important to do this review

Due to the unique production cycle of influenza vaccines (they are produced and tested using surrogate outcomes - antibody stimulation - ahead of each influenza 'season'), past performance is probably the only reliable way to predict future performance. Of the two existing systematic reviews looking at the effects of influenza vaccines in the elderly, one is now over a decade old and its conclusions may be affected by the lack of inclusion of recent evidence (Gross 1995). The other review has several methodological weaknesses which may affect the authors' conclusions (for example, the exclusion of studies with denominators smaller than 30 and pooling of studies using different designs). This review also includes a limited number of studies (Vu 2002). An accurate assessment of the effects (efficacy, effectiveness and safety profile) of influenza vaccines is essential to allow rational choice between alternative strategies.

OBJECTIVES

1. To identify and appraise all the comparative studies evaluating the effects of influenza vaccines in the elderly (aged 65 years and older), irrespective of setting.

2. To assess the effectiveness of vaccines in preventing influenza, influenza-like illness (ILI), hospital admissions, complications and mortality in the elderly.

3. To document the types and frequency of adverse effects associated with influenza vaccines in the elderly.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs), quasi-RCTs, cohort and case-control studies. For study design definitions see Appendix 1. To assess rare adverse effects we also looked for surveillance studies. Despite being non-comparative, they provide information about rare and severe events, possibly related to influenza vaccines.

Types of participants

Elderly participants aged 65 years or older, irrespective of settings. Studies which assessed efficacy in selected groups affected by a specific chronic pathology (i.e. diabetes or cardiac disease) were excluded 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, types of vaccines (for example, 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 authors presented data according to different levels of viral circulation, we only included data restricted to higher viral circulation.

1. 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 states have their own official definition.
2. Cases of influenza, laboratory confirmed (by means of viral isolation, serological supporting evidence, or both).
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, hospitalisation due to heart disease.

We excluded studies with generic outcomes (deaths from all causes, for example) 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, hoarseness) within seven days of vaccination.
2. Local events for parenteral vaccines (tenderness/soreness, erythema, induration, arm stiffness) within seven days from vaccination.
3. Systemic events (myalgia, fever, headache, fatigue, indisposition, rash, angioedema, asthma) within seven days from vaccination.
4. Rare events (thrombocytopenia, neurological disorders, Guillan Barré Syndrome (GBS).

Search methods for identification of studies

Electronic searches

For this 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 following search terms 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 2008). This search was adapted for EMBASE (Appendix 5) and Web of Science (see Appendix 6). The below search terms were also combined with the SIGN (SIGN 2009) search strategy for identifying observational studies (see Appendix 7) and MEDLINE, EMBASE and Web of Science were searched for observational studies. Details of the previous search are in Appendix 4.

MEDLINE (OVID)

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

Searching other resources

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:

- we used the Science Citation Index to identify articles that cite the relevant studies;
- we keyed the relevant studies into PubMed and used the Related Articles feature;
- we searched the bibliographies of all relevant articles obtained, any published reviews and proceedings from relevant conferences for additional studies;
- we explored Internet sources: NHS National Research Register (http://www.update-software.com/national/), the *meta*Register of Clinical Trials (http://www.controlled-

trials.com/) and the digital dissertations web site (http://wwwlib.umi.com/dissertations);

- we searched the Vaccine Adverse Event Reporting System web site (http://www.vaers.org); and
- we contacted vaccine manufacturers listed at the WHO web site.

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 3). Two review authors (TOJ, CDP) checked data and entered these into customised software.
We extracted data on the following:

- methodological quality of studies;
- study design (Appendix 1);
- description of setting;
- characteristics of participants;
- description of vaccines (content and antigenic match);
- description of viral circulation degree;
- description of outcomes;
- length of the follow up;
- publication status;
- date of study; and
- 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 2008) 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, for example, table of random numbers or computer-generated random numbers.
B = inadequate, for example, alternation, date of birth, day of the week or case record number.
C = not described.

Allocation concealment

A = adequate - for example, 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 - for example, sealed envelopes that are not sequentially numbered or opaque.
C = inadequate - for example, open table of random numbers.
D = not described.

Blinding

A = adequate double-blinding - for example, placebo vaccine.
B = single-blind - that is to say, blinded outcome assessment.
C = no blinding.

Follow up

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

Non-experimental studies

We made quality assessment of non-RCT studies in relation to the presence of potential confounders which could make interpretation of the results difficult. The quality of case-control and cohort studies (prospective and retrospective) was evaluated using the appropriate Newcastle-Ottawa Scales (NOS) (Appendix 2). Because of 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.

Unit of analysis issues

Aggregation of data was dependent on the sensitivity and homogeneity of definitions of exposure, populations and outcomes used. Where studies were found to be homogenous, we carried out a meta-analysis of these studies within each design category.

We analysed non-RCT and quasi-RCT evidence separately from RCT evidence. The study results are described individually in the Results section.

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, only data relating to higher viral circulation were included). A period was considered '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).

When possible, we did 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. 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 (CIs) (Greenland 1987) and did quantitative analysis with the inverse of the variance (Higgins 2008).

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

Dealing with missing data

Whenever we identified non-reporting or partial reporting of data we tried to contact the first or corresponding author of the study and requested missing data.

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

We assessed possible publication bias through visual inspection of funnel plots. We also carried out a complete re-extraction of all studies and re-assessed 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 Discussion - 'Potential biases in the review section').

Data synthesis

We pooled whole, split and sub-unit 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. We used random-effect models throughout to take account of the between-study variance in our findings (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

To investigate the causes of heterogeneity we did a further analysis. 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

A sub-analysis of studies describing a better defined epidemic period was performed 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.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

In the 2009 updated search, we identified 1435 reports of potentially relevant studies. We retrieved 18 studies for further evaluation; four were included and 14 excluded for various reasons. For the 2009 update we identified two case-control studies (Jordan 2007; Puig-Barbera 2007) and two cohort studies (Hara 2006; Leung 2007) fulfilling the inclusion criteria.

In the 2005 review, we identified 4400 titles of reports of potentially relevant studies and screened these for retrieval. We excluded 4088 reports by screening of titles and abstracts; we retrieved 312 reports for detailed assessment; 241 reports did not fulfil inclusion criteria.

Included studies

We included 75 studies in this review: 68 studies were used to assess efficacy/effectiveness and eight were included in the safety assessment (one RCT was included in both assessments).

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.

Five RCTs resulted in five data sets (Allsup 2001; Edmondson 1971; Govaert 1994; Rudenko 2001; Stuart 1969).

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; Kaway 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 1999; Ohmit 1995a; Ohmit 1995b; 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 did not provide sufficient information on circulating subtypes.

Twenty-four studies, resulting in 39 data sets, collected information about the health conditions of vaccinated and unvaccinated persons 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. Included studies used the recommended and licensed vaccine formulation even if some authors did not declare vaccine composition.

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

Seven studies included in our safety assessment are described below:

Four RCTs (Govaert 1993; Keitel 1996; Margolis 1990a; Treanor 1994).

Three surveillance studies with a non-comparative design assessing rare events (Guillan Barré Syndrome (GBS)) (Kaplan 1982; Lasky 1998; Schonberger 1979) were commented on in the text but were not included in our meta-analysis. One RCT assessed a vaccine which has not been in production for decades (Stuart 1969). Its harms data were not extracted.

Excluded studies

The most frequent reasons for 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 available 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

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

Surveillance studies

For three surveillance studies assessing rare side effects, we did not perform quality evaluation. All were population-based studies 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 Discussion 'Potential biases in the review process'.

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 had difficulty in understanding what went on (Jefferson 2009).

Selective reporting

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

Other potential sources of bias

See Discussion 'Potential biases in the review process'.

Effects of interventions

RCTs

We identified five RCTs published over four decades and just over 5000 observations (Allsup 2004; Edmondson 1971; Govaert 1994; Rudenko 2001; Stuart 1969). Given the heterogeneous nature of the vaccines tested (monovalent, trivalent, live, or inactivated aerosol vaccines), setting, follow up and outcome definition, no firm conclusions can be drawn from this body of evidence. Follow up is only specified in three trials (Govaert 1994; Rudenko 2001; Stuart 1969) and ranges from 42 to 180 days. Two trials had adequate randomisation and allocation concealment, and one trial had adequate measures to prevent attrition bias. The results of the most recent trial (Allsup 2004) are difficult to interpret because of the presence of selection bias. Based on the results of a meta-analysis of two trials (Allsup 2004; Govaert 1994), inactivated vaccines were more effective than placebo against influenza-like illness (ILI) in conditions of high viral circulation among elderly individuals living in the community (vaccine efficacy (VE) 43%; 21% to 58%; Analysis 13.1.1). The vaccines were also effective against influenza (VE 58%; 34% to 73%; Analysis 13.2) (Edmondson 1971; Govaert 1994; Rudenko 2001).

Cohort studies in long-term care facilities

Thirty cohort studies in long-term care facilities contributed data to 41 data sets (Arden 1988; Arroyo 1984; Aymard 1979a; Aymard 1979b; Cartter 1990a; Cartter 1990b; Cartter 1990c; Coles 1992; Cuneo Crovari 1980; Currier 1988; Taylor 1992; 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) and over 34,000 observations. 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). They 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.

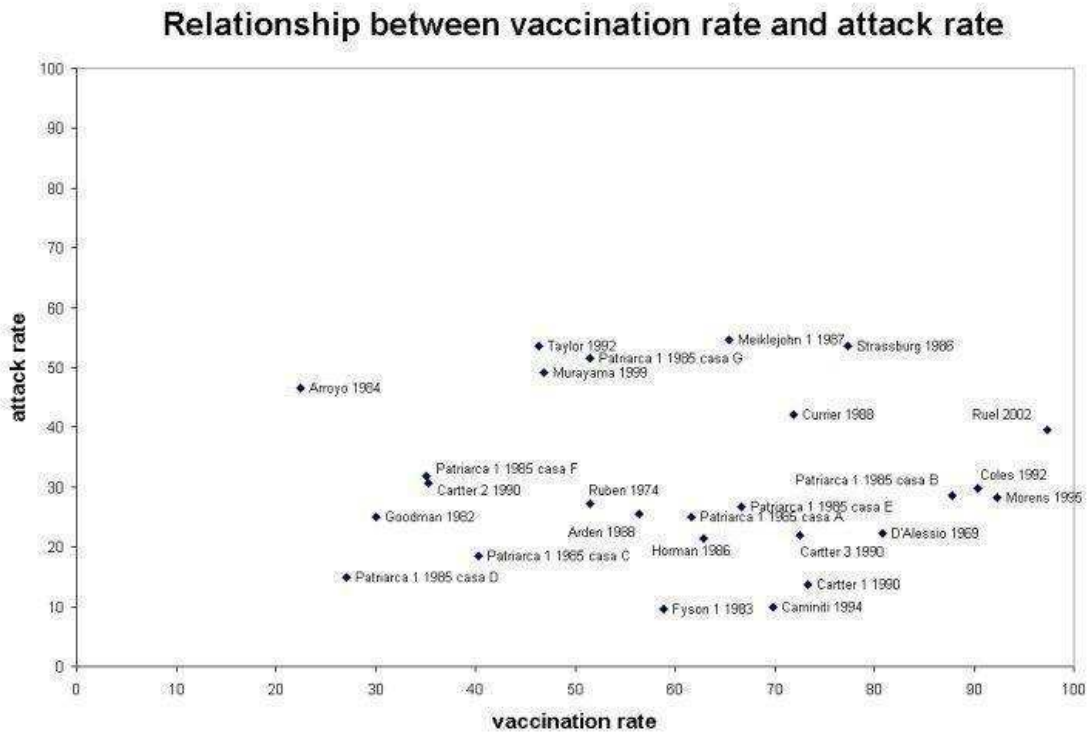
Studies recorded during outbreaks or periods of high viral circulation

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

Twenty-two data sets assessed the effectiveness of influenza vac-

cines in preventing influenza-like illnesses (Analysis 1.1 and Analysis 1.2). In these data sets, follow up was restricted to an outbreak period (mean duration 443,116 days) and authors reported a virologic surveillance that confirmed influenza virus circulation. The overall effectiveness of vaccines (VE) against influenza-like illnesses was 23% (6% to 36%; Analysis 1.1.1) when vaccine matching was good and not significantly different from no vaccination (RR 0.80; 95% CI 0.60 to 1.05; Analysis 1.1.2) 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 influenza-like illness (Figure 1).

Figure 1.



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 1.2.1) and when matching was absent or unknown (RR 0.47; 95% CI 0.22 to 1.04; Analysis 1.2.2).

The effectiveness of the vaccines in preventing pneumonia was assessed in 13 data sets (Analysis 1.3.1 and Analysis 1.3.2; 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 1.3.1) effective in preventing pneumonia (Gross 1988; Horman 1986; Meiklejohn 1987; Morens 1995; Monto 2001; Patriarca 1985a; Saah 1986b; Taylor 1992). When matching was poor or unknown (Arroyo 1984; Currier 1988; Coles 1992; Leung 2007; Saah 1986a), vaccines had no effect (RR 0.68; 95% CI 0.39 to 1.21; Analysis 1.3.2). Excluding studies with the longest follow up (Gross 1988; Saah 1986a; Saah 1986b: six months) did not affect our conclusions.

Eight data sets (Arden 1988; Cartter 1990a; Cartter 1990b; Cartter 1990c; Meiklejohn 1987; Murayama 1999; Patriarca 1985a; Taylor 1992) assessed the effectiveness of well-matched vaccines in preventing hospitalisation for influenza or pneumonia. All of them had a brief and well-defined follow up; effectiveness was 45% (16% to 64%; Analysis 1.4.1). Two studies reported a non-significant effect (Coles 1992; Leung 2007, Analysis 1.4.2) when the vaccine did not match the circulating strain or was not reported.

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 (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; Analysis 1.5.1 and Analysis 1.5.2). 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 six-month follow up (Saah 1986a; Saah 1986b).

The vaccine was effective if it was a good match (VE 42%; 17% to 59%; Analysis 1.5.1), otherwise it was not effective (RR 0.34; 95% CI 0.11 to 1.02; Analysis 1.5.2).

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

The effectiveness in reducing all-cause mortality was assessed in only one small study with a six-month follow up (Gross 1988) and was significant (60%; 23% to 79%; Analysis 1.6.1).

Studies carried out during low viral circulation

Eleven data sets assessing the effects of influenza vaccines in 350 institutional facilities during low viral circulation comprised of 27,283 observations (Caminiti 1994; Deguchi 2001; Howarth 1987a; Howarth 1987b; Howells 1975a; Howells 1975b; Howells 1975c; Patriarca 1985b; Saito 2002a; Saito 2002b; Saah 1986c). 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 (Deguchi 2001; Saah 1986c) did not report virologic surveillance.

The vaccines were 33% effective (2% to 54%; Analysis 1.1.3) in preventing influenza-like illnesses (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 1.2.3). 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 (Howells 1975a; Howells 1975b; Howells 1975c; Saah 1986c) carried out in situations of low viral circulation and poor vaccine matching report a combined effectiveness of 65% (32% to 82%; Analysis 1.3.4) in preventing pneumonia.

During periods of low viral circulation, vaccines did prevent hospital admission for pneumonia or influenza (VE 68%; 24% to 86%; Analysis 1.4.3). However, one of the included studies (Deguchi 2001) is at high risk of bias - meaning that this outcome may not be accurate. 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 1.5.3 and Analysis 1.5.4) (Caminiti 1994; Deguchi 2001; Howells 1975a; Howells 1975b; Howells 1975c; Patriarca 1985b; Saah 1986c).

Cohort studies in community-dwelling elderly

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, Kaway 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 three million observations mainly collected using data-linkage from insurance reimbursement, hospital or primary care data bases; 13 of them 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 =< three months, 13 data sets had a follow up ranging from four to five months, eight data sets had a follow up ranging from six to seven months; four data sets had a follow up ranging from eight to 12 months and two 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

Our second comparison relies on one 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, Kaway 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 2.4.1) but not for cardiac disease (RR 0.87; 95% CI 0.67 to 1.12; Analysis 2.9). Excluding the only study with a one-year follow up (Christenson 2004a), effectiveness in preventing hospital admissions is increased to 29% (95% CI 14 to 42).

Death from respiratory disease was not significantly affected. Seven data sets (Fleming 1995; Gené Badia 1991; Lopez Hernandez 1994; Nichol 2003a; Nichol 2003b; Shapiro 2003; Voordouw 2003) with a follow up ranging from 75 to 210 days, assessed the effect on mortality for all causes (VE: 42%; 24% to 55%; Analysis 2.8). 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

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. Patients 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 3.6) from 68,032 observations with high heterogeneity (I^2 statistic 94.1%) (Fleming 1995; Shapiro 2003; Voordouw 2003).

Inactivated influenza vaccines in community-dwelling elderly without risk of influenza complications

In this stratum, six studies with seven data sets (Fleming 1995; Hak 2002a; Hak 2002b; Mangtani 2004a; Nichol 1998a; Shapiro 2003; Voordouw 2003) contributed several hundred thousand observations. However, most outcomes were only assessed by one study. The only notable results are the vaccines' effectiveness in preventing hospital admission for influenza or pneumonia (VE: 50%; 37% to 60%; Analysis 4.3) although this observation is based only on one data set Nichol 1998a with 101,619 observations, and there is a lack of effect on all-cause mortality (RR 0.65; 95% CI 0.33 to 1.29; 43,821 observations; Analysis 4.6) (Fleming 1995; Shapiro 2003; Voordouw 2003).

Inactivated influenza vaccines in all community-dwelling elderly (adjusted for confounders)

This is another data set with seven studies contributing 19 data sets (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) with over a million observations from several consecutive influenza seasons. Most of the studies included in this analysis used data linkage and adjusted their OR calculations to allow for the effect of confounding of several variables (sex, age, smoking, co-morbidities). The effects of the vaccines are all significant.

Hospitalisations for influenza or pneumonia: eight data sets, all but one with a follow up lasting 135 days (Davis 2001a; Davis 2001b; Davis 2001c; Nichol 1998a; Nichol 2003a; Nichol 2003b; Nordin 2001b) (OR 0.73; 95% CI 0.67 to 0.79, based on 949,215 observations (Analysis 7.1)). Excluding the only data set (Nordin 2001a) with the longest follow up (eight months) does not change the result.

Hospitalisations for respiratory diseases: OR 0.78; 95% CI 0.72 to 0.85 (Analysis 7.2). 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 07.3). Data sets have a follow up of 135 days or less, so a sensitivity analysis appears to be superfluous.

Mortality for all causes: seven data sets (Fleming 1995; Nichol 1998a; Nichol 2003a; Nichol 2003b; Nordin 2001a; Nordin 2001b; Voordouw 2003) with follow up ranging from 75 to 240 days (OR 0.53; 95% CI 0.46 to 0.61 (Analysis 7.4)). Excluding data sets with a follow-up period equal to or longer than six months (Nordin 2001a; Voordouw 2003) does not change the final result.

Inactivated influenza and polysaccharide vaccine (PPV) on community-dwelling elderly

Three studies assessed the impact of inactivated influenza and concomitant PPV (Christenson 2001b; Christenson 2004b; Consonni 2004b) on hospitalisations for influenza or pneumonia or respiratory diseases (VE = 33%; 30 to 36 %, based on 518,748 observations; Analysis 5.2) and two data sets (Christenson 2001b; Consonni 2004b) assessed the effect on all causes mortality (VE = 56%; 54% to 59%; Analysis 5.4).

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

Adjuvant influenza vaccines in all community-dwelling elderly

Two small studies with a combined denominator of 498 assessed the impact of vaccines containing a virosomal adjuvant in preventing influenza-like illness (ILI) (VE 70%, 44% to 84%; Analysis 6.1) and hospitalisations (RR 0.17; 95% CI 0.02 to 1.28; Analysis 6.2.3) 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 mortality for all causes and found no effect (RR 2.10; 95% CI 0.10 to 43.10; Analysis 6.3.3). This is not surprising given its population size of 129 patients (too small for any significant effect to be evident).

Case-control studies

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; Puig-Barberà 1997; Jordan 2007, Puig-Barbera 2007), five looked at the co-administration of inactivated influenza with polysaccharide vaccine (PPV) on institutionalised elderly (Foster 1992; Mullooly 1994; Ohmit 1995a; Ohmit 1995b; Ohmit 1999), one of adjuvant influenza with PPV on community-dwelling elderly (Puig-Barberà 2004) and one of adjuvanted influenza vaccines (MF59) alone Puig-Barbera 2007. Only three of these studies, all assessing 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

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 8.2.1) (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 8.1) (Crocetti 2001; Puig-Barberà 1997) or affect hospitalisation for influenza-like illness (Analysis 8.2.2) (Jordan 2007) or affect mortality from influenza and pneumonia, though this conclusion is based on a relatively small data set of 1092 observations (Ahmed 1995; Analysis 8.3.1). The single study on adjuvanted vaccines showed no effect on pneumonia no better defined (Analysis 8.4.1) (Puig-Barbera 2007).

Inactivated influenza vaccines on community-dwelling elderly - adjusted analysis

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 11.3) (Ahmed 1995; Mullooly 1994) and prevent admission for influenza and pneumonia (OR 0.59; 95% CI 0.47 to 0.74; Analysis 11.01) (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 11.02) (Ahmed 1997; Fedson 1993a; Fedson 1993b).

Inactivated influenza and (PPV) vaccines

Similarly, before adjustment inactivated influenza and concomitant PPV in individuals living in the community did not prevent hospital admission for influenza and pneumonia (OR 0.97; 95% CI 0.85 to 1.09; Analysis 9.1) (Foster 1992; Ohmit 1995a; Ohmit 1995b; Puig-Barberà 2004), whereas after adjustment they did (OR 0.68; 95% CI 0.54 to 0.86; Analysis 12.1) (Ohmit 1995a; Ohmit 1995b). One study assessed the effect of influenza and PPV vaccines on influenza-like illness: VE 48%; 32% to 60%; 1198 observations; Analysis 10.1 (Ohmit 1999).

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 of 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 side effects. For local side effects 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.

Four RCTs (Govaert 1993; Keitel 1996; Margolis 1990a; Treanor 1994; Analysis 17) reported data about local and systemic adverse events observed within a week from administration of parenteral inactivated vaccine (2606 observations). Treanor 1994 also reported data about live aerosol vaccine (Analysis 18). All side effects reported in trials were included in the analysis, even if they were not significant. Vaccines usually induced systemic side effects (general malaise, fever, nausea, headache) more frequently than placebo, but no outcome showed statistically significant results. Local adverse events, such as tenderness and sore arm, were significantly more frequent in the treatment arm than in the placebo arm. The only studies assessing rare adverse events were three surveillance studies assessing Guillan Barré Syndrome with neither cohort nor

case-control design (Kaplan 1982; Lasky 1998; Schonberger 1979) (Table 1). 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 the 'Guillain Barré Syndrome' table (Table 1). The strong and significant association between A/New Jersey/76 swine vaccine and Guillan 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.

Table 1. 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 pop.	> 64 years	5.2 (3.9 to 7.0)
Kaplan 1982	1979 to 1980	Inactivated trivalent	All the USA pop.	> 18 years	0.6 (0.45 to 1.32)
Kaplan 1982	1980 to 1981	Inactivated trivalent	All the USA pop.	> 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)

DISCUSSION

Summary of main results

Our findings show that according to reliable evidence, the effectiveness of trivalent inactivated influenza vaccines in elderly individuals is modest, irrespective of setting, outcome, population and study design. Our estimates are 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 aid comparability. We also performed sub-analysis 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 influenza-like illness (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 on the basis of the results from 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 who live in long-term care facilities are different from

those drawn from studies in individuals who live 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 a 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, but have greater effect on its complications. 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 most need it 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.

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

Quality of the evidence

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

Our main concern was the quality of the non-RCTs which probably affected the estimates of effect reported in our review. The findings of the cohort studies that we included are likely to have been affected to a varying degree 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 (Gené Badia 1991) had difficulties achieving high coverage in those most at need. 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 counter-intuitive 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-RCT studies 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.

Potential biases in the review process

The publication of our 2006 review (Rivetti 2006) sparked a discussion which continues to this day. 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 datasets). 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 (odds ratio 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 2009).

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 its status (registration trials using surrogate outcomes such as antibody titres were not included in the review). As our elderly dataset formed a major part of our overview of influenza vaccines studies, it is likely that that data presented in this review are so biased as to be virtually uninterpretable.

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 (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.

AUTHORS' CONCLUSIONS

Implications for practice

Until such time as the role of vaccines for preventing influenza in the elderly is clarified, more comprehensive and effective strategies for the control of acute respiratory infections should be implemented. These should rely on several preventive interventions that take into account the multi-agent nature of influenza-like illness (ILI) and its context (such as personal hygiene, provision of electricity and adequate food, water and sanitation). The effect of vaccination of high-risk groups should also be further assessed.

Implications for research

Investment in the development of better vaccines than are presently 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.

To resolve the uncertainty of the role of vaccines, an adequately powered, publicly-funded, high quality placebo-controlled trial run over several seasons should be undertaken.

ACKNOWLEDGEMENTS

The authors also wish to thank the following people for commenting on the draft of earlier reviews: Amy Zelmer, Laila Tata, Wendy Keitel, Lohne Simonsen, Sree Nair and Geoff Spurling. Vittorio Demicheli, Roger Thomas, Daniela Rivetti, Melanie Rudin and Alessandro Rivetti contributed to the earlier version of the review. For this 2009 update we wish to thank Maryann Napoli, Anne Lyddiat, Wendy Keitel, Ludovic Reveiz, Mark Jones and Chris Del Mar for commenting on the updated draft.

REFERENCES

References to studies included in this review

Ahmed 1995 *{published data only}*
Ahmed AE, Nicholson KG, Nguyen-Van-Tam JS. Reduction in mortality associated with influenza vaccine during 1989-90 epidemic. *Lancet* 1995;**346**(8975):591–5.

Ahmed 1997 *{published data only}*
Ahmed AH, Nicholson KG, Nguyen-van Tam JS, Pearson JC. Effectiveness of influenza vaccine in reducing hospital admissions during the 1989-90 epidemic. *Epidemiology and Infection* 1997;**118** (1):27–33.

Allsup 2004 *{published data only}*
Allsup S, Haycox A, Regan M, Gosney M. Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial. *Vaccine* 2004;**23**(5):639–45.

Arden 1988 *{published data only}*
Arden NH, Patriarca PA, Fasano MB, Lui KJ, Harmon MW, Kendal AP, et al.The roles of vaccination and amantadine prophylaxis in controlling an outbreak of influenza A (H3N2) in a nursing home. *Archive of Internal Medicine* 1988;**148**(4):865–8.

Arroyo 1984 *{published data only}*
Arroyo JC, Postic B, Brown A, Harrison K, Birgenheier R, Dowda H. Influenza A/Philippines/2/82 outbreak in a nursing home: limitations of influenza vaccination in the aged. *American Journal of Infection Control* 1984;**12**(6):329–34.

Aymard 1979a *{published data only}*
Aymard M, Bentejac MC, Larbaigt G, Michaut D, Triau R. Efficacy of the antiinfluenza A vaccination during epidemics due to A/VIC/3/75 and A/Texas/1/77 viruses. *Developments in Biological Standardization* 1979;**43**:231–9.

Aymard 1979b *{published data only}*
Aymard M, Bentejac MC, Larbaigt G, Michaut D, Triau R. Efficacy of the antiinfluenza A vaccination during epidemics due to A/VIC/3/75 and A/Texas/1/77 viruses. *Developments in biological standardization* 1979;**43**:231–9.

Caminiti 1994 *{published data only}*
Caminiti C, Ricco D, Tanzi ML, Borrini B, Corsello A, Biasio LR, et al.Field evaluation of influenza vaccine efficacy in a population of institutionalized elderly. *L'igiene Moderna* 1994;**101**(2):163–75.

Cartter 1990a *{published data only}*
Cartter ML, Renzullo PO, Helgerson SD, Martin SM, Jekel JF. Influenza outbreaks in nursing homes: how effective is influenza vaccine in the institutionalized elderly?. *Infection Control and Hospital Epidemiology* 1990;**11**(9):473–8.

Cartter 1990b *{published data only}*
Cartter ML, Renzullo PO, Helgerson SD, Martin SM, Jekel JF. Influenza outbreaks in nursing homes: how effective is influenza vaccine in the institutionalized elderly?. *Infection Control and Hospital Epidemiology* 1990;**11**(9):473–8.

Cartter 1990c *{published data only}*
Cartter ML, Renzullo PO, Helgerson SD, Martin SM, Jekel JF. Influenza outbreaks in nursing homes: how effective is influenza vaccine in the institutionalized elderly?. *Infection Control and Hospital Epidemiology* 1990;**11**(9):473–8.

Christenson 2001a *{published data only}*
Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet* 2001;**357**(9261):1008–11.

Christenson 2001b *{published data only}*
Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet* 2001;**357**(9261):1008–11.

Christenson 2004a *{published data only}*
Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. *European Respiratory Journal* 2004;**23**(3):363–8.

Christenson 2004b *{published data only}*
Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. *European Respiratory Journal* 2004;**23**(3):363–8.

Coles 1992 *{published data only}*
Coles FB, Balzano GJ, Morse DL. An outbreak of influenza A (H3N2) in a well immunized nursing home population. *Journal of the American Geriatrics Society* 1992;**40**(6):589–92.

Comeri 1995 *{published data only}*
Comeri L, Tinella M, Croce E, Arzese M. Protective efficacy of antiinfluenza vaccination in the elderly. *L'igiene Moderna* 1995;**103** (6):651–6.

Consonni 2004a *{published data only}*
Consonni S, Sandrini C, Segato E, Perruchini E, Bergamaschini L, Vergani C. Tolerability and efficacy of anti-influenza vaccination alone and associated with antipneumococcal vaccination in an elderly ambulatory population and adherence to the vaccination campaign. *Journal of Preventive Medicine and Hygiene* 2004;**45**: 45–50.

Consonni 2004b *{published data only}*
Consonni S, Sandrini C, Segato E, Perruchini E, Bergamaschini L, Vergani C. Tolerability and efficacy of anti-influenza vaccination alone and associated with antipneumococcal vaccination in an elderly ambulatory population and adherence to the vaccination campaign. *Journal of Preventive Medicine and Hygiene* 2004;**45**: 45–50.

Crocetti 2001 *{published data only}*
Crocetti E, Arniani S, Bordoni F, Maciocco G, Zappa M, Buiatti E. Effectiveness of influenza vaccination in the elderly in a community in Italy. *European Journal of Epidemiology* 2001;**17**(2):163–8.

Cuneo Crovari 1980 *{published data only}*
Cuneo Crovari P, Gasparini R, Crovari P. Efficacy of influenza vaccination: results in a community controlled for 2 years. *Bollettino dell'Istituto Sieroterapico Milanese* 1980;**59**(4):306–13.

Currier 1988 *{published data only}*
Currier M, Coffman T, Boyd P, Fremd B, Israel E. Influenza vaccine efficacy in a Maryland nursing home. *Maryland Medical Journal* 1988;**37**(10):781–3.

D'Alessio 1969 *{published data only}*
D'Alessio DJ, Cox PM Jr, Dick EC. Failure of inactivated influenza vaccine to protect an aged population. *JAMA* 1969;**210**(3):485–9.

Davis 2001a *{published data only}*
Davis JW, Lee E, Taira DA, Chung RS. Influenza vaccination, hospitalizations, and costs among members of a Medicare managed care plan. *Medical Care* 2001;**39**(12):1273–80.

Davis 2001b *{published data only}*
Davis JW, Lee E, Taira DA, Chung RS. Influenza vaccination, hospitalizations, and costs among members of a Medicare managed care plan. *Medical Care* 2001;**39**(12):1273–80.

Davis 2001c *{published data only}*
Davis JW, Lee E, Taira DA, Chung RS. Influenza vaccination, hospitalizations, and costs among members of a Medicare managed care plan. *Medical Care* 2001;**39**(12):1273–80.

Deguchi 2001 *{published data only}*
Deguchi Y, Nishimura K. Efficacy of influenza vaccine in elderly persons in welfare nursing homes: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 2001; **56**(6):M391–4.

Edmondson 1971 *{published data only}*
Edmondson WP Jr, Rothenberg R, White PW, Gwaltney JM Jr. A comparison of subcutaneous, nasal, and combined influenza vaccination. II. Protection against natural challenge. *American Journal of Epidemiology* 1971;**93**(6):480–6.

Fedson 1993a *{published data only}*
Fedson DS, Wajda A, Nicol JP, Hammond GW, Kaiser DL, Roos LL. Clinical effectiveness of influenza vaccination in Manitoba. *JAMA* 1993;**270**(16):1956–61.

Fedson 1993b *{published data only}*
Fedson DS, Wajda A, Nicol JP, Hammond GW, Kaiser DL, Roos LL. Clinical effectiveness of influenza vaccination in Manitoba. *JAMA* 1993;**270**(16):1956–61.

Feery 1976 *{published data only}*
Feery BJ, Evered MG, Morrison EI. Different protection rates in various groups of volunteers given subunit influenza virus vaccine in 1976. *Journal of Infectious Diseases* 1979;**139**(2):237–41.

Fleming 1995 *{published data only}*
Fleming DM, Watson JM, Nicholas S, Smith GE, Swan AV. Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989-90 using a general practice database. *Epidemiology and Infection* 1995;**115**(3):581–9.

Foster 1992 *{published data only}*
Foster DA, Talsma A, Furumoto-Dawson A, Ohmit SE, Margulies JR, Arden NH, et al.Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. *American Journal of Epidemiology* 1992;**136**(3):296–307.

Fyson 1983a *{published data only}*
Fyson RE. Influenza outbreaks in two institutions for the elderly - Ontari. *Canadian Diseases Weekly Report* 1983;**9**:37.

Fyson 1983b *{published data only}*
Fyson RE. Influenza outbreaks in two institutions for the elderly - Ontario. *Canadian Diseases Weekly Report* 1983;**9**:37.

Gavira Iglesias 1987 *{published data only}*
Gavira Iglesias FJ, Rodriguez Lopez FC, Berni Maestre RM. Analysis of an influenza vaccination campaign in rural environment. *Revista de Sanidad e Higiene Publica* 1987;**61**(7-8):759–81.

Gené Badia 1991 *{published data only}*
Gene Badia J, Calero Munoz S, Castanera Ribe C, Gran Rovireta A. Effectiveness of an anti-influenza vaccination program in 4 primary care centers. *Gaceta Sanitaria* 1991;**5**(26):203–8.

Goodman 1982 *{published data only}*
Goodman RA, Orenstein WA, Munro TF, Smith SC, Sikes RK. Impact of influenza A in a nursing home. *JAMA* 1982;**247**(10): 1451–3.

Govaert 1993 *{published data only}*
Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. *BMJ* 1993;**307**(6910):988–90.

Govaert 1994 *{published data only}*
Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994;**272**(21):1661–5.

Gross 1988 *{published data only}*
Gross PA, Quinnan GV, Rodstein M, LaMontagne JR, Kaslow RA, Saah AJ, et al.Association of influenza immunization with reduction in mortality in an elderly population. A prospective study. *Archives of Internal Medicine* 1988;**148**(3):562–5.

Hak 2002a *{published data only}*
Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, et al.Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clinical Infectious Diseases* 2002;**35**(4):370–7.

Hak 2002b *{published data only}*
Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, et al.Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clinical Infectious Diseases* 2002;**35**(4):370–7.

Hara 2006 *{published data only}*
Hara M, Sakamoto T, Tanaka K. Effectiveness of influenza vaccination in preventing influenza-like illness among community-dwelling elderly: population-based cohort study in Japan. *Vaccine* 2006;**24**(27-8):5546–51.

Horman 1986 *{published data only}*
Horman JT, Stetler HC, Israel E, Sorley D, Schipper MT, Joseph JM. An outbreak of influenza A in a nursing home. *American Journal of Public Health* 1986;**76**(5):501–4.

Howarth 1987a *{published data only}*
Howarth DM, Chaston TM, Lickiss K, Weekes JR, O'Doherty C, Foster RE, et al.Age-related responses to influenza vaccination in the Newcastle region during 1983 and 1984. *Medical Journal of Australia* 1987;**146**(10):514–7.

Howarth 1987b *{published data only}*
Howarth DM, Chaston TM, Lickiss K, Weekes JR, O'Doherty C, Foster RE, et al.Age-related responses to influenza vaccination in the Newcastle region during 1983 and 1984. *Medical Journal of Australia* 1987;**146**(10):514–7.

Howells 1975a *{published data only}*
Howells CH, Vesselinova-Jenkins CK, Evans AD, James J. Influenza vaccination and mortality from bronchopneumonia in the elderly. *Lancet* 1975;**1**(7903):381–3.

Howells 1975b *{published data only}*
Howells CH, Vesselinova-Jenkins CK, Evans AD, James J. Influenza vaccination and mortality from bronchopneumonia in the elderly. *Lancet* 1975;**1**(7903):381–3.

Howells 1975c *{published data only}*
Howells CH, Vesselinova-Jenkins CK, Evans AD, James J. Influenza vaccination and mortality from bronchopneumonia in the elderly. *Lancet* 1975;**1**(7903):381–3.

Isaacs 1997 *{published data only}*
Isaacs S, Dickinson C, Brimmer G. Outbreak of influenza A in an Ontario nursing home - January 1997. *Canada Communicable Disease Report* 1997;**23**(14):105–8.

Jordan 2007 *{published data only}*
Jordan RE, Hawker JI, Ayres JG, Tunnicliffe W, Adab P, Olowokure B, et al.A case-control study of elderly patients with acute respiratory illness: effect of influenza vaccination on admission to hospital in winter 2003-2004. *Vaccine* 2007;**25**(46):7909–13.

Kaplan 1982 *{published data only}*
Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. *JAMA* 1982;**248**(6): 698–700.

Kaway 2003 *{published data only}*
Kawai N, Ikematsu H, Iwaki N, Satoh I, Kawashima T, Tsuchimoto T, et al.A prospective, internet-based study of the effectiveness and safety of influenza vaccination in the 2001-2002 influenza season. *Vaccine* 2003;**21**(31):4507–13.

Keitel 1996 *{published data only}*
Keitel WA, Cate TR, Atmar RL, Turner CS, Nino D, Dukes CM, et al.Increasing doses of purified influenza virus hemagglutinin and subvirion vaccines enhance antibody responses in the elderly. *Clinical and Diagnostic Laboratory Immunology* 1996;**3**(5):507–10.

Lasky 1998 *{published data only}*
Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al.The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *New England Journal of Medicine* 1998;**339**(25):1797–802.

Leung 2007 *{published data only}*
Leung JCK. Effectiveness of influenza vaccination among elderly home residents in Hong Kong: a retrospective cohort study. *Hong Kong Practitioner* 2007;**29**(4):123–33.

Lopez Hernandez 1994 *{published data only}*
Lopez Hernandez B, Vazquez J, Fernandez E, Martinez B, Romero J, Arribas L. Effectiveness of anti-flu vaccine in the elderly. *Atencion Primaria* 1994;**14**(1):532–6.

Mangtani 2004a *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004b *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004c *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004d *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004e *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004f *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004g *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004h *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004i *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Mangtani 2004j *{published data only}*
Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *Journal of Infectious Diseases* 2004;**190**(1):1–10.

Margolis 1990a *{published data only}*
Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. *JAMA* 1990;**264**(9):1139–41.

Meiklejohn 1987 *{published data only}*
Meiklejohn G, Hall H. Unusual outbreak of influenza A in a Wyoming nursing home. *Journal of the American Geriatric Society* 1987;**35**(8):742–6.

Monto 2001 *{published data only}*
Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. *American Journal of Epidemiology* 2001;**154**(2):155–60.

Morens 1995 *{published data only}*
Morens DM, Rash VM. Lessons from a nursing home outbreak of influenza A. *Infection Control and Hospital Epidemiology* 1995;**16**(5):275–80.

Mukerjee 1994 *{published data only}*
Mukerjee A. Spread of influenza: a study of risk factors in homes for the elderly in Wales. *Journal of Epidemiology and Community Health* 1994;**48**(6):602–3.

Mullooly 1994 *{published data only}*
Mullooly JP, Bennett MD, Hornbrook MC, Barker WH, Williams WW, Patriarca PA, et al.Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. *Annals of Internal Medicine* 1994;**121**(12):947–52.

Murayama 1999 *{published data only}*
Murayama N, Suzuki H, Arakawa M, Nerome K, Mizuta K, Kameyama K. Two outbreaks of influenza A (H3N2) in a Japanese nursing home in the winter of 1996-1997, with differing vaccine efficacy. *Tohoku Journal of Experimental Medicine* 1999;**188**(4):289–98.

Nichol 1994a *{published data only}*
Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *New England Journal of Medicine* 1994;**331**(12):778–84.

Nichol 1994b *{published data only}*
Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *New England Journal of Medicine* 1994;**331**(12):778–84.

Nichol 1994c *{published data only}*
Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *New England Journal of Medicine* 1994;**331**(12):778–84.

Nichol 1998a *{published data only}*
Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Archives of Internal Medicine* 1998;**158**(16):1769–76.

Nichol 1998b *{published data only}*
Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Archives of Internal Medicine* 1998;**158**(16):1769–76.

Nichol 2003a *{published data only}*
Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *New England Journal of Medicine* 2003;**348**(14):1322–32.

Nichol 2003b *{published data only}*
Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *New England Journal of Medicine* 2003;**348**(14):1322–32.

Nicholson 1999 *{published data only}*
Nicholson KG, Kent J, Hammersley V. Influenza A among community-dwelling elderly persons in Leicestershire during winter 1993-4; cigarette smoking as a risk factor and the efficacy of influenza vaccination. *Epidemiology and Infection* 1999;**123**(1):103–8.

Nordin 2001a *{published data only}*
Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Wei F, et al.Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *Journal of Infectious Diseases* 2001;**184**(6):665–70.

Nordin 2001b *{published data only}*
Nordin J, Mullooly J, Poblete S, Strikas R, Petrucci R, Wei F, et al.Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *Journal of Infectious Diseases* 2001;**184**(6):665–70.

Ohmit 1995a *{published data only}*
Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalization among the elderly during influenza type A and type B seasons. *International Journal of Epidemiology* 1995;**24**(6):1240–8.

Ohmit 1995b *{published data only}*
Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalization among the elderly during influenza type A and type B seasons. *International Journal of Epidemiology* 1995;**24**(6):1240–8.

Ohmit 1999 *{published data only}*
Ohmit SE, Arden NH, Monto AS. Effectiveness of inactivated influenza vaccine among nursing home residents during an influenza type A (H3N2) epidemic. *Journal of the American Geriatric Society* 1999;**47**(2):165–71.

Patriarca 1985a *{published data only}*
Patriarca PA, Weber JA, Parker RA, Hall WN, Kendal AP, Bregman DJ, et al.Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic. *JAMA* 1985;**253**(8):1136–9.

Patriarca 1985b *{published data only}*
Patriarca PA, Weber JA, Parker RA, Hall WN, Kendal AP, Bregman DJ, et al.Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic. *JAMA* 1985;**253**(8):1136–9.

Pregliasco 2002 *{published data only}*
Pregliasco F, Giardini G, Sandrini MC, Perucchini E, Vergani C. Efficacia protettiva di Inflexal V nel pazinte anziano. *Vaccine at a Glance* 2002;**1**(1):2–5.

Puig-Barbera 2007 *{published data only}*
Puig-Barberà J, Díez-Domingo J, Varea AB, Chavarri GS, Rodrigo JA, Hoyos SP, et al.Effectiveness of MF59-adjuvanted subunit

influenza vaccine in preventing hospitalisations for cardiovascular disease, cerebrovascular disease and pneumonia in the elderly. *Vaccine* 2007;**25**(42):7313–21.

Puig-Barberà 1997 *{published data only}*
Puig-Barbera J, Marquez-Calderon S, Masoliver-Fores A, Lloria-Paes F, Ortega-Dicha A, Gil-Martin M, et al.Reduction in hospital admissions for pneumonia in non-institutionalised elderly people as a result of influenza vaccination: a case-control study in Spain. *Journal of Epidemiology and Community Health* 1997;**51**(5):526–30.

Puig-Barberà 2004 *{published data only}*
Puig-Barbera J, Diez-Domingo J, Perez Hoyos S, Belenguer Varea A, Gonzalez Vidal D. Effectiveness of the MF59-adjuvanted influenza vaccine in preventing emergency admissions for pneumonia in the elderly over 64 years of age. *Vaccine* 2004;**23**(3):283–9.

Ruben 1974 *{published data only}*
Ruben FL, Johnston F, Streiff EJ. Influenza in a partially immunized aged population. Effectiveness of killed Hong Kong vaccine against infection with the England strain. *JAMA* 1974;**230**(6):863–6.

Rudenko 2001 *{published data only}*
Rudenko LG, Arden NH, Grigorieva E, Naychin A, Rekstin A, Klimov AI, et al.Immunogenicity and efficacy of Russian live attenuated and US inactivated influenza vaccines used alone and in combination in nursing home residents. *Vaccine* 2000;**19**(2-3): 308–18.

Saah 1986a *{published data only}*
Saah AJ, Neufeld R, Rodstein M, La Montagne JR, Blackwelder WC, Gross P, et al.Influenza vaccine and pneumonia mortality in a nursing home population. *Archive of Internal Medicine* 1986;**146** (12):2353–7.

Saah 1986b *{published data only}*
Saah AJ, Neufeld R, Rodstein M, La Montagne JR, Blackwelder WC, Gross P, et al.Influenza vaccine and pneumonia mortality in a nursing home population. *Archive of Internal Medicine* 1986;**146** (12):2353–7.

Saah 1986c *{published data only}*
Saah AJ, Neufeld R, Rodstein M, La Montagne JR, Blackwelder WC, Gross P, et al.Influenza vaccine and pneumonia mortality in a nursing home population. *Archive of Internal Medicine* 1986;**146** (12):2353–7.

Saito 2002a *{published data only}*
Saito R, Suzuki H, Oshitani H, Sakai T, Seki N, Tanabe N. The effectiveness of influenza vaccine against influenza a (H3N2) virus infections in nursing homes in Niigata, Japan, during the 1998-1999 and 1999-2000 seasons. *Infection Control and Hospital Epidemiology* 2002;**23**(2):82–6.

Saito 2002b *{published data only}*
Saito R, Suzuki H, Oshitani H, Sakai T, Seki N, Tanabe N. The effectiveness of influenza vaccine against influenza a (H3N2) virus infections in nursing homes in Niigata, Japan, during the 1998-1999 and 1999-2000 seasons. *Infection Control and Hospital Epidemiology* 2002;**23**(2):82–6.

Schonberger 1979 *{published data only}*
Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al.Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *American Journal of Epidemiology* 1979; **110**(2):105–23.

Shapiro 2003 *{published data only}*
Shapiro Y, Shemer J, Heymann A, Shalev V, Maharshak N, Chodik G, et al.Influenza vaccination: reduction in hospitalizations and death rates among members of "Maccabi Healthcare Services" during the 2000-2001 influenza season. *Israel Medical Association Journal* 2003;**5**(10):706–8.

Strassburg 1986 *{published data only}*
Strassburg MA, Greenland S, Sorvillo FJ, Lieb LE, Habel LA. Influenza in the elderly: report of an outbreak and a review of vaccine effectiveness reports. *Vaccine* 1986;**4**(1):38–44.

Stuart 1969 *{published data only}*
Stuart WH, Dull HB, Newton LH, McQueen JL, Schiff ER. Evaluation of monovalent influenza vaccine in a retirement community during the epidemic of 1965-66. *JAMA* 1969;**209**(2): 232–8.

Taylor 1992 *{published data only}*
Taylor JL, Dwyer DM, Coffman T, Groves C, Patel J, Israel E. Nursing home outbreak of influenza A (H3N2): evaluation of vaccine efficacy and influenza case definitions. *Infection Control and Hospital Epidemiology* 1992;**13**(2):93–7.

Treanor 1994 *{published data only}*
Treanor J, Dumyati G, O'Brien D, Riley MA, Riley G, Erb S, et al.Evaluation of cold-adapted, reassortant influenza B virus vaccines in elderly and chronically ill adults. *Journal of Infectious Diseases* 1994;**169**(2):402–7.

Voordouw 2003 *{published data only}*
Voordouw BC, van der Linden PD, Simonian S, van der Lei J, Sturkenboom MC, Stricker BH. Influenza vaccination in community-dwelling elderly: impact on mortality and influenza-associated morbidity. *Archives of Internal Medicine* 2003;**163**(9): 1089–94.

References to studies excluded from this review

Allsup 2001 *{published data only}*
Allsup SJ, Gosney M, Regan M, Haycox A, Fear S, Johnstone FC. Side effects of influenza vaccination in healthy older people: a randomised single-blind placebo-controlled trial. *Gerontology* 2001; **47**(6):311–4.

Allsup 2003 *{published data only}*
Allsup S, Gosney M, Haycox A, Regan M. Cost-benefit evaluation of routine influenza immunisation in people 65-74 years of age. *Health Technology Assessment* 2003;**7**(24):iii-x, 1-65.

Anonymous 1995 *{published data only}*
Anonymous. Influenza vaccination in the elderly: a bona fide clinical trial. *Hospital Practice* 1995;**30**(2):100.

Anonymous 2004b *{published data only}*
Anonymous. Vaccination protects against influenza deaths in elderly. *Pharmaceutical Journal* 2004;**273**(7318):410.

Ansaldi 2002 *{published data only}*
Ansaldi F, Tominz R, D'Agaro P, Michieletto F, Quadranti M, Cornelio G, et al.Influenza vaccination among the elderly in Trieste: comparison of a cross-sectional study and routine public health surveillance [Vaccinazione anti–influenzale negli anziani a

Trieste: confronto fra uno studio trasversale ed il sistema di sorveglianza passivo]. *Annali di Igiene: Medicina Preventiva e di Comunita'* 2002;**14**(4):305–11.

Arden 1986 ***{published data only}***
Arden NH, Patriarca PA, Kendal P. Experiences in the use and efficacy of inactivated influenza vaccine in nursing homes. In: Kendal AP, Patriarca PA editor(s). *Options for the Control of Influenza*. New York: Alan R. Liss, 1986:155–68.

Armstrong 2004 ***{published data only}***
Armstrong BG, Mangtani P, Fletcher A, Kovats S, McMichael A, Pattenden S, et al.Effect of influenza vaccination on excess deaths occurring during periods of high circulation of influenza: cohort study in elderly people. *BMJ* 2004;**329**(7467):660.

Arroyo 1988 ***{published data only}***
Arroyo JC, Jordan W, Milligan L. Upper respiratory tract infection and serum antibody responses in nursing home patients. *American Journal of Infection Control* 1988;**16**(4):152–8.

Arya 2003 ***{published data only}***
Arya SC. Influenza and other vaccine uptake in the elderly in England. *Vaccine* 2003;**21**(25-6):3527.

Ayala-Montiel 2004 ***{published data only}***
Ayala-Montiel O, Mascarenas de los Santos C, Garcia-Hernandez D, Rendon-Muniz J, Garcia-Olvera L. Reactogenicity of the simultaneous administration of influenza and pneumococcal vaccines in adults over 55 years of age. *Revista de Investigacion Clinica* 2004;**56**(1):27–31.

Baldo 1999 ***{published data only}***
Baldo V, Menegon T, Buoro S, Scalici C, Vesco A, Perale S, et al.Vaccination against influenza in the elderly. Experience with adjuvant vaccines. *Annali di Igiene: Medicina Preventiva e di Comunita'* 1999;**11**(5):369–74.

Barker 1980 ***{published data only}***
Barker WH, Mullooly JP. Influenza vaccination of elderly persons. Reduction in pneumonia and influenza hospitalizations and deaths. *JAMA* 1980;**244**(22):2547–9.

Bektimirov 1993 ***{published data only}***
Bektimirov TA. The immunization of elderly people against influenza. *Voprosy Virusologii* 1993;**38**(6):242–5.

Belshe 2004 ***{published data only}***
Belshe RB, Nichol KL, Black SB, Shinefield H, Cordova J, Walker R, et al.Safety, efficacy, and effectiveness of live, attenuated, cold-adapted influenza vaccine in an indicated population aged 5-49 years. *Clinical Infectious Diseases* 2004;**39**(7):920–7.

Ben-Yehuda 2003 ***{published data only}***
Ben-Yehuda A, Joseph A, Barenholz Y, Zeira E, Even-Chen S, Louria-Hayon I, et al.Immunogenicity and safety of a novel IL-2-supplemented liposomal influenza vaccine (INFLUSOME-VAC) in nursing-home residents. *Vaccine* 2003;**21**(23):3169–78.

Berg 2004 ***{published data only}***
Berg GD, Thomas E, Silverstein S, Neel CL, Mireles M. Reducing medical service utilization by encouraging vaccines: randomized controlled trial. *American Journal of Preventive Medicine* 2004;**27**(4):284–8.

Buxton 2001 ***{published data only}***
Buxton JA, Skowronski DM, Ng H, Marion SA, Li Y, King A, et al.Influenza revaccination of elderly travelers: antibody response to single influenza vaccination and revaccination at 12 weeks. *Journal of Infectious Diseases* 2001;**184**(2):188–91.

Carman 2000 ***{published data only}***
Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, et al.Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000;**355**(9198):93–7.

Castilla 2006 ***{published data only}***
Castilla J, Arregui L, Baleztena J, Barricarte A, Brugos A, Carpintero M, et al.Incidence of influenza and influenza vaccine effectiveness in the 2004-2005 season. *Anales del Sistema Sanitario de Navarra* 2006;**29**(1):97–106.

Chen 2004 ***{published data only}***
Chen YH, Liou SH, Chou CC, Su WL, Loh CH, Lin SH. Influenza and pneumococcal vaccination of the elderly in Taiwan. *Vaccine* 2004;**22**(21-2):2806–11.

Chlibek 2002 ***{published data only}***
Chlibek R, Beran J, Splino M. Effectiveness of influenza vaccination in healthy adults--a fourfold decrease in influenza morbidity during one influenza season. *Epidemiologie, Mikrobiologie, Imunologie* 2002;**51**(2):47–51.

Christenson 2002 ***{published data only}***
Christenson B, Lundbergh P. Comparison between cohorts vaccinated and unvaccinated against influenza and pneumococcal infection. *Epidemiology and Infection* 2002;**129**(3):515–24.

Chumakov 1992 ***{published data only}***
Chumakov MP, Beregovskii NA, Linev MB, Reizin FN, Malyshkina LP, Matrosovich MN, et al.Use of highly purified subvirion trivalent flue vaccine ("Grippovak") in groups with a high risk of complications. *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 1992;**3**:55–7.

Cohen 2004 ***{published data only}***
Cohen J. Vaccine policy. Immunizing kids against flu may prevent deaths among the elderly. *Science* 2004;**306**(5699):1123.

Conne 1997 ***{published data only}***
Conne P, Gauthey L, Vernet P, Althaus B, Que JU, Finkel B, Gluck R, et al.Immunogenicity of trivalent subunit versus virosome-formulated influenza vaccines in geriatric patients. *Vaccine* 1997;**15**(15):1675–9.

Cruijff 1999 ***{published data only}***
Cruijff M, Thijs C, Govaert T, Aretz K, Dinant GJ, Knottnerus A. The effect of smoking on influenza, influenza vaccination efficacy and on the antibody response to influenza vaccination. *Vaccine* 1999;**17**(5):426–32.

D'Alessandro 2004 ***{published data only}***
D'Alessandro D, Ciriminna S, Rossini A, Bossa MC, Fara GM. Requests of medical examinations after pneumococcal & influenza vaccination in the elderly. *Indian Journal of Medical Research* 2004;**119**(Suppl):108–14.

de Bernardi 2002 ***{published data only}***
de Bernardi di Valserra M, Zanasi A, Ragusa S, Gluck R, Herzog C. An open-label comparison of the immunogenicity and tolerability

of intranasal and intramuscular formulations of virosomal influenza vaccine in healthy adults. *Clinical Therapeutics* 2002;**24**(1):100–11.

de Bruijn 2004 ***{published data only}***
de Bruijn IA, Nauta J, Gerez L, Palache AM. Virosomal influenza vaccine: a safe and effective influenza vaccine with high efficacy in elderly and subjects with low pre-vaccination antibody titers. *Virus Research* 2004;**103**(1-2):139–45.

De Serres 2004 ***{published data only}***
De Serres G, Skowronski DM, Guay M, Rochette L, Jacobsen K, Fuller T, et al.Recurrence risk of oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons. *Archive of Internal Medicine* 2004;**164**(20): 2266–72.

Deguchi 2000 ***{published data only}***
Deguchi Y, Takasugi Y. Efficacy of influenza vaccine in the elderly: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic for the elderly in nursing homes. *International Journal of Clinical & Laboratory Research* 2000;**30**(1):1–4.

Deguchi 2000a ***{published data only}***
Deguchi Y, Takasugi Y, Tatara K. Efficacy of influenza vaccine in the elderly in welfare nursing homes: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic. *Journal of Medical Microbiology* 2000;**49**(6):553–6.

Deguchi 2000b ***{published data only}***
Deguchi Y, Takasugi Y, Nishimura K. Vaccine effectiveness for influenza in the elderly in welfare nursing homes during an influenza A (H3N2) epidemic. *Epidemiology and Infection* 2000; **125**(2):393–7.

Deibel 1970 ***{published data only}***
Deibel R, Decher W, Jacobs J. Observations during Hong Kong influenza epidemic. *New York State Journal of Medicine* 1970;**70** (22):2799–805.

Elder 1996 ***{published data only}***
Elder AG, O'Donnell B, McCruden EA, Symington IS, Carman WF. Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993-4 epidemic: results of serum testing and questionnaire. *BMJ* 1996;**313**(7067):1241–2.

Ender 2001 ***{published data only}***
Ender PT, DeRussy PK, Caldwell MM, Taylor SE, Trevino SC, Ybarra D. The effect of a multivitamin on the immunologic response to the influenza vaccine in the elderly. *Infectious Diseases in Clinical Practice*. Vol. **10**, Lippincott Williams & Wilkins, Inc., 2001:81–5.

Erofeeva 2001 ***{published data only}***
Erofeeva MK, Paramonova MS, Maksakova VL, Kolyvanova IL, Nikolaeva EV, Shadrin AS. Vaccine prophylaxis in elderly patients. *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 2001;**3**: 91–3.

Fedson 1992 ***{published data only}***
Fedson DS, Wajda A, Nicol JP, Roos LL. Disparity between influenza vaccination rates and risks for influenza-associated hospital discharge and death in Manitoba in 1982-1983. *Annals of Internal Medicine* 1992;**116**(7):550–5.

Fedson 1993 ***{published data only}***
Fedson DS, Waida A, Nicol JP, Roos LL. "The old man's friend". *Lancet* 1993;**342**(8870):561.

Fitzner 2001 ***{published data only}***
Fitzner KA, Shortridge KF, McGhee SM, Hedley AJ. Cost-effectiveness study on influenza prevention in Hong Kong. *Health Policy* 2001;**56**(3):215–34.

Fukumi 1969 ***{published data only}***
Fukumi H. Interpretation of influenza antibody patterns in man. Existence and significance of Hong Kong antibody in old people prior to the Hong Kong influenza epidemic. *Bulletin of the World Health Organization* 1969;**41**(3):469–73.

Fukushima 1999 ***{published data only}***
Fukushima T, Nakayama K, Monma M, Sekizawa K, Sasaki H. Influenza vaccination in bedridden patients. *Archives of Internal Medicine* 1999;**159**(3):316–7.

Galanti 1976 ***{published data only}***
Galanti B, Picciotto L, Ruggiero G, Romano E, Vaccaro L. Homologous and heterologous antibody response induced in man by anti-influenza vaccine containing A/England/42/72 and b/ Massachusetts/71. *Bollettino dell'Istituto Sieroterapico Milanese* 1976;**55**(71):13–7.

Galasso 1977 ***{published data only}***
Galasso GJ, Tyeryar FJ Jr, La Montagne JR. Overview of clinical trials of influenza vaccines, 1976. *Journal of Infectious Diseases* 1977;**136**(Suppl):425–8.

Garcia Garcia 2009 ***{published data only}***
Garcia-Garcia L, Valdespino-Gómez JL, Lazcano-Ponce E, Jiminez-Corona A, Higuera-Iglesias A, Cruz-Hervert P, et al.Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. *BMJ* 2009;**339**:3928. [: 10.1136/bmj.b3928]

Garcia-Doval 2001 ***{published data only}***
Garcia-Doval I, Roson E, Feal C, De la Torre C, Rodriguez T, Cruces MJ. Generalized bullous fixed drug eruption after influenza vaccination, simulating bullous pemphigoid. *Acta Dermato-Venereologica* 2001;**81**(6):450–1.

Gasparini 2002 ***{published data only}***
Gasparini R, Lucioni C, Lai P, Maggioni P, Sticchi L, Durando P. Cost-benefit evaluation of influenza vaccination in the elderly in the Italian region of Liguria. *Vaccine* 2002;**20**(Suppl 5):B50–4.

Gavira 1990 ***{published data only}***
Gavira FJ, Lardinois R. Cost-effectiveness analysis of antigrippal vaccination in a rural population (La Victoria, Cordoba). *Medicina Clinica* 1990;**94**(20):777–81.

Gendon 1988 ***{published data only}***
Gendon I. Prevention of influenza in the aged. *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 1988;**9**(9):93–6.

Giglio 1994 ***{published data only}***
Giglio E, Roggi L, Bonanni P, Giacchi M, Gasparini R. Influenza vaccination in subjects of the local health unit of Arezzo (Tuscany - Italy) during the winter 1990/91. *Journal of Preventive Medicine and Hygiene* 1994;**35**(3-4):125–30.

Glass 1978 ***{published data only}***
Glass RI, Brann EA, Slade JD, Jones WE, Scally MJ, Craven RB, et al.Community-wide surveillance of influenza after outbreaks due to H3N2 (A/Victoria/75 and A/Texas/77) and H1N1 (A/USSR/77)

influenza viruses, Mercer County, New Jersey, 1978. *Journal of Infectious Diseases* 1978;**138**(5):703–6.

Glezen 1987 ***{published data only}***
Glezen WP, Decker M, Joseph SW, Mercready RG Jr. Acute respiratory disease associated with influenza epidemics in Houston, 1981-1983. *Journal of Infectious Diseases* 1987;**155**(6):1119–26.

Gomez de Caso 1996 ***{published data only}***
Gomez de Caso JA, Franco Yague JA, Castillo Izquierdo JM, Ruiz Cosin C. Study of a disease outbreak in a home for the aged. *Atencion Primaria* 1996;**17**(3):211–4.

Govaert 1994 2 ***{published data only}***
Govaert TM, Sprenger MJ, Dinant GJ, Aretz K, Masurel N, Knottnerus JA. Immune response to influenza vaccination of elderly people. A randomized double-blind placebo-controlled trial. *Vaccine* 1994;**12**(13):1185–9.

Gowda 1979 ***{published data only}***
Gowda HT. Influenza in a geriatric unit. *Postgraduate Medical Journal* 1979;**55**(641):188–91.

Grigor'eva 1994 ***{published data only}***
Grigor'eva EP, Rekstin AR, Rudenko LG, Ramirez A, Barro M, Lisovskaia KV, et al.The immunogenic properties and prophylactic efficacy of a live polyvalent influenza vaccine in children 5 to 14 years old. *Voprosy Virusologii* 1994;**39**(1):26–9.

Grigor'eva 2002 ***{published data only}***
Grigor'eva EP, Desheva IuA, Donina SA, Naikhin AN, Rekstin AR, Barantseva IB, et al.The comparative characteristics of the safety, immunogenic activity and prophylactic potency of the adult and children types of live influenza vaccine in schoolchildren aged 7-14 years. *Voprosy Virusologii* 2002;**47**(4):24–7.

Gross 1977 ***{published data only}***
Gross PA. Reactogenicity and immunogenicity of bivalent influenza vaccine in one- and two-dose trials in children: a summary. *Journal of Infectious Diseases* 1977;**136**(Suppl):616–25.

Gross 1995 ***{published data only}***
Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Annals of Internal Medicine* 1995;**123**(7):518–27.

Guarino 1977 ***{published data only}***
Guarino F, Di Peppe C, D'Antonio D, Melena E, Lattanzio FM. Immunity to the HSW1N1 virus in the older population of Chieti. *Bollettino della Societa Italiana di Biologia Sperimentale* 1977;**53**(21):1942–4.

Guillevin 1983 ***{published data only}***
Guillevin L, Levy Y. Hypersensitivity reaction following vaccination against influenza. *Presse Medicale* 1983;**12**(26):1668–9.

Gutierrez 2001 ***{published data only}***
Gutierrez EB, Li HY, Santos AC, Lopes MH. Effectiveness of influenza vaccination in elderly outpatients in Sao Paulo city, Brazil. *Revista do Instituto de Medicina Tropical de Sao Paulo* 2001;**43**(6):317–20.

Hak 1998 ***{published data only}***
Hak E, van Essen GA, Buskens E, Stalman W, de Melker RA. Is immunising all patients with chronic lung disease in the community against influenza cost effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, The Netherlands. *Journal of Epidemiology and Community Health* 1998;**52**(2):120–5.

Hall 1981 ***{published data only}***
Hall WN, Goodman RA, Noble GR, Kendal AP, Steece RS. An outbreak of influenza B in an elderly population. *Journal of Infectious Diseases* 1981;**144**(4):297–302.

Hampson 1997 ***{published data only}***
Hampson AW, Irving LB. Influenza vaccination: cost-effective health care for the older adult?. *Journal of Quality in Clinical Practice* 1997;**17**(1):3–11.

Hara 2008 ***{published data only}***
Hara M, Sakamoto T, Tanaka K. Influenza vaccine effectiveness among elderly persons living in the community during the 2003-2004 season. *Vaccine* 2008;**26**(50):6477–80.

Harling 2004 ***{published data only}***
Harling R, Hayward A, Watson JM. Implications of the incidence of influenza-like illness in nursing homes for influenza chemoprophylaxis: descriptive study. *BMJ* 2004;**329**(7467):663–4.

Harper 1985 ***{published data only}***
Harper C, Gibson J. Re: Efficacy of influenza vaccine. *JAMA* 1985;**254**(11):1451–2.

Hedlund 2003 ***{published data only}***
Hedlund J, Christenson B, Lundbergh P, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. *Vaccine* 2003;**21**(25-6):3906–11.

Helliwell 1988 ***{published data only}***
Helliwell BE, Drummond MF. The costs and benefits of preventing influenza in Ontario's elderly. *Canadian Journal of Public Health* 1988;**79**(3):175–80.

Hennessen 1978 ***{published data only}***
Hennessen W, Jacob H, Quast U. Neurologic affections after influenza inoculation (author's transl). *Der Nervenarzt* 1978;**49**(2):90–6.

Herzog 2003 ***{published data only}***
Herzog NS, Bratzler DW, Houck PM, Jiang H, Nsa W, Shook C, et al.Effects of previous influenza vaccination on subsequent readmission and mortality in elderly patients hospitalized with pneumonia. *American Journal of Medicine* 2003;**115**(6):454–61.

Heymann 2004 ***{published data only}***
Heymann AD, Shapiro Y, Chodick G, Shalev V, Kokia E, Kramer E, et al.Reduced hospitalizations and death associated with influenza vaccination among patients with and without diabetes. *Diabetes Care* 2004;**27**(11):2581–4.

Hirota 1997 ***{published data only}***
Hirota Y, Kaji M, Ide S, Kajiwara J, Kataoka K, Goto S, et al.Antibody efficacy as a keen index to evaluate influenza vaccine effectiveness. *Vaccine* 1997;**15**(9):962–7.

Hoberman 2003 ***{published data only}***
Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, et al.Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA* 2003;**290**(12):1608–16.

Hope-Simpson 1970 *{published data only}*
Hope-Simpson RE. First outbreak of Hong Kong influenza in a general practice population in Great Britain. A field and laboratory study. *British Medical Journal* 1970;**3**(714):74–7.

Howell 1967 *{published data only}*
Howell RW. Long-term efficacy of oil-adjuvant influenza vaccine in an industrial population. *British Journal of Industrial Medicine* 1967;**24**(1):66–70.

Hurwitz 1983 *{published data only}*
Hurwitz ES, Holman RC, Nelson DB, Schonberger LB. National surveillance for Guillain-Barre syndrome: January 1978-March 1979. *Neurology* 1983;**33**(2):150–7.

Icardi 2002 *{published data only}*
Icardi G, Durando P, Marasso P, Lai P. Vaccinations for adults at risk and the elderly. *Annali di Igiene: Medicina Preventiva e di Comunita* 2002;**14**(Suppl 3):51–8.

Ikematsu 1998 *{published data only}*
Ikematsu H, Nabeshima A, Kakuda K, Yamaji K, Hayashi J, Goto S, et al.Impact of influenza epidemics and efficacy of vaccination among geriatric inpatients. *Kansenshogaku Zasshi* 1998;**72**(1):60–6.

Ikematsu 2000 *{published data only}*
Ikematsu H, Nabeshima A, Yong C, Hayashi J, Goto S, Oka T, et al.The efficacy of influenza vaccine among geriatric inpatients. *Kansenshogaku Zasshi* 2000;**74**(1):17–23.

Isahak 2007 *{published data only}*
Isahak I, Mahayiddin AA, Ismail R. Effectiveness of influenza vaccination in prevention of influenza-like illness among inhabitants of old folk homes. *Southeast Asian Journal of Tropical Medicine & Public Health* 2007;**38**(5):841–8.

Jackson 1999 *{published data only}*
Jackson LA, Holmes SJ, Mendelman PM, Huggins L, Cho I, Rhorer J. Safety of a trivalent live attenuated intranasal influenza vaccine, FluMist, administered in addition to parenteral trivalent inactivated influenza vaccine to seniors with chronic medical conditions. *Vaccine* 1999;**17**(15-6):1905–9.

Jackson 2002 *{published data only}*
Jackson LA, Yu O, Heckbert SR, Psaty BM, Malais D, Barlow WE, et al.Influenza vaccination is not associated with a reduction in the risk of recurrent coronary events. *American Journal of Epidemiology* 2002;**156**(7):634–40.

Jahnz-Rozyk 2003 *{published data only}*
Jahnz-Rozyk K. Pharmaco-economics of anti-influenza vaccinations. *Polski Merkuriusz Lekarski* 2003;**14**(84):679–81.

Jani 1994 *{published data only}*
Jani FM, Gray JP, Lanham J. Influenza vaccine and dermatomyositis. *Vaccine* 1994;**12**(15):1484.

Jarstrand 1974 *{published data only}*
Jarstrand C, Tunevall G. The significance of bacterial superinfection in influenza. *Scandinavian Journal of Infectious Diseases* 1974;**6**(2):137–44.

Jovanovic 1977 *{published data only}*
Jovanovic D, Delvaux AM. Clinical acceptability of live influenza vaccine in high risk subjects and children. Experience with three consecutive recombinant strains. *Developments in Biological Standardization* 1977;**39**:105–12.

Kaplan 1983 *{published data only}*
Kaplan JE, Schonberger LB, Hurwitz ES, Katona P. Guillain-Barre syndrome in the United States, 1978-1981: additional observations from the national surveillance system. *Neurology* 1983;**33**(5): 633–7.

Keavey 1999 *{published data only}*
Keavey S. Preparing for the next influenza outbreak--or (inevitably) pandemic. *JAAPA* 1999;**12**(11):28-30, 33-4, 37-40.

King 1997 *{published data only}*
King D, Morgan R. Giving influenza vaccination to all elderly people would raise ethical issues. *BMJ* 1997;**314**(7077):373.

Knight 1984 *{published data only}*
Knight RS, Duncan JS, Davis CJ, Warlow CP. Influenza vaccination and Guillain-Barre syndrome. *Lancet* 1984;**1**(8373):394.

Knottnerus 1996 *{published data only}*
Knottnerus JA. Influenza in The Netherlands. *Pharmacoeconomics* 1996;**9**(Suppl 3):46-9; discussion 50-3.

Kurland 1984 *{published data only}*
Kurland LT, Molgaard CA, Kurland EM, Erdtmann FJ, Stebbing GE. Lack of association of swine flu vaccine and rheumatoid arthritis. *Mayo Clinic Proceedings* 1984;**59**(12):816–21.

Landi 2003 *{published data only}*
Landi F, Onder G, Cesari M, Gravina EM, Lattanzio F, Russo A, et al.Effects of influenza vaccination on mortality among frail, community-living elderly patients: an observational study. *Aging Clinical and Experimental Research* 2003;**15**(3):254–8.

Landi 2006 *{published data only}*
Landi F, Onder G, Cesari M, Russo A, Barillaro C, Bernabei R, et al.In a prospective observational study, influenza vaccination prevented hospitalization among older home care patients. *Journal of Clinical Epidemiology* 2006;**59**(10):1072–7.

Lavergne 1980 *{published data only}*
Lavergne B, Frappier-Davignon L, Chagnon A, Burr-Paxton M, Quevillon M, Pavilanis V, et al.Reactogenicity and serologic response to trivalent inactivated A/Texas, A/USSR and B/Hong Kong whole-virus influenza vaccine in human volunteers. *Canadian Journal of Public Health* 1980;**71**(1):25–31.

Lawson 2000 *{published data only}*
Lawson F, Baker V, Au D, McElhaney JE. Standing orders for influenza vaccination increased vaccination rates in inpatient settings compared with community rates. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 2000;**55**(9): M522–6.

Lindahl 1999 *{published data only}*
Lindahl G, Perman E. Influenza vaccine caused problems in joints. Compensation from the drug insurance authority. *Lakartidningen* 1999;**96**(37):3912–4.

Lohse 1999 *{published data only}*
Lohse A, Michel F, Auge B, Toussirot E, Wendling D. Vascular purpura and cryoglobulinemia after influenza vaccination. Case-report and literature review. *Revue du Rhumatisme (English ed.)* 1999;**66**(6):359–60.

Luce 2001 *{published data only}*
Luce BR, Zangwill KM, Palmer CS, Mendelman PM, Yan L, Wolff MC, et al.Cost-effectiveness analysis of an intranasal influenza

vaccine for the prevention of influenza in healthy children. *Pediatrics* 2001;**108**(2):E24.

Mair 1974 ***{published data only}***
Mair HJ, Sansome DA, Tillett HE. A controlled trial of inactivated monovalent influenza A vaccines in general practice. *Journal of Hygiene* 1974;**73**(2):317–27.

Mandal 1973 ***{published data only}***
Mandal SK. Influenza outbreak. *British Medical Journal* 1973;**1**(5851):481.

Manzano 2000 ***{published data only}***
Manzano E, Grau A, Sequeira E, Valles JA. Possible toxicoderma secondary to influenza vaccination. *Atencion Primaria* 2000;**26**(6):429.

Manzoli 2007 ***{published data only}***
Manzoli L, Villari P, Granchelli C, Savino A, Carunchio C, Pacifico D, et al.Cohort analysis on influenza vaccine effectiveness for the elderly as a study case to evaluate an alternative approach involving general practitioners for routine assessment of vaccination impact. *European Journal of Public Health* 2007;**17**:28–9.

Margolis 1990b ***{published data only}***
Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. *JAMA* 1990;**264**(9):1139–41.

Marine 1973 ***{published data only}***
Marine WM, Thomas JE. Age-related response to 1000 CCA unit zonally purified, inactivated influenza vaccines in volunteers in the U.S.A. *Postgraduate Medical Journal* 1973;**49**(569):164–8.

Marinich 1997 ***{published data only}***
Marinich IG, Paramonova MS, Erofeeva MK, Maksakova VL, Nikolaeva VM, Naikhin AN, et al.The immunoprophylaxis of influenza among elderly persons. *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 1997;**3**:60–4.

Martin 1997 ***{published data only}***
Martin JT. Development of an adjuvant to enhance the immune response to influenza vaccine in the elderly. *Biologicals* 1997;**25**(2):209–13.

Marwick 1995 ***{published data only}***
Marwick C. Influenza vaccine first to reach immunization goal. *JAMA* 1995;**273**(10):765.

Masurel 1979 ***{published data only}***
Masurel N. Immunization of elderly subjects with subunit and total virus vaccine containing H1N1 influenza virus. *Nederlands Tijdschrift Voor Geneeskunde* 1979;**123**(6):196–9.

Maxim 1998 ***{published data only}***
Maxim R. Adult immunization. *Medicine and Health, Rhode Island* 1998;**81**(8):272–3.

Mayon-White 1994 ***{published data only}***
Mayon-White RT. Vaccination for the elderly. *British Journal of Hospital Medicine* 1994;**51**(6):265, 267.

McCall 1996 ***{published data only}***
McCall TB. Vaccination against influenza in healthy adults. *New England Journal of Medicine* 1996;**334**(6):403–4.

McCarthy 1978 ***{published data only}***
McCarthy NJ. Influenza 1978. *Medical Journal of Australia* 1978;**1**(6):314.

McElhaney 2002 ***{published data only}***
McElhaney JE. Influenza: a preventable lethal disease. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 2002;**57**(10):M627–8.

McGuffey 1993 ***{published data only}***
McGuffey EC. Flu vaccinations. *American Pharmacy* 1993;**NS33**(11):24.

Meiklejohn 1989 ***{published data only}***
Meiklejohn G, Hoffman R, Graves P. Effectiveness of influenza vaccine when given during an outbreak of influenza A/H3N2 in a nursing home. *Journal of the American Geriatrics Society* 1989;**37**(5):407–10.

Mendelman 2001 ***{published data only}***
Mendelman PM, Cordova J, Cho I. Safety, efficacy and effectiveness of the influenza virus vaccine, trivalent, types A and B, live, cold-adapted (CAIV-T) in healthy children and healthy adults. *Vaccine* 2001;**19**(17-9):2221–6.

Meynaar 1991 ***{published data only}***
Meynaar IA, van't Wout JW, Vandenbroucke JP, van Furth R. Use of influenza vaccine in The Netherlands. *BMJ* 1991;**303**(6801):508.

Mignogna 2000 ***{published data only}***
Mignogna MD, Lo Muzio L, Ruocco E. Pemphigus induction by influenza vaccination. *International Journal of Dermatology* 2000;**39**(10):800.

Miller 1975 ***{published data only}***
Miller LW, Hume EB, O'Brien FR, Togo Y, Hornick RB. Alice strain live attenuated influenza (H3N2) vaccine in an elderly population. *American Journal of Epidemiology* 1975;**101**(4):340–6.

Modlin 1977 ***{published data only}***
Modlin JF, Smith DH, Harding L. Clinical trials of bivalent A/New Jersey/76-A/Victoria/75 influenza vaccines in high-risk children. *Journal of Infectious Diseases* 1977;**136**(Suppl):626–31.

Monto 1994 ***{published data only}***
Monto AS. Influenza vaccines for the elderly. *New England Journal of Medicine* 1994;**331**(12):807–8.

Moreno 2009 ***{published data only}***
Moreno J, De la Hoz F, Rico A, Cotes K, Porras A. Flu vaccine effectiveness: a metaanalysis. *Biomedica* 2009;**29**(1):87–97.

Mostow 1969 ***{published data only}***
Mostow SR, Schoenbaum SC, Dowdle WR, Coleman MT, Kaye HS. Studies with inactivated influenza vaccines purified by zonal centrifugation. 1. Adverse reactions and serological responses. *Bulletin of the World Health Organization* 1969;**41**(3):525–30.

Mostow 1988 ***{published data only}***
Mostow SR. Influenza--a controllable disease?. *Journal of the American Geriatrics Society* 1988;**36**(3):281–3.

Nguyen-van-Tam 1992 ***{published data only}***
Nguyen-van-Tam JS, Nicholson KG. Influenza deaths in Leicestershire during the 1989-90 epidemic: implications for prevention. *Epidemiology and Infection* 1992;**108**(3):537–45.

Nichol 1996 ***{published data only}***
Nichol KL, Margolis KL, Wouremna J, von Sternberg T. Effectiveness of influenza vaccine in the elderly. *Gerontology* 1996;**42**(5):274–9.

Nichol 1999a *{published data only}*
Nichol KL, Goodman M. The health and economic benefits of influenza vaccination for healthy and at-risk persons aged 65 to 74 years. *Pharmacoeconomics* 1999;**16**(Suppl 1):63–71.

Nichol 1999b *{published data only}*
Nichol KL. Complications of influenza and benefits of vaccination. *Vaccine* 1999;**17**(Suppl 1):47–52.

Nichol 1999c *{published data only}*
Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Annals of Internal Medicine* 1999;**130**(5):397–403.

Nichol 1999d *{published data only}*
Nichol KL, Mendelman PM, Mallon KP, Jackson LA, Gorse GJ, Belshe RB, et al.Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. *JAMA* 1999;**282**(2):137–44.

Nichol 2002 *{published data only}*
Nichol KL, Goodman M. Cost effectiveness of influenza vaccination for healthy persons between ages 65 and 74 years. *Vaccine* 2002;**20**(Suppl 2):21–4.

Nichol 2007 *{published data only}*
Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly [see comment]. *New England Journal of Medicine* 2007;**357**(14):1373–81.

Nicholson 1979 *{published data only}*
Nicholson KG, Tyrrell DA, Harrison P, Potter CW, Jennings R, Clark A, et al.Clinical studies of monovalent inactivated whole virus and subunit A/USSR/77 (H1N1) vaccine: serological responses and clinical reactions. *Journal of Biological Standardization* 1979;**7**(2):123–36.

Nicholson 1983 *{published data only}*
Nicholson KG, Tyrrell DA, Howells CH, Schild GC, Oxford J. Live influenza vaccines. *Lancet* 1983;**2**(8349):564–5.

Nicholson 1990a *{published data only}*
Nicholson KG, Baker DJ, Farquhar A, Hurd D, Kent J, Smith SH. Acute upper respiratory tract viral illness and influenza immunization in homes for the elderly. *Epidemiology and Infection* 1990;**105**(3):609–18.

Nicholson 1990b *{published data only}*
Nicholson KG. Influenza vaccination and the elderly. *BMJ* 1990;**301**(6753):617–8.

Nicholson 1992 *{published data only}*
Nicholson KG, Baker DJ, Chakraverty P, Farquhar A, Hurd D, Kent J, et al.Immunogenicity of inactivated influenza vaccine in residential homes for elderly people. *Age and Ageing* 1992;**21**(3):182–8.

Nielsen 1996 *{published data only}*
Nielsen PV. Vaccination against influenza of the elderly population of Copenhagen. *Ugeskrift for Laeger* 1996;**158**(48):6928.

Nygaard 1999 *{published data only}*
Nygaard HA. Prevention of influenza in nursing homes. *Tidsskrift for den Norske Laegeforening* 1999;**119**(14):2079.

Odelin 1993 *{published data only}*
Odelin MF, Pozzetto B, Aymard M, Defayolle M, Jolly-Million J. Role of influenza vaccination in the elderly during an epidemic of A/H1N1 virus in 1988-1989: clinical and serological data. *Gerontology* 1993;**39**(2):109–16.

Odelin 2003 *{published data only}*
Odelin MF, Momplot C, Bourlet T, Gonthier R, Aymard M, Pozzetto B. Temporal surveillance of the humoral immunity against influenza vaccine in the elderly over 9 consecutive years. *Gerontology* 2003;**49**(4):233–9.

Ohmit 1995 *{published data only}*
Ohmit SE, Furumoto-Dawson A, Monto AS, Fasano N. Influenza vaccine use among an elderly population in a community intervention. *American Journal of Preventive Medicine* 1995;**11**(4):271–6.

Ortqvist 2007 *{published data only}*
Ortqvist A, Granath F, Askling J, Hedlund J. Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area [see comment]. *European Respiratory Journal* 2007;**30**(3):414–22.

Oshitani 2000 *{published data only}*
Oshitani H, Saito R, Seki N, Tanabe N, Yamazaki O, Hayashi S, et al.Influenza vaccination levels and influenza-like illness in long-term-care facilities for elderly people in Niigata, Japan, during an influenza A (H3N2) epidemic. *Infection Control and Hospital Epidemiology* 2000;**21**(11):728–30.

Parkin 1978 *{published data only}*
Parkin WE, Beecham HJ, Streiff E, Sharrar RG, Harris JC. Relationship studied in Pennsylvania. Guillain-Barre syndrome and influenza immunization. *Pennsylvania Medicine* 1978;**81**(4):47-8, 50-2.

Parsons 1997 *{published data only}*
Parsons JE, Wilson DH, Luke KF, Carrangis J. Influenza vaccination among the elderly in South Australia. *Medical Journal of Australia* 1997;**167**(8):456.

Patel 1988 *{published data only}*
Patel U, Bradley JR, Hamilton DV. Henoch-Schonlein purpura after influenza vaccination. *BMJ* 1988;**296**(6639):1800.

Patriarca 1985 *{published data only}*
Patriarca PA, Weber JA, Meissner MK, Stricof RL, Dateno B, Braun JE. Use of influenza vaccine in nursing homes. *Journal of the American Geriatrics Society* 1985;**33**(7):463–6.

Patriarca 1994 *{published data only}*
Patriarca PA. A randomized controlled trial of influenza vaccine in the elderly. Scientific scrutiny and ethical responsibility. *JAMA* 1994;**272**(21):1700–1.

Pena-Rey 2003 *{published data only}*
Pena-Rey I, Perez-Farinos N, Sarria-Santamera A. Determinants of flu vaccination in Galician women over 65 years old. *Atencion Primaria* 2003;**31**(7):462–3.

Perez 2000 *{published data only}*
Perez C, Loza E, Tinture T. Giant cell arteritis after influenza vaccination. *Archive of Internal Medicine* 2000;**160**(17):2677.

Perez-Tirse 1992 *{published data only}*
Perez-Tirse J, Gross PA. Review of cost-benefit analyses of influenza vaccine. *Pharmacoeconomics* 1992;**2**(3):198–206.

Perucchini 2004 *{published data only}*
Perucchini E, Consonni S, Sandrini MC, Bergamaschini L, Vergani C. Adverse reactions to influenza vaccine alone or with pneumococcal vaccine in the elderly. *Journal of the American Geriatrics Society* 2004;**52**(7):1219–20.

Peters 1988 *{published data only}*
Peters NL, Meiklejohn G, Jahnigen DW. Antibody response of an elderly population to a supplemental dose of influenza B vaccine. *Journal of the American Geriatrics Society* 1988;**36**(7):593–9.

Philip 1969 *{published data only}*
Philip RN, Bell JA, Davis DJ, Beem MO, Beigelman PM, Engler JI, et al.Epidemiologic studies on influenza in familial and general population groups, 1951-1956. V. Effectiveness of adjuvant vaccines. *American Journal of Epidemiology* 1969;**90**(6):471–83.

Phillips 1970 *{published data only}*
Phillips CA, Forsyth BR, Christmas WA, Gump DW, Whorton EB, Rogers I, et al.Purified influenza vaccine: clinical and serologic responses to varying doses and different routes of immunization. *Journal of Infectious Diseases* 1970;**122**(1):26–32.

Phillips 1971 *{published data only}*
Phillips WP, Hughes JN. Immunization against influenza. *Community Health (Bristol)* 1971;**2**(5):245–9.

Piedra 2002 *{published data only}*
Piedra PA, Yan L, Kotloff K, Zangwill K, Bernstein DI, King J, et al.Safety of the trivalent, cold-adapted influenza vaccine in preschool-aged children. *Pediatrics* 2002;**110**(4):662–72.

Poe 1977 *{published data only}*
Poe GS, Massey JT. Estimating influenza cases and vaccinations by means of weekly rapid reporting system; methodological considerations and results obtained in the U.S. health interview survey. *Public Health Reports* 1977;**92**(4):299–306.

Poland 2002 *{published data only}*
Poland GA. If you could halve the mortality rate, would you do it?. *Clinical Infectious Diseases* 2002;**35**(4):378–80.

Potter 1997 *{published data only}*
Potter J, Stott DJ, Roberts MA, Elder AG, O'Donnell B, Knight PV, et al.Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *Journal of Infectious Diseases* 1997;**175**(1):1–6.

Powers 1991 *{published data only}*
Powers DC, Fries LF, Murphy BR, Thumar B, Clements ML. In elderly persons live attenuated influenza A virus vaccines do not offer an advantage over inactivated virus vaccine in inducing serum or secretory antibodies or local immunologic memory. *Journal of Clinical Microbiology* 1991;**29**(3):498–505.

Pregliasco 1997 *{published data only}*
Pregliasco F, Sodano L, Mensi C, Borghetti MC, Camorali L, D'Argenio P. Anti-influenza vaccination: knowledge, attitude and practice of the elderly residing in the city of Milan. *Annali di Igiene: Medicina Preventiva e di Comunita* 1997;**9**(2):127–31.

Pregliasco 1999 *{published data only}*
Pregliasco F, Sodano L, Mensi C, Selvaggi MT, Adamo B, D'Argenio P, et al.Influenza vaccination among the elderly in Italy. *Bulletin of the World Health Organization* 1999;**77**(2):127–31.

Profeta 1987 *{published data only}*
Profeta ML, Guidi G, Meroni PL, Palmieri R, Palladino G, Cantone V, et al.Influenza vaccination with adjuvant RU41740 in the elderly. *Lancet* 1987;**1**(8539):973.

Provinciali 1994 *{published data only}*
Provinciali M, Di Stefano G, Muzzioli M, Scarpazza P, Colombo D, Migliorino M, et al.Impaired antibody response to influenza vaccine in institutionalized elderly. *Annals of the New York Academy of Sciences* 1994;**717**:307–14.

Puig Barberà 1995 *{published data only}*
Puig Barbera J, Marquez Calderon S. Effectiveness of influenza vaccine in the elderly. A critical review of the bibliography. *Medicina Clinica* 1995;**105**(17):645–8.

Puretz 1979 *{published data only}*
Puretz DH. Some thoughts on the 1976 swine flu immunization program: what went wrong?. *Journal of School Health* 1979;**49**(7): 410–2.

Pyhala 1997 *{published data only}*
Pyhala R, Hovi T. Influenza vaccinations--use with care. *Duodecim* 1997;**113**(21):2129, 2131.

Quinlisk 1990 *{published data only}*
Quinlisk P, Smithee L. Shanghai in Oklahoma?. *Journal of the Oklahoma State Medical Association* 1990;**83**(11):562–4.

Quinnan 1983 *{published data only}*
Quinnan GV, Schooley R, Dolin R, Ennis FA, Gross P, Gwaltney JM. Serologic responses and systemic reactions in adults after vaccination with monovalent A/USSR/77 and trivalent A/USSR/77, A/Texas/77, B/Hong Kong/72 influenza vaccines. *Reviews of Infectious Diseases* 1983;**5**(4):748–57.

Rao 1982 *{published data only}*
Rao BL, Kadam SS, Pavri KM, Kothavale VS. Epidemiological, clinical, and virological features of influenza outbreaks in Pune, India, 1980. *Bulletin of the World Health Organization* 1982;**60**(4): 639–42.

Read 2000 *{published data only}*
Read CA, Mohsen A, Nguyen-Van-Tam JS, McKendrick M, Kudesia G. Outbreaks of influenza A in nursing homes in Sheffield during the 1997-1998 season: implications for diagnosis and control. *Journal of Public Health Medicine* 2000;**22**(1):116–20.

Reedy 2000 *{published data only}*
Reedy JL, Paul SM, Zanna MT. Influenza: prevention and treatment. *New Jersey Medicine* 2000;**97**(11):41–50.

Ruben 1973 *{published data only}*
Ruben FL. Effectiveness of current killed influenza vaccines against influenza A-England-42-72. *Journal of Infectious Diseases* 1973;**127** (5):576–7.

Rubin 1973 *{published data only}*
Rubin RJ, Gregg MB. "English flu"--a primer. *New England Journal of Medicine* 1973;**288**(9):467–8.

Rudenko 1981 *{published data only}*
Rudenko LG, Zykov MP. Protection of the elderly against influenza (a review of the literature). *Vrachebnoe Delo* 1981;**12**:8–11.

Rudenko 1993 *{published data only}*
Rudenko LG, Slepushkin AN, Monto AS, Kendal AP, Grigorieva EP, Burtseva EP, et al.Efficacy of live attenuated and inactivated influenza vaccines in schoolchildren and their unvaccinated contacts in Novgorod, Russia. *Journal of Infectious Diseases* 1993; **168**(4):881–7.

Ruel 2002 *{published data only}*
Ruel N, Odelin MF, Jolly J, Momplot C, Diana MC, Bourlet T, et al.Outbreaks due to respiratory syncytial virus and influenza virus A/H3N in institutionalized aged. Role of immunological status to influenza vaccine and possible implication of caregivers in the transmission. *Presse Medicale* 2002;**31**(8):349–55.

Ruf 2004 *{published data only}*
Ruf BR, Colberg K, Frick M, Preusche A. Open, randomized study to compare the immunogenicity and reactogenicity of an influenza split vaccine with an MF59-adjuvanted subunit vaccine and a virosome-based subunit vaccine in elderly. *Infection* 2004;**32**(4): 191–8.

Runehagen 2002 *{published data only}*
Runehagen A, Petersson C. Free vaccine and increased information suggested to increase the vaccination coverage. A questionnaire study concerning influenza vaccination of elderly persons and other risk groups. *Lakartidningen* 2002;**99**(6):496–7.

Russell 2001 *{published data only}*
Russell ML, Ferguson CA. Improving population influenza vaccine coverage through provider feedback and best practice identification. *Canadian Journal of Public Health* 2001;**92**(5):345–6.

Ryan 1984 *{published data only}*
Ryan MP, MacLeod AF. A comparison of adverse effects of two influenza vaccines, and the influence on subsequent uptake. *Journal of the Royal College of General Practitioners* 1984;**34**(265):442–4.

Sadler 2000 *{published data only}*
Sadler C. Needle work. *Nursing Standard* 2000;**15**(7):18–9.

Sandrini 1997 *{published data only}*
Sandrini MC, Pregliasco F, Mensi C, Giardini G, Lucchi T, Santambrogio D, et al.Immunogenicity and efficacy field evaluation (1994-1995 season) of influenza vaccine in a noninstitutionalized elderly population. *Annali di Igiene: Medicina Preventiva e di Comunita* 1997;**9**(5):373–9.

Saslaw 1966 *{published data only}*
Saslaw S, Carlisle HN, Perkins RL. Effect of dosage and influenza vaccine content on antibody response in an aged population. *American Journal of the Medical Sciences* 1966;**251**(2):195–206.

Satsuta 1985 *{published data only}*
Satsuta K, Ogawa M, Makabe A, Ichinose T. On death due to influenza. *Nippon Ika Daigaku Zasshi* 1985;**52**(3):347–51.

Schoenbaum 1969 *{published data only}*
Schoenbaum SC, Mostow SR, Dowdle WR, Coleman MT, Kaye HS. Studies with inactivated influenza vaccines purified by zonal centrifugation. 2. Efficacy. *Bulletin of the World Health Organization* 1969;**41**(3):531–5.

Schwartz 1995 *{published data only}*
Schwartz K. Efficacy of influenza vaccine in the elderly. *Journal of Family Practice* 1995;**40**(3):298–9.

Selvaraj 1998 *{published data only}*
Selvaraj N, Moonis M, Ravin P. Hemiparesis following influenza vaccination. *Postgraduate Medical Journal* 1998;**74**(876):633–5.

Serie 1977 *{published data only}*
Serie C, Barme M, Hannoun C, Thibon M, Beck H, Aquino JP. Effects of vaccination on an influenza epidemic in a geriatric hospital. *Developments in Biological Standardization* 1977;**39**: 317–21.

Sethi 2002 *{published data only}*
Sethi S. Bacterial pneumonia. Managing a deadly complication of influenza in older adults with comorbid disease. *Geriatrics* 2002;**57** (3):56–61.

Sharbaugh 1997 *{published data only}*
Sharbaugh RJ. Influenza--it's that time again. *Home Care Provider* 1997;**2**(5):227–8.

Shinkawa 2002 *{published data only}*
Shinkawa M, Nakayama K, Hirai H, Monma M, Sasaki H. Depression and immunoreactivity in disabled older patients. *Journal of the American Geriatrics Society* 2002;**50**(1):198–9.

Shoji 2003 *{published data only}*
Shoji H, Kaji M. The influenza vaccination and neurological complications. *Internal Medicine* 2003;**42**(2):139.

Siewert 1988 *{published data only}*
Siewert M, Drinka P, Langer E. High rates of immunization in a nursing home. *American Journal of Infection Control* 1988;**16**(5): 228–30.

Simonsen 2005 *{published data only}*
Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Archive of Internal Medicine* 2005; **165**(3):265–72.

Skowronski 2003 *{published data only}*
Skowronski DM, De Serres G, Scheifele D, Russell ML, Warrington R, Davies HD, et al.Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clinical Infectious Diseases* 2003;**37**(8):1059–66.

Skull 2009 *{published data only}*
Skull SA, Andrews RM, Byrnes GB, Campbell DA, Kelly HA, Brown GV, et al.Hospitalized community-acquired pneumonia in the elderly: an Australian case-cohort study. *Epidemiology & Infection* 2009;**137**(2):194–202.

Slepuskin 1967 *{published data only}*
Slepuskin AN, Bobyleva TK, Russina AE, Vitkina BS, Ellengorn NS, Zdanov VM. Evaluation of the effectiveness of large-scale vaccination against influenza in the USSR. *Bulletin of the World Health Organization* 1967;**36**(3):385–95.

Sloan 1993 *{published data only}*
Sloan DS. Influenza immunization in elderly people. *BMJ* 1993; **307**(6913):1213–4.

Socan 2004 *{published data only}*
Socan M, Frelih T, Janet E, Petras T, Peternelj B. Reactions after pneumococcal vaccine alone or in combination with influenza vaccine. *Vaccine* 2004;**22**(23-24):3087–91.

Solomon 1984 *{published data only}*
Solomon R, Morlino J, Martucci M, Ney D. Adverse drug reaction after administration of influenza vaccine. *Journal of the Medical Society of New Jersey* 1984;**81**(7):573–4.

Solomon 1996 *{published data only}*
Solomon A, Frucht-Pery J. Bilateral simultaneous corneal graft rejection after influenza vaccination. *American Journal of Ophthalmology* 1996;**121**(6):708–9.

Solomon 1999 *{published data only}*
Solomon A, Siganos CS, Frucht-Pery J. Adverse ocular effects following influenza vaccination. *Eye* 1999;**13**(Pt 3a):381–2.

Spencer 1979 *{published data only}*
Spencer MJ, Cherry JD, Powell KR, Sumaya CV. A clinical trial with Alice/R-75 strain, live attenuated serum inhibitor-resistant intranasal bivalent influenza A/B vaccine. *Medical Microbiology and Immunology* 1979;**167**(1):1–9.

Sprenger 1990 *{published data only}*
Sprenger MJ, Diepersloot RJ, Beyer WE, Masurel N. Influenza-related excess mortality in The Netherlands 1989/90. *Lancet* 1990; **336**(8711):382.

Squarcione 2003 *{published data only}*
Squarcione S, Sgricia S, Biasio LR, Perinetti E. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. *Vaccine* 2003;**21** (11-2):1268–74.

Stamboulian 1999 *{published data only}*
Stamboulian D, Bonvehi PE, Nacinovich FM, Ruttimann RW. Immunization against influenza in the elderly: the Argentinian experience, 1993-1997. *Vaccine* 1999;**17**(Suppl 1):53–6.

Stott 2001 *{published data only}*
Stott DJ, Carman WF, Elder AG. Influenza in old age. *Age and Ageing* 2001;**30**(5):361–3.

Tamblyn 1997 *{published data only}*
Tamblyn SE. Preventing influenza outbreaks in long-term care facilities. *Canadian Medical Association Journal* 1997;**157**(7):927–8.

Thompson 1988 *{published data only}*
Thompson MP. Is routine influenza immunization indicated for people over 65 years of age? An affirmative view. *Journal of Family Practice* 1988;**26**(2):211–4.

Treanor 1992 *{published data only}*
Treanor JJ, Mattison HR, Dumyati G, Yinnon A, Erb S, O'Brien D, et al.Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. *Annals of Internal Medicine* 1992;**117**(8):625–33.

Treanor 1998 *{published data only}*
Treanor JJ, Betts RF. Evaluation of live, cold-adapted influenza A and B virus vaccines in elderly and high-risk subjects. *Vaccine* 1998; **16**(18):1756–60.

Tsai 2007 *{published data only}*
Tsai Y-W, Huang W-F, Wen Y-W, Chen P-F. The relationship between influenza vaccination and outpatient visits for upper respiratory infection by the elderly in Taiwan. *Value in Health* 2007;**10**(2):117–27.

Upshur 2000 *{published data only}*
Upshur RE, Goel V. Measuring the impact of influenza on the hospital admission rates of the elderly in Ontario: a five-year admission rate analysis, 1988-1993. *Canadian Journal of Public Health* 2000;**91**(2):144–7.

Urquhart 1974 *{published data only}*
Urquhart GE. Serum IgM and IgA responses in influenza A infections. *Journal of Clinical Pathology* 1974;**27**(3):198–201.

Uyeki 2003 *{published data only}*
Uyeki TM, Zane SB, Bodnar UR, Fielding KL, Buxton JA, Miller JM, et al.Large summertime influenza A outbreak among tourists in Alaska and the Yukon Territory. *Clinical Infectious Diseases* 2003;**36** (9):1095–102.

Vallee 2000 *{published data only}*
Vallee JP. Flu and antiviral agents..... *Presse Medicale* 2000;**29**(2): 84–5.

Van Horren 1976 *{published data only}*
Van Horren J. Letter: Influenza vaccine and P.P.D. skin-test reactivity. *Lancet* 1976;**1**(7949):44.

van Vuuren 2009 *{published data only}*
van Vuuren A, Rheeder P, Hak E. Effectiveness of influenza vaccination in the elderly in South Africa. *Epidemiology & Infection* 2009;**137**(7):994–1002.

Verde 1973 *{published data only}*
Verde F, Frezza G, Russo V, Visconti M. Antibody response to anti-influenza vaccination with vaccine purified by differential ultracentrifugation and with vaccine purified by zonal ultracentrifugation. *Bollettino della Societa Italiana di Biologia Sperimentale* 1973;**49**(4):178–81.

Verweij 2002 *{published data only}*
Verweij M, van Den Hoven M. Influenza vaccination rates and informed consent in Dutch nursing homes: survey of nursing home physicians. *BMJ* 2002;**324**(7333):328.

Vila-Corcoles 2005 *{published data only}*
Vila-Corcoles A, Ochoa-Gondar O, Ansa-Echeverria X, Gomez-Sorribes A, Espelt-Aluja P, Pascual-Moron I. Influenza vaccination and mortality in the elderly [see comment]. *Medicina Clinica* 2005; **125**(18):689–91.

Visconti 1973 *{published data only}*
Visconti M, Verde F, Frezza G, Russo V. Persistence of antibodies inhibiting hemagglutination by influenza viruses in aged vaccinated women. Changes in antibody titer after re-vaccination. *Bollettino della Societa Italiana di Biologia Sperimentale* 1973;**49**(4):173–7.

Voordouw 2004 *{published data only}*
Voordouw AC, Sturkenboom MC, Dieleman JP, Stijnen T, Smith DJ, van der Lei J, et al.Annual revaccination against influenza and mortality risk in community-dwelling elderly persons. *JAMA* 2004; **292**(17):2089–95.

Voordouw 2006 *{published data only}*
Voordouw BC, Sturkenboom MC, Dieleman JP, Stijnen T, van der Lei J, Stricker BH. Annual influenza vaccination in community-dwelling elderly individuals and the risk of lower respiratory tract

infections or pneumonia. *Archives of Internal Medicine* 2006;**166** (18):1980–5.

Vu 2002 ***{published data only}***
Vu T, Farish S, Jenkins M, Kelly H. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. *Vaccine* 2002;**20**(13-4):1831–6.

Wagner 1993 ***{published data only}***
Wagner TA, Skiba R. Tolerance of preventive influenza vaccination with a subunit vaccine. *Bevolkerung und Kultur. Reihe 7: Gesundheitswesen* 1993;**55**(11):587–8.

Wagner 1994 ***{published data only}***
Wagner TA. Placebo-controlled study on effectiveness of influenza vaccination?. *Deutsche Medizinische Wochenschrift* 1994;**119**(30): 1057–8.

Wakefield 1990 ***{published data only}***
Wakefield IR. Influenza vaccination and the elderly. *BMJ* 1990;**301** (6762):1216.

Wang 1986 ***{published data only}***
Wang A, Hannoun C, Cadiot P. Theoretical and practical prospects of influenza vaccination in aged persons [Perspectives theoriques et pratiques de la vaccination antigrippale chez la personne agee]. *Medecine et Hygiene* 1986;**44**(1656):1373–6.

Wang 2002 ***{published data only}***
Wang CS, Wang ST, Chou P. Efficacy and cost-effectiveness of influenza vaccination of the elderly in a densely populated and unvaccinated community. *Vaccine* 2002;**20**(19-20):2494–9.

Warburton 1972 ***{published data only}***
Warburton MF, Jacobs DS, Langsford WA, White GE. Herd immunity following subunit influenza vaccine administration. *Medical Journal of Australia* 1972;**2**(2):67–70.

Wareing 2001 ***{published data only}***
Wareing MD, Tannock GA. Live attenuated vaccines against influenza; an historical review. *Vaccine* 2001;**19**(25-26):3320–30.

Watson 1997 ***{published data only}***
Watson JM, Cordier JF, Nicholson KG. Does influenza immunisation cause exacerbations of chronic airflow obstruction or asthma?. *Thorax* 1997;**52**(2):190–4.

Weaver 2001 ***{published data only}***
Weaver M, Krieger J, Castorina J, Walls M, Ciske S. Cost-effectiveness of combined outreach for the pneumococcal and influenza vaccines. *Archive of Internal Medicine* 2001;**161**(1): 111–20.

Wiehl 2001 ***{published data only}***
Wiehl M. Influenza vaccination. Even colleagues try and avoid it. *MMW Fortschritte der Medizin* 2001;**143**(43):14.

Williams 1980 ***{published data only}***
Williams GO. Vaccines in older patients: combating the risk of mortality. *Geriatrics* 1980;**35**(11):55-7, 63-4.

Wilson 1994 ***{published data only}***
Wilson R. Influenza vaccination. *Thorax* 1994;**49**(11):1079–80.

Winer 1984 ***{published data only}***
Winer JB, Hughes RA, Bradley GW, Scadding JW. Guillain-Barre syndrome and influenza vaccine. *Lancet* 1984;**1**(8387):1182.

Wise 1977 ***{published data only}***
Wise TG, Dolin R, Mazur MH, Top FH Jr, Edelman R, Ennis FA. Serologic responses and systemic reactions in adults after vaccination with bivalent A/Victoria/75-A/New Jersey/76 and monovalent B/Hong Kong/72 influenza vaccines. *Journal of Infectious Diseases* 1977;**136**(Suppl):507–17.

Wood 2000 ***{published data only}***
Wood SC, Nguyen VH, Schmidt C. Economic evaluations of influenza vaccination in the elderly: impact on public health policy (for bibl. only). *Disease Management and Health Outcomes* 2000;**8** (5):273–85.

Woratz 1984 ***{published data only}***
Woratz C, Sinnecker H, Woratz G, Giard W, Muller D, Hajduk F, et al.Use of excess mortality as a criterion of effectiveness in vaccination for the prevention of influenza. *Zeitschrift fur die Gesamte Hygiene und ihre Grenzgebiete* 1984;**30**(9):488–90.

Yassi 1993 ***{published data only}***
Yassi A, Mcgill M, Holton C, Nicolle L. Morbidity, cost and role of health care worker transmission in an outbreak in a tertiary care hospital. *Canadian Journal of Infectious Diseases* 1993;**4**(1):52–6.

Zambon 2001 ***{published data only}***
Zambon M, Hays J, Webster A, Newman R, Keene O. Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serologic, or molecular detection of influenza. *Archives of Internal Medicine* 2001;**161**(17):2116–22.

Zimmerman 2004 ***{published data only}***
Zimmerman RK, Nowalk MP, Bardella IJ, Fine MJ, Janosky JE, Santibanez TA, et al.Physician and practice factors related to influenza vaccination among the elderly. *American Journal of Preventive Medicine* 2004;**26**(1):1–10.

Zoffmann 1977 ***{published data only}***
Zoffmann H, Von Magnus H. Swine influenza. *Ugeskrift for Laeger* 1977;**139**(5):259–61.

Zourbas 1973 ***{published data only}***
Zourbas J, Barme M, Paillard R, Reynaud R, Morvan A, Megret P. New advance in influenza vaccination. 2. Clinical and immunologic study, in Rennes, of a Pasteur 30-c strain. *Nouvelle Presse Medicale* 1973;**2**(29):1939–43.

Zuckerman 1990 ***{published data only}***
Zuckerman M, Oxford J, Wood J, Taylor J. Influenza A (H3N2) component of recommended vaccine induces antibody to current virus. *Lancet* 1990;**335**(8682):179–80.

Zuckerman 1992 ***{published data only}***
Zuckerman M, Cox R, Oxford J, Taylor J, Wood J, Haaheim L. Activity of influenza vaccine against virus strains now circulating. *Lancet* 1992;**339**(8785):118.

Zuckerman 1993 ***{published data only}***
Zuckerman M, Cox R, Taylor J, Wood J, Haaheim L, Oxford J. Rapid immune response to influenza vaccination. *Lancet* 1993;**342** (8879):1113.

Additional references

ACIP 2005
Advisory Committee on Immunization Practices. Prevention and control of influenza. Recommendations of the Advisory

Committee on Immunization Practices (ACIP). *MMWR. Morbidity and Mortality Weekly Report* 2005;**54**(RR-8):1–40.

CDC 2004
Centers for Disease Control. Updated interim influenza vaccination recommendations : 2004-2005 influenza season. http://www.cdc.gov/flu (accessed 31 December 2004) 2004.

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Dickersin 1994
Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

Eurich 2008
Eurich DT, Marrie TJ, Johnstone J, Majumdar SR. Mortality reduction with influenza vaccine in patients with pneumonia outside "flu" season: pleiotropic benefits or residual confounding? [see comment]. *American Journal of Respiratory & Critical Care Medicine* 2008;**178**(5):527–33.

Fukushima 2008
Fukushima W, Hayashi Y, Mizuno Y, Suzuki K, Kase T, Ohfuji S, et al.Selection bias in evaluating of influenza vaccine effectiveness: a lesson from an observational study of elderly nursing home residents. *Vaccine* 2008;**26**(50):6466–9.

Glezen 2006
Glezen WP, Simonsen L. Commentary: benefits of influenza vaccine in US elderly--new studies raise questions. *International Journal of Epidemiology* 2006;**35**(2):352–3. [: doi:10.1093/ije/dyi293]

Greenland 1987
Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiologic Reviews* 1987;**9**:1–30.

Groenwold 2008
Groenwold RHH, Hoes AW, Nichol KL, Hak E. Quantifying the potential role of unmeasured confounders: the example of influenza vaccination. *International Journal of Epidemiology* 2008;**37**(6):1422–9.

Groenwold 2009
Groenwold RHH, Hak E, Hoes AW. Pooling of confounders did not induce residual confounding in influenza vaccination studies. *Annals of Epidemiology* 2009;**19**(6):432–6.

Hak 2006
Hak E, Hoes AW, Nordin J, Nichol KL. Benefits of influenza vaccine in US elderly - appreciating issues of confounding bias and precision. *International Journal of Epidemiology* 2006;**35**(3):800–2.

Higgins 2002
Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539–58.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2008
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008] The Cochrane Collaboration (available from www.cochrane-handbook.org.)*. Chichester, UK: Wiley-Blackwell, 2008.

Hirota 2008
Hirota Y. Ecological fallacy and scepticism about influenza vaccine efficacy in Japan: the Maebashi study. *Vaccine* 2008;**26**(50):6473–6.

Jackson 2006a
Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *International Journal of Epidemiology* 2006;**35**(2):337–44. [: doi:10.1093/ije/dyi274]

Jackson 2006b
Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, et al.Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *International Journal of Epidemiology* 2005;**35**(2):345–52. [: doi:10.1093/ije/dyi275]

Jackson 2006c
Jackson LA, Jackson ML, Weiss NS. Bias in studies of influenza vaccine effectiveness: the authors reply to Hak et al. *International Journal of Epidemiology* 2006;**35**(3):799–800.

Jackson 2006d
Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, et al.Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors [see comment]. *International Journal of Epidemiology* 2006;**35**(2):345–52.

Jackson 2006e
Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors [see comment]. *International Journal of Epidemiology* 2006;**35**(2):337–44.

Jefferson 2009
Jefferson T, Di Pietrantonj C, Debalini MG, Rivetti A, Demicheli V. Study quality, concordance, take home message, funding and impact: their relationship in influenza vaccines studies. *BMJ (available http://www.bmj.com/cgi/content/abstract/338/feb12˙2/b354?ct=ct)* 2009;**338**:354.

Lefebvre 2008
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews*. Chichester, UK: Wiley-Blackwell, 2008.

Nichol 2008
Nichol KL. Efficacy and effectiveness of influenza vaccination. *Vaccine* 2008;**26**:D17–22.

SIGN 2009
Scottish Intercollegiate Guideline Network. Search Filters, Methodology. http://www.sign.ac.uk/methodology/filters.html (last modified 3 August 2009; accessed 2 October 2009) 2009.

Thomas 2010
Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2. [DOI: 10.1002/14651858.CD005187.pub2]

van Essen 2003

van Essen GA, Palache AM, Forleo E, Fedson DS. Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. *Vaccine* 2003;**21**(16): 1780–5.

WHO 2005

WHO global influenza programme. Number of influenza vaccine doses distributed in various regions. http: // www.who.int/cst/diseases/influenz/fluenumber2005˙02˙25.JPG (accessed 18 August 2005) 2005.

References to other published versions of this review

Jefferson 2005

Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet* 2005;**366**(9492): 1165–74.

Rivetti 2006

Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di Pietrantonj C, et al.Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD004876.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ahmed 1995

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	Two 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ahmed 1997

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 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	Two 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

Ahmed 1997 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Allsup 2004

Methods	Experimental study conducted in Liverpool, UK during the 1999 to 2000 influenza season, randomised, single-blind, placebo-controlled. Computer random number generation. Opaque envelopes were sealed and serially numbered to assign participants to intervention. 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/Sidney/5/97: B/Beijing/184/93. All patients received pneumococcal vaccine too. 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
Notes	The study year was an epidemic one; the vaccine was the recommended one

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Arden 1988

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 26/1/85 to 1/2/85. 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/URSS/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 outcome were not accounted for. The circulating strain was related to A/Philippines/2/82

Arden 1988 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Arroyo 1984

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 patients 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 patients were given amantadine: not indicated if vaccinees or unvaccinated. The circulating strain was related to A/Philippines/2/82

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Aymard 1979a

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

Aymard 1979a (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Aymard 1979b

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 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/Tex/1/77 like

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Caminiti 1994

Methods	Prospective 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 subjects 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 persons had more chronic respiratory diseases. The influenza season was relatively mild. Data were reported by health status

Risk of bias

Caminiti 1994 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cartter 1990a

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/URSS/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 occurred within 2 weeks of ILI with no different explanation
Notes	Amantadine was not used. There was serological evidence of A(H3N2) influenza infections

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cartter 1990b

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/URSS/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 occurred within 2 weeks of ILI with no different explanation
Notes	9 days after the outbreak started amantadine prophylaxis was given to most of the remaining well residents. Successive outcome were not accounted for. The circulating strain was related to A/Philippines/2/82

Risk of bias

Cartter 1990b (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cartter 1990c

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/URSS/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 occurred within 2 weeks of ILI with no different 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Christenson 2001a

Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1998 to 1999 influenza season, in the community. Data sources were: vaccination database; 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 persons 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

Christenson 2001a (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Christenson 2001b

Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1998 to 1999 influenza season in the community. Data sources were: vaccination database; 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 persons 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Christenson 2004a

Methods	Prospective cohort study conducted in Sweden, Stockholm, during the 1999 to 2000 influenza season, in the community. Data sources were: vaccination database; 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 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

Christenson 2004a (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Christenson 2004b

Methods	Prospective cohort study conducted in Stockholm, Sweden during the 1999 to 2000 influenza season, in the community. Data sources were: vaccination database; 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Coles 1992

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Comeri 1995

Methods	Retrospective cohort study conducted in Italy, during the 1991 to 1992 influenza season, in the community. Data sources were: self-administered questionnaire; vaccination registry. Follow-up period was 1 December 1991 to 29 February 1992. Random samples of vaccinated and control subjects were extracted from vaccination and population registries
Participants	213 community-dwelling elderly (150 treated and 63 controls; number of subjects 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

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Consonni 2004a

Methods	Prospective cohort study conducted in Italy, during the 2002 to 2003 influenza season, in the community. Data sources were: self-administered questionnaire; phone interviews. Follow-up period went from enrollment 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 congestion); hospitalisation for all respiratory diseases, all deaths. ARI (acute respiratory infection) was also defined
Notes	Vaccinated people had higher impairment. None information about flu activity: probably not epidemic year

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Consonni 2004b

Methods	Prospective cohort study conducted in Italy, during the 2002 to 2003 influenza season, in the community. Data sources were: self-administered questionnaire; phone interviews. Follow-up period went from enrollment 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; anti-pneumococcal 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. ARI (acute respiratory infection) was also defined
Notes	Vaccinated people had higher impairment. None information about flu activity: probably not epidemic year

Risk of bias

Item	Authors' judgement	Description

Consonni 2004b (*Continued*)

Allocation concealment?	Unclear	D - Not used

Crocetti 2001

Methods	Case-control study conducted in Italy, during the 1994 to 1995 influenza season, in the community. Data sources were: database discharge diagnoses, mailed questionnaire. Follow-up period was 1 December 1994 to 31 March 1995. Cases were resident discharged from hospital with pneumonia and influenza; community controls were matched for age, sex and residence
Participants	825 residents in 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Cuneo Crovari 1980

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/URSS/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

Item	**Authors' judgement**	**Description**

Cuneo Crovari 1980 (*Continued*)

Allocation concealment?	No	C - Inadequate

Currier 1988

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
Participants	126 nursing home residents (87 treated and 34 controls were included in the analysis, for 5 residents data on immunisation status 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 throat positive culture; pneumonia; deaths were also reported but not by immunisation status
Notes	Vaccinated and not vaccinated subjects were similar as underlying conditions, only senile dementia was more frequent in vaccinees. The circulating strain was A/Leningrad-like

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

D'Alessio 1969

Methods	Prospective outbreak investigation study conducted in 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, for 14 residents data on immunisation status 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

Item	**Authors' judgement**	**Description**

D'Alessio 1969 (*Continued*)

Allocation concealment?	No	C - Inadequate

Davis 2001a

Methods	Prospective cohort study conducted in Hawaii, during the 1994 to 1995 influenza season, in the community. Data sources were: insurance claim records. Follow-up period was 15 November 1994 to 31 March 1995. Only 10% of vaccinated subjects and 3% of unvaccinated subjects received pneumococcal vaccination
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 460-62, 465-466, 480-487, 500-518), hospitalisation from congestive heart failure (ICD 428)
Notes	OR 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Davis 2001b

Methods	Prospective cohort study conducted in Hawaii, during the 1995 to 1996 influenza season, in the community. Data sources were: insurance claim records. Follow-up period was 15 November 1995 to 31 March 1996. Only 10% of vaccinated subjects and 3% of unvaccinated subjects 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 460-62, 465-466, 480-487, 500-518), hospitalisation from congestive heart failure (ICD 428)
Notes	OR 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

Davis 2001b (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Davis 2001c

Methods	Prospective cohort study conducted in Hawaii, during the 1996 to 1997 influenza season, in the community. Data sources were: insurance claim records. Follow-up period was 15 November 1996 to 31 March 1997. Only 10% of vaccinated subjects and 3% of unvaccinated subjects 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 460-62, 465-466, 480-487, 500-518), hospitalisation from congestive heart failure (ICD 428)
Notes	OR 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Deguchi 2001

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 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

Deguchi 2001 (*Continued*)

Notes	Poor description of methods, poor definitions, some cases were laboratory confirmed, but number of cases was not indicated. Groups were comparable as age and gender. Health status was not investigated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Edmondson 1971

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 work
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Fedson 1993a

Methods	Case-controlled study conducted in Manitoba, Canada during the 1982 to 1983 influenza season, in the community. Data sources were: 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 persons, 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

Fedson 1993a (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Fedson 1993b

Methods	Case-control study conducted in Manitoba, Canada during the 1985 to 1986 influenza season, in the community. Data sources were: 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 persons, 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Feery 1976

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

Feery 1976 (*Continued*)

Notes	Poor reporting; no confounders control. The circulating strain was A/Victoria/3/75

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Fleming 1995

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 vaccine used in 1988 and 1989 were antigenically closely related, 2 exposure definitions were used: recently vaccinated and previously vaccinated
Participants	9391 residents 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. Subjects vaccinated during the previous year are considered as "non vaccinated". Quantitative analysis was also performed

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Foster 1992

Methods	Case-controlled 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 persons (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

Foster 1992 (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Fyson 1983a

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Fyson 1983b

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

Fyson 1983b (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gavira Iglesias 1987

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

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Gené Badia 1991

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 residents were enrolled; in the others only patients approaching the center 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

Gené Badia 1991 (*Continued*)

Outcomes	All hospitalisations and hospitalisation from cardio respiratory causes (ICD 401-414 and 460-519); death from all causes. Only deaths for all causes are included in analysis
Notes	The season was an epidemic one

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Goodman 1982

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). Patients 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 teste were negative for other pathogens

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Govaert 1993

Methods	Experimental study conducted in 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 reaction were self-reported on postal questionnaire completed 4 weeks after vaccination
Participants	1838 not known as belonging to high-risk group (927 treated and 911 controls; 23 and 9 dropped out respectively), 60 years or older

Govaert 1993 (*Continued*)

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	Side effects were reported for all subjects and by risk condition. Data regarding all population were included

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Govaert 1994

Methods	Experimental study conducted in Netherlands, during the 1991 to 1992 period, 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 persons not known as belonging to high-risk group (927 treated and 911 controls; 25 and 22 drop 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 definition 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gross 1988

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 to 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), Rx 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hak 2002a

Methods	Prospective cohort study conducted in 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. None information about pneumococcal vaccination. The season was an epidemic one"

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hak 2002b

Methods	Prospective cohort study conducted in 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
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. None information about pneumococcal vaccination. The season was an epidemic one; circulating strain: A/Sydney-like

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Hara 2006

Methods	Prospective cohort study conducted in Saga, Japan. 10,000 community-dwelling elderly were randomly selected from a population registry, and a letter was sent to them about the explanation for the study and request for participation. The eligibility criteria to participate to study were as follows: not being hospitalised, not being institutionalised, not being having any long-term absence, not living alone, and possible to contact by telephone at least once a month
Participants	Among 10,000 elderly citizens, 7357 responded and 4787 agreed to participate and also matched our eligibility criteria. The vaccination status of the study subjects was identified by self-reporting verification and a list of recipients of partially funded vaccination. After all 3240 subjects (3230 subjects were self-reported and 10 subjects 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 (IP), and total death
Notes	The author concludes that influenza vaccination was found to be associated with a 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 are not closely matched.

Horman 1986

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 resident were chronically ill; risk status did not vary 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 attempt for other pathogens were unsuccessful

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Howarth 1987a

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. None information about flu activity

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Howarth 1987b

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. None information about flu activity

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Howells 1975a

Methods	Prospective cohort study conducted in 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Howells 1975b

Methods	Prospective cohort study conducted in 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. None information about flu activity and laboratory confirmation

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Howells 1975c

Methods	Prospective cohort study conducted in 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. None information about flu activity and laboratory confirmation

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Isaacs 1997

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. One positive result was obtained by rapid testing. Poor reporting

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Jordan 2007

Methods	Case-control study nested within a cohort of older people registered with 79 participating general practices in central England. Patients were included in the identified cohort if aged 65 to 89 years and if they consulted their GP (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. Patients with simple upper respiratory tract infections were excluded
Participants	Description of cases Cases were defined as all patients admitted to hospital with acute respiratory disease. The first admission during the study period only was included. Surviving cases were invited for interview. Description of controls Controls were defined as patients 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 four 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) There were 3970 eligible patients identified. 500 patients 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
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 patients clinically ill with acute respiratory disease, although there was a possible effect during the peak weeks of influenza activity. Solely relying on the influenza vaccine to control the annual winter bed pressures in hospitals is unlikely to be a sufficiently effective yearly strategy and that continuing attention to other factors (e.g. the effective vaccination

	of healthcare workers, treatment of comorbidities, indoor housing conditions) is essential

Kaplan 1982

Methods	Surveillance population-based study conducted in USA, during the 1979 to 1980 and 1980 to 1981 influenza season. Case report from 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Kaway 2003

Methods	Prospective cohort study conducted in Japan, during the 2001 to 2002 period in the community. Data sources were: the general practitioner database; self-administered questionnaire. Follow-up period was 31 December 2001 to 31 May 2002. Unvaccinated subjects were matched for sex and age, as closely as possible, to the vaccinated subjects. Laboratory confirmation was performed on 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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Keitel 1996

Methods	Experimental study conducted in USA, Texas, during the 1994 to 1995 influenza season, randomised, placebo-controlled trial; randomisation method and allocation concealment were not described. Subjects 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 persons, 65 years or older
Interventions	Parenteral monovalent subvirion 15 ug (9 participants) and purified HA 15 ug (12 participants) influenza vaccine: A/Singapore/6/86
Outcomes	Discomfort, erythema/induration, headache, malaise without further description
Notes	Different vaccines (HA and SV) were analysed as a single "treatment group"

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Lasky 1998

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 season. Discharge diagnoses database were 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 dialing telephone survey

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Leung 2007

Methods	Retrospective cohort study conducted in 46 elderly homes in Hong Kong, Chinato assess the effectiveness of influenza vaccination on influenza, pneumonia, hospitalisation for influenza and death. Subjects were eligible if they aged 65 years or above. The exposed group comprised subjects who had not received influenza vaccination while the control group comprised subjects who had received influenza vaccination from the department of health or other health care providers in 2004. Information regarding vaccination was based on its documentation in the elderly home records. For resident having unknown history of influenza vaccination in the preceding calendar year he was regarded as being not 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 subjects. More females were vaccinated (67.7%) compared with 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 the protective effect of influenza vaccine against influenza and its complications during outbreaks

Lopez Hernandez 1994

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. Patients 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 for 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Mangtani 2004a

Methods	Retrospective cohort study conducted in UK, during the 1990 to 1998 influenza season, in the community. Data sources were: managed care organisation database. Follow-up period was the epidemic period (period with consultation rate for ILI more than 50/100000 person-weeks). Patients 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mangtani 2004b

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mangtani 2004c

Methods	See Mangtani. Influenza season 1991 to 1992
Participants	See Mangtani

Mangtani 2004c (*Continued*)

Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mangtani 2004d

Methods	See Mangtani. Influenza season 1992 to 1993	
Participants	See Mangtani	
Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Non-epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mangtani 2004e

Methods	See Mangtani. Influenza season 1993 to 1994	
Participants	See Mangtani	
Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**

Mangtani 2004e (*Continued*)

Allocation concealment?	Yes	A - Adequate

Mangtani 2004f

Methods	See Mangtani. Influenza season 1994 to 1995	
Participants	See Mangtani	
Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Non-epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mangtani 2004g

Methods	See Mangtani. Influenza season 1995 to 1996	
Participants	See Mangtani	
Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mangtani 2004h

Methods	See Mangtani. Influenza season 1996 to 1997	
Participants	See Mangtani	

Mangtani 2004h (*Continued*)

Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mangtani 2004i

Methods	See Mangtani. Influenza season 1997 to 1998	
Participants	See Mangtani	
Interventions	See Mangtani. Vaccine did not match the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Non-epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mangtani 2004j

Methods	See Mangtani. Influenza season 1998 to 1999	
Participants	See Mangtani	
Interventions	See Mangtani. Vaccine matched the epidemic strain	
Outcomes	See Mangtani	
Notes	See Mangtani. Epidemic year	
Risk of bias		
Item	**Authors' judgement**	**Description**

Mangtani 2004j (*Continued*)

Allocation concealment?	Yes	A - Adequate

Margolis 1990a

Methods	Experimental study conducted in Minneapolis, USA during the 1988 to 1989 influenza season, randomised, double-blind, placebo-controlled cross-over trial; randomisation method and allocation concealment were not described. 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Meiklejohn 1987

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/URSS/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/Philippine type. No virus strain was isolated from patients but serologic tests confirmed influenza A virus infections. Poor description of methods

Risk of bias

Item	**Authors' judgement**	**Description**

Meiklejohn 1987 (*Continued*)

Allocation concealment?	No	C - Inadequate

Monto 2001

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 coordinator. 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 occurred within 3 months of the onset of respiratory illness. Influenza was considered 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Morens 1995

Methods	Authors investigated an outbreak in a nursing home, in Honolulu, USA during the 1989 to 1990 influenza season; vaccination records, hospital records, residents records were reviewed. Follow-up period was 15 December 1989 to 28 January 1990. Specimens for virus isolation were obtained from 9 ill patients 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

Morens 1995 (*Continued*)

Notes	Amantadine was administered to all patients 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mukerjee 1994

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Mullooly 1994

Methods	Case-controlled study conducted in USA, during the 1981 to 1989 period, in the community. Data sources were: 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; patients received pneumococcal vaccination too. Vaccine strains matched the circulating strain
Outcomes	Pneumonia and influenza without hospitalisation, hospitalisation from pneumonia and influenza (ICD 480-487), hospitalised death

Mullooly 1994 (*Continued*)

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 OR adjusted by risk status was obtained pooling the data reported in the paper using Wolf method

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Murayama 1999

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	Two 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 the 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 virus were not isolated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nichol 1994a

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

Nichol 1994a (*Continued*)

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 are extracted by rates reported in tables. Quantitative analysis with adjusted rates is not performed because data reported and statistical model used are not homogeneous to those reported in the other studies

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nichol 1994b

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, 490-96, 500-518), hospitalisation from congestive heart failure (ICD 428), death from all causes (not reported)
Notes	The season was an epidemic one. Data are extracted by rates reported in tables. Quantitative analysis with adjusted rates is not performed because data reported and statistical model used are not homogeneous to those reported in the other studies

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nichol 1994c

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 unvaccinees 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, 490-96, 500-518), hospitalisation from congestive heart failure (ICD 428), death from all causes (not reported)
Notes	The season was an epidemic one. Data are extracted by rates reported in tables. Quantitative analysis with adjusted rates is not performed because data reported and statistical model used are not homogeneous to those reported in the other studies

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nichol 1998a

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
Interventions	Parenteral influenza vaccine. 11.3% of vaccinees and 4.5% of unvaccinees 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

Item	Authors' judgement	Description

Nichol 1998a (*Continued*)

Allocation concealment?	Yes	A - Adequate

Nichol 1998b

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 unvaccinees 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Nichol 2003a

Methods	Prospective cohort study conducted in 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
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

Item	**Authors' judgement**	**Description**

Nichol 2003a (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Nichol 2003b

Methods	Prospective cohort study conducted in 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Nicholson 1999

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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Nordin 2001a

Methods	Prospective cohort study conducted in 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nordin 2001b

Methods	Prospective cohort study conducted in 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
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ohmit 1995a

Methods	Case-controlled 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 resident 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, subjects 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 had probably 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ohmit 1995b

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 resident 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
Interventions	Parenteral influenza vaccine, subjects 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ohmit 1999

Methods	Case-controlled 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 on or more of the following: cough, sore throat, or 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 does not control by health status

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Patriarca 1985a

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
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), Rx confirmed pneumonia, hospitalisation for ILI, deaths occurred within 2 weeks of onset of ILI. An outbreak was defined by a number of ILI per week 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

Item	Authors' judgement	Description

Patriarca 1985a (*Continued*)

Allocation concealment?	Yes	A - Adequate

Patriarca 1985b

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 occurred 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Pregliasco 2002

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 infections
Notes	Low viral circulation. Cohorts were not significantly different as co-morbidity

Risk of bias

Pregliasco 2002 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Puig-Barbera 2007

Methods	Three case-control studies were performed in the elderly (> 64 years of age) population from 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 patients who had received influenza vaccine and for those who had not been vaccinated against influenza
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 according to 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
Interventions	Influenza vaccination and hospitalisation for ACS, CVA and pneumonia
Outcomes	-
Notes	The authors conclude that the results suggest that MF59TM-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

Puig-Barberà 1997

Methods	Case-controlled 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 residents 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 persons (94 cases and 166 controls, were identified; 83 and 166 were included in analysis respectively), 65 years or older

Puig-Barberà 1997 (*Continued*)

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 had probably low epidemic levels. Quantitative analysis was also performed

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Puig-Barberà 2004

Methods	Case-control study conducted in Spain, Valencia, 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 residents 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 persons: (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 (ICDIX 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ruben 1974

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

Ruben 1974 (*Continued*)

Participants	392 nursing home residents (204 treated and 192 controls, all included in the analysis). Patients were both ambulatory and bed ridden
Interventions	Parenteral influenza vaccine: A/Aichi/2/62; B/Mass/1/71. Vaccine strains did not matched 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rudenko 2001

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 subjects were excluded, 41 to 95, 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 ILI: positive swab or 4-fold increase in antibody titre
Notes	No description of methods; 1 or 2 doses' efficacy was tested; data are extracted irrespective of the number of doses administered

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Saah 1986a

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 patients 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 subjects 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Saah 1986b

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 record were reviewed. Comparability between cohorts was assessed by analysis of the underlying conditions of a sample of the population; 62 patients 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 subjects 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

Saah 1986b (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Saah 1986c

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 patients 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 subjects had very slight excess of underlying conditions; smokers were rare; pneumococcal vaccine was rarely used. The circulating strain was not identified

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Saito 2002a

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/Sidney/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 only in 4 homes. No other respiratory viruses were isolated. Data were extracted by RRs reported in tables

Saito 2002a (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Saito 2002b

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/Sidney/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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Schonberger 1979

Methods	Surveillance population-based study conducted in USA, during the 1976 to 1977 influenza season. Neurologists were directly contacted; physician and hospital records were reviewed. Suspected cases reported to CDC 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

Schonberger 1979 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Shapiro 2003

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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Strassburg 1986

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 persons
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; for 3 residents vaccination status could not be determined)
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 persons. The circulating strain was A/Bangkok/79-like. No other positive laboratory findings were found. Amantadine was not used

Strassburg 1986 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Stuart 1969

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 persons to confirm the infection active surveillance. Follow-up period was 1 February 1966 to 30 April 1966
Participants	4180 residents in the house, 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 Side effects were reported but they were excluded from analysis as they refer to an old oil adjuvant vaccine
Notes	Subjects 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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Taylor 1992

Methods	Authors investigated an outbreak in a nursing home, in Washington, USA during the 1988 to 1989 influenza season; patients 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 or level of care required
Interventions	Parenteral influenza vaccine: A/Taiwan; A/Sichuan; B/Victoria. Vaccine strains probably matched circulating strains

Taylor 1992 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Treanor 1994

Methods	Experimental study conducted in New York, USA during the 1990 to 1991 influenza season, randomised, double-blind, placebo-controlled study; randomisation method and allocation concealment were not described. 34 patients received live vaccine; 30 patients received trivalent vaccine; 11 patients received placebo. Follow-up period was for 7 days after vaccination. Self-administered diary card was filled by participants
Participants	75 outpatients with chronic disease or elderly, mostly 65 years or older
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	Subjects experiencing symptoms within 1 week of vaccination were considered

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Voordouw 2003

Methods	Retrospective cohort study conducted in 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 subject was randomly selected
Participants	17,822 community-dwelling elderly with a permanent status in one of the practices (8911 treated and 8911 controls, all included in the analysis), 65 years or older

Voordouw 2003 (*Continued*)

Interventions	Parenteral influenza vaccine. Vaccine strain matched the circulating strain
Outcomes	Influenza as defined by International Classification for 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

ACS = acute coronary syndromes
CAP = community-acquired pneumonia
CVA = cerebro-vascular accident
HCWs = health care workers
ICD = ischaemic cardiac disease
ILI = influenza-like illness
NI = neurominadase inhibitor
OR = odds ratio
Rx = X-ray
URI = upper respiratory infection
RR = risk ratio

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

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

(*Continued*)

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. 60 ILI cases only 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 adult's review
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 1994
D'Alessandro 2004	Both arms have influenza vaccines, no placebo/do nothing comparator
de Bernardi 2002	Healthy adults; lack of a control group
de Bruijn 2004	Serological outcome only
De Serres 2004	Same data set as Skowronski - high-risk group
Deguchi 2000	Same cohorts of Deguchi 2001

(*Continued*)

Deguchi 2000a	Same cohorts of Deguchi 2001
Deguchi 2000b	Same cohorts of Deguchi 2001
Deibel 1970	The study does not investigate the vaccine efficacy
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 Garcia 2009	Only 16% of participants are over the age of 60
Garcia-Doval 2001	Case report
Gasparini 2002	Economic study; data source not described
Gavira 1990	Economic evaluation
Gendon 1988	No original data presented
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 1994 2	Antibody outcomes only
Gowda 1979	The study does not investigate the vaccine efficacy

(*Continued*)

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
Howell 1967	Not elderly
Hurwitz 1983	Non-comparative data

(*Continued*)

Icardi 2002	Unclear study design: probably cross-sectional
Ikematsu 1998	Poorly described study. ILI was defined only as "fever". Deaths from all causes were referred to a too long period (from January to September)
Ikematsu 2000	Poorly described study. ILI was defined only as "fever". Asymptomatic infections were undistinguishable 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	One-year follow up in a population with important diseases
Landi 2006	Same dataset 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

(*Continued*)

Mair 1974	Lack of a control group
Mandal 1973	Descriptive
Manzano 2000	Case report
Manzoli 2007	Feasibility study of GP 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

(*Continued*)

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
Nichol 1999c	High-risk groups
Nichol 1999d	Adult population
Nichol 2002	Same cohorts of Nichol 1998
Nichol 2007	Data already 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 subjects only
Nicholson 1990b	No data presented
Nicholson 1992	Unclear study design: symptomatic subjects 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 of Ohmit 1995 included
Ortqvist 2007	Data already included in the 2005 review. Re-analysis of the same dataset
Oshitani 2000	Ecological study
Parkin 1978	Case series
Parsons 1997	No data

(*Continued*)

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 by age are not presented
Phillips 1970	Lack of a control group
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

(*Continued*)

Quinnan 1983	Does not report safety outcomes by age groups
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 one subject 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
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

(*Continued*)

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 CAP. 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
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

(*Continued*)

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
Wilson 1994	Comment
Winer 1984	Survey of cases

(*Continued*)

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

GP = general practice

DATA AND ANALYSES

Comparison 1. Influenza vaccines versus no vaccination - Cohort studies in nursing homes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ILI	26	12388	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.66, 0.88]
1.1 Outbreak - vaccine matching (circulating strains)	16	5963	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.94]
1.2 Outbreak - vaccine matching absent or unknown	6	4096	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.60, 1.05]
1.3 No outbreak - vaccine matching	4	2329	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
1.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Influenza	8	1941	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.32, 1.29]
2.1 Outbreak - vaccine matching	4	658	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.43, 2.51]
2.2 Outbreak - vaccine matching absent or unknown	2	592	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 1.04]
2.3 No outbreak - vaccine matching	2	691	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.03]
2.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Pneumonia	17	10274	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.43, 0.66]
3.1 Outbreak - vaccine matching	8	4482	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.42, 0.70]
3.2 Outbreak - vaccine matching absent or unknown	5	3991	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.21]
3.3 No outbreak - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 No outbreak - matching absent or unknown	4	1801	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.18, 0.68]
4 Hospitalisation for ILI or pneumonia	12	28032	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.32, 0.81]
4.1 Outbreak - vaccine matching	8	2027	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.36, 0.84]
4.2 Outbreak - vaccine matching absent or unknown	2	3301	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.43, 1.58]
4.3 No outbreak - vaccine matching	2	22704	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.14, 0.76]
4.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Deaths from flu or pneumonia	27	32179	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.63]
5.1 Outbreak - vaccine matching	16	6127	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.41, 0.83]
5.2 Outbreak - vaccine matching absent or unknown	4	1089	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.11, 1.02]

5.3 No outbreak - vaccine matching	3	23162	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.09, 0.87]
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 All deaths	1	305	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.77]
6.1 Outbreak - vaccine matching	1	305	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.77]
6.2 Outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 No outbreak - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.4 No outbreak - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Influenza cases (clinically defined without clear definition)	7	24238	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 1.02]
7.1 Outbreak - vaccine matching	2	271	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.11, 4.56]
7.2 Outbreak - vaccine matching absent or unknown	1	155	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.09, 0.59]
7.3 No outbreak - vaccine matching	1	22462	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.35, 0.46]
7.4 No outbreak - vaccine matching absent or unknown	3	1350	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.41, 1.28]

Comparison 2. Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ILI	4	9613	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.42, 1.33]
1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Non epidemic year - vaccine matching	2	4636	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.58, 2.03]
1.4 Non epidemic year - vaccine matching absent or unknown	1	268	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.16, 4.55]
1.5 Epidemic year - vaccine not matching	1	4709	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.24, 0.81]
2 Influenza	2	18249	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 2.01]
2.1 Epidemic year - vaccine matching	1	427	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.37]
2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Non epidemic year - vaccine matching	1	17822	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.27, 0.91]

2.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Pneumonia	2	18090	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]
3.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Non epidemic year - vaccine matching	1	17822	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.19]
3.4 Non epidemic year - vaccine matching absent or unknown	1	268	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.16, 57.42]
4 Hospitalisation for flu or pneumonia	9	784643	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.85]
4.1 Epidemic year - vaccine matching	6	727776	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 Non epidemic year - vaccine matching	1	25532	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.83]
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]
4.5 Epidemic year - vaccine not matching	1	4709	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.40]
5 Hospitalisation for any respiratory disease	5	567299	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.54, 1.43]
5.1 Epidemic year - vaccine matching	3	515141	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.64]
5.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.3 Non epidemic year - vaccine matching	1	25532	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.12]
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]
6 Deaths from flu or pneumonia	1	163391	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.09]
6.1 Epidemic year - vaccine matching	1	163391	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.09]
6.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Deaths from respiratory disease	1	426668	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.25, 1.39]
7.1 Epidemic year - vaccine matching	1	426668	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.25, 1.39]
8 All deaths	8	409468	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.47, 0.80]

8.1 Epidemic year - vaccine matching	4	300332	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.50, 0.70]
8.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.3 Non epidemic year - vaccine matching	3	104427	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.30, 1.39]
8.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.5 Epidemic year - vaccine not matching	1	4709	Risk Ratio (M-H, Random, 95% CI)	3.89 [0.90, 16.89]
9 Hospitalisation for heart disease	6	433934	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.12]
9.1 Epidemic year - vaccine matching	4	381776	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.56, 0.97]
9.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
9.3 Non epidemic year - vaccine matching	1	25532	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.81, 1.38]
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]
10 Combined outcome: all deaths or severe respiratory illness	3	290819	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.85]
10.1 Epidemic year - vaccine matching	2	132365	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.55]
10.2 Epidemic year - vaccine matching absent or unknown	1	158454	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.69, 0.80]

Comparison 3. Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	1	6423	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.17]
1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Non epidemic year - vaccine matching	1	6423	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.17]
1.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Pneumonia	1	6423	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

2.3 Non epidemic year - vaccine matching	1	6423	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
2.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Hospitalisation for influenza or pneumonia	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.86]
3.1 Epidemic year - vaccine matching	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.86]
3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Hospitalisation for any respiratory disease	2	189004	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.80, 0.92]
4.1 Epidemic year - vaccine matching	2	189004	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.80, 0.92]
4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Deaths from respiratory disease	1	142464	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
5.1 Epidemic year - vaccine matching	1	142464	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.86, 0.98]
6 All deaths	3	68032	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.16, 0.97]
6.1 Epidemic year - vaccine matching	1	2344	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.92]
6.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Non epidemic year - vaccine matching	2	65688	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.17, 1.28]
6.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Hospitalisation for heart disease	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.03]
7.1 Epidemic year - vaccine matching	1	45932	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.03]
7.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

8 Combined outcome: all deaths or severe respiratory illness	2	146248	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.74]
8.1 Epidemic year - vaccine matching	1	54438	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.49, 0.60]
8.2 Epidemic year - vaccine matching absent or unknown	1	91810	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.61, 0.72]

Comparison 4. Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.17]
1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Non epidemic year - vaccine matching	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.17]
1.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Pneumonia	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.92]
2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Non epidemic year - vaccine matching	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.92]
2.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Hospitalisation for influenza or pneumonia	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.40, 0.63]
3.1 Epidemic year - vaccine matching	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.40, 0.63]
3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Hospitalisation for any respiratory disease	2	376324	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.55, 1.27]
4.1 Epidemic year - vaccine matching	2	376324	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.55, 1.27]

4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Deaths from respiratory disease	1	281424	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.31, 1.53]
5.1 Epidemic year - vaccine matching	1	281424	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.31, 1.53]
6 All deaths	3	43821	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.33, 1.29]
6.1 Epidemic year - vaccine matching	1	7047	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.26, 4.49]
6.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Non epidemic year - vaccine matching	2	36774	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.30]
6.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Hospitalisation for heart disease	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.01]
7.1 Epidemic year - vaccine matching	1	101619	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.01]
7.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.4 Non epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Combined outcome: all deaths or severe respiratory illness	2	135180	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.54, 0.70]
8.1 Epidemic year - vaccine matching	1	68536	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.54, 0.78]
8.2 Epidemic year - vaccine matching absent or unknown	1	66644	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.48, 0.71]

Comparison 5. 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
1 ILI	1	374	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.64]
1.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

1.3 Non epidemic year - vaccine matching	1	374	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.64]
2 Hospitalisation for influenza or pneumonia or respiratory disease	3	518748	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.64, 0.70]
2.1 Epidemic year - vaccine matching	2	518374	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.63, 0.71]
2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Non epidemic year - vaccine matching	1	374	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.10, 7.97]
3 Deaths from influenza or pneumonia	1	259627	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.57]
3.1 Epidemic year - vaccine matching	1	259627	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.57]
3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Non epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 All deaths	2	260001	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.41, 0.46]
4.1 Epidemic year - vaccine matching	1	259627	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.41, 0.46]
4.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 Non epidemic year - vaccine matching	1	374	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.08, 30.65]

Comparison 6. 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
1 ILI	2	498	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.56]
1.1 Epidemic year - vaccine matching	1	263	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.54]
1.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Non epidemic year - vaccine matching	1	235	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.18, 0.82]
2 Hospitalisation for influenza or pneumonia or respiratory disease	2	498	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.28]
2.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Non epidemic year - vaccine matching	2	498	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.28]

3 All deaths	1	235	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.10, 43.10]
3.1 Epidemic year - vaccine matching	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Epidemic year - vaccine matching absent or unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Non epidemic year - vaccine matching	1	235	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.10, 43.10]

Comparison 7. 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
1 Hospitalisation for influenza or pneumonia	8		Odds Ratio (Random, 95% CI)	0.73 [0.67, 0.79]
1.1 Epidemic - vaccine matching	6		Odds Ratio (Random, 95% CI)	0.71 [0.65, 0.77]
1.2 Non epidemic - vaccine not matching	1		Odds Ratio (Random, 95% CI)	0.90 [0.58, 1.38]
1.3 Epidemic year - vaccine matching absent or unknown	1		Odds Ratio (Random, 95% CI)	0.82 [0.68, 0.98]
2 Hospitalisation for any respiratory disease	13		Odds Ratio (Random, 95% CI)	0.78 [0.72, 0.85]
2.1 Epidemic matching vaccine	9		Odds Ratio (Random, 95% CI)	0.71 [0.67, 0.74]
2.2 Non epidemic non matching	2		Odds Ratio (Random, 95% CI)	0.91 [0.76, 1.08]
2.3 Non epidemic year and matching vaccine	2		Odds Ratio (Random, 95% CI)	0.94 [0.84, 1.06]
3 Hospitalisation for heart disease	6		Odds Ratio (Random, 95% CI)	0.76 [0.70, 0.82]
3.1 Epidemic year - vaccine matching	5		Odds Ratio (Random, 95% CI)	0.75 [0.70, 0.82]
3.2 Non epidemic - vaccine not matching	1		Odds Ratio (Random, 95% CI)	0.80 [0.55, 1.16]
4 All deaths	7		Odds Ratio (Random, 95% CI)	0.53 [0.46, 0.61]
4.1 Epidemic year - vaccine matching	5		Odds Ratio (Random, 95% CI)	0.47 [0.42, 0.53]
4.2 Epidemic year - vaccine matching absent or unknown	1		Odds Ratio (Random, 95% CI)	0.65 [0.57, 0.75]
4.3 Non epidemic year - vaccine matching	1		Odds Ratio (Random, 95% CI)	0.76 [0.60, 0.97]
5 Combined outcome: all deaths or severe respiratory illness	1		Odds Ratio (Random, 95% CI)	0.70 [0.37, 1.34]
5.1 Epidemic year - vaccine matching	1		Odds Ratio (Random, 95% CI)	0.70 [0.37, 1.34]

Comparison 8. Influenza vaccines versus no vaccination - Case-control studies in community

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospitalisations for influenza or pneumonia	2	1074	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
1.1 Outbreak - vaccine matching (circulating strains)	0	0	Odds Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Outbreak - vaccine matching absent or unknown	1	825	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.22]
1.3 No outbreak - vaccine matching	1	249	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.48, 1.40]
2 Hospitalisations for any respiratory disease	4	21378	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.95, 1.23]
2.1 Outbreak - vaccine matching	3	20582	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.26]
2.2 No outbreak - not matching	1	796	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.68, 1.52]
3 Deaths from influenza or pneumonia	1	1092	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.04]
3.1 Outbreak - vaccine matching	1	1092	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.04]
4 Pneumonia (no better defined)	1	519	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.33]
4.1 Outbreak - partially matching	1	519	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.33]

Comparison 9. 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
1 Hospitalisations for influenza or pneumonia	4	6629	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.09]
1.1 Outbreak - vaccine matching	2	3617	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.31]
1.2 No outbreak - vaccine matching	2	3012	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.08]

Comparison 10. 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
1 ILI	1	1198	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.68]
1.1 Outbreak - vaccine matching	1	1198	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.40, 0.68]

Comparison 11. 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
1 Hospitalisations for influenza or pneumonia	5		Odds Ratio (Random, 95% CI)	0.59 [0.47, 0.74]
1.1 Epidemic - vaccine matching	1		Odds Ratio (Random, 95% CI)	0.55 [0.36, 0.85]
1.2 Non epidemic - vaccine not matching	0		Odds Ratio (Random, 95% CI)	Not estimable
1.3 Epidemic year - vaccine matching absent or unknown	2		Odds Ratio (Random, 95% CI)	0.68 [0.58, 0.79]
1.4 Non epidemic - vaccine matching	2		Odds Ratio (Random, 95% CI)	0.37 [0.16, 0.87]
2 Hospitalisations for any respiratory disease	3		Odds Ratio (Random, 95% CI)	0.71 [0.56, 0.90]
2.1 Epidemic - vaccine matching	3		Odds Ratio (Random, 95% CI)	0.71 [0.56, 0.90]
2.2 Non epidemic - vaccine matching	0		Odds Ratio (Random, 95% CI)	Not estimable
2.3 Non epidemic year - vaccine matching	0		Odds Ratio (Random, 95% CI)	Not estimable
3 Deaths from pneumonia or influenza	2		Odds Ratio (Random, 95% CI)	0.74 [0.60, 0.92]
3.1 Epidemic year - vaccine matching	1		Odds Ratio (Random, 95% CI)	0.76 [0.60, 0.97]
3.2 Epidemic year - vaccine matching absent or unknown	1		Odds Ratio (Random, 95% CI)	0.67 [0.42, 1.07]

Comparison 12. 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
1 Hospitalisations for influenza or pneumonia	2		Odds Ratio (Random, 95% CI)	0.68 [0.54, 0.86]
1.1 Epidemic - vaccine matching	1		Odds Ratio (Random, 95% CI)	0.68 [0.50, 0.93]
1.2 Non epidemic - vaccine not matching	0		Odds Ratio (Random, 95% CI)	Not estimable
1.3 Epidemic year - vaccine matching absent or unknown	0		Odds Ratio (Random, 95% CI)	Not estimable
1.4 Non epidemic - vaccine matching	1		Odds Ratio (Random, 95% CI)	0.69 [0.49, 0.97]

Comparison 13. Influenza vaccines versus placebo - RCT - parenteral vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ILI	4	6894	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.47, 0.73]
1.1 Outbreak - vaccine matching (circulating strains) - community - healthy	2	2047	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.79]
1.2 Outbreak - vaccine matching - community - risk groups	1	490	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.49, 1.53]
1.3 Outbreak - vaccine matching - nursing home - healthy	1	4180	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.37, 0.80]
1.4 Outbreak - vaccine matching - psychiatric hospital	1	177	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.92]
2 Influenza	3	2217	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.27, 0.66]
2.1 Outbreak - vaccine matching - community - healthy and ill	1	1838	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.74]
2.2 outbreak - vaccine matching - psychiatric hospital	1	177	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.12, 1.06]
2.3 No outbreak - vaccine matching - nursing home - healthy and ill	1	202	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.25]
3 Pneumonia	1	699	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.1 Outbreak - vaccine matching - community - healthy	1	699	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 All deaths	1	699	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.11, 9.72]

4.1 Outbreak - vaccine matching - community - healthy	1	699	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.11, 9.72]

Comparison 14. Vaccine versus placebo - inactivated aerosol vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ILI	1	176	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.71]
1.1 Outbreak - vaccine matching - psychiatric hospital	1	176	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.71]
2 Influenza	1	176	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.40, 1.99]
2.1 outbreak - vaccine matching - psychiatric hospital	1	176	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.40, 1.99]

Comparison 15. Vaccine versus placebo - live aerosol vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	1	220	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.17]
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]

Comparison 16. Sensitivity analysis Comparison 01: subgroup analysis by study quality

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

Comparison 17. Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

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

Comparison 18. Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events

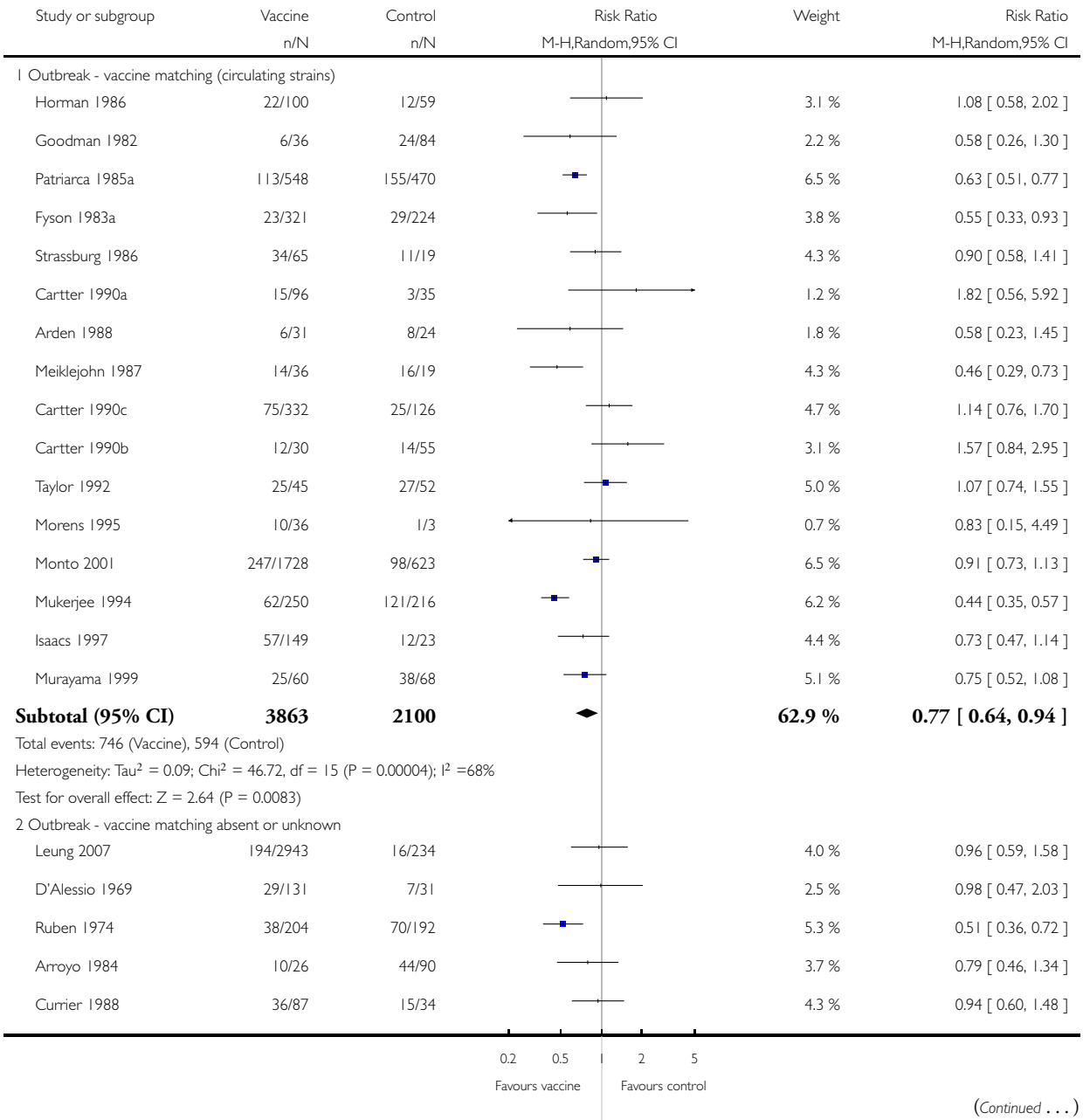
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 General malaise	1	45	Risk Ratio (M-H, Random, 95% CI)	3.09 [0.18, 53.20]
2 Fever	1	45	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.09, 33.24]
3 Upper respiratory tract symptoms	1	45	Risk Ratio (M-H, Random, 95%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

Analysis 1.1. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

Outcome: 1 ILI

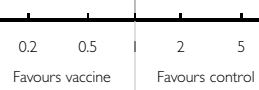


Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching (circulating strains)					
Horman 1986	22/100	12/59		3.1 %	1.08 [0.58, 2.02]
Goodman 1982	6/36	24/84		2.2 %	0.58 [0.26, 1.30]
Patriarca 1985a	113/548	155/470		6.5 %	0.63 [0.51, 0.77]
Fyson 1983a	23/321	29/224		3.8 %	0.55 [0.33, 0.93]
Strassburg 1986	34/65	11/19		4.3 %	0.90 [0.58, 1.41]
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]
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]
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]
Monto 2001	247/1728	98/623		6.5 %	0.91 [0.73, 1.13]
Mukerjee 1994	62/250	121/216		6.2 %	0.44 [0.35, 0.57]
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 (Vaccine), 594 (Control)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 46.72$, df = 15 (P = 0.00004); $I^2 = 68\%$					
Test for overall effect: Z = 2.64 (P = 0.0083)					
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]

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 155 (Control)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.18$, df = 5 (P = 0.15); $I^2 = 39\%$					
Test for overall effect: Z = 1.62 (P = 0.11)					
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 (Vaccine), 158 (Control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.91$, df = 3 (P = 0.07); $I^2 = 57\%$					
Test for overall effect: Z = 2.09 (P = 0.037)					
4 No outbreak - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 907 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 62.97$, df = 25 (P = 0.00004); $I^2 = 60\%$					
Test for overall effect: Z = 3.79 (P = 0.00015)					



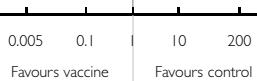
Analysis 1.2. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

Outcome: 2 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 27 (Control)					
Heterogeneity: Tau^2 = 0.40; Chi^2 = 7.39, df = 3 (P = 0.06); I^2 =59%					
Test for overall effect: Z = 0.09 (P = 0.92)					
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 (Vaccine), 20 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 1.87 (P = 0.061)					
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 (Vaccine), 5 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 1.92 (P = 0.055)					
4 No outbreak - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 52 (Control)					
Heterogeneity: Tau^2 = 0.45; Chi^2 = 16.15, df = 7 (P = 0.02); I^2 =57%					
Test for overall effect: Z = 1.23 (P = 0.22)					



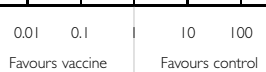
Analysis 1.3. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 3 Pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

Outcome: 3 Pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching					
Horman 1986	6/100	5/59		3.5 %	0.71 [0.23, 2.22]
Saah 1986b	12/244	11/214		7.2 %	0.96 [0.43, 2.12]
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 (Vaccine), 122 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.04$, df = 7 (P = 0.54); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.80 (P < 0.00001)					
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 (Vaccine), 36 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.76$, df = 4 (P = 0.78); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.30 (P = 0.19)					
3 No outbreak - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 No outbreak - matching absent or unknown					
Howells 1975a	2/134	18/356		2.2 %	0.30 [0.07, 1.26]



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 %	0.57 [0.26, 1.25]
Subtotal (95% CI)	**665**	**1136**		**13.3 %**	**0.35 [0.18, 0.68]**
Total events: 14 (Vaccine), 73 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 3.44$, df = 3 (P = 0.33); $I^2 = 13\%$					
Test for overall effect: Z = 3.10 (P = 0.0020)					
Total (95% CI)	**6970**	**3304**		**100.0 %**	**0.53 [0.43, 0.66]**
Total events: 178 (Vaccine), 231 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 13.29$, df = 16 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.79 (P < 0.00001)					

Analysis 1.4. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 4 Hospitalisation for ILI or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

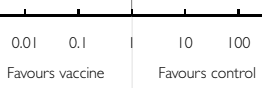
Outcome: 4 Hospitalisation for ILI or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Patriarca 1985a	19/548	31/470		0.53 [0.30, 0.92]
Cartter 1990b	0/30	0/55		0.0 [0.0, 0.0]
Arden 1988	0/31	5/24		0.07 [0.00, 1.22]
Cartter 1990c	6/332	5/126		0.46 [0.14, 1.47]
Meiklejohn 1987	5/36	5/19		0.53 [0.17, 1.60]
Cartter 1990a	0/96	0/35		0.0 [0.0, 0.0]
Taylor 1992	2/45	1/52		2.31 [0.22, 24.65]
Murayama 1999	4/60	5/68		0.91 [0.26, 3.22]
Subtotal (95% CI)	**1178**	**849**		**0.55 [0.36, 0.84]**

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total events: 36 (Vaccine), 52 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.16, df = 5 (P = 0.53); I^2 =0.0%				
Test for overall effect: Z = 2.80 (P = 0.0052)				
2 Outbreak - vaccine matching absent or unknown				
Leung 2007	91/2943	9/234		0.80 [0.41, 1.57]
Coles 1992	5/112	0/12		1.27 [0.07, 21.61]
Subtotal (95% CI)	**3055**	**246**		**0.82 [0.43, 1.58]**
Total events: 96 (Vaccine), 9 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				
3 No outbreak - vaccine matching				
Caminiti 1994	8/169	6/73		0.58 [0.21, 1.60]
Deguchi 2001	32/10739	150/11723		0.23 [0.16, 0.34]
Subtotal (95% CI)	**10908**	**11796**		**0.32 [0.14, 0.76]**
Total events: 40 (Vaccine), 156 (Control)				
Heterogeneity: Tau^2 = 0.26; Chi^2 = 2.68, df = 1 (P = 0.10); I^2 =63%				
Test for overall effect: Z = 2.59 (P = 0.0095)				
4 No outbreak - vaccine matching absent or unknown				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**15141**	**12891**		**0.51 [0.32, 0.81]**
Total events: 172 (Vaccine), 217 (Control)				
Heterogeneity: Tau^2 = 0.24; Chi^2 = 19.87, df = 9 (P = 0.02); I^2 =55%				
Test for overall effect: Z = 2.85 (P = 0.0043)				



Analysis 1.5. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 5 Deaths from flu or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

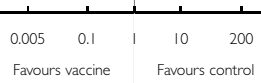
Outcome: 5 Deaths from flu or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 1983a	4/321	5/224		5.2 %	0.56 [0.15, 2.06]
Patriarca 1985a	6/548	21/470		9.4 %	0.25 [0.10, 0.60]
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]
Fyson 1983b	3/53	0/118		1.1 %	15.43 [0.81, 293.46]
Meiklejohn 1987	1/36	3/19		2.0 %	0.18 [0.02, 1.58]
Cartter 1990c	3/332	2/126		3.0 %	0.57 [0.10, 3.37]
Cartter 1990a	2/96	0/46		1.1 %	2.42 [0.12, 49.46]
Cartter 1990b	0/30	1/55		1.0 %	0.60 [0.03, 14.34]
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 (Vaccine), 86 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 15.62, df = 15 (P = 0.41); I^2 =4%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
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]**

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 9 (Vaccine), 31 (Control)					
Heterogeneity: Tau² = 0.48; Chi² = 4.92, df = 3 (P = 0.18); I² =39%					
Test for overall effect: Z = 1.92 (P = 0.055)					
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 (Vaccine), 10 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 1.20, df = 2 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 2.20 (P = 0.028)					
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 (Vaccine), 53 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 2.44, df = 3 (P = 0.49); I² =0.0%					
Test for overall effect: Z = 2.93 (P = 0.0034)					
Total (95% CI)	**16357**	**15822**		**100.0 %**	**0.46 [0.33, 0.63]**
Total events: 121 (Vaccine), 180 (Control)					
Heterogeneity: Tau² = 0.07; Chi² = 29.31, df = 26 (P = 0.30); I² =11%					
Test for overall effect: Z = 4.79 (P < 0.00001)					



Analysis 1.6. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 6 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

Outcome: 6 All deaths

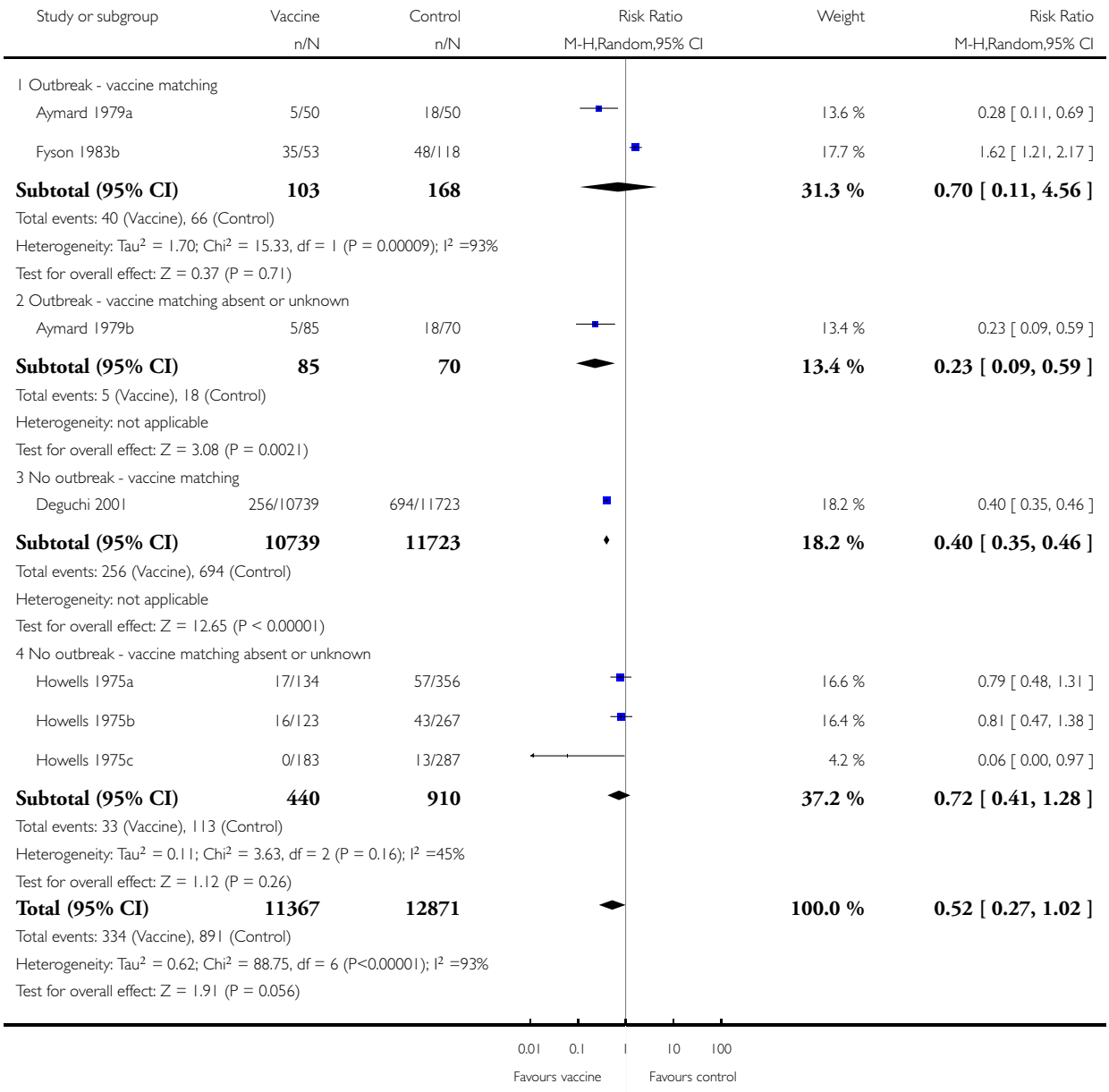
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching					
Gross 1988	13/181	22/124		100.0 %	0.40 [0.21, 0.77]
Subtotal (95% CI)	**181**	**124**		**100.0 %**	**0.40 [0.21, 0.77]**
Total events: 13 (Vaccine), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.74 (P = 0.0061)					
2 Outbreak - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 No outbreak - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 No outbreak - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.74 (P = 0.0061)					

Analysis 1.7. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 7 Influenza cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in the elderly

Comparison: 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes

Outcome: 7 Influenza cases (clinically defined without clear definition)

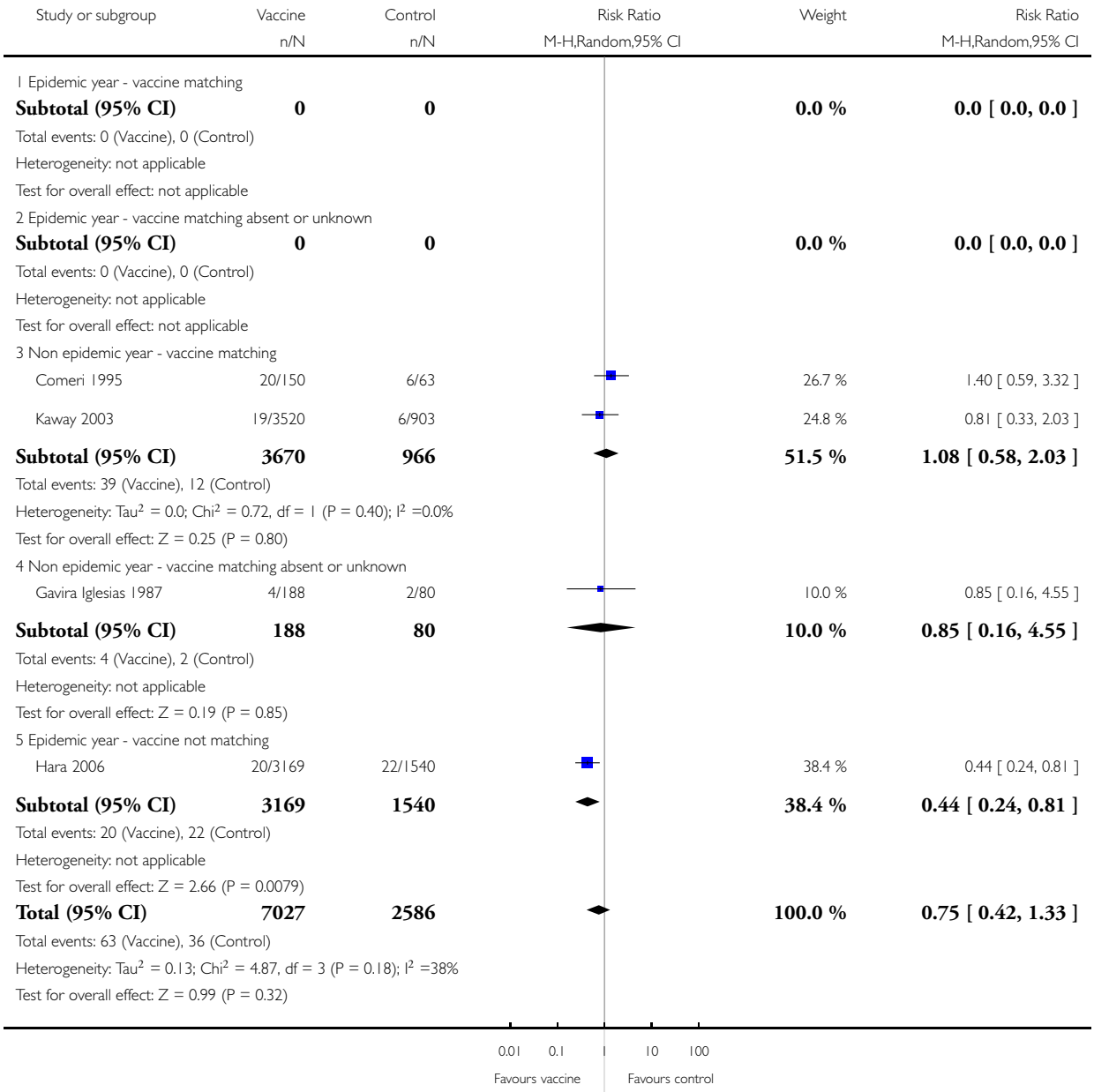


Analysis 2.1. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 1 ILI



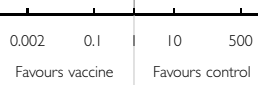
Analysis 2.2. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 2 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0035)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 32 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 51 (Control)					
Heterogeneity: Tau^2 = 2.40; Chi^2 = 5.22, df = 1 (P = 0.02); I^2 =81%					
Test for overall effect: Z = 1.38 (P = 0.17)					



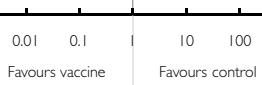
Analysis 2.3. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 3 Pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 3 Pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 83 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.38)					
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 (Vaccine), 0 (Control)					
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 (Vaccine), 83 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.67, df = 1 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					



Analysis 2.4. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 4 Hospitalisation for flu or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 4 Hospitalisation for flu or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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]
Christenson 2004a	672/29346	3305/134045		14.8 %	0.93 [0.86, 1.01]
Nichol 2003b	589/87357	501/58971		14.1 %	0.79 [0.70, 0.89]
Subtotal (95% CI)	**279433**	**448343**		**80.8 %**	**0.74 [0.62, 0.88]**
Total events: 2481 (Vaccine), 7598 (Control)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 58.24$, df = 5 (P<0.00001); $I^2 = 91\%$					
Test for overall effect: Z = 3.33 (P = 0.00087)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 75 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.86 (P = 0.0043)					
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 (Vaccine), 87 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.00 (P = 0.046)					
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]**

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 11 (Vaccine), 6 (Control)					
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 (Vaccine), 7766 (Control)					
Heterogeneity: Tau² = 0.04; Chi² = 61.76, df = 8 (P<0.00001); I² =87%					
Test for overall effect: Z = 4.03 (P = 0.000055)					

Analysis 2.5. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 5 Hospitalisation for any respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 5 Hospitalisation for any respiratory disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 4558 (Control)					
Heterogeneity: Tau² = 0.42; Chi² = 419.59, df = 2 (P<0.00001); I² =100%					
Test for overall effect: Z = 0.65 (P = 0.51)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 288 (Control)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
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 (Vaccine), 317 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.039)					
Total (95% CI)	**233604**	**333695**		**100.0 %**	**0.88 [0.54, 1.43]**
Total events: 3997 (Vaccine), 5163 (Control)					
Heterogeneity: Tau^2 = 0.30; Chi^2 = 432.59, df = 4 (P<0.00001); I^2 =99%					
Test for overall effect: Z = 0.52 (P = 0.60)					

Analysis 2.6. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 6 Deaths from flu or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

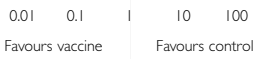
Outcome: 6 Deaths from flu or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 472 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.20 (P = 0.23)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 472 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.20 (P = 0.23)					



Analysis 2.7. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 7 Deaths from respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 7 Deaths from respiratory disease

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

Analysis 2.8. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 8 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 8 All deaths

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Gen 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 (Vaccine), 2534 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.54$, df = 3 (P = 0.01); $I^2 = 74\%$					
Test for overall effect: Z = 6.07 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 1252 (Control)					
Heterogeneity: $Tau^2 = 0.44$; $Chi^2 = 61.64$, df = 2 (P<0.00001); $I^2 = 97\%$					
Test for overall effect: Z = 1.11 (P = 0.27)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 2 (Control)					
Heterogeneity: not applicable					

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.81 (P = 0.070)					
Total (95% CI)	**217147**	**192321**	◆	**100.0 %**	**0.61 [0.47, 0.80]**
Total events: 2432 (Vaccine), 3788 (Control)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 101.29, df = 7 (P<0.00001); I^2 =93%					
Test for overall effect: Z = 3.59 (P = 0.00033)					

Analysis 2.9. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 9 Hospitalisation for heart disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 9 Hospitalisation for heart disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 2448 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 62.97, df = 3 (P<0.00001); I^2 =95%					
Test for overall effect: Z = 2.16 (P = 0.031)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 118 (Control)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.68)					
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 (Vaccine), 37 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.021)					
Total (95% CI)	**252993**	**180941**		**100.0 %**	**0.87 [0.67, 1.12]**
Total events: 2726 (Vaccine), 2603 (Control)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 87.72, df = 5 (P<0.00001); I^2 =94%					
Test for overall effect: Z = 1.08 (P = 0.28)					

Analysis 2.10. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 10 Combined outcome: all deaths or severe respiratory illness.

Review: Vaccines for preventing influenza in the elderly

Comparison: 2 Influenza vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 10 Combined outcome: all deaths or severe respiratory illness

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Fleming 1995	10/599	120/8792		7.5 %	1.22 [0.65, 2.32]
Hak 2002a	896/71005	1065/51969		45.7 %	0.62 [0.56, 0.67]
Subtotal (95% CI)	**71604**	**60761**		**53.2 %**	**0.80 [0.42, 1.55]**
Total events: 906 (Vaccine), 1185 (Control)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 4.34, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 0.65 (P = 0.51)					
2 Epidemic year - vaccine matching absent or unknown					
Hak 2002b	1293/92001	1262/66453		46.8 %	0.74 [0.69, 0.80]
Subtotal (95% CI)	**92001**	**66453**		**46.8 %**	**0.74 [0.69, 0.80]**
Total events: 1293 (Vaccine), 1262 (Control)					
Heterogeneity: not applicable					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 7.67 (P < 0.00001)					
Total (95% CI)	**163605**	**127214**	♦	**100.0 %**	**0.71 [0.58, 0.85]**
Total events: 2199 (Vaccine), 2447 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 12.64, df = 2 (P = 0.002); I^2 =84%					
Test for overall effect: Z = 3.59 (P = 0.00033)					

0.01 0.1 1 10 100

Favours vaccine Favours control

Analysis 3.1. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 1 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.095)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					

0.01 0.1 1 10 100

Favours vaccine Favours control

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					
Total (95% CI)	**3562**	**2861**		**100.0 %**	**0.40 [0.14, 1.17]**
Total events: 5 (Vaccine), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.095)					

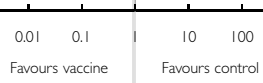
Analysis 3.2. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 2 Pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 2 Pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 29 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					
Total (95% CI)	**3562**	**2861**		**100.0 %**	**1.22 [0.76, 1.94]**
Total events: 44 (Vaccine), 29 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					

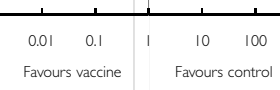
Analysis 3.3. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 3 Hospitalisation for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 3 Hospitalisation for influenza or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 278 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.97 (P = 0.000072)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					
Total (95% CI)	**30840**	**15092**	♦	**100.0 %**	**0.74 [0.63, 0.86]**
Total events: 419 (Vaccine), 278 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.97 (P = 0.000072)					

0.01 0.1 1 10 100

Favours vaccine Favours control

Analysis 3.4. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 4 Hospitalisation for any respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 4 Hospitalisation for any respiratory disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Mangtani 2004a	1426/67877	1785/75195	■	50.5 %	0.89 [0.83, 0.95]
Nichol 1998a	1937/30840	1150/15092	■	49.5 %	0.82 [0.77, 0.88]
Subtotal (95% CI)	**98717**	**90287**	♦	**100.0 %**	**0.85 [0.80, 0.92]**
Total events: 3363 (Vaccine), 2935 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.01, df = 1 (P = 0.16); I^2 =50%					
Test for overall effect: Z = 4.42 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					

0.01 0.1 1 10 100

Favours vaccine Favours control

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 2935 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.01$, df = 1 (P = 0.16); $I^2 = 50\%$					
Test for overall effect: Z = 4.42 (P < 0.00001)					

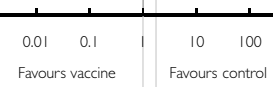
Analysis 3.5. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 5 Deaths from respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 5 Deaths from respiratory disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Mangtani 2004a	1653/66850	2029/75614		100.0 %	0.92 [0.86, 0.98]
Total (95% CI)	**66850**	**75614**		**100.0 %**	**0.92 [0.86, 0.98]**
Total events: 1653 (Vaccine), 2029 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.50 (P = 0.012)					



Analysis 3.6. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 6 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 6 All deaths

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Fleming 1995	1/265	61/2079		14.4 %	0.13 [0.02, 0.92]
Subtotal (95% CI)	**265**	**2079**		**14.4 %**	**0.13 [0.02, 0.92]**
Total events: 1 (Vaccine), 61 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.041)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Voordouw 2003	75/3562	76/2861		41.9 %	0.79 [0.58, 1.09]
Shapiro 2003	238/28853	872/30412		43.7 %	0.29 [0.25, 0.33]
Subtotal (95% CI)	**32415**	**33273**		**85.6 %**	**0.47 [0.17, 1.28]**
Total events: 313 (Vaccine), 948 (Control)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 33.12, df = 1 (P<0.00001); I^2 =97%					
Test for overall effect: Z = 1.48 (P = 0.14)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**32680**	**35352**		**100.0 %**	**0.39 [0.16, 0.97]**
Total events: 314 (Vaccine), 1009 (Control)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 34.12, df = 2 (P<0.00001); I^2 =94%					
Test for overall effect: Z = 2.02 (P = 0.044)					

Analysis 3.7. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 7 Hospitalisation for heart disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 7 Hospitalisation for heart disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 487 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 487 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					

Analysis 3.8. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups, Outcome 8 Combined outcome: all deaths or severe respiratory illness.

Review: Vaccines for preventing influenza in the elderly

Comparison: 3 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - risk groups

Outcome: 8 Combined outcome: all deaths or severe respiratory illness

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 811 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 11.97 (P < 0.00001)					
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 (Vaccine), 995 (Control)					
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 (Vaccine), 1806 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 9.34, df = 1 (P = 0.002); I^2 =89%					
Test for overall effect: Z = 4.97 (P < 0.00001)					

Analysis 4.1. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 1 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					

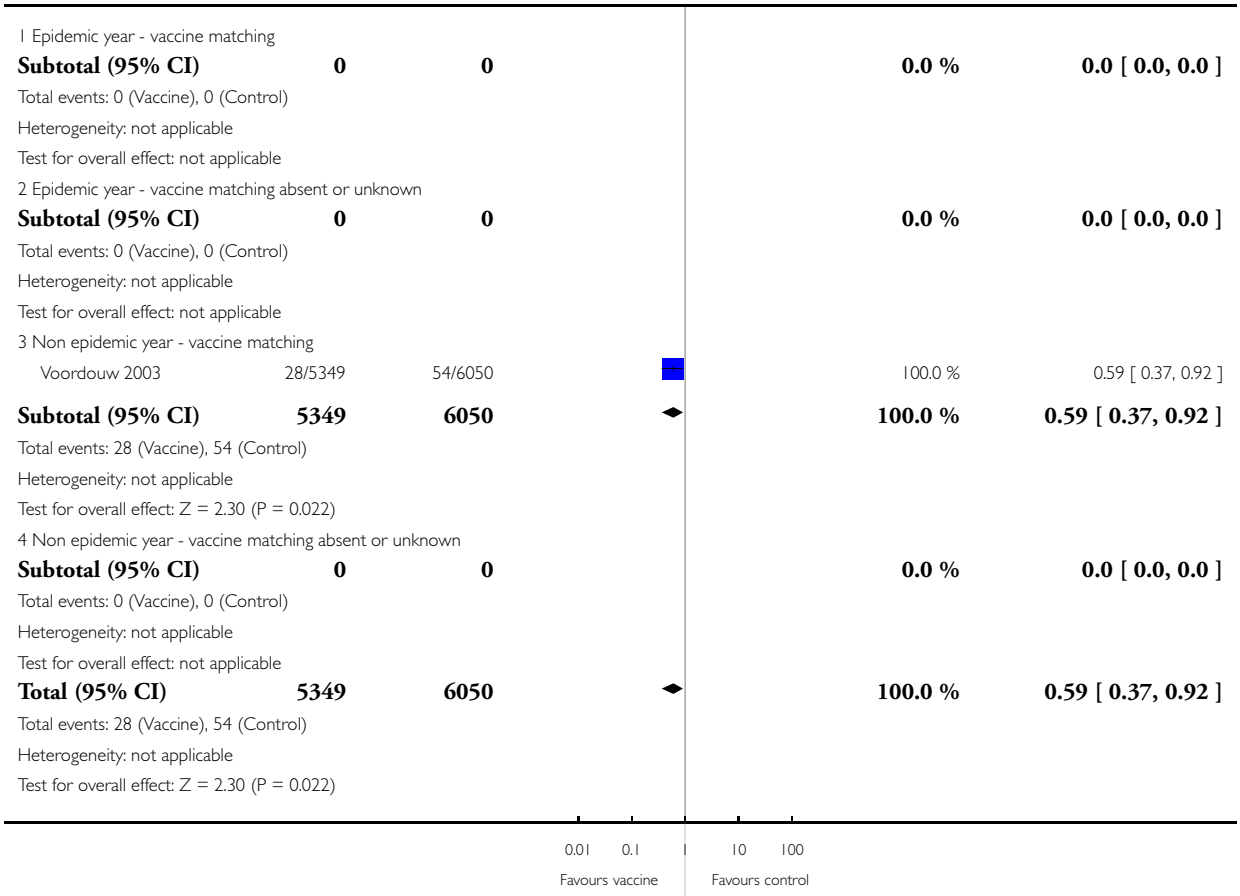
Analysis 4.2. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 2 Pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 2 Pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 54 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.022)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 54 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.022)					



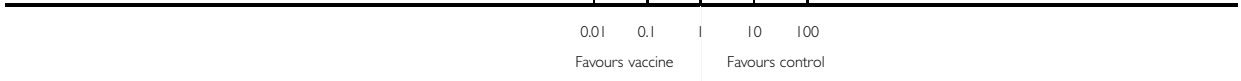
Analysis 4.3. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 3 Hospitalisation for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 3 Hospitalisation for influenza or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 196 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.04 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 196 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.04 (P < 0.00001)					



Analysis 4.4. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 4 Hospitalisation for any respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 4 Hospitalisation for any respiratory disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Mangtani 2004a	567/77722	1392/196983		50.4 %	1.03 [0.94, 1.14]
Nichol 1998a	491/57058	566/44561		49.6 %	0.68 [0.60, 0.76]
Subtotal (95% CI)	**134780**	**241544**		**100.0 %**	**0.84 [0.55, 1.27]**
Total events: 1058 (Vaccine), 1958 (Control)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 28.49$, df = 1 (P<0.00001); $I^2 = 96\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 1958 (Control)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 28.49$, df = 1 (P<0.00001); $I^2 = 96\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					

Analysis 4.5. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 5 Deaths from respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 5 Deaths from respiratory disease

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

Analysis 4.6. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 6 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 6 All deaths

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 37 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 268 (Control)					
Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 10.32$, df = 1 (P = 0.001); $I^2 = 90\%$					
Test for overall effect: Z = 1.31 (P = 0.19)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 305 (Control)					
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 10.88$, df = 2 (P = 0.004); $I^2 = 82\%$					
Test for overall effect: Z = 1.24 (P = 0.22)					

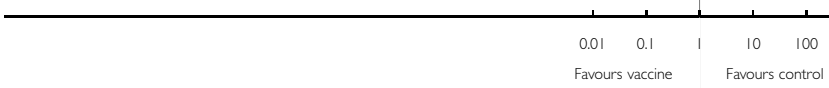
Analysis 4.7. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 7 Hospitalisation for heart disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 7 Hospitalisation for heart disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 125 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.058)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 125 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.058)					



Analysis 4.8. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups, Outcome 8 Combined outcome: all deaths or severe respiratory illness.

Review: Vaccines for preventing influenza in the elderly

Comparison: 4 Influenza vaccines versus no vaccination - Cohort studies - community-dwellers - no risk groups

Outcome: 8 Combined outcome: all deaths or severe respiratory illness

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Hak 2002a	201/37693	254/30843		52.5 %	0.65 [0.54, 0.78]
Subtotal (95% CI)	**37693**	**30843**		**52.5 %**	**0.65 [0.54, 0.78]**
Total events: 201 (Vaccine), 254 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.62 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Hak 2002b	164/34155	267/32489		47.5 %	0.58 [0.48, 0.71]
Subtotal (95% CI)	**34155**	**32489**		**47.5 %**	**0.58 [0.48, 0.71]**
Total events: 164 (Vaccine), 267 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.43 (P < 0.00001)					
Total (95% CI)	**71848**	**63332**		**100.0 %**	**0.62 [0.54, 0.70]**
Total events: 365 (Vaccine), 521 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.57, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 7.09 (P < 0.00001)					

Analysis 5.1. Comparison 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.23 (P = 0.0013)					
Total (95% CI)	**305**	**69**		**100.0 %**	**0.32 [0.16, 0.64]**
Total events: 17 (Vaccine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.23 (P = 0.0013)					

Analysis 5.2. Comparison 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 2 Hospitalisation for influenza or pneumonia or respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 5 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 n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 4960 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.60$, df = 1 (P = 0.21); $I^2 = 38\%$					
Test for overall effect: Z = 13.07 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 1 (Control)					
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 (Vaccine), 4961 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.68$, df = 2 (P = 0.43); $I^2 = 0.0\%$					
Test for overall effect: Z = 16.54 (P < 0.00001)					

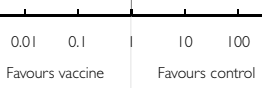
Analysis 5.3. Comparison 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 3 Deaths from influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 3 Deaths from influenza or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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 (Vaccine), 245 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.04 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
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 (Vaccine), 245 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.04 (P < 0.00001)					



Analysis 5.4. Comparison 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers, Outcome 4 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community-dwellers

Outcome: 4 All deaths

Study or subgroup	Vaccinne n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Christenson 2001b	1514/100242	5531/159385		100.0 %	0.44 [0.41, 0.46]
Subtotal (95% CI)	**100242**	**159385**		**100.0 %**	**0.44 [0.41, 0.46]**
Total events: 1514 (Vaccinne), 5531 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 28.96 (P < 0.00001)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccinne), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Consonni 2004b	3/305	0/69		0.0 %	1.60 [0.08, 30.65]
Subtotal (95% CI)	**305**	**69**		**0.0 %**	**1.60 [0.08, 30.65]**
Total events: 3 (Vaccinne), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.75)					
Total (95% CI)	**100547**	**159454**		**100.0 %**	**0.44 [0.41, 0.46]**
Total events: 1517 (Vaccinne), 5531 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.75, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 28.95 (P < 0.00001)					

Analysis 6.1. Comparison 6 Influenza vaccines with adjuvant versus no vaccination - Cohort studies in community-dwellers, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 6 Influenza vaccines with adjuvant versus no vaccination - Cohort studies in community-dwellers

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Pregliasco 2002	5/184	11/79		36.8 %	0.20 [0.07, 0.54]
Subtotal (95% CI)	**184**	**79**		**36.8 %**	**0.20 [0.07, 0.54]**
Total events: 5 (Vaccine), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.13 (P = 0.0018)					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Consonni 2004a	11/166	12/69		63.2 %	0.38 [0.18, 0.82]
Subtotal (95% CI)	**166**	**69**		**63.2 %**	**0.38 [0.18, 0.82]**
Total events: 11 (Vaccine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.46 (P = 0.014)					
Total (95% CI)	**350**	**148**		**100.0 %**	**0.30 [0.16, 0.56]**
Total events: 16 (Vaccine), 23 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.05, df = 1 (P = 0.30); I^2 =5%					
Test for overall effect: Z = 3.74 (P = 0.00018)					

Analysis 6.2. Comparison 6 Influenza vaccines with adjuvant versus no vaccination - Cohort studies in community-dwellers, Outcome 2 Hospitalisation for influenza or pneumonia or respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 6 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 n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 4 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.89$, df = 1 (P = 0.35); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.72 (P = 0.086)					
Total (95% CI)	**350**	**148**		**100.0 %**	**0.17 [0.02, 1.28]**
Total events: 1 (Vaccine), 4 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.89$, df = 1 (P = 0.35); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.72 (P = 0.086)					

Analysis 6.3. Comparison 6 Influenza vaccines with adjuvant versus no vaccination - Cohort studies in community-dwellers, Outcome 3 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 6 Influenza vaccines with adjuvant versus no vaccination - Cohort studies in community-dwellers

Outcome: 3 All deaths

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Consonni 2004a	2/166	0/69		100.0 %	2.10 [0.10, 43.10]
Subtotal (95% CI)	**166**	**69**		**100.0 %**	**2.10 [0.10, 43.10]**
Total events: 2 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
Total (95% CI)	**166**	**69**		**100.0 %**	**2.10 [0.10, 43.10]**
Total events: 2 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					

Analysis 7.1. Comparison 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates, Outcome 1 Hospitalisation for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates

Outcome: 1 Hospitalisation for influenza or pneumonia

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
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: $Tau^2 = 0.00$; $Chi^2 = 5.95$, df = 5 (P = 0.31); $I^2 = 16\%$				
Test for overall effect: Z = 7.97 (P < 0.00001)				
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)				
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 = 0.033)				
Total (95% CI)			**100.0 %**	**0.73 [0.67, 0.79]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.18$, df = 7 (P = 0.24); $I^2 = 24\%$				
Test for overall effect: Z = 7.40 (P < 0.00001)				

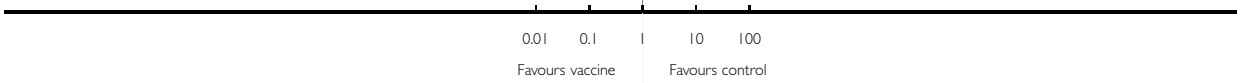
Analysis 7.2. Comparison 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates, Outcome 2 Hospitalisation for any respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates

Outcome: 2 Hospitalisation for any respiratory disease

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Epidemic matching vaccine				
Mangtani 2004b	-0.1744 (0.1209)		6.4 %	0.84 [0.66, 1.06]
Nichol 1998a	-0.3857 (0.0429)		11.6 %	0.68 [0.63, 0.74]
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]
Davis 2001c	-0.36 (0.18)		4.0 %	0.70 [0.49, 0.99]
Mangtani 2004h	-0.4155 (0.0656)		10.0 %	0.66 [0.58, 0.75]
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: Tau^2 = 0.0; Chi^2 = 7.64, df = 8 (P = 0.47); I^2 =0.0%				
Test for overall effect: Z = 13.17 (P < 0.00001)				
2 Non epidemic non 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: Tau^2 = 0.00; Chi^2 = 1.09, df = 1 (P = 0.30); I^2 =8%				
Test for overall effect: Z = 1.05 (P = 0.30)				
3 Non epidemic year and matching vaccine				
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: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
Total (95% CI)			**100.0 %**	**0.78 [0.72, 0.85]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 34.73, df = 12 (P = 0.00052); I^2 =65%				
Test for overall effect: Z = 5.74 (P < 0.00001)				



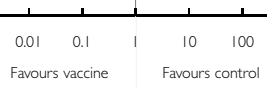
Analysis 7.3. Comparison 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates, Outcome 3 Hospitalisation for heart disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates

Outcome: 3 Hospitalisation for heart disease

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
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: $Tau^2 = 0.0$; $Chi^2 = 1.69$, df = 4 (P = 0.79); $I^2 = 0.0\%$				
Test for overall effect: Z = 6.91 (P < 0.00001)				
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: $Tau^2 = 0.0$; $Chi^2 = 1.80$, df = 5 (P = 0.88); $I^2 = 0.0\%$				
Test for overall effect: Z = 7.00 (P < 0.00001)				

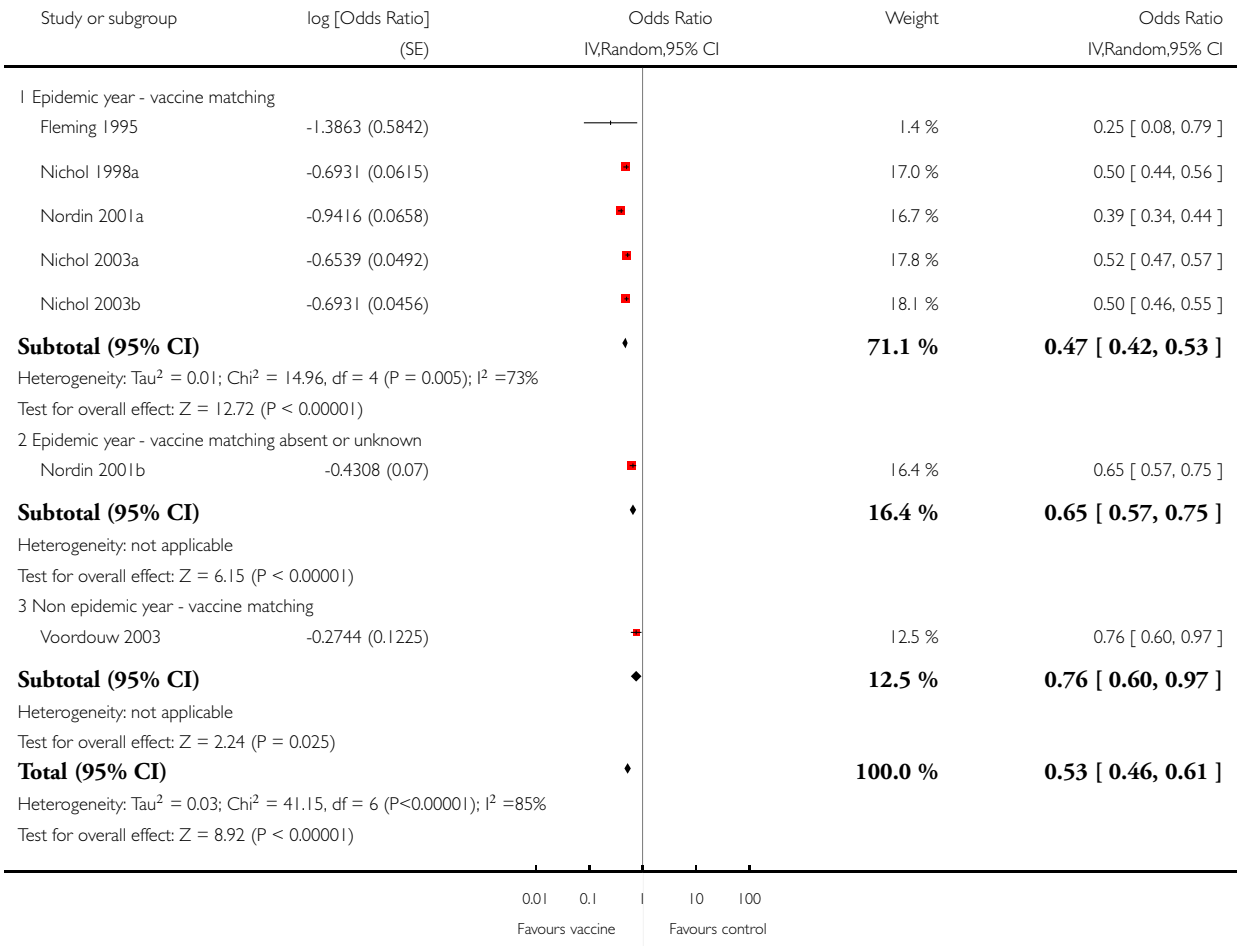


Analysis 7.4. Comparison 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates, Outcome 4 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates

Outcome: 4 All deaths



Analysis 7.5. Comparison 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates, Outcome 5 Combined outcome: all deaths or severe respiratory illness.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza vaccines versus no vaccination - Cohort studies in community - adjusted rates

Outcome: 5 Combined outcome: all deaths or severe respiratory illness

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Epidemic year - vaccine matching				
Fleming 1995	-0.3567 (0.3321)		100.0 %	0.70 [0.37, 1.34]
Total (95% CI)			**100.0 %**	**0.70 [0.37, 1.34]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.07 (P = 0.28)				

Analysis 8.1. Comparison 8 Influenza vaccines versus no vaccination - Case-control studies in community, Outcome 1 Hospitalisations for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 8 Influenza vaccines versus no vaccination - Case-control studies in community

Outcome: 1 Hospitalisations for influenza or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching (circulating strains)					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 (Vaccine), 278 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.55)					
3 No outbreak - vaccine matching					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Puig-Barber 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 (Vaccine), 102 (Control)					
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 (Vaccine), 380 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.87 (P = 0.39)					

Analysis 8.2. Comparison 8 Influenza vaccines versus no vaccination - Case-control studies in community, Outcome 2 Hospitalisations for any respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 8 Influenza vaccines versus no vaccination - Case-control studies in community

Outcome: 2 Hospitalisations for any respiratory disease

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
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 (Vaccine), 1831 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.20, df = 2 (P = 0.12); I^2 =52%					
Test for overall effect: Z = 0.91 (P = 0.36)					
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 (Vaccine), 474 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Total (95% CI)	**5349**	**16029**		**100.0 %**	**1.08 [0.95, 1.23]**
Total events: 797 (Vaccine), 2305 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.36$, df = 3 (P = 0.22); $I^2 = 31\%$					
Test for overall effect: Z = 1.22 (P = 0.22)					

Analysis 8.3. Comparison 8 Influenza vaccines versus no vaccination - Case-control studies in community, Outcome 3 Deaths from influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 8 Influenza vaccines versus no vaccination - Case-control studies in community

Outcome: 3 Deaths from influenza or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching					
Ahmed 1995	57/315	178/777		100.0 %	0.74 [0.53, 1.04]
Total (95% CI)	**315**	**777**		**100.0 %**	**0.74 [0.53, 1.04]**
Total events: 57 (Vaccine), 178 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.080)					

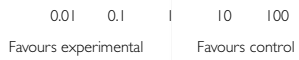
Analysis 8.4. Comparison 8 Influenza vaccines versus no vaccination - Case-control studies in community, Outcome 4 Pneumonia (no better defined).

Review: Vaccines for preventing influenza in the elderly

Comparison: 8 Influenza vaccines versus no vaccination - Case-control studies in community

Outcome: 4 Pneumonia (no better defined)

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Outbreak - partially matching					
Puig-Barbera 2007	150/198	251/321		100.0 %	0.87 [0.57, 1.33]
Total (95% CI)	**198**	**321**		**100.0 %**	**0.87 [0.57, 1.33]**
Total events: 150 (Vaccine), 251 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					



Analysis 9.1. Comparison 9 Influenza and pneumococcal vaccines versus no vaccination - Case-control studies in community, Outcome 1 Hospitalisations for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 9 Influenza and pneumococcal vaccines versus no vaccination - Case-control studies in community

Outcome: 1 Hospitalisations for influenza or pneumonia

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
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 (Vaccine), 1236 (Control)					
Heterogeneity: Tau² = 0.04; Chi² = 2.92, df = 1 (P = 0.09); I² =66%					
Test for overall effect: Z = 0.30 (P = 0.76)					
2 No outbreak - vaccine matching					
Ohmit 1995a	314/667	743/1530		33.2 %	0.94 [0.79, 1.13]
Puig-Barber 2004	168/290	318/525		15.6 %	0.90 [0.67, 1.20]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**957**	**2055**		**48.8 %**	**0.93 [0.80, 1.08]**
Total events: 482 (Vaccine), 1061 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
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 (Vaccine), 2297 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.77, df = 3 (P = 0.29); I^2 =21%					
Test for overall effect: Z = 0.54 (P = 0.59)					

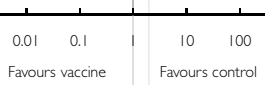
Analysis 10.1. Comparison 10 Influenza and pneumococcal vaccines versus no vaccination - Case-control studies in nursing homes, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 10 Influenza and pneumococcal vaccines versus no vaccination - Case-control studies in nursing homes

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching					
Ohmit 1999	220/361	628/837		100.0 %	0.52 [0.40, 0.68]
Total (95% CI)	**361**	**837**		**100.0 %**	**0.52 [0.40, 0.68]**
Total events: 220 (Vaccine), 628 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.88 (P < 0.00001)					



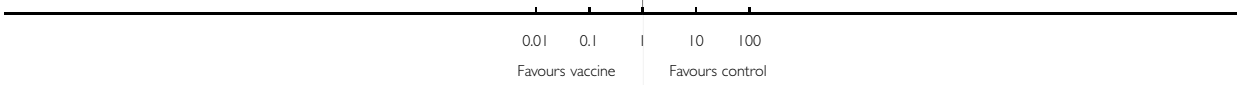
Analysis 11.1. Comparison 11 Influenza vaccines versus no vaccination - Case-control studies in community - adjusted rates, Outcome 1 Hospitalisations for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 11 Influenza vaccines versus no vaccination - Case-control studies in community - adjusted rates

Outcome: 1 Hospitalisations for influenza or pneumonia

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
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 = 0.0071)				
2 Non epidemic - vaccine not matching				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
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: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%				
Test for overall effect: Z = 4.92 (P < 0.00001)				
4 Non epidemic - vaccine matching				
Puig-Barber 1997	-1.5606 (0.4918)		4.8 %	0.21 [0.08, 0.55]
Puig-Barber 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: Tau^2 = 0.27; Chi^2 = 2.84, df = 1 (P = 0.09); I^2 =65%				
Test for overall effect: Z = 2.27 (P = 0.023)				
Total (95% CI)			**100.0 %**	**0.59 [0.47, 0.74]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 7.08, df = 4 (P = 0.13); I^2 =44%				
Test for overall effect: Z = 4.65 (P < 0.00001)				



Analysis 11.2. Comparison 11 Influenza vaccines versus no vaccination - Case-control studies in community - adjusted rates, Outcome 2 Hospitalisations for any respiratory disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 11 Influenza vaccines versus no vaccination - Case-control studies in community - adjusted rates

Outcome: 2 Hospitalisations for any respiratory disease

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
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: $Tau^2 = 0.02$; $Chi^2 = 5.09$, df = 2 (P = 0.08); $I^2 = 61\%$				
Test for overall effect: Z = 2.79 (P = 0.0053)				
2 Non epidemic - vaccine matching				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
3 Non epidemic year - vaccine matching				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)			**100.0 %**	**0.71 [0.56, 0.90]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.09$, df = 2 (P = 0.08); $I^2 = 61\%$				
Test for overall effect: Z = 2.79 (P = 0.0053)				

Analysis 11.3. Comparison 11 Influenza vaccines versus no vaccination - Case-control studies in community - adjusted rates, Outcome 3 Deaths from pneumonia or influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 11 Influenza vaccines versus no vaccination - Case-control studies in community - adjusted rates

Outcome: 3 Deaths from pneumonia or influenza

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Epidemic year - vaccine matching				
Ahmed 1995	-0.2744 (0.1225)		78.9 %	0.76 [0.60, 0.97]
Subtotal (95% CI)			**78.9 %**	**0.76 [0.60, 0.97]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.24 (P = 0.025)				
2 Epidemic year - vaccine matching absent or unknown				
Mullooly 1994	-0.3988 (0.237)		21.1 %	0.67 [0.42, 1.07]
Subtotal (95% CI)			**21.1 %**	**0.67 [0.42, 1.07]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.68 (P = 0.092)				
Total (95% CI)			**100.0 %**	**0.74 [0.60, 0.92]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%				
Test for overall effect: Z = 2.76 (P = 0.0057)				

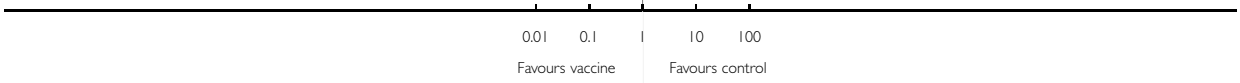
Analysis 12.1. Comparison 12 Influenza and pneumococcal vaccines versus no vaccination - Case-control studies in community - adjusted rates, Outcome 1 Hospitalisations for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 12 Influenza and pneumococcal vaccines versus no vaccination - Case-control studies in community - adjusted rates

Outcome: 1 Hospitalisations for influenza or pneumonia

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Epidemic - vaccine matching				
Ohmit 1995b	-0.3857 (0.1583)		54.0 %	0.68 [0.50, 0.93]
Subtotal (95% CI)			**54.0 %**	**0.68 [0.50, 0.93]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.44 (P = 0.015)				
2 Non epidemic - vaccine not matching				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
3 Epidemic year - vaccine matching absent or unknown				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
4 Non epidemic - vaccine matching				
Ohmit 1995a	-0.3711 (0.1716)		46.0 %	0.69 [0.49, 0.97]
Subtotal (95% CI)			**46.0 %**	**0.69 [0.49, 0.97]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.16 (P = 0.031)				
Total (95% CI)			**100.0 %**	**0.68 [0.54, 0.86]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 3.26 (P = 0.0011)				

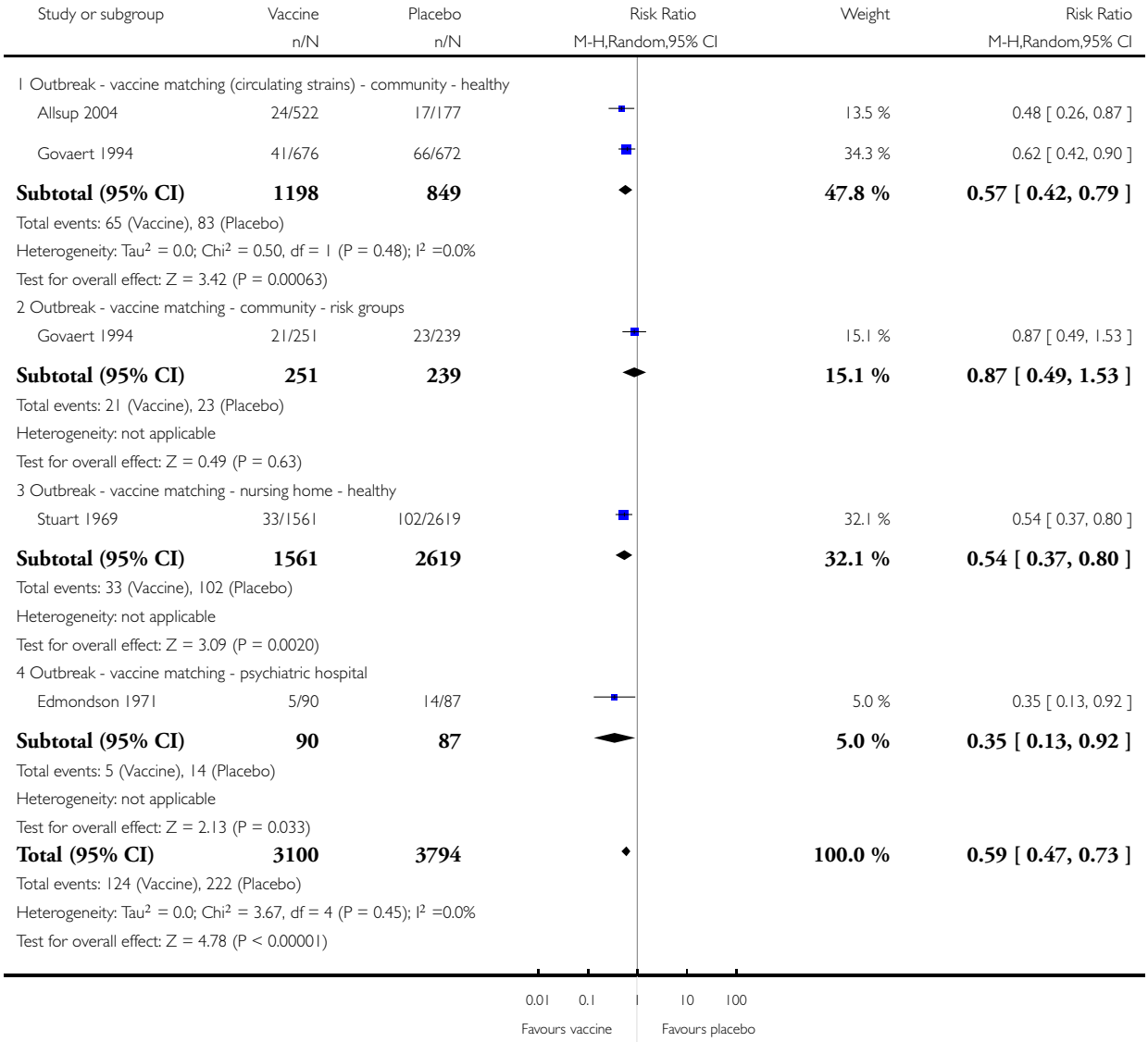


Analysis 13.1. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 13 Influenza vaccines versus placebo - RCT - parenteral vaccine

Outcome: 1 ILI



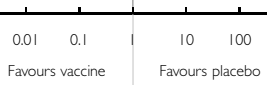
Analysis 13.2. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 13 Influenza vaccines versus placebo - RCT - parenteral vaccine

Outcome: 2 Influenza

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching - community - healthy and ill					
Govaert 1994	16/927	38/911		59.9 %	0.41 [0.23, 0.74]
Subtotal (95% CI)	**927**	**911**		**59.9 %**	**0.41 [0.23, 0.74]**
Total events: 16 (Vaccine), 38 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.0027)					
2 outbreak - vaccine matching - psychiatric hospital					
Edmondson 1971	4/90	11/87		16.3 %	0.35 [0.12, 1.06]
Subtotal (95% CI)	**90**	**87**		**16.3 %**	**0.35 [0.12, 1.06]**
Total events: 4 (Vaccine), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.064)					
3 No outbreak - vaccine matching - nursing home - healthy and ill					
Rudenko 2001	6/93	14/109		23.8 %	0.50 [0.20, 1.25]
Subtotal (95% CI)	**93**	**109**		**23.8 %**	**0.50 [0.20, 1.25]**
Total events: 6 (Vaccine), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
Total (95% CI)	**1110**	**1107**		**100.0 %**	**0.42 [0.27, 0.66]**
Total events: 26 (Vaccine), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.25, df = 2 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 3.79 (P = 0.00015)					



Analysis 13.3. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 3 Pneumonia.

Review: Vaccines for preventing influenza in the elderly

Comparison: 13 Influenza vaccines versus placebo - RCT - parenteral vaccine

Outcome: 3 Pneumonia

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching - community - healthy				
Allsup 2004	0/522	0/177		0.0 [0.0, 0.0]
Total (95% CI)	**522**	**177**		**0.0 [0.0, 0.0]**
Total events: 0 (Vaccine), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 13.4. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 4 All deaths.

Review: Vaccines for preventing influenza in the elderly

Comparison: 13 Influenza vaccines versus placebo - RCT - parenteral vaccine

Outcome: 4 All deaths

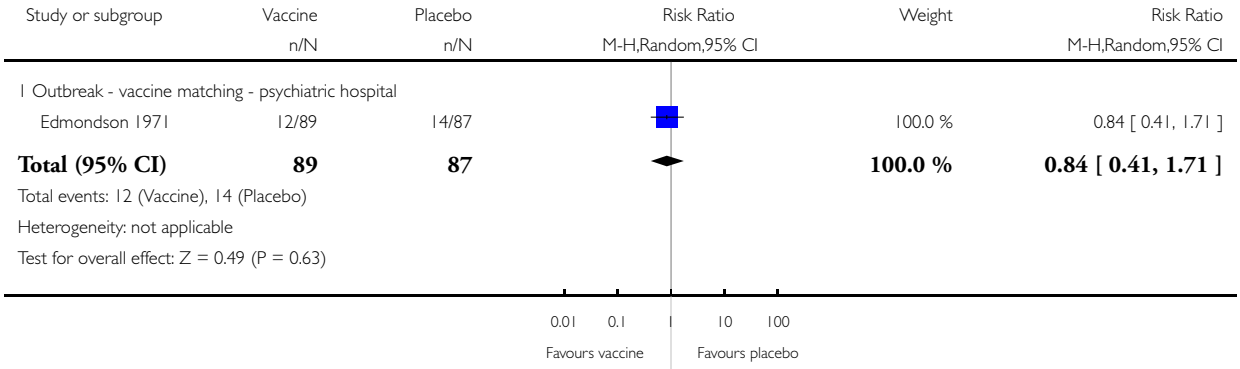
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching - community - healthy					
Allsup 2004	3/522	1/177		100.0 %	1.02 [0.11, 9.72]
Total (95% CI)	**522**	**177**		**100.0 %**	**1.02 [0.11, 9.72]**
Total events: 3 (Vaccine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					

Analysis 14.1. Comparison 14 Vaccine versus placebo - inactivated aerosol vaccine, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 14 Vaccine versus placebo - inactivated aerosol vaccine

Outcome: 1 ILI

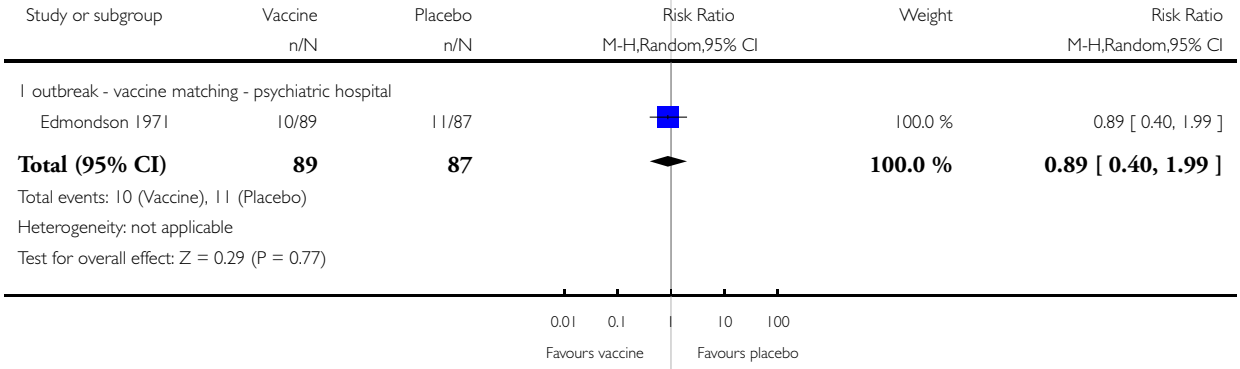


Analysis 14.2. Comparison 14 Vaccine versus placebo - inactivated aerosol vaccine, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 14 Vaccine versus placebo - inactivated aerosol vaccine

Outcome: 2 Influenza



Analysis 15.1. Comparison 15 Vaccine versus placebo - live aerosol vaccine, Outcome 1 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 15 Vaccine versus placebo - live aerosol vaccine

Outcome: 1 Influenza

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

Analysis 16.1. Comparison 16 Sensitivity analysis Comparison 01: subgroup analysis by study quality, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

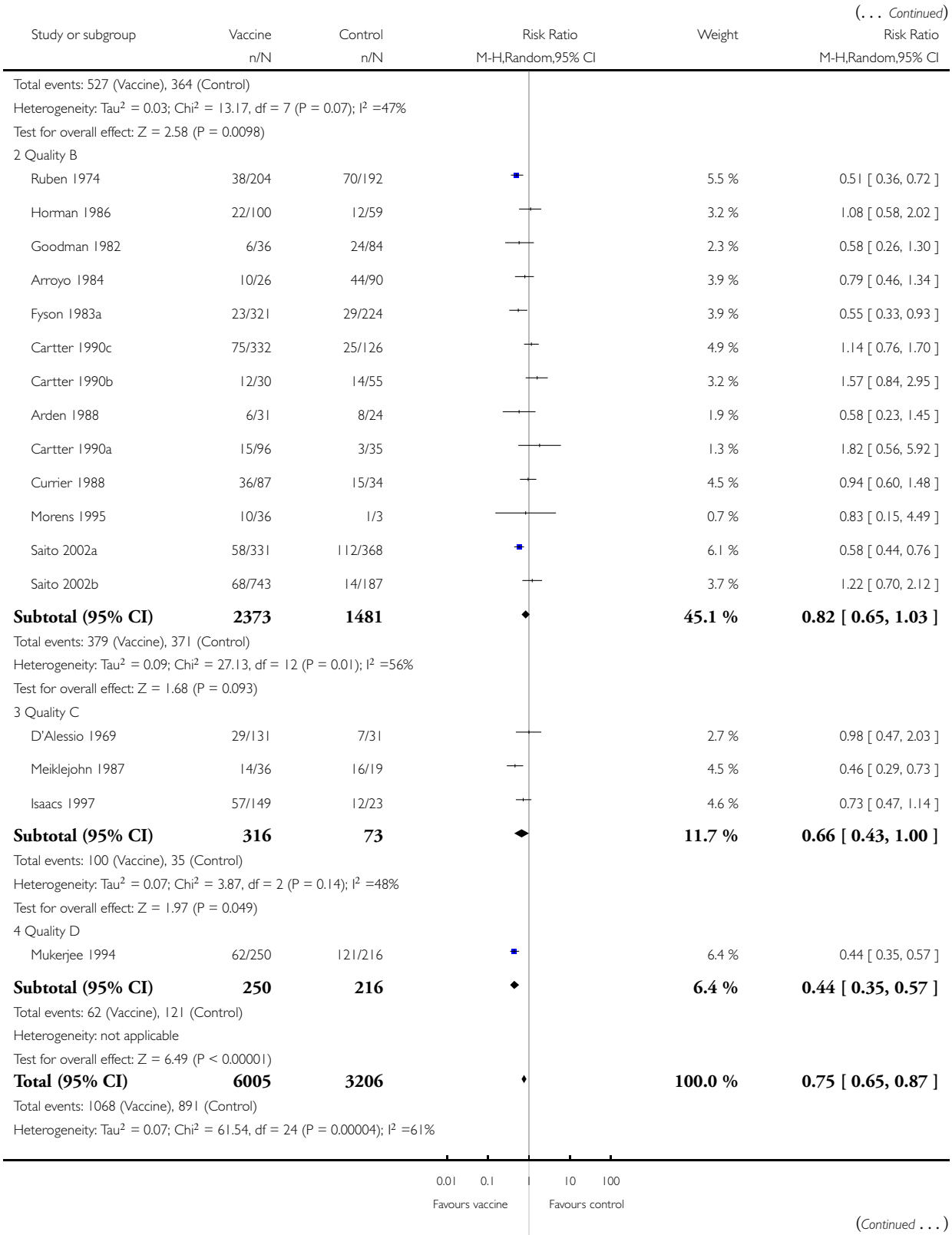
Comparison: 16 Sensitivity analysis Comparison 01: subgroup analysis by study quality

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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]**

(*Continued . . .*)

(. . . *Continued*)



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 3.82 (P = 0.00014)					

Analysis 17.1. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 1 General malaise.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

Outcome: 1 General malaise

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Margolis 1990a	24/336	20/336		1.20 [0.68, 2.13]
Treanor 1994	3/30	0/11		2.71 [0.15, 48.62]
Govaert 1993	58/904	50/902		1.16 [0.80, 1.67]
Keitel 1996	0/21	0/20		0.0 [0.0, 0.0]
Total (95% CI)	**1291**	**1269**		**1.18 [0.87, 1.61]**
Total events: 85 (Vaccine), 70 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.33, df = 2 (P = 0.85); I^2 =0.0%				
Test for overall effect: Z = 1.06 (P = 0.29)				

Analysis 17.2. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 2 Fever.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

Outcome: 2 Fever

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 20 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.35$, df = 2 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 1.64 (P = 0.10)

Analysis 17.3. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 3 Upper respiratory tract symptoms.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

Outcome: 3 Upper respiratory tract symptoms

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Margolis 1990a	44/336	34/336		91.0 %	1.29 [0.85, 1.97]
Treanor 1994	1/30	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 (Vaccine), 36 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.38$, df = 1 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 1.45 (P = 0.15)

Analysis 17.4. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 4 Headache.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

Outcome: 4 Headache

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 61 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.17$, df = 2 (P = 0.34); $I^2 = 8\%$

Test for overall effect: Z = 0.48 (P = 0.63)

Analysis 17.5. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 5 Nausea.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

Outcome: 5 Nausea

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 8 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Analysis 17.6. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 6 Local tenderness/sore arm.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

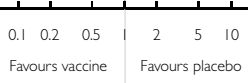
Outcome: 6 Local tenderness/sore arm

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 47 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.80$, df = 3 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 7.99 (P < 0.00001)



Analysis 17.7. Comparison 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events, Outcome 7 Swelling - erythema - induration.

Review: Vaccines for preventing influenza in the elderly

Comparison: 17 Influenza vaccines versus placebo - RCT - parenteral vaccine - adverse events

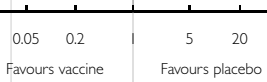
Outcome: 7 Swelling - erythema - induration

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Govaert 1993	66/904	8/902		8.23 [3.98, 17.05]
Keitel 1996	0/21	0/20		0.0 [0.0, 0.0]
Total (95% CI)	**925**	**922**		**8.23 [3.98, 17.05]**

Total events: 66 (Vaccine), 8 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 5.68 (P < 0.00001)



Analysis 18.1. Comparison 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events, Outcome 1 General malaise.

Review: Vaccines for preventing influenza in the elderly

Comparison: 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events

Outcome: 1 General malaise

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.44)					

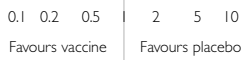
Analysis 18.2. Comparison 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events, Outcome 2 Fever.

Review: Vaccines for preventing influenza in the elderly

Comparison: 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events

Outcome: 2 Fever

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					



Analysis 18.3. Comparison 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events, Outcome 3 Upper respiratory tract symptoms.

Review: Vaccines for preventing influenza in the elderly

Comparison: 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events

Outcome: 3 Upper respiratory tract symptoms

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					

Analysis 18.4. Comparison 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events, Outcome 4 Lower respiratory tract symptoms.

Review: Vaccines for preventing influenza in the elderly

Comparison: 18 Influenza vaccines versus placebo - RCT - live aerosol vaccine - adverse events

Outcome: 4 Lower respiratory tract symptoms

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	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 (Vaccine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					

APPENDICES

Appendix 1. Included studies design

A case-control study is a retrospective epidemiological study usually used to investigate the association between two variables (for example 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.

A cohort study is an epidemiological study where groups of individuals are identified who vary in their exposure to an intervention or hazard, and 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.

A randomised controlled trial (RCT) is 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.

A quasi-randomised clinical trial is 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. Methodological quality of non-randomised studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE-CONTROL STUDIES
Selection

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

Comparability

1. Comparability of cases and controls on the basis of the design or analysis
    i) study controls for ..... (select the most important factor)
    ii) 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
    i) secure record (e.g. surgical records)
    ii) structured interview where blind to case/control status
    iii) interview not blinded to case/control status
    iv) written self-report or medical record only
    v) no description
2. Same method of ascertainment for cases and controls
    i) yes
    ii) no

1. Non-response rate
    i) same rate for both groups
    ii) non-respondents described

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

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   i) study controls for ····· (select the most important factor)
   ii) 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
   i) independent blind assessment
   ii) record linkage
   iii) self-report
   iv) no description
2. Was follow up long enough for outcomes to occur
   i) yes (select an adequate follow-up period for outcome of interest)
   ii) no
3. Adequacy of follow up of cohorts
   i) complete follow up - all subjects accounted for
   ii) subjects lost to follow up unlikely to introduce bias - small number lost - > ···· % (select an adequate %) follow up, or description provided of those lost) *
   iii) follow up rate < ····% (select an adequate %) and no description of those lost
   iv) no statement

Appendix 3. 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 2)

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 4. Previous search

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)

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 5. EMBASE 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 6. 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 7. 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 http://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.
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 favorable 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

Last assessed as up-to-date: 6 October 2009.

7 October 2009	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 partly changed. In part this was due to the re-evaluation of the whole topic and partly because of the ambiguity in the previous text which readers found confusing.
7 October 2009	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 (Vila-Corcoles 2005) was formerly awaiting classification.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2006

8 May 2008	Amended	Converted to new review format.
25 July 2007	Feedback has been incorporated	Feedback comment and reply added to review.
29 March 2006	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ) and Daniela Rivetti (DR) wrote the original protocol.

Roger E Thomas (RT) participated in the final draft of the original protocol and the review.

TOJ, DR and Vittorio Demicheli (VD) designed the original review.

Alessandro Rivetti (AR) conducted the original searches.

TOJ, DR and VD applied inclusion criteria.

TOJ, DR and Melanie Rudin (MR) extracted the original data.

VD arbitrated and checked the data extraction.

For this 2009 update:

Carlo Di Pietrantonj (CDP) undertook the meta-analysis and did statistical testing of the reviews and its 2009 update.

TOJ wrote the first review and its update.

Lubna Al Ansary (LAA) and Eliana Ferroni (EF) extracted the data.

Sarah Thorning (ST) conducted the updated searches.

All authors contributed to the final updated review.

DECLARATIONS OF INTEREST

TOJ owned shares in Glaxo SmithKline and received consultancy fees from Sanofi Synthelabo and Roche. All other review authors have no conflicts to declare.

See Appendix 1 for included studies designs.

See Appendix 2 for methodological quality of non-randomised studies.

See Appendix 3 for the data extraction form.

SOURCES OF SUPPORT

Internal sources

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

External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

Influenza, Human [*prevention & control]; Influenza Vaccines [*administration & dosage; adverse effects]; Vaccines, Inactivated [administration & dosage]

MeSH check words

Aged; Humans