Vaccines for preventing influenza in the elderly (Review)

Rivetti D, Jefferson T, Thomas RE, Rudin M, Rivetti A, Di Pietrantonj C, Demicheli V

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[Intervention review]

Vaccines for preventing influenza in the elderly

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ABSTRACT

Background

Influenza vaccination of elderly individuals is recommended worldwide and has been targeted toward the elderly and those at serious risk of complications.

Objectives

Our aim was to review the evidence of efficacy, effectiveness and safety of influenza vaccines in individuals aged 65 years or older.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infection (ARI) Group's specialized register, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness, (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).

Selection criteria

We considered randomised, quasi-randomised, 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

Sixty-four studies were included in the efficacy / effectiveness assessment, resulting in 96 data sets. In homes for elderly individuals (with good vaccine match and high viral circulation) the effectiveness of vaccines against ILI was 23% (6% to 36%) and non-significant against influenza (RR 1.04: 95% CI 0.43 to 2.51). We found no correlation between vaccine coverage and ILI attack rate. Well matched vaccines prevented pneumonia (VE 46%; 30% to 58%), hospital admission (VE 45%; 16% to 64%) and deaths from influenza or pneumonia (VE 42%, 17% to 59%). In elderly individuals living in the community, vaccines were not significantly effective against influenza (RR 0.19; 95% CI 0.02 to 2.01), ILI (RR 1.05: 95% CI 0.58 to 1.89), or pneumonia (RR 0.88; 95% CI 0.64 to 1.20). Well matched vaccines prevented hospital admission for influenza and pneumonia (VE 26%; 12% to 38%) and all-cause mortality (VE 42%; 24% to 55%). After adjustment for confounders, vaccine performance was improved for admissions to hospital for influenza or pneumonia (VE* 27%; 21% to 33%), respiratory diseases (VE* 22%; 15% to 28%) and cardiac disease (VE* 24%; 18% to 30%); and for all-cause mortality (VE* 47%; 39% to 54%). The public health safety profiles of the vaccines appear to be acceptable.

Authors' conclusions

In long-term care facilities, where vaccination is most effective against complications, the aims of the vaccination campaign are fulfilled, at least in part. However, according to reliable evidence the usefulness of vaccines in the community is modest. The apparent high effectiveness of the vaccines in preventing death from all causes may reflect a baseline imbalance in health status and other systematic differences in the two groups of participants.

PLAIN LANGUAGE SUMMARY

The review looked at whether vaccines prevented 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 highest risk for complications, hospitalisations and deaths from influenza.

The review looked at evidence from experimental and non-experimental studies carried out over 40 years of influenza vaccination. Seventy-one studies were included and were grouped first according to study design and then to setting (community or long-term care facilities). The results of the review 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 are the most commonly used influenza vaccines. Best effectiveness of current vaccines in preventing clinical illness and its complications was seen in long-term care facilities (for example nursing homes) where vaccines prevented about 45% of pneumonia cases, hospital admissions and influenza-related deaths. This compared to about 25% vaccine efficacy in preventing hospitalisation from influenza or respiratory illness in open community settings. The public health safety profile of the vaccines appears to be acceptable.

BACKGROUND

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 developed or rapidly developing 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. Currently there is no up-to-date comprehensive assessment of the effects of influenza vaccines in the elderly. 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

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.

To assess the effectiveness of vaccines in preventing influenza, ILI, hospital admissions, complications and mortality in the elderly.

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, quasi-randomised, 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 more, 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

Vaccination with any influenza vaccine given independently, in any dose, preparation or time schedule, compared with placebo, or with no intervention.

New as yet unlicensed types of vaccines were also considered (for example, live attenuated and DNA vaccines).

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 2005).

Studies in which vaccine was administered after the beginning of the epidemic period were excluded.

Old oil adjuvant vaccine or vaccines with a content greater than 15 µg of hemagglutinin / strain / dose were excluded from the safety assessment.

Types of outcome measures

Primary outcome measures for treatment efficacy and effectiveness

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

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 and/or serological supporting evidence).
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.

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

Outcome measures 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 Barrè Syndrome (GBS)).

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infection (ARI) Group's specialized register, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness, (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
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:
- the Science Citation Index was used to identify articles that cite the relevant studies;
- the relevant studies were also keyed into PubMed and the Related Articles feature used;
- bibliographies of all relevant articles obtained, any published review and proceedings from relevant conferences were assessed for additional studies;
- Internet sources were also explored: NHS National Research Register (http://www.update-software.com/national/) ; the Meta-register of Clinical Trials (http://www.controlled-trials.com/) the digital dissertations website (http://wwwlib.umi.com/dissertations);
- the Vaccine Adverse Event Reporting System website was searched (http://www.vaers.org);
- first or corresponding authors of relevant studies was contacted to identify further published or unpublished trials;
- vaccine manufacturers listed at the WHO web site were also contacted.

Data collection and analysis

Inclusion procedure

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

Assessment of methodological quality

Experimental studies

The review authors independently assessed the methodological quality of the included studies using criteria from the Cochrane Reviewers' Handbook (Deeks 2004) and results were introduced into the sensitivity analysis.
Studies were classified 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

Quality assessment of non-randomised studies was made 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) (*see* Appendix 2). Because of the lack of empirical evidence on the impact that the methodological quality has on the results of non-randomised studies, 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).

Arbitration procedure

In case of disagreement between two review authors VD arbitrated.

Data collection

Data extraction was performed by three review authors (TOJ, DR, and MR) using a data extraction form (*see* Appendix 3).
Data were checked and entered onto customised software.
Data on the following were extracted:
Methodological quality of studies
Study design (see 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

Location of study

Data analysis

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, a meta-analysis of these studies was carried out within each design category.

Non-randomised and quasi-randomised evidence was analysed separately from randomised controlled trial 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). We pooled whole, split and subunit vaccines, as in community studies this information was not reported. When a study reported data for more than one influenza season or for more than one setting, we considered these separately, creating separate data sets. We calculated the statistic I^2 for every pooled estimate to assess the effect on statistical heterogeneity. I^2 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 I^2 is less than 30% there is little concern about statistical heterogeneity (Higgins 2002; Higgins 2003). We used random-effect models throughout to take account of the between-study variance in our findings (DerSimonian 1986).

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 (Deeks 2004).

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.

We summarised efficacy (against influenza) and effectiveness (against influenza-like illness) estimates as relative risk (RR) using a 95% 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.

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). A sub-analysis of studies describing better defined epidemic period was performed for most significant comparisons. We then tested effect size from cohort studies done 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.

Efficacy and effectiveness evaluation

4400 titles of reports of potentially relevant studies were identified and screened for retrieval; 4088 reports were excluded by screening of titles and abstracts; 312 reports were retrieved for detailed assessment; 241 reports did not fulfil inclusion criteria. 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 tables.

Seventy-one studies were included in systematic review: 64 studies were used to assess efficacy / effectiveness and eight were included in safety assessment (one randomised controlled trial (RCT) was included in both assessments).

Sixty-four studies included in efficacy / effectiveness assessment were split into subsets by influenza season or setting or vaccine type, resulting in 96 data sets as described below:

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

Forty-nine cohort studies resulted in 79 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; Horman 1986; Howarth 1987a; Howarth 1987b; Howells 1975a; Howells 1975b; Howells 1975c; Isaacs 1997; Kaway 2003; 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);

Ten case-control studies resulted in 12 data sets (Ahmed 1995; Ahmed 1997; Crocetti 2001; Fedson 1993a; Fedson 1993b; Foster 1992; Mullooly 1994; Ohmit 1999; Ohmit 1995a; Ohmit 1995b; Puig-Barberà 1997; Puig-Barberà 2004).

Half (n = 48) 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 data sets did not provide sufficient information on circulating subtypes.

Twenty-three studies resulting in 38 data sets collected information about health conditions of vaccinated and unvaccinated persons and reported stratified results or adjusted rates. Subjects 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 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:

Five randomised controlled trials (Govaert 1993; Keitel 1996; Margolis 1990a; Treanor 1994; Stuart 1969);

Three surveillance studies with a non-comparative design assessing rare events (GBS) (Kaplan 1982; Lasky 1998; Schonberger 1979) were commented on in the text but were not included in our meta-analysis.

See the description of the studies in the 'Characteristics of included studies' table.

Risk of bias in included studies

Quality was as follows:

Experimental

Allocation concealment: Adequate 3
Allocation concealment: Unclear 1
Allocation concealment: Inadequate 0
Allocation concealment: Not described 5

Cohort / case control

Low risk of bias 18
Medium risk of bias 29
High risk of bias 9
Very high risk of bias 3

Surveillance studies

For three surveillance studies assessing rare side effects, quality evaluation was not performed. All were population-based studies with good case findings and case-definitions.

Effects of interventions

Efficacy / effectiveness

Cohort studies in long-term care facilities

Twenty-nine cohort studies in long-term care facilities contributed data to 40 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; 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 33,985 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.

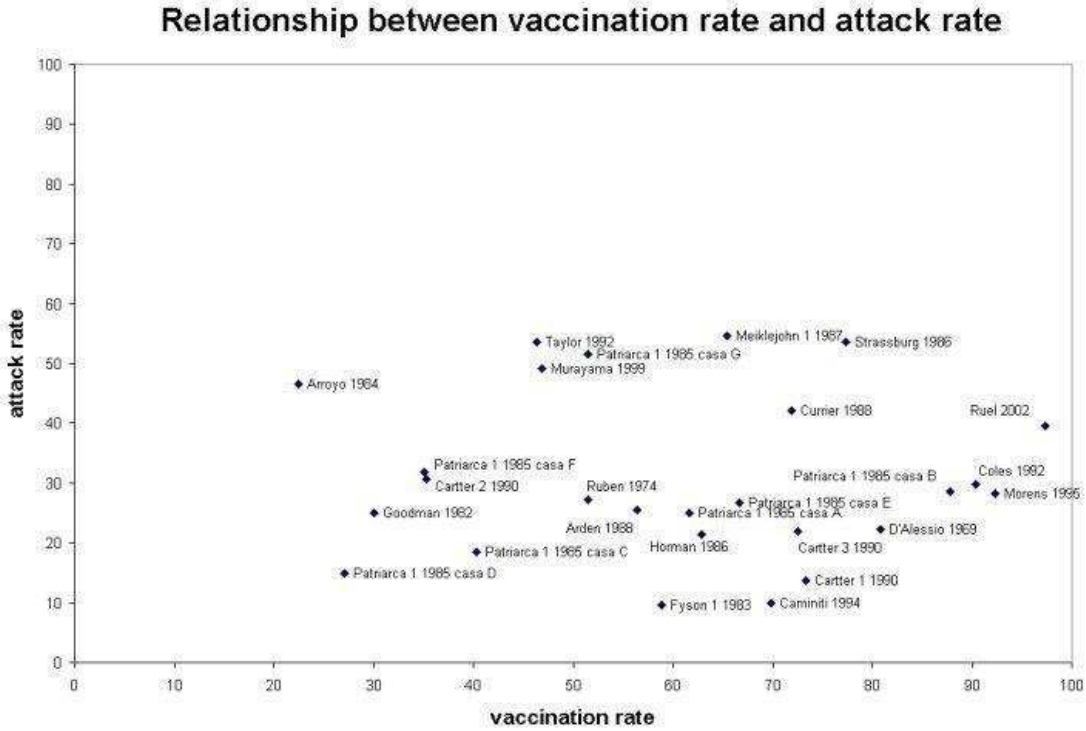
Studies recorded during outbreaks or periods of high viral circulation

Of the 40 data sets, 29 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; 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 6702 observations, were recorded during outbreaks or periods of high viral circulation. In 26 data sets the influenza virus subtype is positively identified (A/H3N2 in 23 data sets). The focus of 23 data sets (Arden 1988; Arroyo 1984; Cartter 1990a; Cartter 1990b; Cartter 1990c; Coles 1992; Cuneo Crovari 1980; Currier 1988; Taylor 1992; 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-one data sets (Arden 1988; Aymard 1979a; Cartter 1990a; Cartter 1990b; Cartter 1990c; 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; Saah 1986b; Strassburg 1986; Taylor 1992) from 17 studies provided information about vaccine content match with circulating influenza viruses. We thus grouped our analyses by viral circulation and vaccine match.

Twenty-one data sets assessed the effectiveness of influenza vaccines in preventing influenza-like illnesses (comparison 01.01.01 and comparison 01.01.02). 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%; comparison 01.01.01) when vaccine matching was good and not significantly different from no vaccination (RR 0.77; 95% CI 0.56 to 1.06; comparison 01.01.02) 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 (*see* Additional 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; comparison 01.02.01) and when matching was absent or unknown (RR 0.47; 95% CI 0.22 to 1.04; comparison 01.02.02).
The effectiveness of the vaccines in preventing pneumonia was assessed in 12 data sets (comparison 01.03.01 and comparison 01.03.02; 5296 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%; comparison 01.03.01) 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; Saah 1986a), vaccines had no effect (RR 0.64; 95% CI 0.35 to 1.16; comparison 01.03.02). 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%; comparison 01.04.01). One small study reported a non-significant effect (Coles 1992 ; comparison 01.04.02) when the vaccine did not match the circulating strain.
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; comparison 01.05.01 and comparison 01.05.02). Eighteen studies reported virologic surveillance to confirm influenza virus circulation; of these, 16 had a follow up shorter than 3 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% ; comparison 01.05.01), otherwise it was not effective (RR 0.34; 95% CI 0.11 to 1.02; comparison 01.05.02).
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% (CI 95% 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%; comparison 01.06.01).

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%; comparison 01.01.03) 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; comparison 01.02.03). 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 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%; comparison 01.03.04) in preventing pneumonia.
During periods of low viral circulation, vaccines did prevent hospital admission for pneumonia or influenza (VE 68%; 24% to 86%; comparison 01.04.03). 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%; comparisons 01.05.03 and 01.05.04) (Caminiti 1994; Deguchi 2001; Howells 1975a; Howells 1975b; Howells 1975c; Patriarca 1985b; Saah 1986c).

Cohort studies in community-dwelling elderly

We included 20 studies with 39 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 ; 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 =< 3 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 8 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 1 million observations in 18 data sets from 15 studies (Christenson 2001a; Christenson 2004a; Comeri 1995; Davis 2001c; Fleming 1995; Gavira Iglesias 1987; Gené Badia 1991; 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 (779,934 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%; comparison 02.04.01) but not for cardiac disease (RR 0.87; 95% CI 0.67 to 1.12; comparison 02.09). 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%; comparison 02.08). 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%; comparison 03.06) from 68,032 observations with high heterogeneity (I^2 94.1%) (Fleming 1995; Shapiro 2003; Voordouw 2003).

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

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%; comparison 04.03) 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; comparison 04.06) (Fleming 1995; Shapiro 2003; Voordouw 2003).

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

This is another data set with 7 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: 8 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 (comparison 07.01). 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 (comparison 07.02). 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 (comparison 07.03). 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(comparison 07.04). Excluding data sets with a follow up period equal to or longer than 6 months (Nordin 2001a ; Voordouw 2003) does not change the final result .

Inactivated influenza and 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; comparison 05.02) and two data sets (Christenson 2001b; Consonni 2004b) assessed the effect on all causes mortality (VE = 56%; 54% to 59%; comparison 05.04).
The addition of PPV did not appear to significantly improve the performance of influenza vaccines.

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 ILI (VE 70%, 44% to 84%; comparison 06.01) and hospitalisations (RR 0.17; 95% CI 0.02 to 1.28; comparison 06.02.03) 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; comparison 06.03.03). 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 10 studies contributing 12 data sets (Ahmed 1995; Ahmed 1997; Crocetti 2001; Fedson 1993a; Fedson 1993b; Foster 1992; Mullooly 1994; Ohmit 1995a; Ohmit 1995b; Ohmit 1999; Puig-Barberà 1997 ; Puig-Barberà 2004). Six data sets from five 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), five looked at the co-administration of inactivated influenza with PPV on institutionalised elderly (Foster 1992; Mullooly 1994; Ohmit 1995a; Ohmit 1995b; Ohmit 1999) and one of adjuvant influenza with PPV on community-dwelling elderly (Puig-Barberà 2004). 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; comparison 08.02.01) (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; comparison 08.01) (Crocetti 2001 ; Puig-Barberà 1997) or affect mortality from influenza and pneumonia, though this conclusion is based on a relatively small data set of 1092 observations (Ahmed 1995; comparison 08.03.01).

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; comparison 11.03) (Ahmed 1995 ; Mullooly 1994) and prevent admission for influenza and pneumonia (OR 0.59; 95% CI 0.47 to 0.74; comparison 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; comparison 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; comparison 09.01) (Foster 1992; Ohmit 1995a; Ohmit 1995b; Puig-Barberà 2004), whereas after adjustment they did (OR 0.68; 95% CI 0.54 to 0.86; comparison 12.01) (Ohmit 1995a; Ohmit 1995b). One study assessed effect of influenza and PPV vaccines on ILI: VE 48%; 32% to 60%; 1198 observations; comparison 10.01(Ohmit 1999).

RCTs

We identified five randomised controlled trials published over four decades and including 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 ILI in conditions of high viral circulation

among elderly individuals living in the community (VE 43%; 21% to 58%; comparison 13.01.01). The vaccines were also effective against influenza (VE 58%; 34% to 73%; comparison 13.02) (Edmondson 1971; Govaert 1994; Rudenko 2001).

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 of greater than 30% and that the heterogeneity of these studies could be explained by grouping by viral circulation and vaccine matching. In additional tables we reported comparisons in which statistical heterogeneity could be explained by differences in viral circulation and degree of vaccine matching or study quality. We used the following keys: statistical heterogeneity could be explained by: (*) differences in viral circulation and degree of vaccine matching; (°) differences in study quality; (+) insufficient data, ( ) not statistically significant (that is, heterogeneity in outcomes not explained by either viral circulation, vaccine matching or study quality groupings). All tests performed were performed at the 10% level of significance

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; comparison 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 (comparison 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 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 GBS with neither cohort nor case control design (Kaplan 1982; Lasky 1998; Schonberger 1979 ; Table 1). Case finding was carried on 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 results of these studies in 'Guillain Barré Syndrome' table. The strong and significant association between A/New Jersey/76 swine vaccine and GBS, 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

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 decision or economic model making. In view of the known variability of incidence and effect of influenza, we constructed a large number of comparisons and strata to reduce possible heterogeneity between studies to a minimum and aid comparability. We also performed sub-analysis of studies describing better defined epidemic periods. Despite our attempts, we noted significant residual heterogeneity between studies that could be explained only in part by different study designs, methodological quality, settings, viral circulation, vaccine types and matching, age, population types and risk factors. We think the residual heterogeneity could be the result of the unpredictable nature of the spread of influenza and ILI and the bias caused by the non-randomised nature of our evidence base. Our sensitivity analysis did not affect the final result.

Our main concern was the quality of included studies 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. 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 further example of the potential effect of such bias is the apparently counter-intuitive effectiveness of the vaccines in elderly individuals living in the community. In this population, 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.

It cannot be discounted that such differences are the result of a baseline imbalance in health status and other systematic differences in the two groups of participants. Recently, empirical confirmation of the presence of selection bias in cohort studies assessing the effectiveness of influenza vaccines has been presented. 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; Simonsen 2005). Proof of bias was provided by a study evaluating the risk of hospitalisation and death in vaccinated compared with unvaccinated seniors in both 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 influenza the season, vaccination was associated with a 61% reduction in risk of this outcome. The reduction in risk before 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 influenza season. In a second, nested case-control, seniors with functional markers of frailty (such as dependence on washing) were found to be at 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). Until improvement of cohort study design is available, the use in non-randomised studies of highly non specific outcome indicators - such as all-cause mortality - are 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 possible on ethical grounds.

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, reporting observations from a few seasons, but that 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 to those drawn from studies in individuals who live in the community. Whereas studies done in residents of care homes often indicate the inevitably improvised nature of efforts to study the effect of vaccines during an epidemic. Often concurrently in several locations, 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 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 and the possible benefits of vaccination are highest.

Safety does not appear to be a particular problem: the public health safety profile of the vaccines is acceptable.

AUTHORS' CONCLUSIONS

Implications for practice

Efforts should be concentrated on achieving high vaccination coverage in long-term care facilities coupled with a systematic assessment of the effect of such a policy. One possible way to improve this strategy may be to also vaccinate carers in an effort to reduce transmission. More comprehensive and effective strategies for the control of acute respiratory infections should be implemented, which may rely on several preventive interventions that take into account the multi-agent nature of 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.

Investment in the development of better vaccines than available at present 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.

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* *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 4/11/89 to 23/2/90. 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 1/12/89 to 31/1/90. 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

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 day 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

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 31/1/83 to 25/2/83. 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

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 1/12/90 to 30/4/91. 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 two 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

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 1/12/84 to 15/1/85. 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 15/1/85 to 15/2/85. 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 day 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

Cartter 1990b

(*Continued*)

Risk of bias

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 1/2/85 to 10/4/85. 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 day 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 1/12/98 to 31/5/99. 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
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 1/12/98 to 31/5/99. 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 Dec 1999 to Nov 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
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

Christenson 2004a

(*Continued*)

	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 Dec 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 26/12/87 to 25/1/88. Throat swab and paired sera specimens were obtained from some ill residents

Coles 1992

(*Continued*)

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 one 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 01/12/91 to 29/02/92. 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

Consonni 2004a

(*Continued*)	
	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 one systemic symptom: headache, discomfort, myalgia, chills or sweating, weakness + at least one 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 one systemic symptom: headache, discomfort, myalgia, chills or sweating, weakness + at least one 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	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 1/12/94 to 31/3/95. 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 1/11/78 to 31/5/79. 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 4fold 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
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 8/1/88 to 26/1/88. Throat swab 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 + one 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
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 15/11/94 to 31/3/95. 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 15/11/95 to 31/3/96. 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 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

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 15/11/96 to 31/3/97. 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 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 1/11/98 to 31/3/99. 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
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 1/12/82 to 28/2/83. 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 institutionalized 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
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 1/12/85 to 15/2/86. 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 swab and paired sera specimens were obtained from residents
Participants	222 nursing home residents (154 treated and 68 controls, all included in the analysis); elderly
Interventions	Parenteral influenza vaccine: A/Victoria/3/75; A/Scotland/840/74; B/Hong Kong/8/73 . Vaccine strains matched circulating strains
Outcomes	Laboratory confirmed influenza, deaths from influenza
Notes	Poor reporting; no confounder's 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 1/11/89 to 15/1/90. As vaccine used in 1988 and 1989 were antigenically closely related, two 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 1/11/89 to 30/4/90. 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
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 3/11/82-17/1/83. 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 confounder's 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 30/11/82 to 9/1/83. Throat swab and paired sera specimens were obtained from some residents
Participants	171 female, chronically ill nursing home residents (53 treated and 118 controls, all included in the analysis); 19 to 105 years old
Interventions	Parenteral whole influenza vaccine: A/Brazil/11/78; A/Bangkok/1/79; B/Singapore/222/80. Vaccine strains probably matched circulating strains
Outcomes	Clinically defined ILI without further specification; death from pneumonia
Notes	Poor reporting; no confounder's 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 1/11/88 to 30/5/89. 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
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

Goodman 1982

(*Continued*)

	season; medical charts and hospital charts were reviewed. Follow up period was 12/12/80 to 21/1/81. 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 (12/12/80 to 21/1/81), 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, randomized, 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
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 1/11/91 to 30/4/92. 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 1/11/82 to 30/4/83. 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 3 managed care organisation database. Follow up period was 5/10/96 to 3/5/97
Participants	122,974 members of a medical care program 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 3 managed care organisation database. Follow up period was 23/11/97 to 4/4/98
Participants	158,454 members of a medical care program 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

Horman 1986

Methods	Authors investigated an outbreak in a nursing home, in Maryland, USA during the 1980 to 1981 influenza season; resident's medical records were reviewed. Follow up period was 8/12/80 to 13/1/81. Throat swab

Horman 1986

(*Continued*)

	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 (two 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

Howarth 1987b

(*Continued*)

Participants	365 residents in 17 nursing homes (184 treated and 181 controls, all included in the analysis), 44 to 99
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. None 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 1972-1973 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 1/1/97 to 11/1/97. 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

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 01/09/79 to 31/03/80 and 01/09/80 to 31/03/81
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 eight-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 31/12/01 to 31/5/02. 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

Keitel 1996

(*Continued*)

	were allocated to receive ascending doses (15- 45- 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 (four 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 01/09/92 to 28/02/93 and 01/09/93 to 28/02/94
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 six-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

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

Mangtani 2004b

(*Continued*)

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
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
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

Mangtani 2004g

(*Continued*)

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

Mangtani 2004h

Methods	See Mangtani. Influenza season 1996 to 1997
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 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
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 2/1/85 to 3/3/85. 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

Meiklejohn 1987

(*Continued*)	
	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
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 1/11/91 to 29/2/92.
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 seven day period during community documented virus circulation or when virus was isolated from cases
Notes	Both influenza A (H3N2) and A (H1N1) cocirculated 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

Morens 1995

(*Continued*)	
	was 15/12/89 to 28/1/90. 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
Notes	Amantadine was administered to all patients over a one 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 15/12/91 to 28/2/92. Paired sera specimens were collected from 7 cases in two 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

Mullooly 1994

(*Continued*)	
	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), hospitalized death
Notes	Most of the seasons were epidemic, and vaccine strains did not match the circulating strains. The study controls for confounders in analysis (age, sex, pneumococcal vaccination). Data are stratified by health status, but allow only quantitative analysis. The 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 two consecutive outbreaks in the same nursing home in Japan, during the 1996 to 1997 influenza season; patients records were reviewed. Follow up period was 25/12/96 to 14/1/97 and 19/2/97 to 26/2/97. 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 1/10/90 to 31/3/91. The rate was adjusted for age, sex, health status, pneumococcal vaccination
Participants	25,532 members of a medical care program continuously enrolled for the 1 year period (11,483 treated and 14,049 controls, all included in the analysis), 65 years or older
Interventions	Parenteral influenza vaccine. 3% of vaccinees and 1% of unvaccinated received pneumococcal vaccination. Vaccine strains matched the circulating strain
Outcomes	Hospitalisation from pneumonia and influenza (ICD 480-487), hospitalisation from all respiratory conditions (ICD 460, 462, 465-466, 480-487, 490-96, 500-518), hospitalisation from congestive heart failure (ICD 428), death from all causes (not reported)
Notes	The season was an epidemic one. Data 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 1/10/91 to 31/3/92. 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 1/10/92 to 31/3/93. 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 omogeneous 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 15/11 to 31/2. A sub-group 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
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 15/11 to 31/3. 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 15/11 to 31/2. 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
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 15/11 to 31/3. 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 18/10/93 to 19/12/93. 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 5/10/96 to 3/5/97

Nordin 2001a

(*Continued*)

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 3 managed care organisation database. Follow up period was 23/11/97 to 4/4/98
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 1/11/90 to 30/4/91. 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

Ohmit 1995a

(*Continued*)

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 USA Michigan, during the 1991-1992 influenza season, in the community. Data sources were: database discharge diagnoses, mailed questionnaire. Follow up period was 1/11/91-30/4/92. 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 10/12/82 to 4/3/83
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
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 10/12/82 to 4/3/83
Participants	458 residents in 6 nursing homes without outbreak (339 treated and 119 controls, all included in the analysis)

Patriarca 1985b

(*Continued*)

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 30/11/00 to 31/3/01
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 one systemic symptom: headache, myalgia, chills, weakness + at least one 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

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

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 15/11/94 to 31/3/95. 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 istitutionalised persons (94 cases and 166 controls, were identified; 83 and 166 were included in

Puig-Barberà 1997

(*Continued*)	
	analysis respectively), 65 years or older
Interventions	Parenteral influenza vaccine. Vaccine strains matched the circulating strain
Outcomes	Hospitalisation for pneumonia; pneumonia was clinically defined and radiologically confirmed
Notes	The study controls for confounders in analysis: health status, age, socio-economic factors. The season 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 15/11/02 to 31/03/03. 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 20/12/72 to 28/1/73. Throat swab were obtained from ill residents
Participants	392 nursing home residents (204 treated and 192 controls, all included in the analysis). Patients were both

Ruben 1974

(*Continued*)	
	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, randomized, double blind, placebo controlled; random sample stratified by age and underlying health conditions. Follow up period was 20/1/97 2/3/97
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 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 1/11/79 to 30/4/80
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 1/11/80 to 30/4/81
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

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 1/11/81 to 30/4/82
Participants	451 residents in nursing home for healthy and ill elderly (225 treated and 226 controls, all included in the

Saah 1986c

(*Continued*)	
	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

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

Saito 2002b

(*Continued*)	
	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 01/10/76 to 31/01/77
Participants	USA population
Interventions	Monovalent A/New Jersey/76 or bivalent A/New Jersey/76 and A/Victoria/75 parenteral vaccine
Outcomes	Cases of Guillain-Barré syndrome.
Notes	Results were stratified by age group and vaccine type. Vaccination rates in population were obtained from national immunisation survey

Risk of bias

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 strais probably matched the circulating strain (literature)
Outcomes	Hospitalisation for any reason; deaths from all causes
Notes	Very poor description of methods; none 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 1/2/83 to 31/3/83. 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

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 1/2/66 to 30/4/66
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

Stuart 1969

(*Continued*)	
	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 29/1/89 to 1/3/89. 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 as age, gender or level of care required
Interventions	Parenteral influenza vaccine: A/Taiwan; A/Sichuan; B/Victoria. Vaccine strains probably matched circulating strains
Outcomes	Outbreak associated cases: clinically defined ILI (fever + cough) or laboratory confirmed influenza (4-fold increase in antibody titre); pneumonia, hospitalisation from ILI or pneumonia, deaths from ILI or pneumonia
Notes	Vaccination was not offered to staff. Positive specimens showed a diagnostic titre rise to A/Sichuan, but no virus was isolated: matching was only hypothetic. Amantadine was not used. Laboratory confirmed cases were analysed by intention-to-treat

Risk of bias

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 dyspnea), 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 1/9/96 to 1/6/97. For every individuals who had received an influenza vaccination, one 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
Interventions	Parenteral influenza vaccine. Vaccine strais 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

[a] OR = odds ratio
Rx = X-ray
HCWs = health care workers

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

Study	Reason for exclusion
Allsup 2001	Elderly denominator 19 and no breakdown of cases by age groups is given
Allsup 2003	See Allsup 2004
Anonymous 1995	Comment
Anonymous 2004a	Elderly denominator 19 and no breakdown of cases by age groups is given
Anonymous 2004b	No data presented
Ansaldi 2002	Cross-sectional study
Arden 1986	Review
Armstrong 2004	Data presented cannot be used in the analysis. The statistical model is not comparable with that used in the other studies
Arroyo 1988	Description of epidemic
Arya 2003	No data presented
Ayala-Montiel 2004	No placebo / do nothing comparator : influenza + pneumococcus versus influenza vaccine
Baldo 1999	Lack of a control group
Barker 1980	Cross-sectional study
Bektimirov 1993	No original data presented
Belshe 2004	Children and adults
Ben-Yehuda 2003	No placebo / do nothing comparator
Berg 2004	The study does not investigate the vaccine efficacy
Buxton 2001	Lack of a control group
Carman 2000	Data are not presented by vaccine condition
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

(*Continued*)

Study	Reason for exclusion
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
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-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
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
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
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
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

(*Continued*)

Study	Reason for exclusion
Knottnerus 1996	Cost of illness study
Kurland 1984	Non-comparative study
Landi 2003	One-year follow up in a population with important diseases
Lavergne 1980	No placebo /do nothing comparator, serological responses and age group?
Lawson 2000	Frequency data not reported
Lindahl 1999	Case report
Lohse 1999	Case report
Luce 2001	Economic evaluation
Mair 1974	Lack of a control group
Mandal 1973	Descriptive
Manzano 2000	Case report
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
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
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
Oshitani 2000	Ecological study
Parkin 1978	Case series
Parsons 1997	No data
Patel 1988	Case report
Patriarca 1985	The study does not investigate the vaccine efficacy
Patriarca 1994	Comment
Pena-Rey 2003	The study does not investigate the vaccine efficacy
Perez 2000	Case report
Perez-Tirse 1992	Review of economic evaluations
Perucchini 2004	Lack of a control group
Peters 1988	Serological outcomes
Philip 1969	Data by age are not presented
Phillips 1970	Lack of a control group
Phillips 1971	Comment
Piedra 2002	Study population is children

(*Continued*)

Study	Reason for exclusion
Poe 1977	Not about vaccine effectiveness
Poland 2002	Review
Potter 1997	Data are not presented by vaccine condition
Powers 1991	Serological outcome only
Pregliasco 1997	Not about vaccine effectiveness
Pregliasco 1999	The study does not investigate the vaccine efficacy
Profeta 1987	Serological outcome only
Provinciali 1994	Unclear study design
Puig Barberà 1995	Review
Puretz 1979	Review
Pyhala 1997	Guideline
Quinlisk 1990	Not about vaccines
Quinnan 1983	Does not report safety outcomes by age 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 descripion; absence of definitions, incoherence between data reported in text and data reported in tables
Sethi 2002	Not about vaccines
Sharbaugh 1997	Descriptive study
Shinkawa 2002	No data
Shoji 2003	Comment
Siewert 1988	The study does not investigate the vaccine efficacy
Simonsen 2005	Ecological study
Skowronski 2003	High risk groups
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
Upshur 2000	Descriptive study
Urquhart 1974	Antibody titres
Uyeki 2003	The study does not investigate the vaccine efficacy
Vallee 2000	No data presented
Van Horren 1976	Not about effectiveness
Verde 1973	Serological outcomes
Verweij 2002	Ethical study
Visconti 1973	Serological outcomes

(*Continued*)

Study	Reason for exclusion
Voordouw 2004	Lack of a control group
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	One-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
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

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	25	9211	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.65, 0.87]
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	5	919	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.06]
1.3 No outbreak - vaccine matching	4	2329	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
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]
3 Pneumonia	16	7097	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.42, 0.65]
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	4	814	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.16]
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 flu or pneumonia	11	24855	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.29, 0.74]
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	1	124	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.07, 21.61]
4.3 No outbreak - vaccine matching	2	22704	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.14, 0.76]
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]

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	3	4904	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.58, 1.89]
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]
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]
2.3 Non epidemic year - vaccine matching	1	17822	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.27, 0.91]
3 Pneumonia	2	18090	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]
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)	3.00 [0.16, 57.42]
4 Hospitalisation for flu or pneumonia	8	779934	Risk Ratio (M-H, Random, 95% CI)	0.72 [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]
4.3 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]
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]
5.3 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]
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	7	404759	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.45, 0.76]
8.1 Epidemic year - vaccine matching	4	300332	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.50, 0.70]
8.3 Non epidemic year - vaccine matching	3	104427	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.30, 1.39]
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]
9.3 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]
1.3 Non epidemic year - vaccine matching	1	6423	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.17]
2 Pneumonia	1	6423	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
2.3 Non epidemic year - vaccine matching	1	6423	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
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]
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]
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]
6.3 Non epidemic year - vaccine matching	2	65688	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.17, 1.28]
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]
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]
1.3 Non epidemic year - vaccine matching	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.17]
2 Pneumonia	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.92]
2.3 Non epidemic year - vaccine matching	1	11399	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.92]
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]
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]
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]
6.3 Non epidemic year - vaccine matching	2	36774	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.30]
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]
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]
1.3 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 disesase	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]
2.3 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]
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]
4.3 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]
1.3 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 disesase	2	498	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.28]
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]

3.3 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]
1.2 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	3	20582	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.26]
2.1 Outbreak - vaccine matching	3	20582	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.26]
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]

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]
1.3 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]
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]
1.4 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 - healty 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 Hospitalisations for influenza or pneumonia	2	4879	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.30, 0.90]
4.1 Outbreak - vaccine matching - community - healthy	1	699	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 Outbreak - vaccine matching - nursing home - healthy	1	4180	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.30, 0.90]
5 Deaths from influenza or pneumonia	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 All deaths	1	699	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.11, 9.72]
6.1 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 - healty and ill	1	220	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.17]

Comparison 16. Sensitivity analysis Comparison 01: subgoups 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)	1.76 [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]

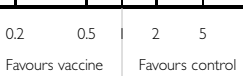
Analysis 1.1. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 1 ILI.

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)					
Goodman 1982	6/36	24/84		2.3 %	0.58 [0.26, 1.30]
Horman 1986	22/100	12/59		3.2 %	1.08 [0.58, 2.02]
Strassburg 1986	34/65	11/19		4.5 %	0.90 [0.58, 1.41]
Patriarca 1985a	113/548	155/470		6.8 %	0.63 [0.51, 0.77]
Fyson 1983a	23/321	29/224		3.9 %	0.55 [0.33, 0.93]
Meiklejohn 1987	14/36	16/19		4.5 %	0.46 [0.29, 0.73]
Cartter 1990c	75/332	25/126		4.9 %	1.14 [0.76, 1.70]
Arden 1988	6/31	8/24		1.9 %	0.58 [0.23, 1.45]
Cartter 1990a	15/96	3/35		1.3 %	1.82 [0.56, 5.92]
Cartter 1990b	12/30	14/55		3.2 %	1.57 [0.84, 2.95]
Taylor 1992	25/45	27/52		5.2 %	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		6.7 %	0.91 [0.73, 1.13]
Mukerjee 1994	62/250	121/216		6.4 %	0.44 [0.35, 0.57]



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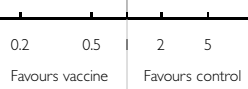
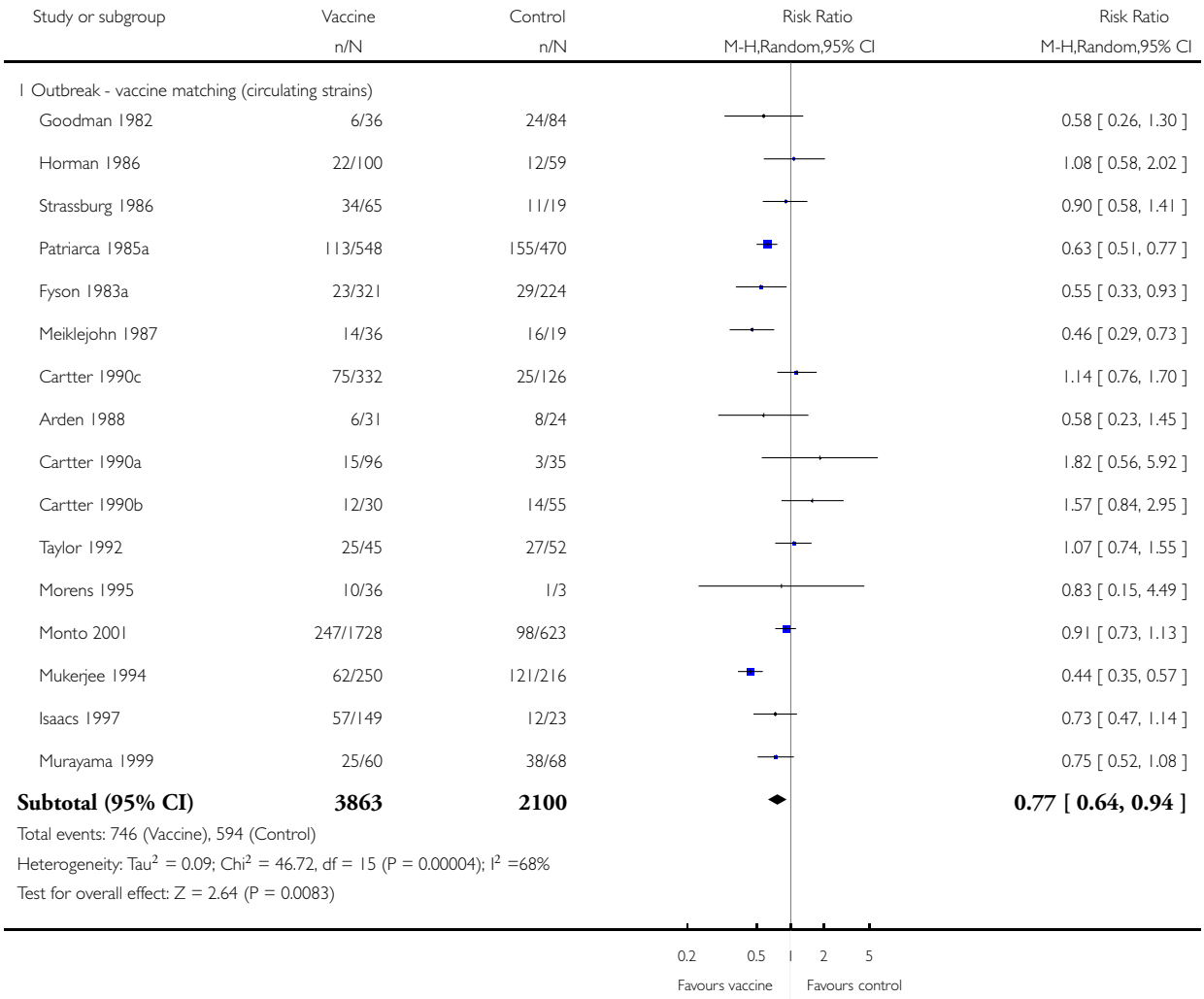
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Isaacs 1997	57/149	12/23		4.6 %	0.73 [0.47, 1.14]
Murayama 1999	25/60	38/68		5.3 %	0.75 [0.52, 1.08]
Subtotal (95% CI)	**3863**	**2100**		**65.5 %**	**0.77 [0.64, 0.94]**
Total events: 746 (Vaccine), 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					
D'Alessio 1969	29/131	7/31		2.7 %	0.98 [0.47, 2.03]
Ruben 1974	38/204	70/192		5.5 %	0.51 [0.36, 0.72]
Arroyo 1984	10/26	44/90		3.9 %	0.79 [0.46, 1.34]
Coles 1992	34/112	3/12		1.6 %	1.21 [0.44, 3.37]
Currier 1988	36/87	15/34		4.5 %	0.94 [0.60, 1.48]
Subtotal (95% CI)	**560**	**359**		**18.1 %**	**0.77 [0.56, 1.06]**
Total events: 147 (Vaccine), 139 (Control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 7.01, df = 4 (P = 0.14); I^2 =43%					
Test for overall effect: Z = 1.61 (P = 0.11)					
3 No outbreak - vaccine matching					
Patriarca 1985b	37/339	20/119		4.1 %	0.65 [0.39, 1.07]
Caminiti 1994	12/169	12/73		2.5 %	0.43 [0.20, 0.92]
Saito 2002a	58/331	112/368		6.1 %	0.58 [0.44, 0.76]
Saito 2002b	68/743	14/187		3.7 %	1.22 [0.70, 2.12]
Subtotal (95% CI)	**1582**	**747**		**16.4 %**	**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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**6005**	**3206**		**100.0 %**	**0.75 [0.65, 0.87]**
Total events: 1068 (Vaccine), 891 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 61.54, df = 24 (P = 0.00004); I^2 =61%					
Test for overall effect: Z = 3.82 (P = 0.00014)					



Review: Vaccines for preventing influenza in the elderly

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

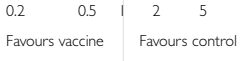
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching absent or unknown				
D'Alessio 1969	29/131	7/31		0.98 [0.47, 2.03]
Ruben 1974	38/204	70/192		0.51 [0.36, 0.72]
Arroyo 1984	10/26	44/90		0.79 [0.46, 1.34]
Coles 1992	34/112	3/12		1.21 [0.44, 3.37]
Currier 1988	36/87	15/34		0.94 [0.60, 1.48]
Subtotal (95% CI)	**560**	**359**		**0.77 [0.56, 1.06]**
Total events: 147 (Vaccine), 139 (Control)				
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.01$, df = 4 (P = 0.14); I^2 =43%				
Test for overall effect: Z = 1.61 (P = 0.11)				

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	Risk Ratio M-H,Random,95% CI
3 No outbreak - vaccine matching				
Patriarca 1985b	37/339	20/119		0.65 [0.39, 1.07]
Caminiti 1994	12/169	12/73		0.43 [0.20, 0.92]
Saito 2002a	58/331	112/368		0.58 [0.44, 0.76]
Saito 2002b	68/743	14/187		1.22 [0.70, 2.12]
Subtotal (95% CI)	**1582**	**747**		**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)				



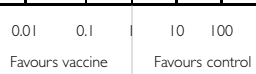
Analysis 1.2. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 2 Influenza.

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 %**	**Not estimable**
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)					



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	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Feery 1976	31/154	12/63		1.06 [0.58, 1.92]
Gross 1988	1/181	6/124		0.11 [0.01, 0.94]
Taylor 1992	16/45	9/52		2.05 [1.01, 4.19]
Morens 1995	6/36	0/3		1.41 [0.10, 20.60]
Subtotal (95% CI)	**416**	**242**		**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)

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	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching absent or unknown				
Ruben 1974	8/204	14/192		0.54 [0.23, 1.25]
Cuneo Crovari 1980	1/86	6/110		0.21 [0.03, 1.74]
Subtotal (95% CI)	**290**	**302**		**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)

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	Risk Ratio M-H,Random,95% CI
3 No outbreak - vaccine matching				
Howarth 1987a	2/229	4/97		0.21 [0.04, 1.14]
Howarth 1987b	0/184	1/181		0.33 [0.01, 8.00]
Subtotal (95% CI)	**413**	**278**		**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)				

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					
Saah 1986b	12/244	11/214		7.3 %	0.96 [0.43, 2.12]
Horman 1986	6/100	5/59		3.5 %	0.71 [0.23, 2.22]
Patriarca 1985a	22/548	45/470		18.9 %	0.42 [0.26, 0.69]
Gross 1988	6/181	8/124		4.3 %	0.51 [0.18, 1.44]
Meiklejohn 1987	4/36	8/19		4.1 %	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		32.0 %	0.57 [0.39, 0.84]
Subtotal (95% CI)	**2918**	**1564**		**73.5 %**	**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)					

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching absent or unknown					
Saah 1986a	11/219	20/234		9.1 %	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)	**444**	**370**		**13.0 %**	**0.64 [0.35, 1.16]**
Total events: 23 (Vaccine), 35 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.19$, df = 3 (P = 0.76); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.46 (P = 0.14)					
3 No outbreak - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
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]
Howells 1975b	3/123	28/267		3.4 %	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		7.3 %	0.57 [0.26, 1.25]
Subtotal (95% CI)	**665**	**1136**		**13.5 %**	**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)	**4027**	**3070**		**100.0 %**	**0.53 [0.42, 0.65]**
Total events: 160 (Vaccine), 230 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 12.36$, df = 15 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.86 (P < 0.00001)					

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	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Saah 1986b	12/244	11/214		0.96 [0.43, 2.12]
Horman 1986	6/100	5/59		0.71 [0.23, 2.22]
Patriarca 1985a	22/548	45/470		0.42 [0.26, 0.69]
Gross 1988	6/181	8/124		0.51 [0.18, 1.44]
Meiklejohn 1987	4/36	8/19		0.26 [0.09, 0.76]
Taylor 1992	3/45	3/52		1.16 [0.25, 5.44]
Morens 1995	5/36	1/3		0.42 [0.07, 2.51]
Monto 2001	65/1728	41/623		0.57 [0.39, 0.84]
Subtotal (95% CI)	**2918**	**1564**		**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)

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	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching absent or unknown				
Saah 1986a	11/219	20/234		0.59 [0.29, 1.20]
Arroyo 1984	2/26	14/90		0.49 [0.12, 2.04]
Currier 1988	4/87	1/34		1.56 [0.18, 13.49]
Coles 1992	6/112	0/12		1.50 [0.09, 25.06]
Subtotal (95% CI)	**444**	**370**		**0.64 [0.35, 1.16]**

Total events: 23 (Vaccine), 35 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.19$, df = 3 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 1.46 (P = 0.14)

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	Risk Ratio M-H,Random,95% CI
4 No outbreak - matching absent or unknown				
Howells 1975a	2/134	18/356		0.30 [0.07, 1.26]
Howells 1975b	3/123	28/267		0.23 [0.07, 0.75]
Howells 1975c	0/183	11/287		0.07 [0.00, 1.15]
Saah 1986c	9/225	16/226		0.57 [0.26, 1.25]
Subtotal (95% CI)	**665**	**1136**		**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)				

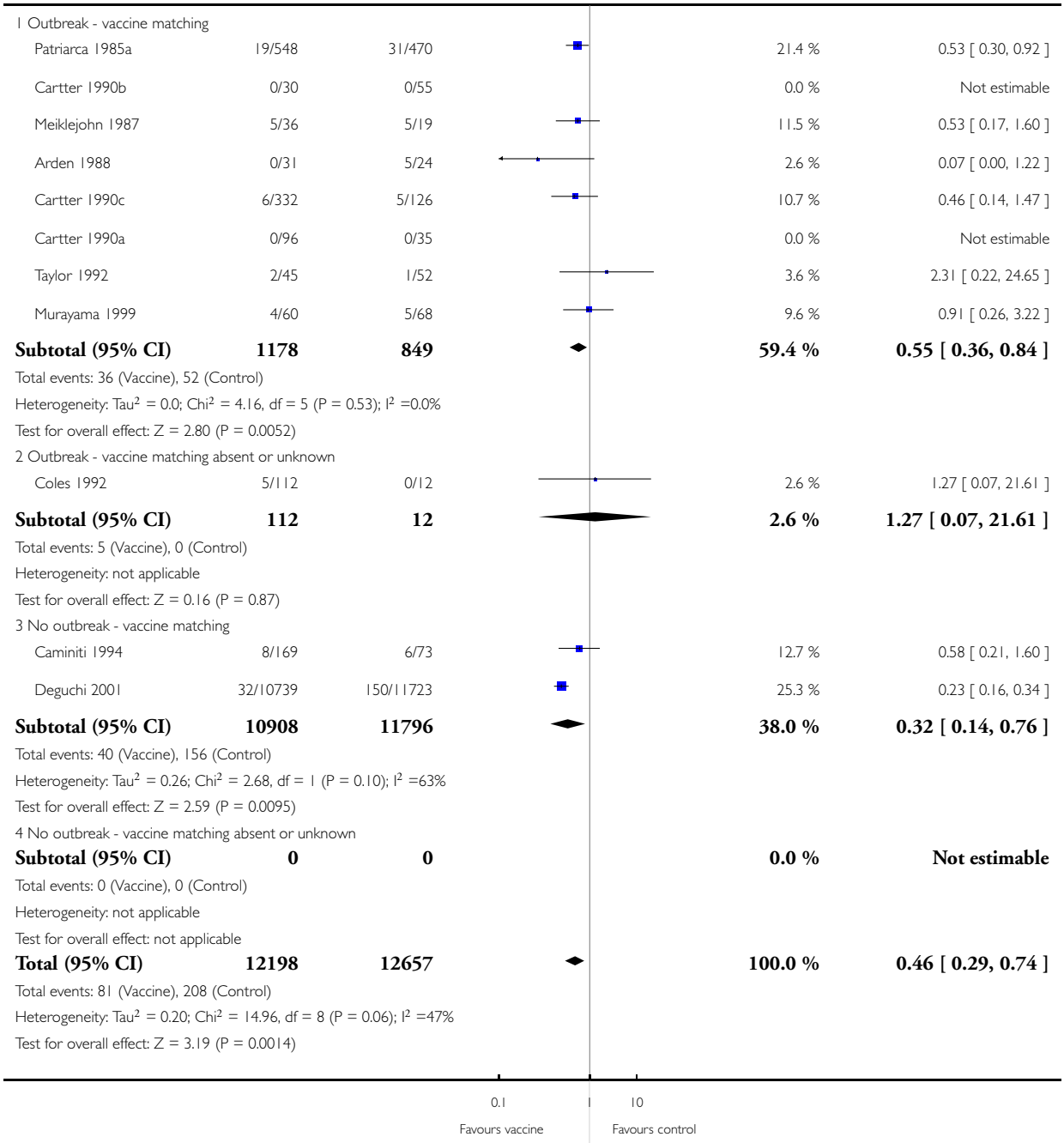
Analysis 1.4. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 4 Hospitalisation for flu or pneumonia.

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisation for 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					
Patriarca 1985a	19/548	31/470		21.4 %	0.53 [0.30, 0.92]
Cartter 1990b	0/30	0/55		0.0 %	Not estimable
Meiklejohn 1987	5/36	5/19		11.5 %	0.53 [0.17, 1.60]
Arden 1988	0/31	5/24		2.6 %	0.07 [0.00, 1.22]
Cartter 1990c	6/332	5/126		10.7 %	0.46 [0.14, 1.47]
Cartter 1990a	0/96	0/35		0.0 %	Not estimable
Taylor 1992	2/45	1/52		3.6 %	2.31 [0.22, 24.65]
Murayama 1999	4/60	5/68		9.6 %	0.91 [0.26, 3.22]
Subtotal (95% CI)	**1178**	**849**		**59.4 %**	**0.55 [0.36, 0.84]**
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					
Coles 1992	5/112	0/12		2.6 %	1.27 [0.07, 21.61]
Subtotal (95% CI)	**112**	**12**		**2.6 %**	**1.27 [0.07, 21.61]**
Total events: 5 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.87)					
3 No outbreak - vaccine matching					
Caminiti 1994	8/169	6/73		12.7 %	0.58 [0.21, 1.60]
Deguchi 2001	32/10739	150/11723		25.3 %	0.23 [0.16, 0.34]
Subtotal (95% CI)	**10908**	**11796**		**38.0 %**	**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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**12198**	**12657**		**100.0 %**	**0.46 [0.29, 0.74]**
Total events: 81 (Vaccine), 208 (Control)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 14.96, df = 8 (P = 0.06); I^2 =47%					
Test for overall effect: Z = 3.19 (P = 0.0014)					



Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisation for flu 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		Not estimable
Meiklejohn 1987	5/36	5/19		0.53 [0.17, 1.60]
Arden 1988	0/31	5/24		0.07 [0.00, 1.22]
Cartter 1990c	6/332	5/126		0.46 [0.14, 1.47]
Cartter 1990a	0/96	0/35		Not estimable
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]**

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)

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisation for flu 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
2 Outbreak - vaccine matching absent or unknown				
Coles 1992	5/112	0/12		1.27 [0.07, 21.61]
Subtotal (95% CI)	**112**	**12**		**1.27 [0.07, 21.61]**

Total events: 5 (Vaccine), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.16 (P = 0.87)

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisation for flu 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
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)				

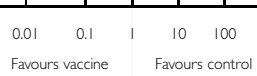
Analysis 1.5. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 5 Deaths from flu or pneumonia.

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]
Horman 1986	5/100	3/59		4.6 %	0.98 [0.24, 3.97]
Saah 1986b	3/244	8/214		5.1 %	0.33 [0.09, 1.22]
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]
Strassburg 1986	4/65	3/19		4.6 %	0.39 [0.10, 1.59]
Goodman 1982	0/36	9/84		1.3 %	0.12 [0.01, 2.02]
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 1990b	0/30	1/55		1.0 %	0.60 [0.03, 14.34]



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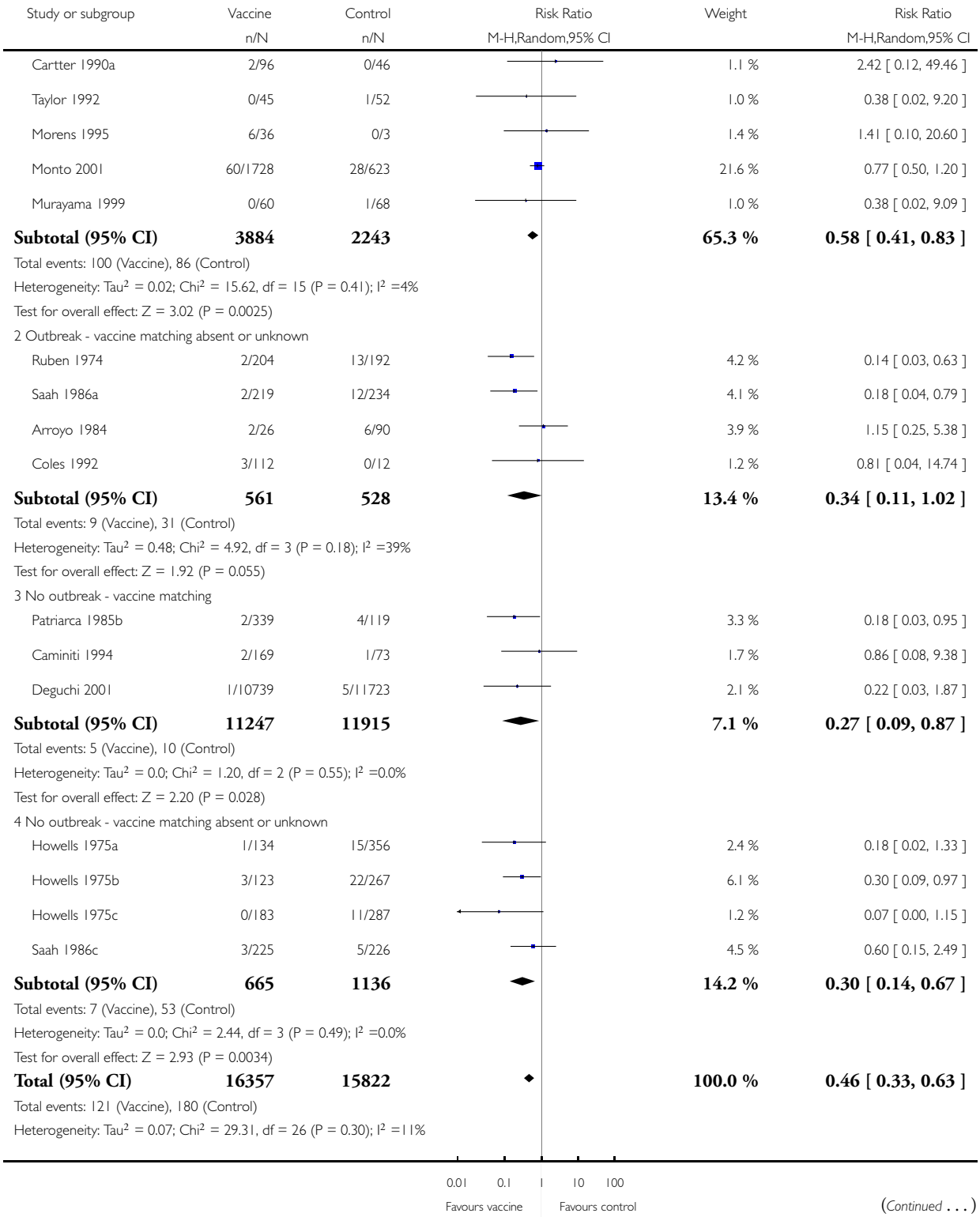

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cartter 1990a	2/96	0/46		1.1 %	2.42 [0.12, 49.46]
Taylor 1992	0/45	1/52		1.0 %	0.38 [0.02, 9.20]
Morens 1995	6/36	0/3		1.4 %	1.41 [0.10, 20.60]
Monto 2001	60/1728	28/623		21.6 %	0.77 [0.50, 1.20]
Murayama 1999	0/60	1/68		1.0 %	0.38 [0.02, 9.09]
Subtotal (95% CI)	**3884**	**2243**		**65.3 %**	**0.58 [0.41, 0.83]**
Total events: 100 (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]**
Total events: 9 (Vaccine), 31 (Control)					
Heterogeneity: Tau^2 = 0.48; Chi^2 = 4.92, df = 3 (P = 0.18); I^2 =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: Tau^2 = 0.0; Chi^2 = 1.20, df = 2 (P = 0.55); I^2 =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: Tau^2 = 0.0; Chi^2 = 2.44, df = 3 (P = 0.49); I^2 =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: Tau^2 = 0.07; Chi^2 = 29.31, df = 26 (P = 0.30); I^2 =11%					

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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 = 4.79 (P < 0.00001)					

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	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Feery 1976	3/154	1/63		1.23 [0.13, 11.58]
Horman 1986	5/100	3/59		0.98 [0.24, 3.97]
Saah 1986b	3/244	8/214		0.33 [0.09, 1.22]
Fyson 1983a	4/321	5/224		0.56 [0.15, 2.06]
Patriarca 1985a	6/548	21/470		0.25 [0.10, 0.60]
Strassburg 1986	4/65	3/19		0.39 [0.10, 1.59]
Goodman 1982	0/36	9/84		0.12 [0.01, 2.02]
Fyson 1983b	3/53	0/118		15.43 [0.81, 293.46]
Meiklejohn 1987	1/36	3/19		0.18 [0.02, 1.58]
Cartter 1990c	3/332	2/126		0.57 [0.10, 3.37]
Cartter 1990b	0/30	1/55		0.60 [0.03, 14.34]
Cartter 1990a	2/96	0/46		2.42 [0.12, 49.46]
Taylor 1992	0/45	1/52		0.38 [0.02, 9.20]
Morens 1995	6/36	0/3		1.41 [0.10, 20.60]
Monto 2001	60/1728	28/623		0.77 [0.50, 1.20]
Murayama 1999	0/60	1/68		0.38 [0.02, 9.09]
Subtotal (95% CI)	**3884**	**2243**		**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)				

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	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching absent or unknown				
Ruben 1974	2/204	13/192		0.14 [0.03, 0.63]
Saah 1986a	2/219	12/234		0.18 [0.04, 0.79]
Arroyo 1984	2/26	6/90		1.15 [0.25, 5.38]
Coles 1992	3/112	0/12		0.81 [0.04, 14.74]
Subtotal (95% CI)	**561**	**528**		**0.34 [0.11, 1.02]**

Total events: 9 (Vaccine), 31 (Control)

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 4.92$, df = 3 (P = 0.18); $I^2 = 39\%$

Test for overall effect: Z = 1.92 (P = 0.055)

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	Risk Ratio M-H,Random,95% CI
3 No outbreak - vaccine matching				
Patriarca 1985b	2/339	4/119		0.18 [0.03, 0.95]
Caminiti 1994	2/169	1/73		0.86 [0.08, 9.38]
Deguchi 2001	1/10739	5/11723		0.22 [0.03, 1.87]
Subtotal (95% CI)	**11247**	**11915**		**0.27 [0.09, 0.87]**

Total events: 5 (Vaccine), 10 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.20$, df = 2 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 2.20 (P = 0.028)

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	Risk Ratio M-H,Random,95% CI
4 No outbreak - vaccine matching absent or unknown				
Howells 1975a	1/134	15/356		0.18 [0.02, 1.33]
Howells 1975b	3/123	22/267		0.30 [0.09, 0.97]
Howells 1975c	0/183	11/287		0.07 [0.00, 1.15]
Saah 1986c	3/225	5/226		0.60 [0.15, 2.49]
Subtotal (95% CI)	**665**	**1136**		**0.30 [0.14, 0.67]**
Total events: 7 (Vaccine), 53 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.44$, df = 3 (P = 0.49); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.93 (P = 0.0034)				

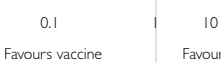
Analysis 1.6. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 6 All deaths.

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 %**	**Not estimable**
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 %**	**Not estimable**



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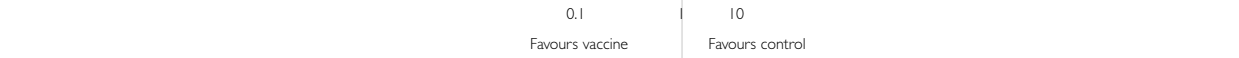
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 No outbreak - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
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)					



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	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Gross 1988	13/181	22/124		0.40 [0.21, 0.77]
Subtotal (95% CI)	**181**	**124**		**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)				

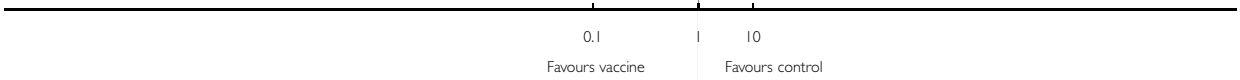
Analysis 1.7. Comparison 1 Influenza vaccines versus no vaccination - Cohort studies in nursing homes, Outcome 7 Influenza cases (clinically defined without clear definition).

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)

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					
Aymard 1979a	5/50	18/50		13.6 %	0.28 [0.11, 0.69]
Fyson 1983b	35/53	48/118		17.7 %	1.62 [1.21, 2.17]
Subtotal (95% CI)	**103**	**168**		**31.3 %**	**0.70 [0.11, 4.56]**
Total events: 40 (Vaccine), 66 (Control)					
Heterogeneity: Tau^2 = 1.70; Chi^2 = 15.33, df = 1 (P = 0.00009); I^2 =93%					
Test for overall effect: Z = 0.37 (P = 0.71)					
2 Outbreak - vaccine matching absent or unknown					
Aymard 1979b	5/85	18/70		13.4 %	0.23 [0.09, 0.59]
Subtotal (95% CI)	**85**	**70**		**13.4 %**	**0.23 [0.09, 0.59]**
Total events: 5 (Vaccine), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.08 (P = 0.0021)					
3 No outbreak - vaccine matching					
Deguchi 2001	256/10739	694/11723		18.2 %	0.40 [0.35, 0.46]
Subtotal (95% CI)	**10739**	**11723**		**18.2 %**	**0.40 [0.35, 0.46]**
Total events: 256 (Vaccine), 694 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 12.65 (P < 0.00001)					
4 No outbreak - vaccine matching absent or unknown					
Howells 1975a	17/134	57/356		16.6 %	0.79 [0.48, 1.31]
Howells 1975b	16/123	43/267		16.4 %	0.81 [0.47, 1.38]
Howells 1975c	0/183	13/287		4.2 %	0.06 [0.00, 0.97]
Subtotal (95% CI)	**440**	**910**		**37.2 %**	**0.72 [0.41, 1.28]**
Total events: 33 (Vaccine), 113 (Control)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 3.63, df = 2 (P = 0.16); I^2 =45%					
Test for overall effect: Z = 1.12 (P = 0.26)					
Total (95% CI)	**11367**	**12871**		**100.0 %**	**0.52 [0.27, 1.02]**
Total events: 334 (Vaccine), 891 (Control)					
Heterogeneity: Tau^2 = 0.62; Chi^2 = 88.75, df = 6 (P<0.00001); I^2 =93%					
Test for overall effect: Z = 1.91 (P = 0.056)					

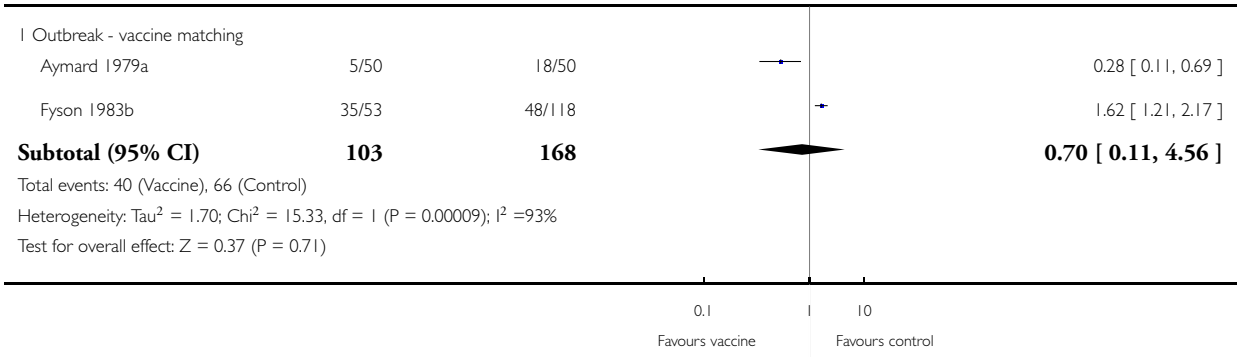


Review: Vaccines for preventing influenza in the elderly

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

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

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				
Aymard 1979a	5/50	18/50		0.28 [0.11, 0.69]
Fyson 1983b	35/53	48/118		1.62 [1.21, 2.17]
Subtotal (95% CI)	**103**	**168**		**0.70 [0.11, 4.56]**
Total events: 40 (Vaccine), 66 (Control)				
Heterogeneity: Tau^2 = 1.70; Chi^2 = 15.33, df = 1 (P = 0.00009); I^2 =93%				
Test for overall effect: Z = 0.37 (P = 0.71)				

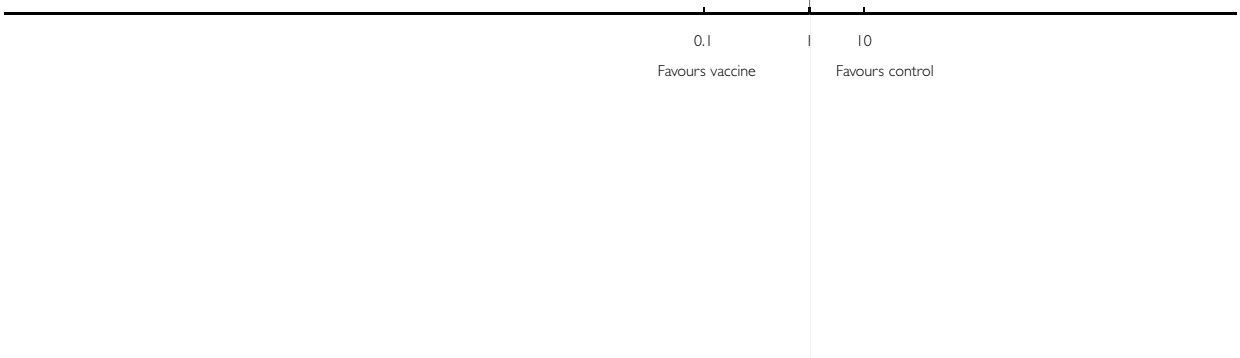


Review: Vaccines for preventing influenza in the elderly

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

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

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching absent or unknown				
Aymard 1979b	5/85	18/70		0.23 [0.09, 0.59]
Subtotal (95% CI)	**85**	**70**		**0.23 [0.09, 0.59]**
Total events: 5 (Vaccine), 18 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 3.08 (P = 0.0021)				



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)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
3 No outbreak - vaccine matching				
Deguchi 2001	256/10739	694/11723		0.40 [0.35, 0.46]
Subtotal (95% CI)	**10739**	**11723**		**0.40 [0.35, 0.46]**
Total events: 256 (Vaccine), 694 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 12.65 (P < 0.00001)				

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)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
4 No outbreak - vaccine matching absent or unknown				
Howells 1975a	17/134	57/356		0.79 [0.48, 1.31]
Howells 1975b	16/123	43/267		0.81 [0.47, 1.38]
Howells 1975c	0/183	13/287		0.06 [0.00, 0.97]
Subtotal (95% CI)	**440**	**910**		**0.72 [0.41, 1.28]**
Total events: 33 (Vaccine), 113 (Control)				
Heterogeneity: Tau^2 = 0.11; Chi^2 = 3.63, df = 2 (P = 0.16); I^2 =45%				
Test for overall effect: Z = 1.12 (P = 0.26)				

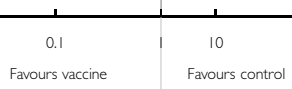
Analysis 2.1. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community - dwellers, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI

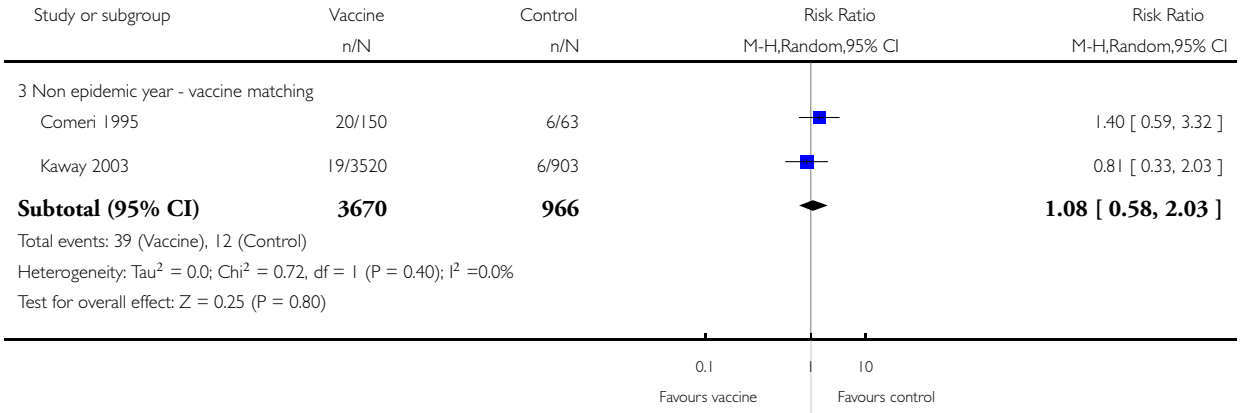
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Non epidemic year - vaccine matching					
Comeri 1995	20/150	6/63		46.4 %	1.40 [0.59, 3.32]
Kaway 2003	19/3520	6/903		41.3 %	0.81 [0.33, 2.03]
Subtotal (95% CI)	**3670**	**966**		**87.7 %**	**1.08 [0.58, 2.03]**
Total events: 39 (Vaccine), 12 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.72$, df = 1 (P = 0.40); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.25 (P = 0.80)					
4 Non epidemic year - vaccine matching absent or unknown					
Gavira Iglesias 1987	4/188	2/80		12.3 %	0.85 [0.16, 4.55]
Subtotal (95% CI)	**188**	**80**		**12.3 %**	**0.85 [0.16, 4.55]**
Total events: 4 (Vaccine), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
Total (95% CI)	**3858**	**1046**		**100.0 %**	**1.05 [0.58, 1.89]**
Total events: 43 (Vaccine), 14 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.79$, df = 2 (P = 0.67); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.17 (P = 0.87)					



Review: Vaccines for preventing influenza in the elderly

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

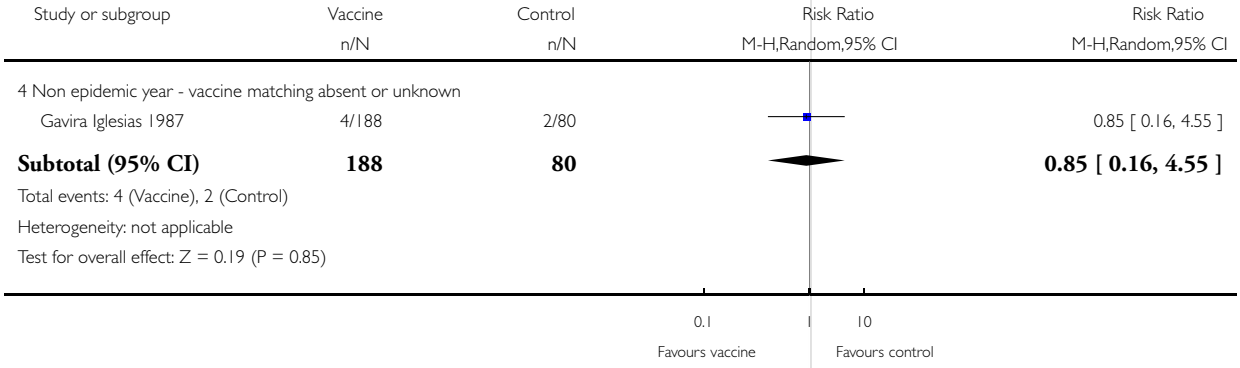
Outcome: 1 ILI



Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI



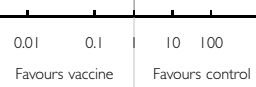
Analysis 2.2. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community - dwellers, Outcome 2 Influenza.

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 %**	**Not estimable**
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 %**	**Not estimable**
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: Tau² = 2.40; Chi² = 5.22, df = 1 (P = 0.02); I² =81%					
Test for overall effect: Z = 1.38 (P = 0.17)					



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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nicholson 1999	1/218	19/209		0.05 [0.01, 0.37]
Subtotal (95% CI)	**218**	**209**		**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)				

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 2 Influenza

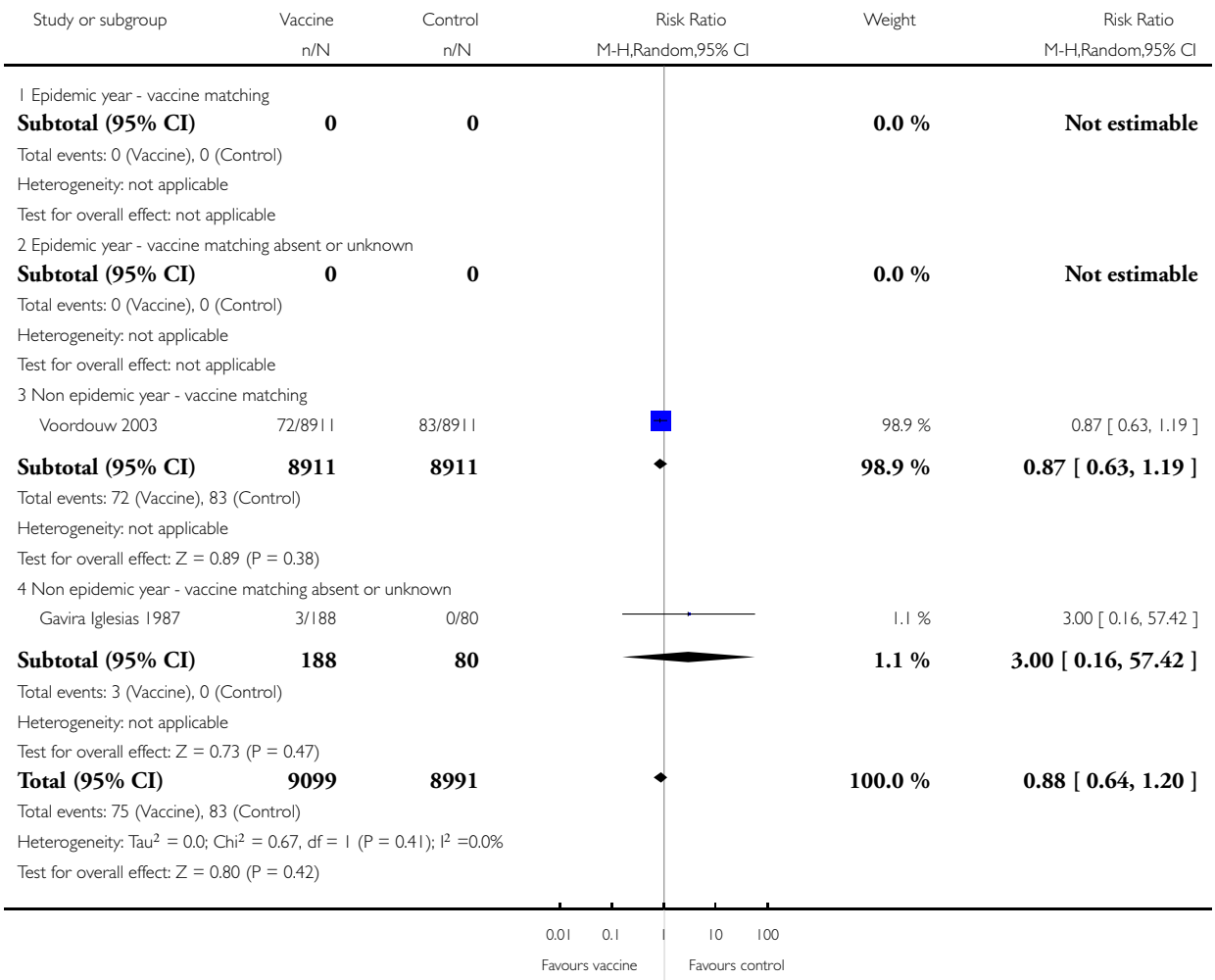
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	16/8911	32/8911		0.50 [0.27, 0.91]
Subtotal (95% CI)	**8911**	**8911**		**0.50 [0.27, 0.91]**
Total events: 16 (Vaccine), 32 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.27 (P = 0.023)				

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

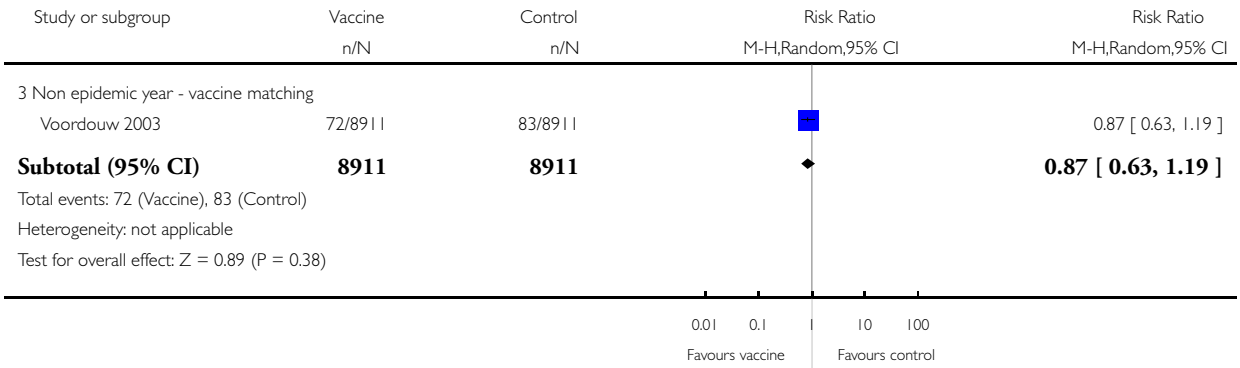
Outcome: 3 Pneumonia



Review: Vaccines for preventing influenza in the elderly

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

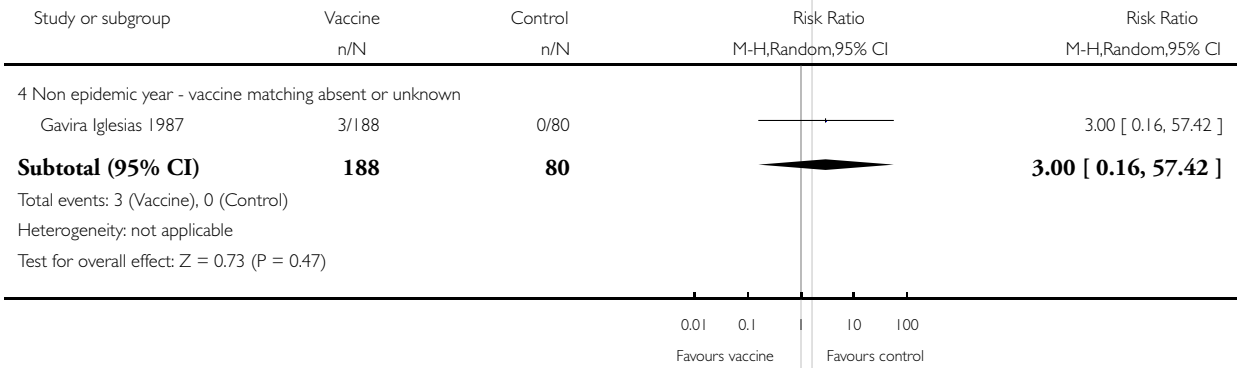
Outcome: 3 Pneumonia



Review: Vaccines for preventing influenza in the elderly

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

Outcome: 3 Pneumonia



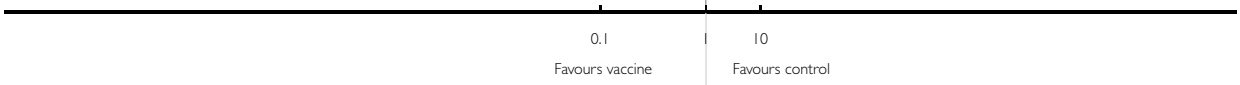
Analysis 2.4. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community - dwellers, Outcome 4 Hospitalisation for flu or pneumonia.

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		10.8 %	0.75 [0.57, 0.97]
Nichol 1998b	246/46480	252/22544		13.1 %	0.47 [0.40, 0.56]
Nichol 2003a	495/77738	581/62317		14.4 %	0.68 [0.61, 0.77]
Christenson 2001a	371/23224	2854/159385		14.6 %	0.89 [0.80, 0.99]
Nichol 2003b	589/87357	501/58971		14.4 %	0.79 [0.70, 0.89]
Christenson 2004a	672/29346	3305/134045		15.1 %	0.93 [0.86, 1.01]
Subtotal (95% CI)	**279433**	**448343**		**82.4 %**	**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 %**	**Not estimable**
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		7.7 %	0.55 [0.37, 0.83]
Subtotal (95% CI)	**11483**	**14049**		**7.7 %**	**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		9.9 %	0.73 [0.54, 0.99]
Subtotal (95% CI)	**14647**	**11979**		**9.9 %**	**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)					
Total (95% CI)	**305563**	**474371**		**100.0 %**	**0.72 [0.62, 0.85]**
Total events: 2593 (Vaccine), 7760 (Control)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 61.71$, df = 7 (P<0.00001); $I^2 = 89\%$					
Test for overall effect: Z = 4.01 (P = 0.000060)					



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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1994b	108/15288	105/11081		0.75 [0.57, 0.97]
Nichol 1998b	246/46480	252/22544		0.47 [0.40, 0.56]
Nichol 2003a	495/77738	581/62317		0.68 [0.61, 0.77]
Christenson 2001a	371/23224	2854/159385		0.89 [0.80, 0.99]
Nichol 2003b	589/87357	501/58971		0.79 [0.70, 0.89]
Christenson 2004a	672/29346	3305/134045		0.93 [0.86, 1.01]
Subtotal (95% CI)	**279433**	**448343**		**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)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Nichol 1994a	34/11483	75/14049		0.55 [0.37, 0.83]
Subtotal (95% CI)	**11483**	**14049**		**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)				

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	Risk Ratio M-H,Random,95% CI
4 Non epidemic year - vaccine matching absent or unknown				
Nichol 1994c	78/14647	87/11979		0.73 [0.54, 0.99]
Subtotal (95% CI)	**14647**	**11979**		**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)				

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 %**	**Not estimable**
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]**

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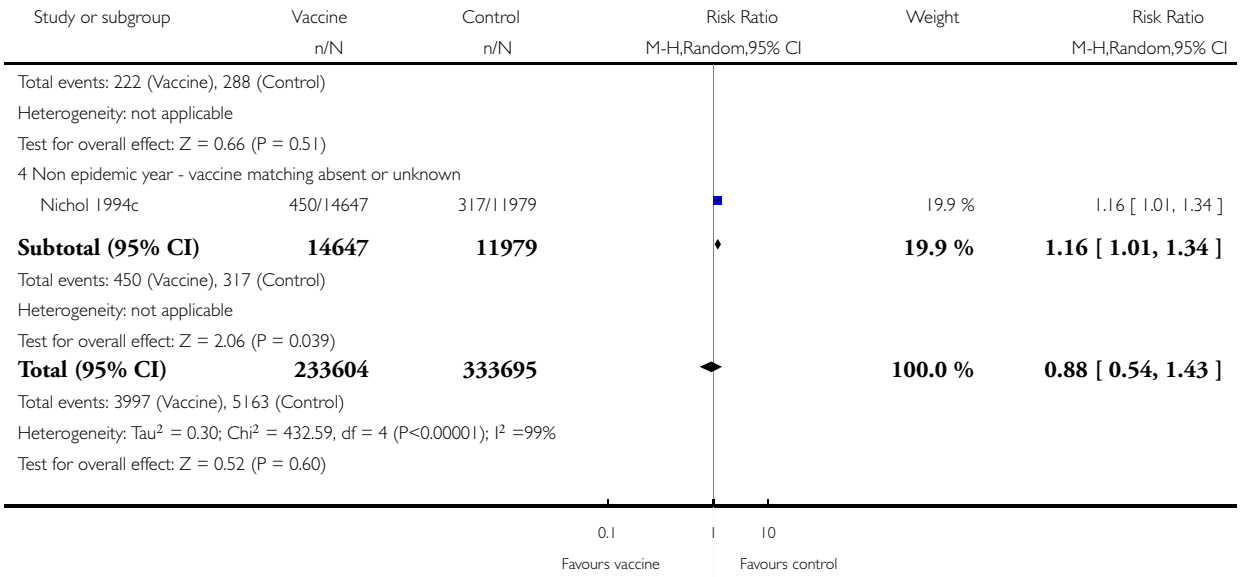
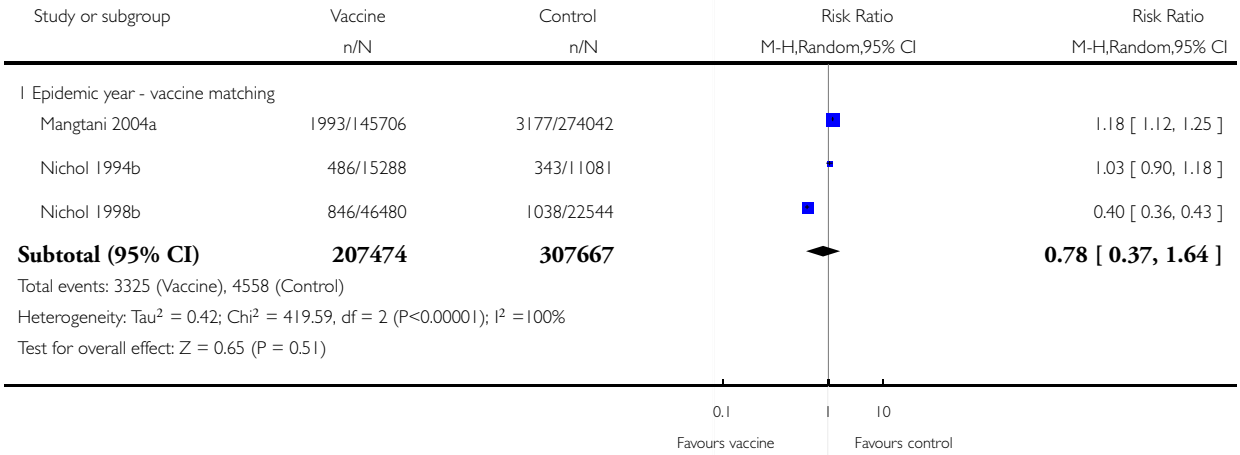


Review: Vaccines for preventing influenza in the elderly

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

Outcome: 5 Hospitalisation for any respiratory disease



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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Nichol 1994a	222/11483	288/14049		0.94 [0.79, 1.12]
Subtotal (95% CI)	**11483**	**14049**		**0.94 [0.79, 1.12]**
Total events: 222 (Vaccine), 288 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.66 (P = 0.51)				

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	Risk Ratio M-H,Random,95% CI
4 Non epidemic year - vaccine matching absent or unknown				
Nichol 1994c	450/14647	317/11979		1.16 [1.01, 1.34]
Subtotal (95% CI)	**14647**	**11979**		**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)				

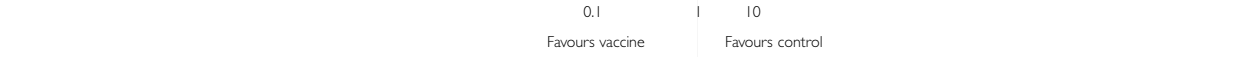
Analysis 2.6. Comparison 2 Influenza vaccines versus no vaccination - Cohort studies in community - dwellers, Outcome 6 Deaths from flu or pneumonia.

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 %**	**Not estimable**
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 %**	**Not estimable**
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 %**	**Not estimable**
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)					



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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Christenson 2004a	90/29346	472/134045		0.87 [0.70, 1.09]
Subtotal (95% CI)	**29346**	**134045**		**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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Mangtani 2004a	2585/147294	3720/279374		1.32 [1.25, 1.39]

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		10.4 %	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		19.2 %	0.56 [0.51, 0.60]
Nichol 2003b	1019/87357	1026/58971		19.2 %	0.67 [0.62, 0.73]
Subtotal (95% CI)	**167692**	**132640**		**53.0 %**	**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 %**	**Not estimable**
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		11.2 %	0.97 [0.58, 1.63]
Voordouw 2003	143/8911	164/8911		17.2 %	0.87 [0.70, 1.09]
Shapiro 2003	269/36596	1052/48044		18.6 %	0.34 [0.29, 0.38]

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**46286**	**58141**		**47.0 %**	**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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**213978**	**190781**		**100.0 %**	**0.58 [0.45, 0.76]**
Total events: 2416 (Vaccine), 3786 (Control)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 94.78, df = 6 (P<0.00001); I^2 =94%					
Test for overall effect: Z = 4.03 (P = 0.000057)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Gen Badia 1991	16/1998	49/2560		0.42 [0.24, 0.73]
Fleming 1995	3/599	98/8792		0.45 [0.14, 1.41]
Nichol 2003a	943/77738	1361/62317		0.56 [0.51, 0.60]
Nichol 2003b	1019/87357	1026/58971		0.67 [0.62, 0.73]
Subtotal (95% CI)	**167692**	**132640**		**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)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Lopez Hernandez 1994	23/779	36/1186		0.97 [0.58, 1.63]
Voordouw 2003	143/8911	164/8911		0.87 [0.70, 1.09]
Shapiro 2003	269/36596	1052/48044		0.34 [0.29, 0.38]
Subtotal (95% CI)	**46286**	**58141**		**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)				

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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					

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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					
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)					
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: Tau² = 0.09; Chi² = 87.72, df = 5 (P<0.00001); I² =94%					
Test for overall effect: Z = 1.08 (P = 0.28)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1994b	81/15288	50/11081		1.17 [0.83, 1.67]
Nichol 1998b	554/46480	553/22544		0.49 [0.43, 0.55]
Nichol 2003a	888/77738	1026/62317		0.69 [0.63, 0.76]
Nichol 2003b	1029/87357	819/58971		0.85 [0.77, 0.93]
Subtotal (95% CI)	**226863**	**154913**		**0.74 [0.56, 0.97]**
Total events: 2552 (Vaccine), 2448 (Control)				
Heterogeneity: Tau² = 0.07; Chi² = 62.97, df = 3 (P<0.00001); I² =95%				
Test for overall effect: Z = 2.16 (P = 0.031)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Nichol 1994a	102/11483	118/14049		1.06 [0.81, 1.38]
Subtotal (95% CI)	**11483**	**14049**		**1.06 [0.81, 1.38]**
Total events: 102 (Vaccine), 118 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.42 (P = 0.68)				

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	Risk Ratio M-H,Random,95% CI
4 Non epidemic year - vaccine matching absent or unknown				
Nichol 1994c	72/14647	37/11979		1.59 [1.07, 2.36]
Subtotal (95% CI)	**14647**	**11979**		**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)				

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					
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)					

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

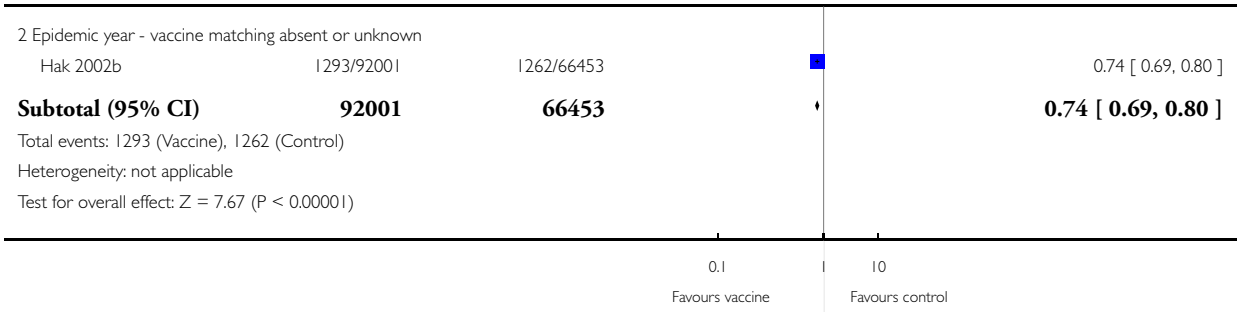
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Fleming 1995	10/599	120/8792		1.22 [0.65, 2.32]
Hak 2002a	896/71005	1065/51969		0.62 [0.56, 0.67]
Subtotal (95% CI)	**71604**	**60761**		**0.80 [0.42, 1.55]**
Total 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)				

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	Risk Ratio M-H,Random,95% CI
2 Epidemic year - vaccine matching absent or unknown				
Hak 2002b	1293/92001	1262/66453		0.74 [0.69, 0.80]
Subtotal (95% CI)	**92001**	**66453**		**0.74 [0.69, 0.80]**
Total events: 1293 (Vaccine), 1262 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 7.67 (P < 0.00001)				



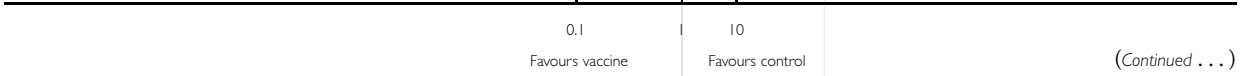
Analysis 3.1. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community dwellers - risk groups, Outcome 1 Influenza.

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 %**	**Not estimable**
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 %**	**Not estimable**
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]



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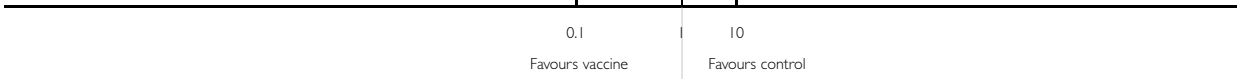
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**3562**	**2861**		**100.0 %**	**0.40 [0.14, 1.17]**
Total events: 5 (Vaccine), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.095)					
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**3562**	**2861**		**100.0 %**	**0.40 [0.14, 1.17]**
Total events: 5 (Vaccine), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.095)					



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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	5/3562	10/2861		0.40 [0.14, 1.17]
Subtotal (95% CI)	**3562**	**2861**		**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 %**	**Not estimable**
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 %**	**Not estimable**
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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**3562**	**2861**		**100.0 %**	**1.22 [0.76, 1.94]**
Total events: 44 (Vaccine), 29 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	44/3562	29/2861		1.22 [0.76, 1.94]
Subtotal (95% CI)	**3562**	**2861**		**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 %**	**Not estimable**
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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**30840**	**15092**	♦	**100.0 %**	**0.74 [0.63, 0.86]**
Total events: 419 (Vaccine), 278 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.97 (P = 0.000072)					

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Favours vaccine Favours control

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1998a	419/30840	278/15092	■	0.74 [0.63, 0.86]
Subtotal (95% CI)	**30840**	**15092**	♦	**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)				

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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 %**	**Not estimable**
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 %**	**Not estimable**
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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
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)					

Review: Vaccines for preventing influenza in the elderly

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

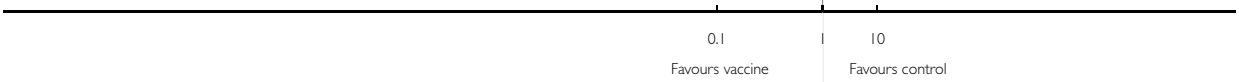
Outcome: 4 Hospitalisation for any respiratory disease

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Mangtani 2004a	1426/67877	1785/75195		0.89 [0.83, 0.95]
Nichol 1998a	1937/30840	1150/15092		0.82 [0.77, 0.88]
Subtotal (95% CI)	**98717**	**90287**		**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

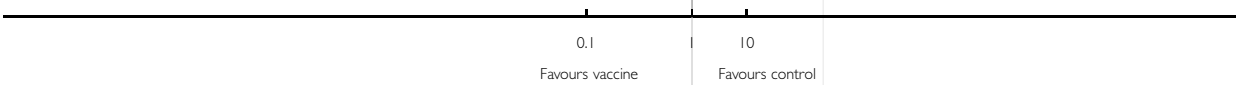
Outcome: 5 Deaths from respiratory disease

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)



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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Mangtani 2004a	1653/66850	2029/75614		0.92 [0.86, 0.98]

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 %**	**Not estimable**
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 %**	**Not estimable**

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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					
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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Fleming 1995	1/265	61/2079		0.13 [0.02, 0.92]
Subtotal (95% CI)	**265**	**2079**		**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)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	75/3562	76/2861		0.79 [0.58, 1.09]
Shapiro 2003	238/28853	872/30412		0.29 [0.25, 0.33]
Subtotal (95% CI)	**32415**	**33273**		**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)				

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 %**	**Not estimable**
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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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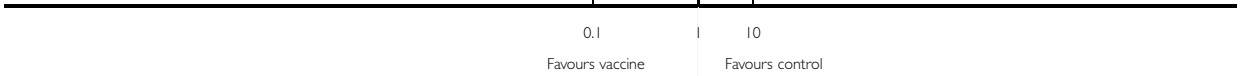
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
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)					

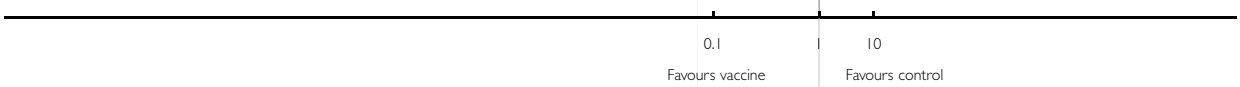


Review: Vaccines for preventing influenza in the elderly

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1998a	917/30840	487/15092		0.92 [0.83, 1.03]
Subtotal (95% CI)	**30840**	**15092**		**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)				



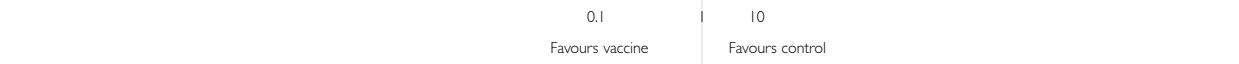
Analysis 3.8. Comparison 3 Influenza vaccines versus no vaccination - Cohort studies - community dwellers - risk groups, Outcome 8 Combined outcome: all deaths or severe respiratory illness.

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)					

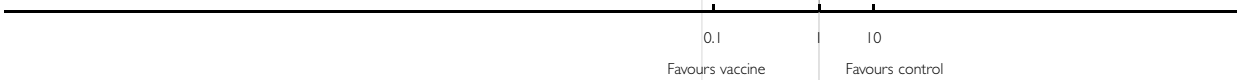


Review: Vaccines for preventing influenza in the elderly

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Hak 2002a	695/33312	811/21126		0.54 [0.49, 0.60]
Subtotal (95% CI)	**33312**	**21126**		**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)				



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	Risk Ratio M-H,Random,95% CI
2 Epidemic year - vaccine matching absent or unknown				
Hak 2002b	1129/57846	995/33964		0.67 [0.61, 0.72]
Subtotal (95% CI)	**57846**	**33964**		**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)				

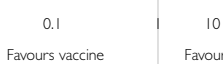
Analysis 4.1. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community dwellers - no risk groups, Outcome 1 Influenza.

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 %**	**Not estimable**
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 %**	**Not estimable**
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					



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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
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)					

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	11/5349	22/6050		0.57 [0.27, 1.17]
Subtotal (95% CI)	**5349**	**6050**		**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 %**	**Not estimable**
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 %**	**Not estimable**
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 %**	**Not estimable**
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)					

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	28/5349	54/6050		0.59 [0.37, 0.92]
Subtotal (95% CI)	**5349**	**6050**		**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 %**	**Not estimable**
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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Non epidemic year - vaccine matching absent or unknown					

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
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)					

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Favours vaccine Favours control

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1998a	126/57058	196/44561	■	0.50 [0.40, 0.63]
Subtotal (95% CI)	**57058**	**44561**	◆	**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)				

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Favours vaccine Favours control

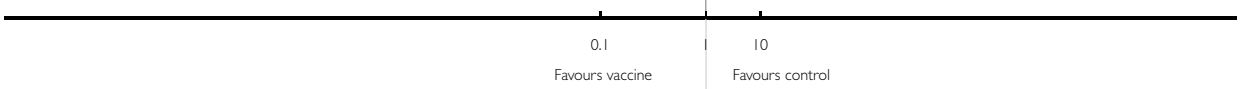
Analysis 4.4. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community dwellers - no risk groups, Outcome 4 Hospitalisation for any respiratory disease.

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					
Nichol 1998a	491/57058	566/44561		49.6 %	0.68 [0.60, 0.76]
Mangtani 2004a	567/77722	1392/196983		50.4 %	1.03 [0.94, 1.14]
Subtotal (95% CI)	**134780**	**241544**		**100.0 %**	**0.84 [0.55, 1.27]**
Total events: 1058 (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 %**	**Not estimable**
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 %**	**Not estimable**
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 %**	**Not estimable**
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)					

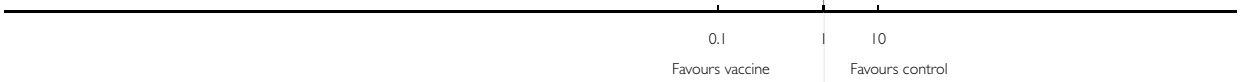


Review: Vaccines for preventing influenza in the elderly

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1998a	491/57058	566/44561		0.68 [0.60, 0.76]
Mangtani 2004a	567/77722	1392/196983		1.03 [0.94, 1.14]
Subtotal (95% CI)	**134780**	**241544**		**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)				



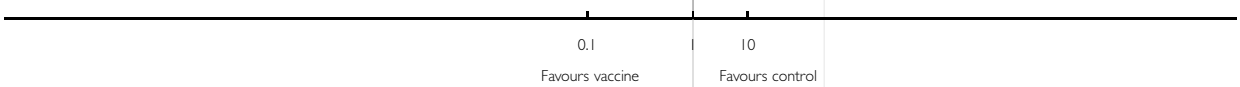
Analysis 4.5. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community dwellers - no risk groups, Outcome 5 Deaths from respiratory disease.

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)					



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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Mangtani 2004a	932/78912	1691/202512		1.41 [1.31, 1.53]

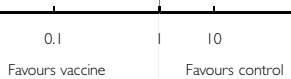
Analysis 4.6. Comparison 4 Influenza vaccines versus no vaccination - Cohort studies - community dwellers - no risk groups, Outcome 6 All deaths.

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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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 %**	**Not estimable**



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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					
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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Fleming 1995	2/334	37/6713		1.09 [0.26, 4.49]
Subtotal (95% CI)	**334**	**6713**		**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)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Voordouw 2003	68/5349	88/6050		0.87 [0.64, 1.20]
Shapiro 2003	31/7743	180/17632		0.39 [0.27, 0.57]
Subtotal (95% CI)	**13092**	**23682**		**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)				

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 %**	**Not estimable**
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 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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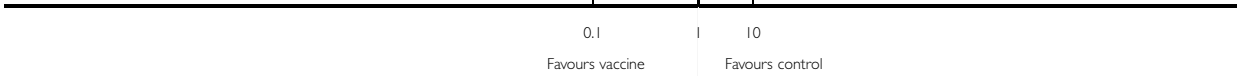
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
4 Non epidemic year - vaccine matching absent or unknown					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
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)					



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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Nichol 1998a	126/57058	125/44561		0.79 [0.61, 1.01]
Subtotal (95% CI)	**57058**	**44561**		**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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Hak 2002a	201/37693	254/30843		0.65 [0.54, 0.78]
Subtotal (95% CI)	**37693**	**30843**		**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)				

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	Risk Ratio M-H,Random,95% CI
2 Epidemic year - vaccine matching absent or unknown				
Hak 2002b	164/34155	267/32489		0.58 [0.48, 0.71]
Subtotal (95% CI)	**34155**	**32489**		**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)				

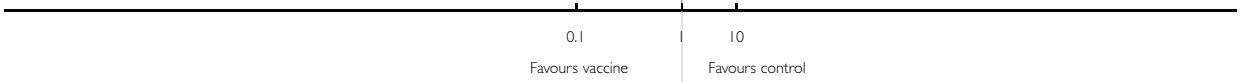
Analysis 5.1. Comparison 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community - dwellers, Outcome 1 ILI.

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 %**	**Not estimable**
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 %**	**Not estimable**
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)					



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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Consonni 2004b	17/305	12/69		0.32 [0.16, 0.64]
Subtotal (95% CI)	**305**	**69**		**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 disesase.

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 disesase

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 %**	**Not estimable**
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)					

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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 = 0.09 (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)					

Review: Vaccines for preventing influenza in the elderly

Comparison: 5 Influenza and pneumococcal vaccines versus no vaccination - Cohort studies in community - dwellers

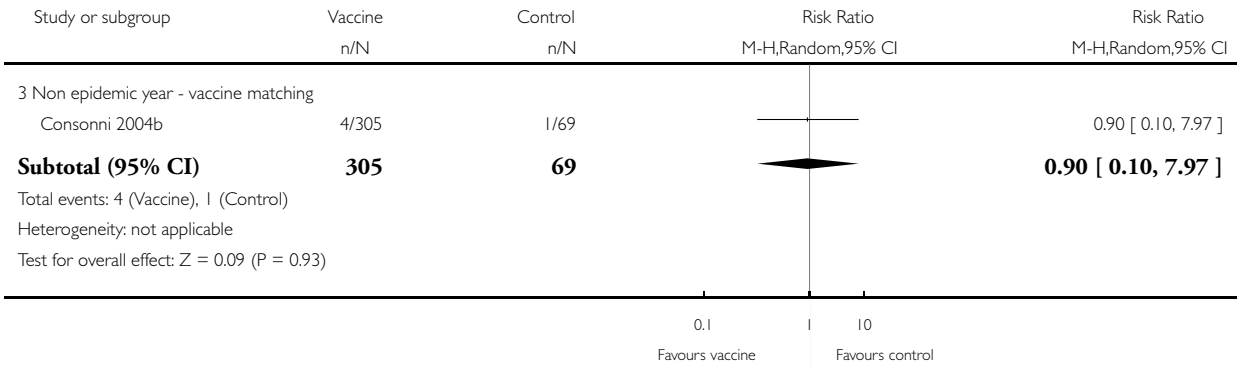
Outcome: 2 Hospitalisation for influenza or pneumonia or respiratory disesase

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Christenson 2001b	1234/100242	2854/159385		0.69 [0.64, 0.73]
Christenson 2004b	1266/124702	2106/134045		0.65 [0.60, 0.69]
Subtotal (95% CI)	**224944**	**293430**		**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)				

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



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 %**	**Not estimable**
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 %**	**Not estimable**
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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Christenson 2001b	67/100242	245/159385		0.43 [0.33, 0.57]
Subtotal (95% CI)	**100242**	**159385**		**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 %**	**Not estimable**
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)					

(*Continued . . .*)

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Study or subgroup	Vaccinne n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Christenson 2001b	1514/100242	5531/159385		0.44 [0.41, 0.46]
Subtotal (95% CI)	**100242**	**159385**		**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)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Consonni 2004b	3/305	0/69		1.60 [0.08, 30.65]
Subtotal (95% CI)	**305**	**69**		**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)				

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 %**	**Not estimable**
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)					

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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 (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)					

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	Risk Ratio M-H,Random,95% CI
1 Epidemic year - vaccine matching				
Pregliasco 2002	5/184	11/79	■	0.20 [0.07, 0.54]
Subtotal (95% CI)	**184**	**79**	◆	**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)				

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Consonni 2004a	11/166	12/69		0.38 [0.18, 0.82]
Subtotal (95% CI)	**166**	**69**		**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)				

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 disesase.

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 disesase

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 %**	**Not estimable**
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 %**	**Not estimable**
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)					

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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 (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)					

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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Pregliasco 2002	0/184	3/79		0.06 [0.00, 1.18]
Consonni 2004a	1/166	1/69		0.42 [0.03, 6.55]
Subtotal (95% CI)	**350**	**148**		**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)				

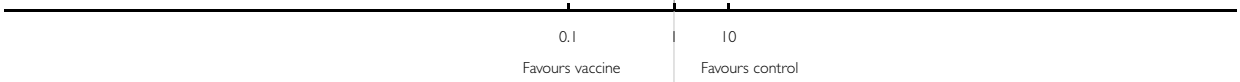
Analysis 6.3. Comparison 6 Influenza vaccines with adjuvant versus no vaccination - Cohort studies in community - dwellers, Outcome 3 All deaths.

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 %**	**Not estimable**
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 %**	**Not estimable**
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)					



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	Risk Ratio M-H,Random,95% CI
3 Non epidemic year - vaccine matching				
Consonni 2004a	2/166	0/69		2.10 [0.10, 43.10]
Subtotal (95% CI)	**166**	**69**		**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)				

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Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
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)				

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

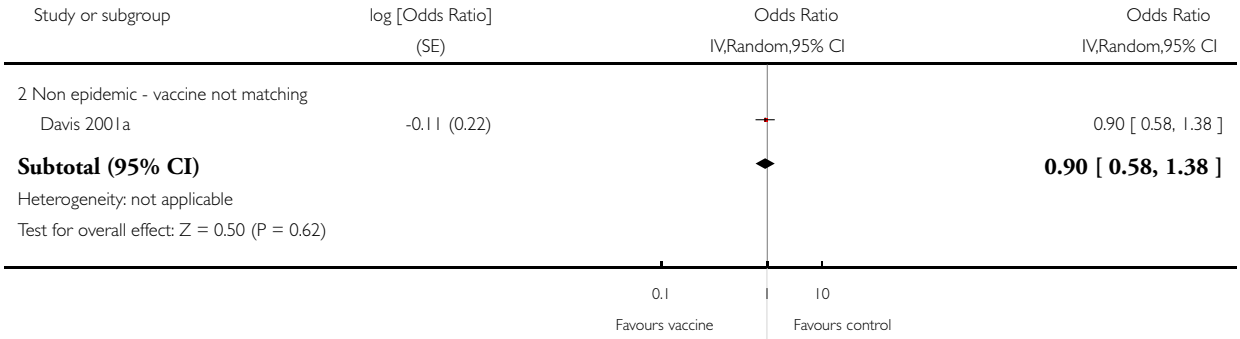
Outcome: 1 Hospitalisation for influenza or pneumonia

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Odds Ratio IV,Random,95% CI
1 Epidemic - vaccine matching			
Nichol 1998a	-0.4943 (0.1104)		0.61 [0.49, 0.76]
Davis 2001b	-0.11 (0.2)		0.90 [0.61, 1.33]
Nordin 2001a	-0.2107 (0.097)		0.81 [0.67, 0.98]
Davis 2001c	-0.51 (0.24)		0.60 [0.38, 0.96]
Nichol 2003a	-0.3857 (0.0669)		0.68 [0.60, 0.78]
Nichol 2003b	-0.3425 (0.065)		0.71 [0.63, 0.81]
Subtotal (95% CI)			**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)			

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

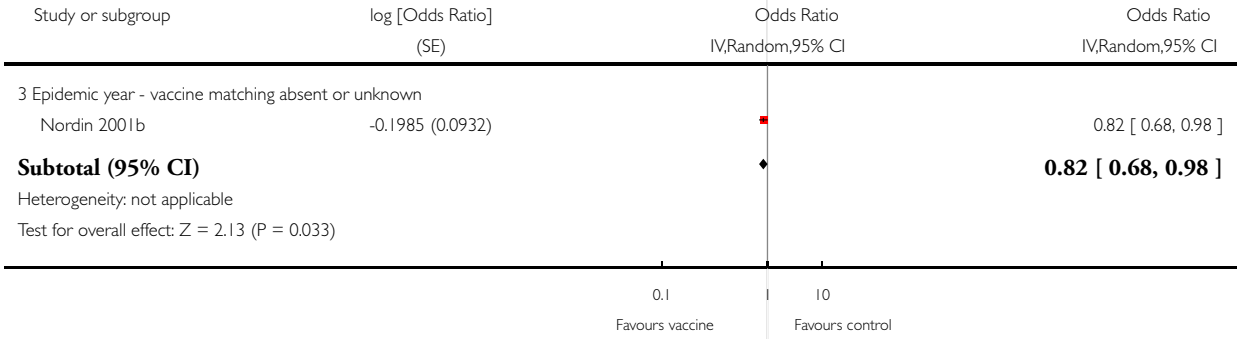
Outcome: 1 Hospitalisation for influenza or pneumonia



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



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)				

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	Odds Ratio IV,Random,95% CI
1 Epidemic matching vaccine			
Mangtani 2004b	-0.1744 (0.1209)		0.84 [0.66, 1.06]
Nichol 1998a	-0.3857 (0.0429)		0.68 [0.63, 0.74]
Mangtani 2004c	-0.3567 (0.084)		0.70 [0.59, 0.83]
Mangtani 2004e	-0.2744 (0.1062)		0.76 [0.62, 0.94]
Davis 2001b	-0.22 (0.15)		0.80 [0.60, 1.08]
Mangtani 2004g	-0.3711 (0.0777)		0.69 [0.59, 0.80]
Davis 2001c	-0.36 (0.18)		0.70 [0.49, 0.99]
Mangtani 2004h	-0.4155 (0.0656)		0.66 [0.58, 0.75]
Mangtani 2004j	-0.1985 (0.0958)		0.82 [0.68, 0.99]
Subtotal (95% CI)			**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)

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	Odds Ratio IV,Random,95% CI
2 Non epidemic non matching			
Davis 2001a	-0.22 (0.15)		0.80 [0.60, 1.08]
Mangtani 2004i	-0.0305 (0.1018)		0.97 [0.79, 1.18]
Subtotal (95% CI)			**0.91 [0.76, 1.08]**

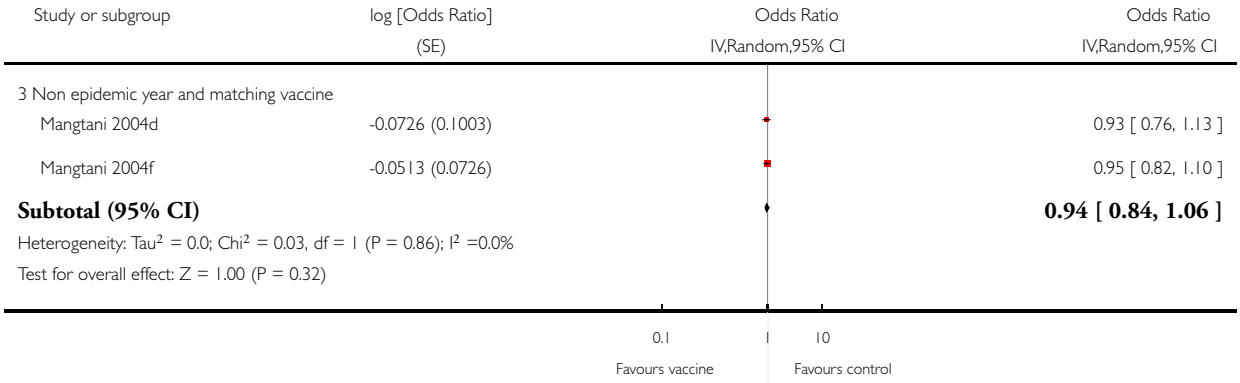
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 1 (P = 0.30); $I^2 = 8\%$

Test for overall effect: Z = 1.05 (P = 0.30)

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

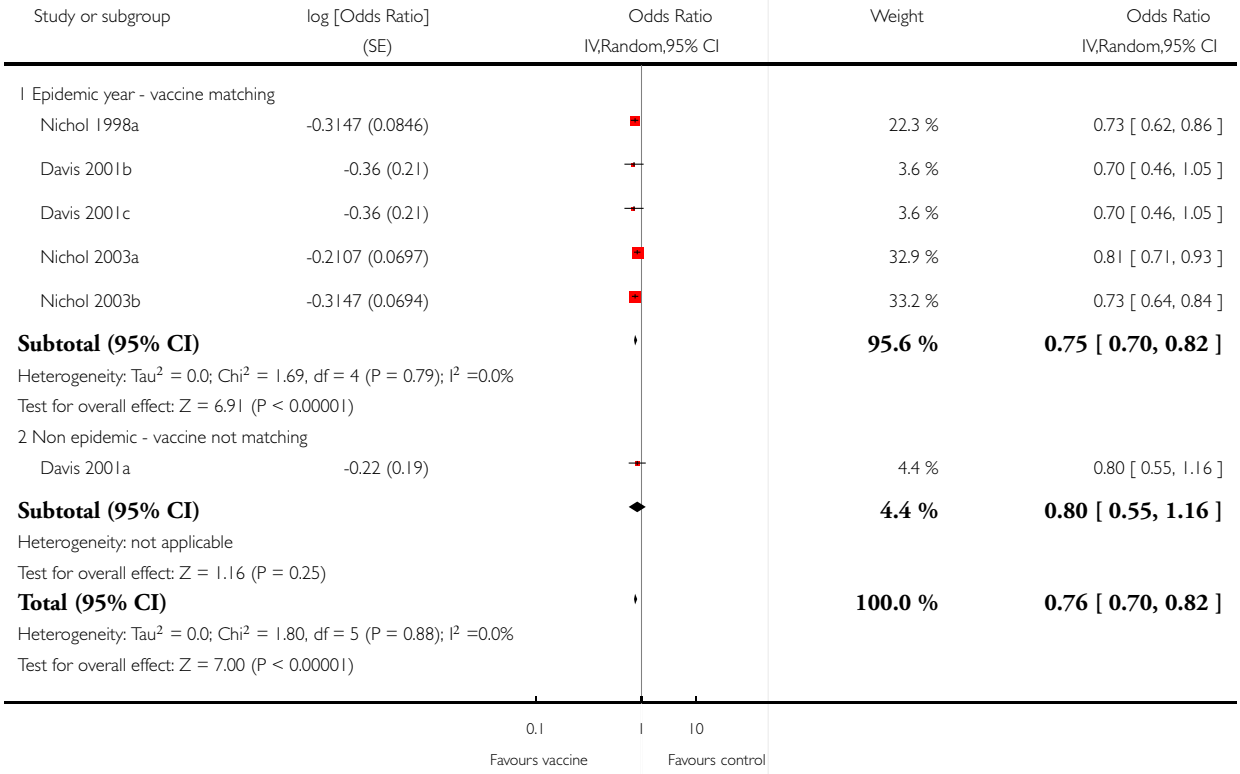


Analysis 7.3. Comparison 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates, Outcome 3 Hospitalisation for heart disease.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

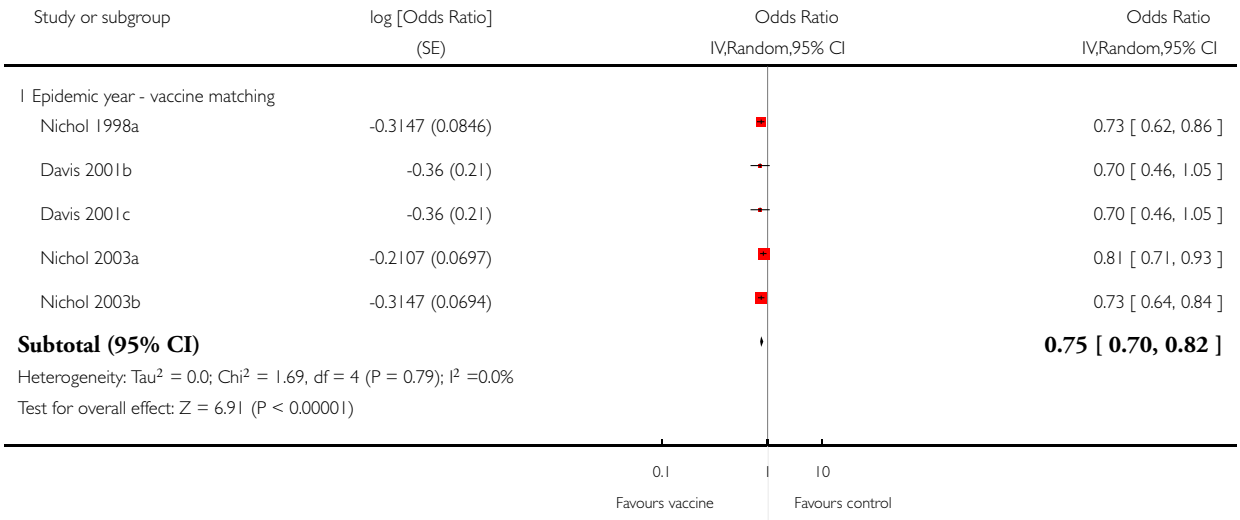
Outcome: 3 Hospitalisation for heart disease



Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

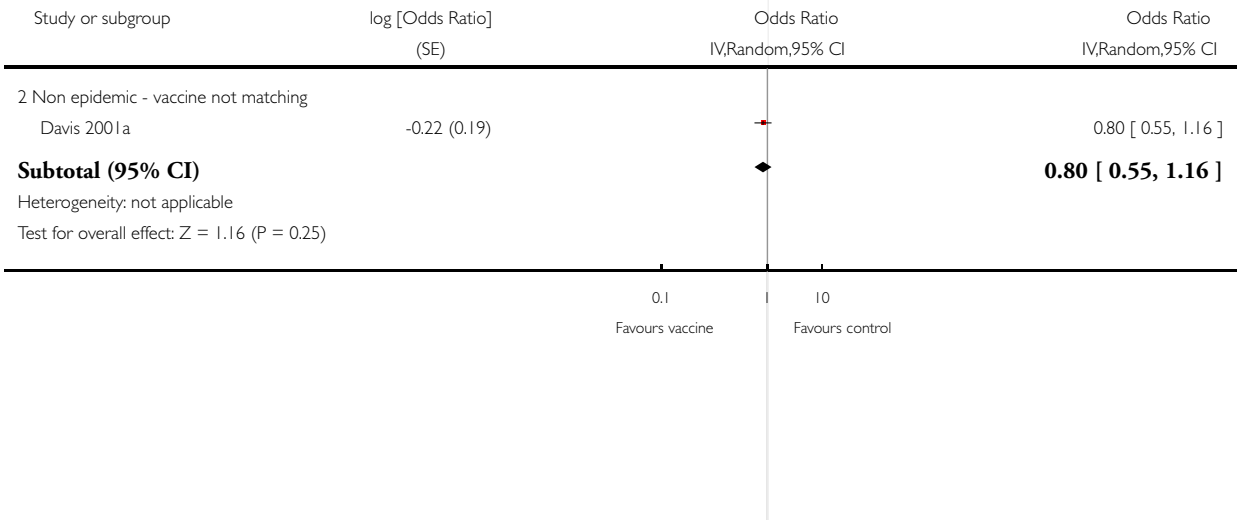
Outcome: 3 Hospitalisation for heart disease



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



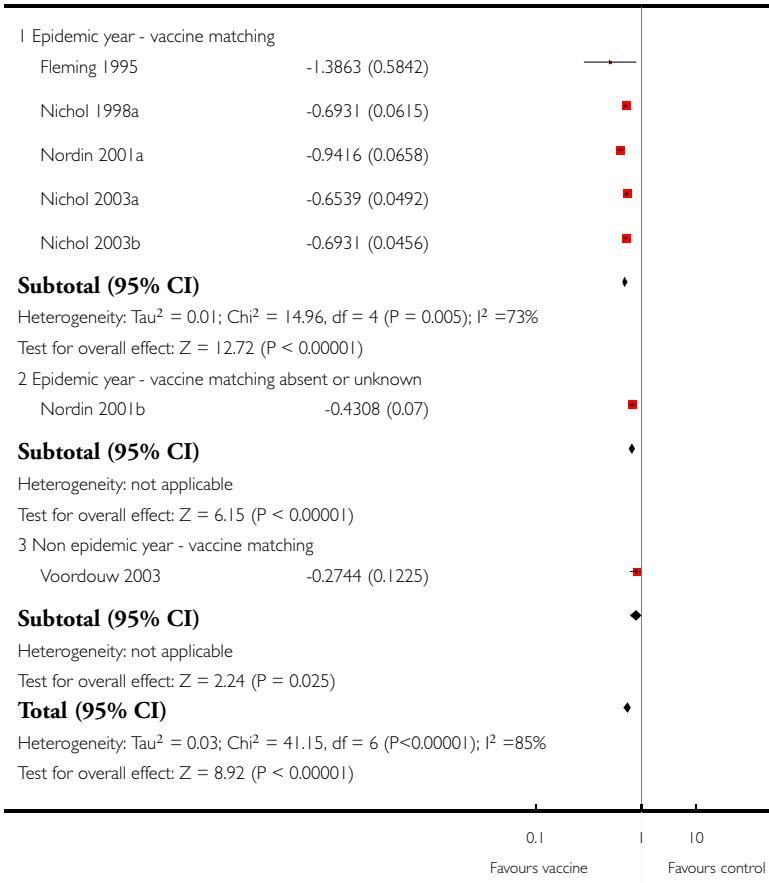
Analysis 7.4. Comparison 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates, Outcome 4 All deaths.

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

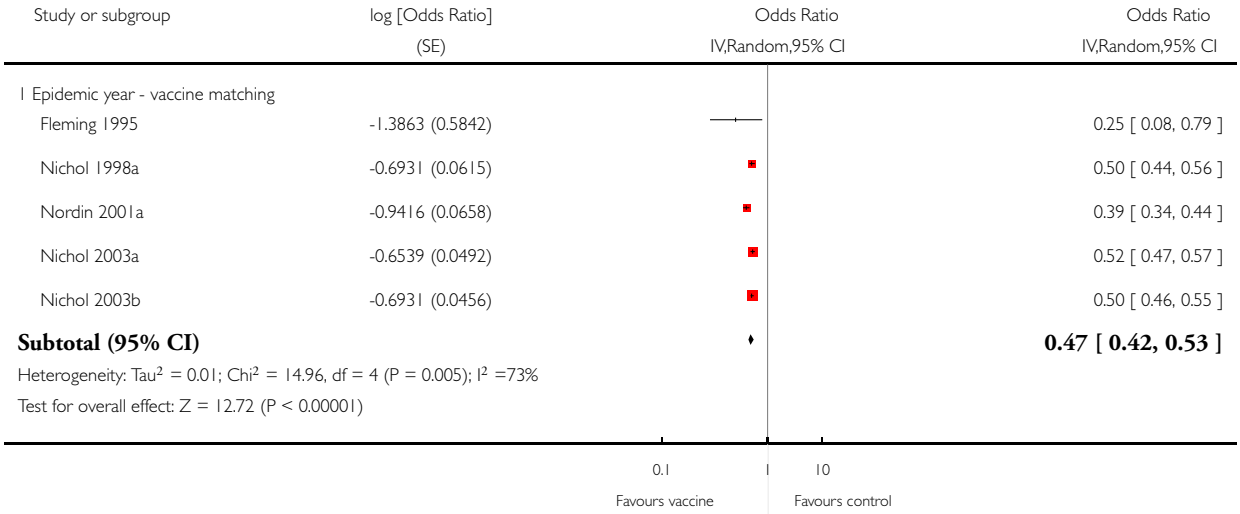
Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Epidemic year - vaccine matching				
Fleming 1995	-1.3863 (0.5842)		1.4 %	0.25 [0.08, 0.79]
Nichol 1998a	-0.6931 (0.0615)		17.0 %	0.50 [0.44, 0.56]
Nordin 2001a	-0.9416 (0.0658)		16.7 %	0.39 [0.34, 0.44]
Nichol 2003a	-0.6539 (0.0492)		17.8 %	0.52 [0.47, 0.57]
Nichol 2003b	-0.6931 (0.0456)		18.1 %	0.50 [0.46, 0.55]
Subtotal (95% CI)			**71.1 %**	**0.47 [0.42, 0.53]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 14.96, df = 4 (P = 0.005); I^2 =73%				
Test for overall effect: Z = 12.72 (P < 0.00001)				
2 Epidemic year - vaccine matching absent or unknown				
Nordin 2001b	-0.4308 (0.07)		16.4 %	0.65 [0.57, 0.75]
Subtotal (95% CI)			**16.4 %**	**0.65 [0.57, 0.75]**
Heterogeneity: not applicable				
Test for overall effect: Z = 6.15 (P < 0.00001)				
3 Non epidemic year - vaccine matching				
Voordouw 2003	-0.2744 (0.1225)		12.5 %	0.76 [0.60, 0.97]
Subtotal (95% CI)			**12.5 %**	**0.76 [0.60, 0.97]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.24 (P = 0.025)				
Total (95% CI)			**100.0 %**	**0.53 [0.46, 0.61]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 41.15, df = 6 (P<0.00001); I^2 =85%				
Test for overall effect: Z = 8.92 (P < 0.00001)				



Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

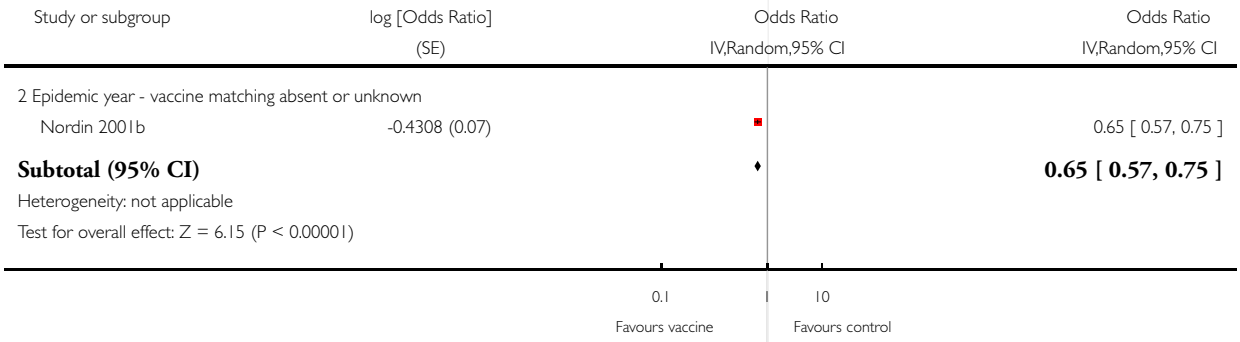
Outcome: 4 All deaths



Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

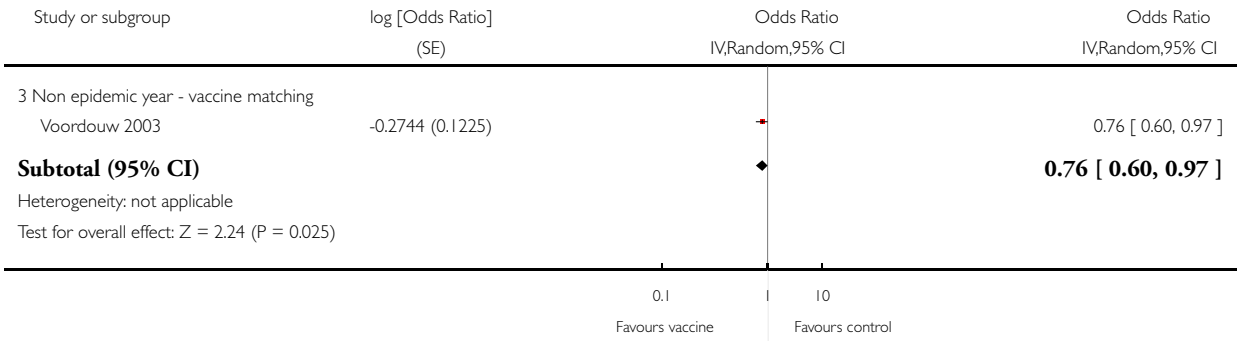
Outcome: 4 All deaths



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

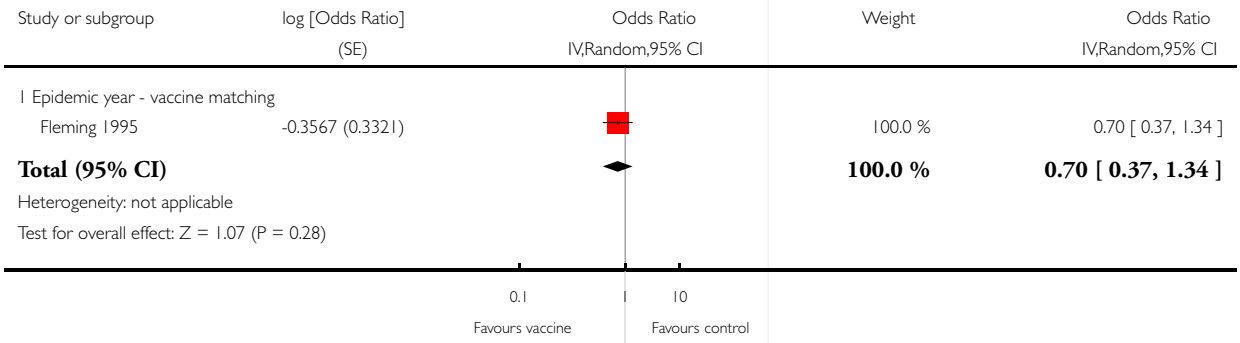


Analysis 7.5. Comparison 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates, Outcome 5 Combined outcome: all deaths or severe respiratory illness.

Review: Vaccines for preventing influenza in the elderly

Comparison: 7 Influenza Vaccines versus no vaccination - Cohort studies in community - Adjusted Rates

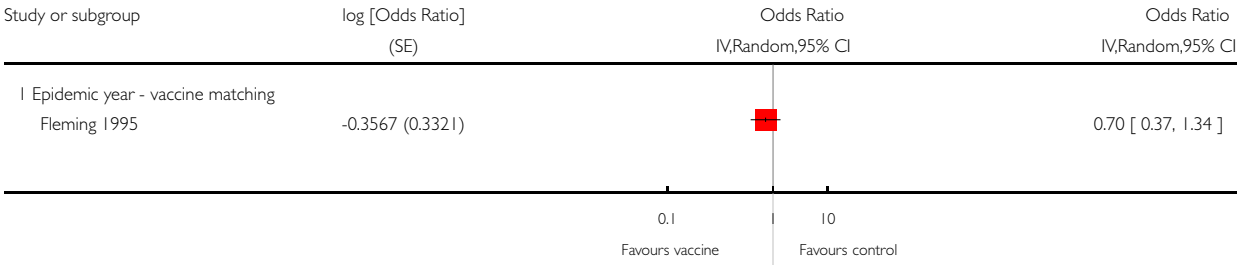
Outcome: 5 Combined outcome: all deaths or severe respiratory illness



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

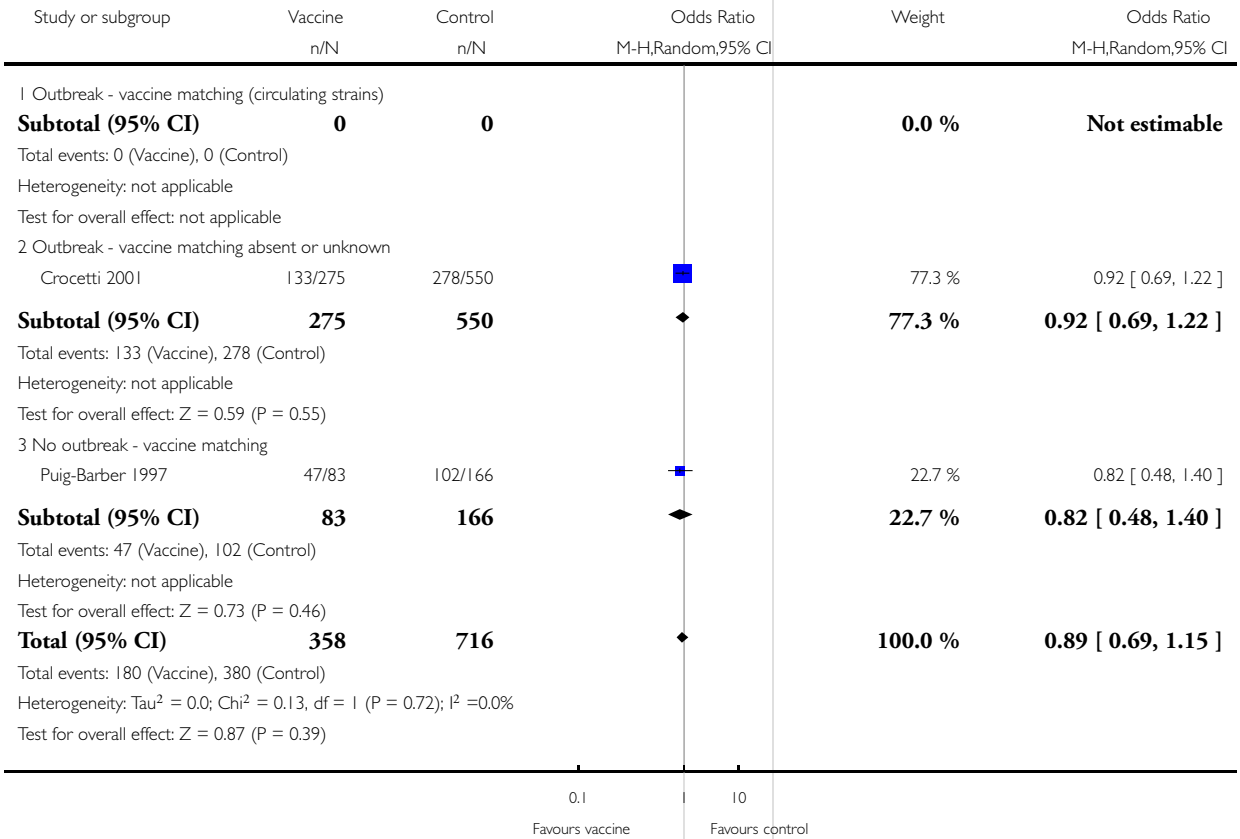


Analysis 8.1. Comparison 8 Influenza vaccines versus no vaccination - Case control studies in community, Outcome 1 Hospitalisations for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

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

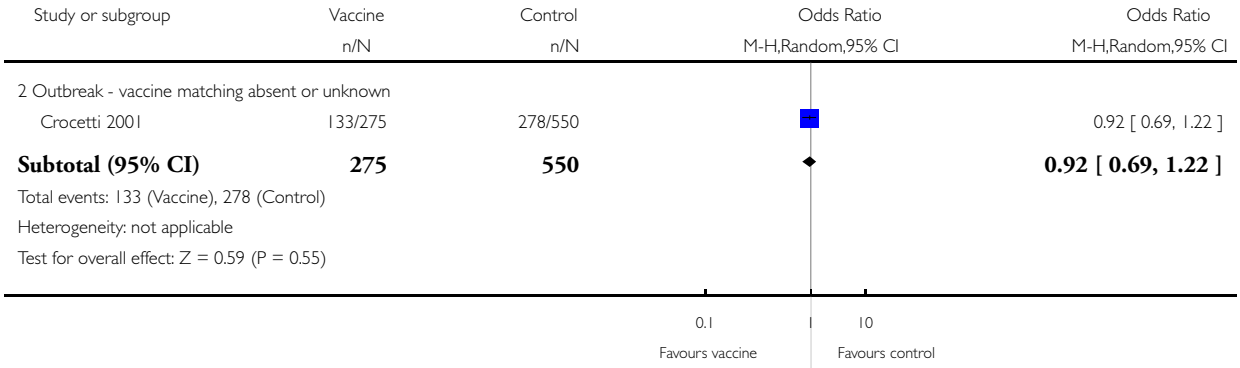
Outcome: 1 Hospitalisations for influenza or pneumonia



Review: Vaccines for preventing influenza in the elderly

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

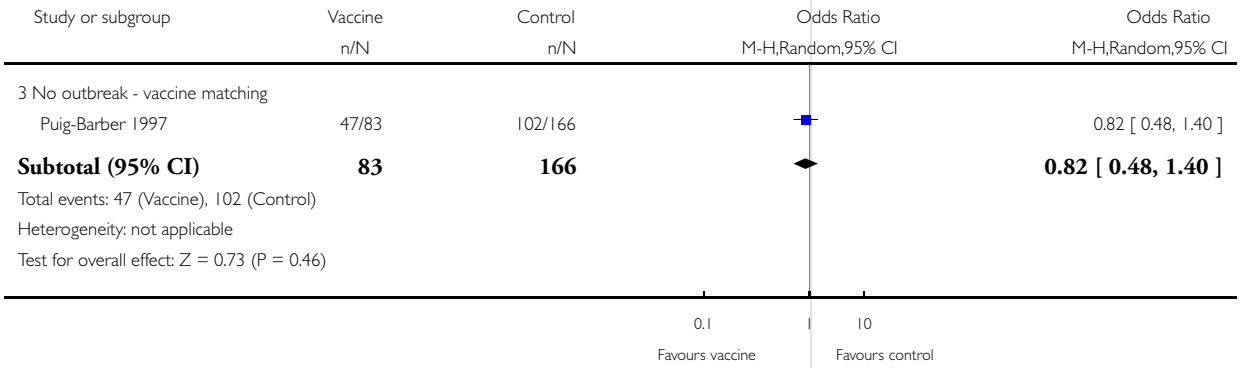
Outcome: 1 Hospitalisations for influenza or pneumonia



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



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		43.8 %	1.14 [0.99, 1.32]
Fedson 1993b	370/2417	1008/7249		47.2 %	1.12 [0.98, 1.27]
Ahmed 1997	27/156	69/289		9.0 %	0.67 [0.41, 1.09]
Total (95% CI)	**5192**	**15390**		**100.0 %**	**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)

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	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Fedson 1993a	283/2619	754/7852		1.14 [0.99, 1.32]
Fedson 1993b	370/2417	1008/7249		1.12 [0.98, 1.27]
Ahmed 1997	27/156	69/289		0.67 [0.41, 1.09]

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

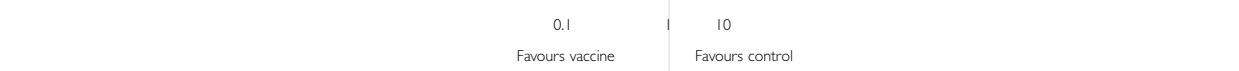
Outcome: 3 Deaths from influenza or pneumonia

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)



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	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Ahmed 1995	57/315	178/777		0.74 [0.53, 1.04]

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: $Tau^2 = 0.04$; $Chi^2 = 2.92$, df = 1 (P = 0.09); $I^2 = 66\%$					
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]
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)					

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	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Foster 1992	60/185	256/671		0.78 [0.55, 1.10]
Ohmit 1995b	484/890	980/1871		1.08 [0.92, 1.27]
Subtotal (95% CI)	**1075**	**2542**		**0.95 [0.69, 1.31]**
Total events: 544 (Vaccine), 1236 (Control)				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.92$, df = 1 (P = 0.09); $I^2 = 66\%$				
Test for overall effect: Z = 0.30 (P = 0.76)				

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	Odds Ratio M-H,Random,95% CI
2 No outbreak - vaccine matching				
Ohmit 1995a	314/667	743/1530		0.94 [0.79, 1.13]
Puig-Barber 2004	168/290	318/525		0.90 [0.67, 1.20]
Subtotal (95% CI)	**957**	**2055**		**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)				

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

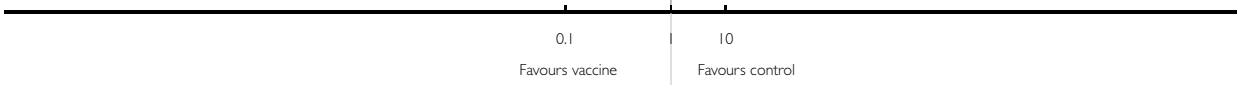
Outcome: 1 ILI

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)



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	Odds Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching				
Ohmit 1999	220/361	628/837		0.52 [0.40, 0.68]

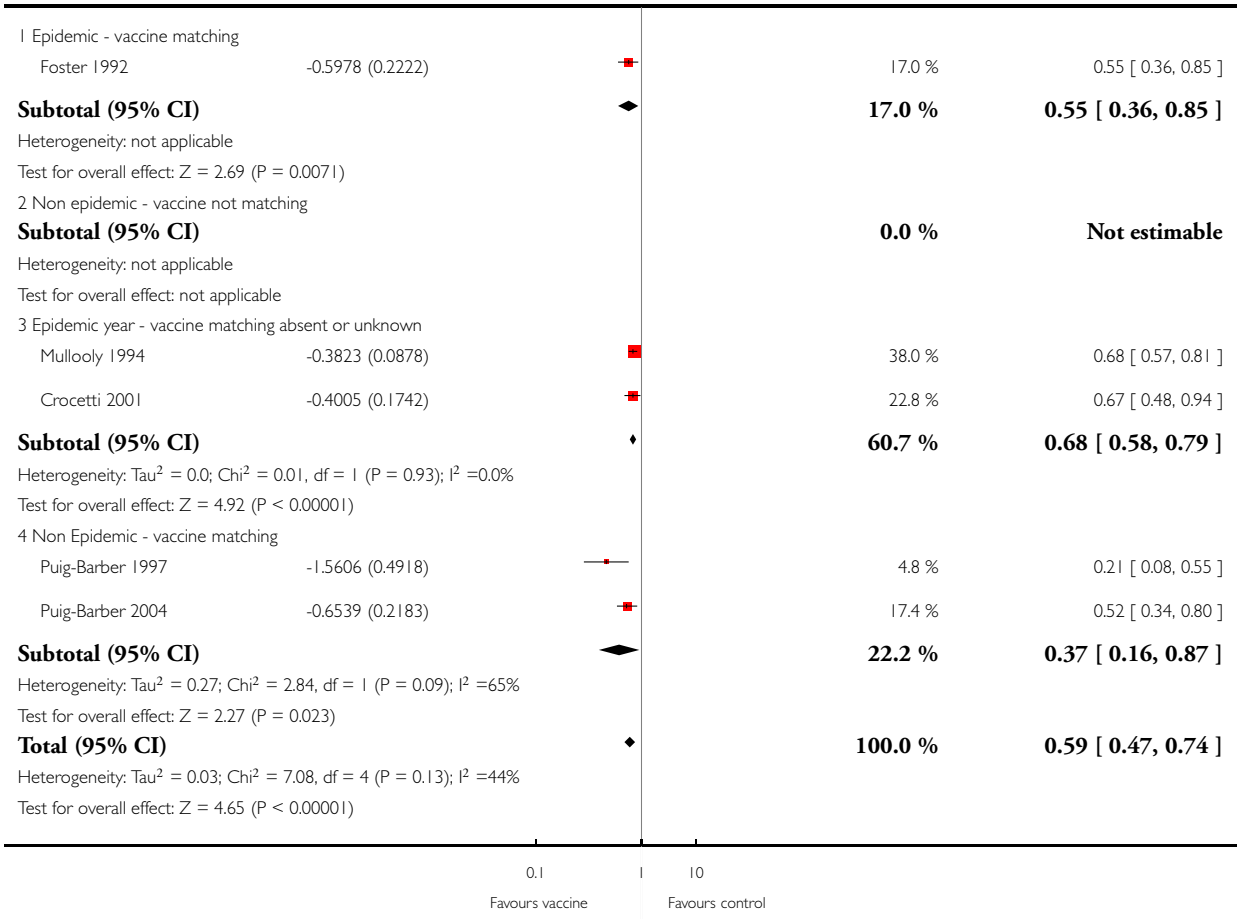
Analysis 11.1. Comparison 11 Influenza vaccines versus no vaccination - Case control studies in community - Adjusted rates, Outcome 1 Hospitalisations for influenza or pneumonia.

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

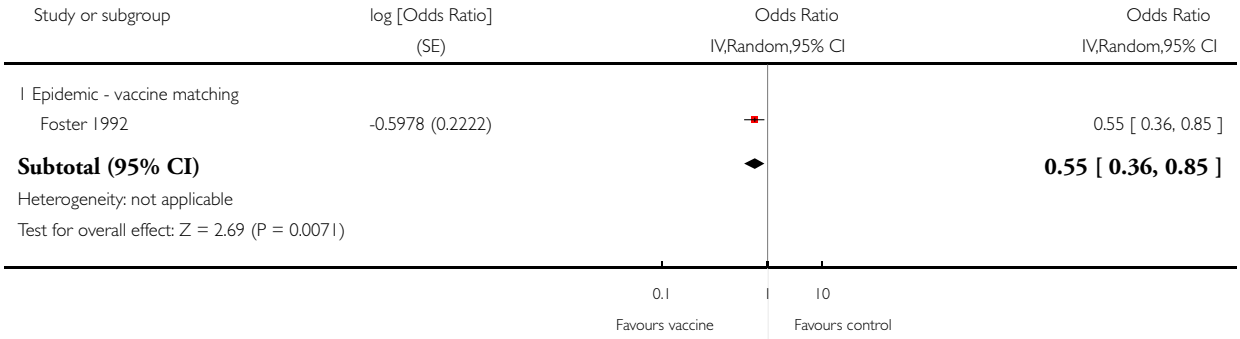
Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Epidemic - vaccine matching				
Foster 1992	-0.5978 (0.2222)		17.0 %	0.55 [0.36, 0.85]
Subtotal (95% CI)			**17.0 %**	**0.55 [0.36, 0.85]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.69 (P = 0.0071)				
2 Non epidemic - vaccine not matching				
Subtotal (95% CI)			**0.0 %**	**Not estimable**
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)				



Review: Vaccines for preventing influenza in the elderly

Comparison: 11 Influenza vaccines versus no vaccination - Case control studies in community - Adjusted rates

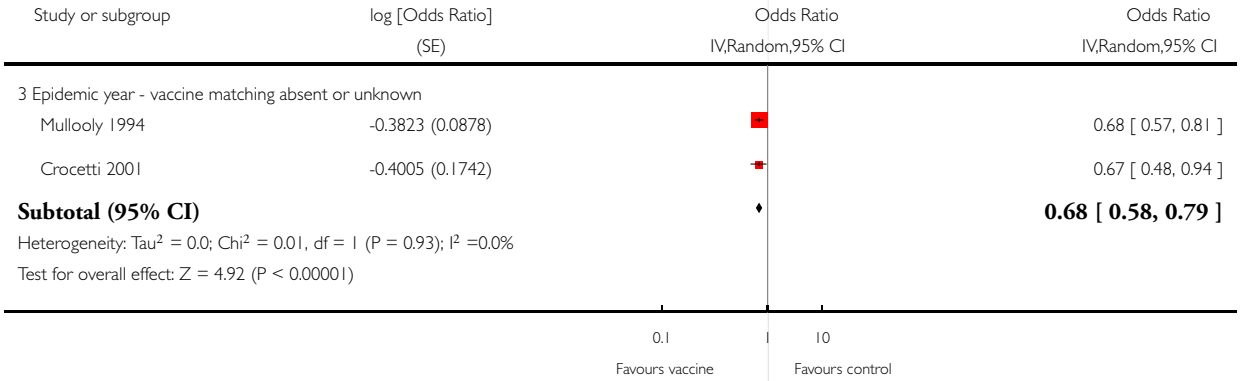
Outcome: 1 Hospitalisations for influenza or pneumonia



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



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	Odds Ratio IV,Random,95% CI
4 Non Epidemic - vaccine matching			
Puig-Barber 1997	-1.5606 (0.4918)		0.21 [0.08, 0.55]
Puig-Barber 2004	-0.6539 (0.2183)		0.52 [0.34, 0.80]
Subtotal (95% CI)			**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)			

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 %**	**Not estimable**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
3 Non epidemic year - vaccine matching				
Subtotal (95% CI)			**0.0 %**	**Not estimable**
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)				

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	Odds Ratio IV,Random,95% CI
1 Epidemic - vaccine matching			
Fedson 1993a	-0.1863 (0.0958)		0.83 [0.69, 1.00]
Fedson 1993b	-0.3857 (0.0865)		0.68 [0.57, 0.81]
Ahmed 1997	-0.9943 (0.42)		0.37 [0.16, 0.84]
Subtotal (95% CI)			**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)				

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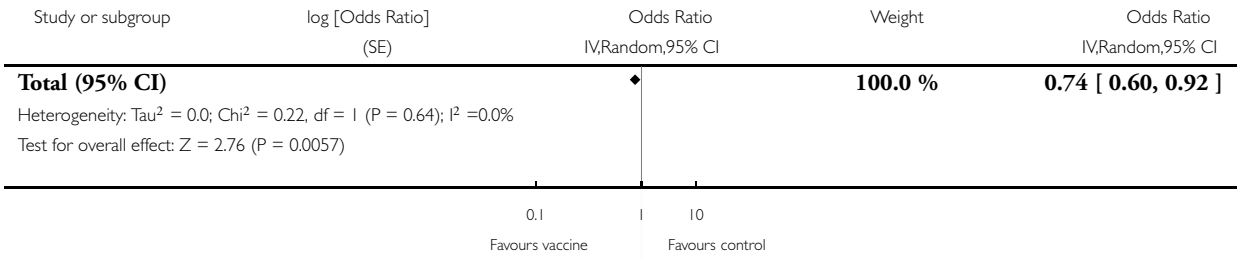
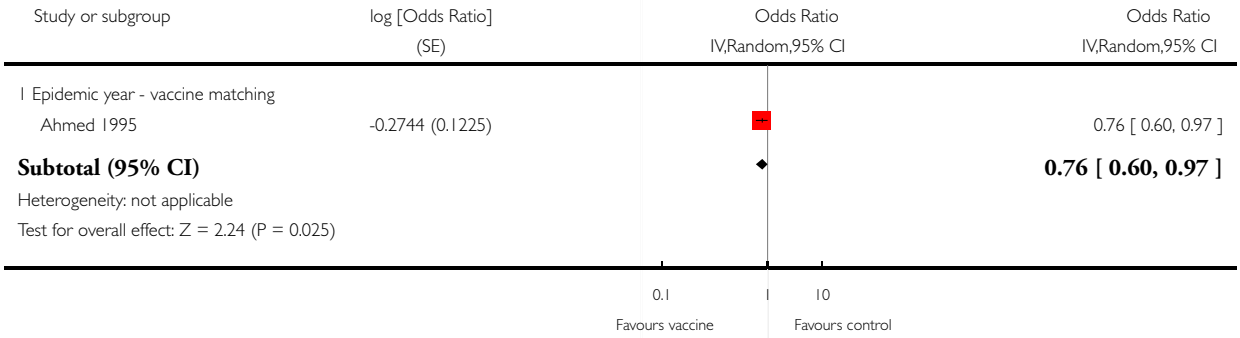


Review: Vaccines for preventing influenza in the elderly

Comparison: 11 Influenza vaccines versus no vaccination - Case control studies in community - Adjusted rates

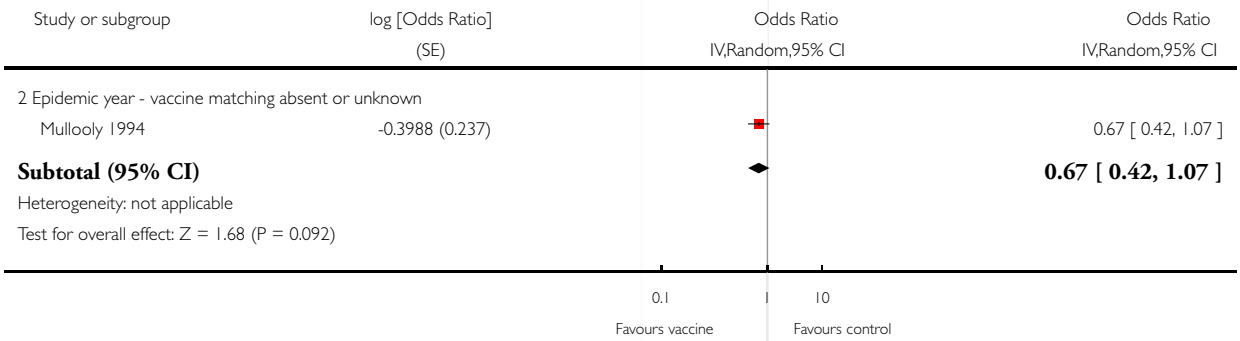
Outcome: 3 Deaths from pneumonia or influenza



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



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

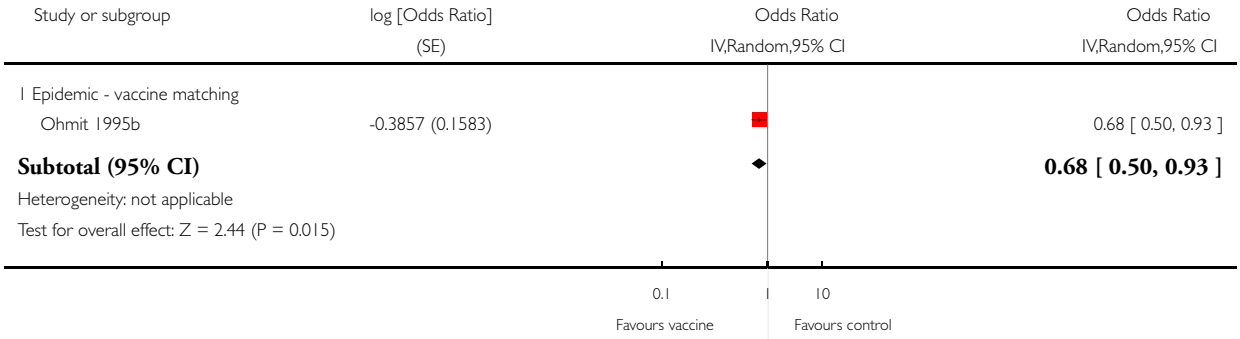
Outcome: 1 Hospitalisations for influenza or pneumonia

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 %**	**Not estimable**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
3 Epidemic year - vaccine matching absent or unknown				
Subtotal (95% CI)			**0.0 %**	**Not estimable**
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)				

Review: Vaccines for preventing influenza in the elderly

Comparison: 12 Influenza and pneumococcal vaccines versus no vaccination - Case control studies in community - Adjusted Rates

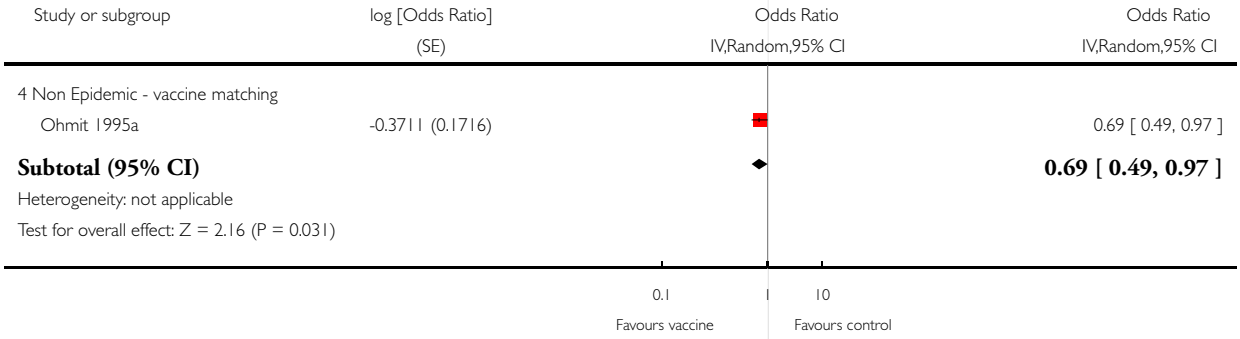
Outcome: 1 Hospitalisations for influenza or pneumonia



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



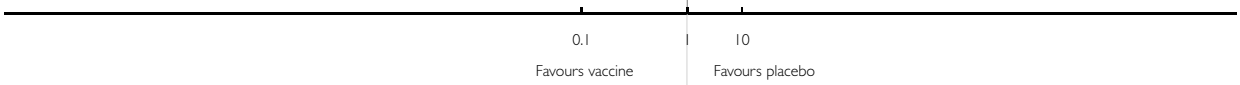
Analysis 13.1. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI

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 (circulating strains) - community - healthy					
Allsup 2004	24/522	17/177		13.5 %	0.48 [0.26, 0.87]
Govaert 1994	41/676	66/672		34.3 %	0.62 [0.42, 0.90]
Subtotal (95% CI)	**1198**	**849**		**47.8 %**	**0.57 [0.42, 0.79]**
Total events: 65 (Vaccine), 83 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.42 (P = 0.00063)					
2 Outbreak - vaccine matching - community - risk groups					
Govaert 1994	21/251	23/239		15.1 %	0.87 [0.49, 1.53]
Subtotal (95% CI)	**251**	**239**		**15.1 %**	**0.87 [0.49, 1.53]**
Total events: 21 (Vaccine), 23 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.63)					
3 Outbreak - vaccine matching - nursing home - healthy					
Stuart 1969	33/1561	102/2619		32.1 %	0.54 [0.37, 0.80]
Subtotal (95% CI)	**1561**	**2619**		**32.1 %**	**0.54 [0.37, 0.80]**
Total events: 33 (Vaccine), 102 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.09 (P = 0.0020)					
4 outbreak - vaccine matching - psychiatric hospital					
Edmondson 1971	5/90	14/87		5.0 %	0.35 [0.13, 0.92]
Subtotal (95% CI)	**90**	**87**		**5.0 %**	**0.35 [0.13, 0.92]**
Total events: 5 (Vaccine), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.13 (P = 0.033)					
Total (95% CI)	**3100**	**3794**		**100.0 %**	**0.59 [0.47, 0.73]**
Total events: 124 (Vaccine), 222 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.67$, df = 4 (P = 0.45); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.78 (P < 0.00001)					

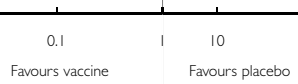


Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI

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 (circulating strains) - community - healthy				
Allsup 2004	24/522	17/177		0.48 [0.26, 0.87]
Govaert 1994	41/676	66/672		0.62 [0.42, 0.90]
Subtotal (95% CI)	**1198**	**849**		**0.57 [0.42, 0.79]**
Total events: 65 (Vaccine), 83 (Placebo)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0.0\%$				
Test for overall effect: Z = 3.42 (P = 0.00063)				



Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
2 Outbreak - vaccine matching - community - risk groups				
Govaert 1994	21/251	23/239		0.87 [0.49, 1.53]
Subtotal (95% CI)	**251**	**239**		**0.87 [0.49, 1.53]**
Total events: 21 (Vaccine), 23 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.49 (P = 0.63)				

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
3 Outbreak - vaccine matching - nursing home - healthy				
Stuart 1969	33/1561	102/2619		0.54 [0.37, 0.80]
Subtotal (95% CI)	**1561**	**2619**		**0.54 [0.37, 0.80]**
Total events: 33 (Vaccine), 102 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 3.09 (P = 0.0020)				

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 1 ILI

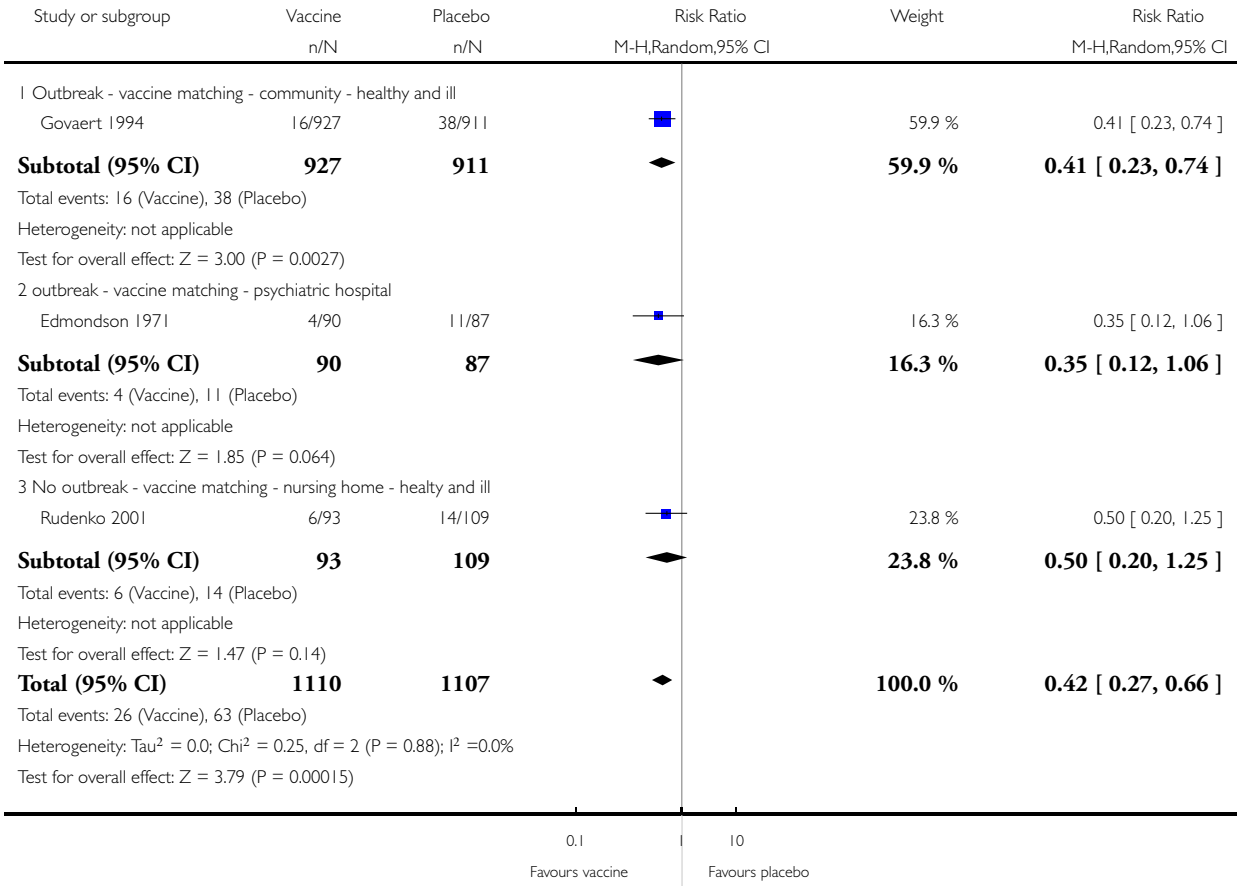
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
4 outbreak - vaccine matching - psychiatric hospital				
Edmondson 1971	5/90	14/87		0.35 [0.13, 0.92]
Subtotal (95% CI)	**90**	**87**		**0.35 [0.13, 0.92]**
Total events: 5 (Vaccine), 14 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.13 (P = 0.033)				

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

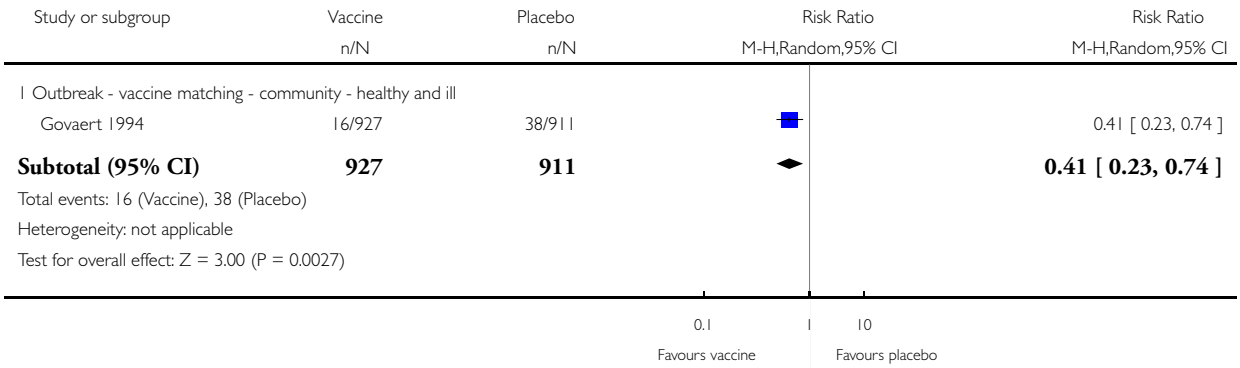
Outcome: 2 Influenza



Review: Vaccines for preventing influenza in the elderly

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

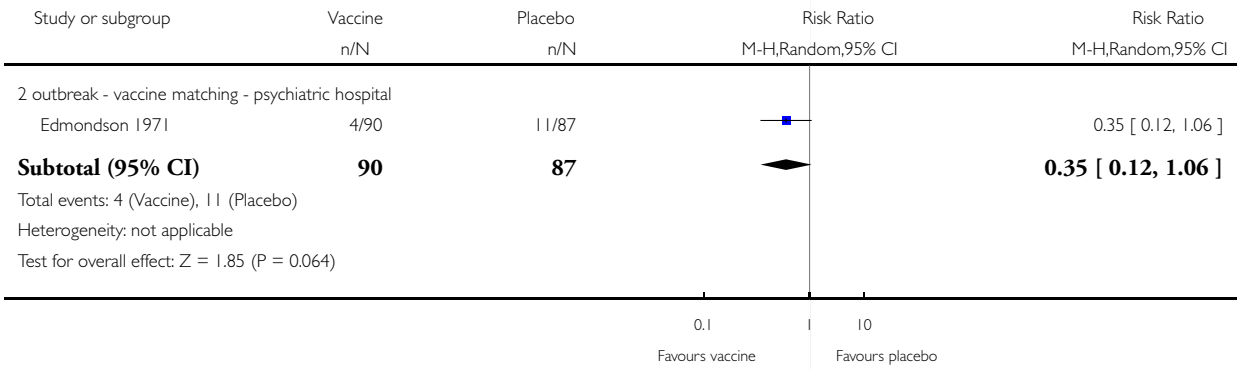
Outcome: 2 Influenza



Review: Vaccines for preventing influenza in the elderly

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

Outcome: 2 Influenza



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	Risk Ratio M-H,Random,95% CI
3 No outbreak - vaccine matching - nursing home - healty and ill				
Rudenko 2001	6/93	14/109		0.50 [0.20, 1.25]
Subtotal (95% CI)	**93**	**109**		**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)				

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	Weight	Risk Ratio M-H,Random,95% CI
1 Outbreak - vaccine matching - community - healthy					
Allsup 2004	0/522	0/177		0.0 %	Not estimable
Subtotal (95% CI)	**522**	**177**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Outbreak - vaccine matching - community - risk groups					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Outbreak - vaccine matching - nursing home - healthy					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**522**	**177**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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		Not estimable
Subtotal (95% CI)	**522**	**177**		**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				

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Favours vaccine Favours placebo

Analysis 13.4. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 4 Hospitalisations for influenza or pneumonia.

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisations for influenza or pneumonia

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	0/522	0/177		0.0 %	Not estimable
Subtotal (95% CI)	**522**	**177**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Outbreak - vaccine matching - community - risk groups					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Outbreak - vaccine matching - nursing home - healthy					

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Favours vaccine Favours placebo

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Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stuart 1969	16/1561	52/2619		100.0 %	0.52 [0.30, 0.90]
Subtotal (95% CI)	**1561**	**2619**		**100.0 %**	**0.52 [0.30, 0.90]**
Total events: 16 (Vaccine), 52 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.33 (P = 0.020)					
Total (95% CI)	**2083**	**2796**		**100.0 %**	**0.52 [0.30, 0.90]**
Total events: 16 (Vaccine), 52 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.33 (P = 0.020)					

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisations for influenza or 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		Not estimable
Subtotal (95% CI)	**522**	**177**		**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 4 Hospitalisations for influenza or pneumonia

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
3 Outbreak - vaccine matching - nursing home - healthy				
Stuart 1969	16/1561	52/2619		0.52 [0.30, 0.90]
Subtotal (95% CI)	**1561**	**2619**		**0.52 [0.30, 0.90]**
Total events: 16 (Vaccine), 52 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.33 (P = 0.020)				

Analysis 13.6. Comparison 13 Influenza vaccines versus placebo - RCT - parenteral vaccine, Outcome 6 All deaths.

Review: Vaccines for preventing influenza in the elderly

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

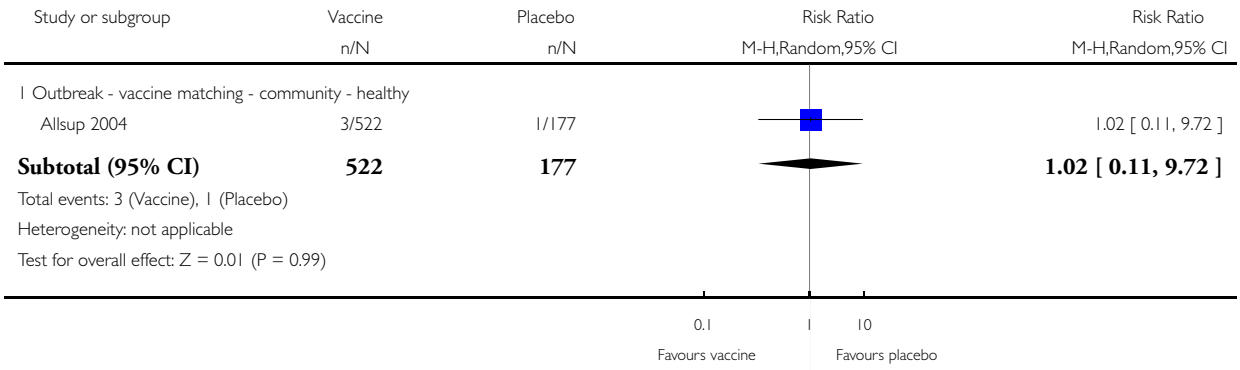
Outcome: 6 All deaths

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]
Subtotal (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)					
2 Outbreak - vaccine matching - community - risk groups					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Outbreak - vaccine matching - nursing home - healthy					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
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)					

Review: Vaccines for preventing influenza in the elderly

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

Outcome: 6 All deaths

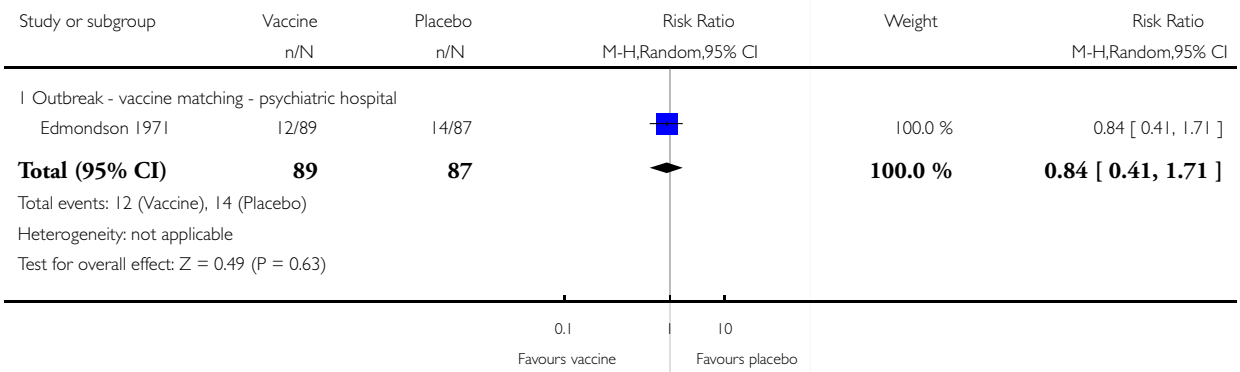


Analysis 14.1. Comparison 14 Vaccine versus placebo - inactivated aerosol vaccine, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 14 Vaccine versus placebo - inactivated aerosol vaccine

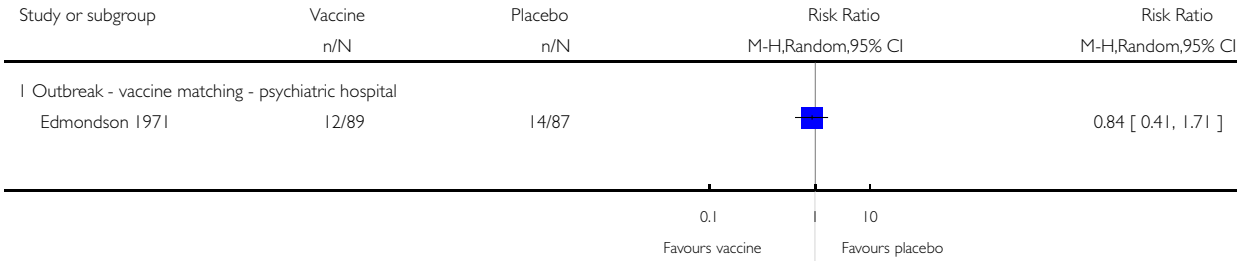
Outcome: 1 ILI



Review: Vaccines for preventing influenza in the elderly

Comparison: 14 Vaccine versus placebo - inactivated aerosol vaccine

Outcome: 1 ILI

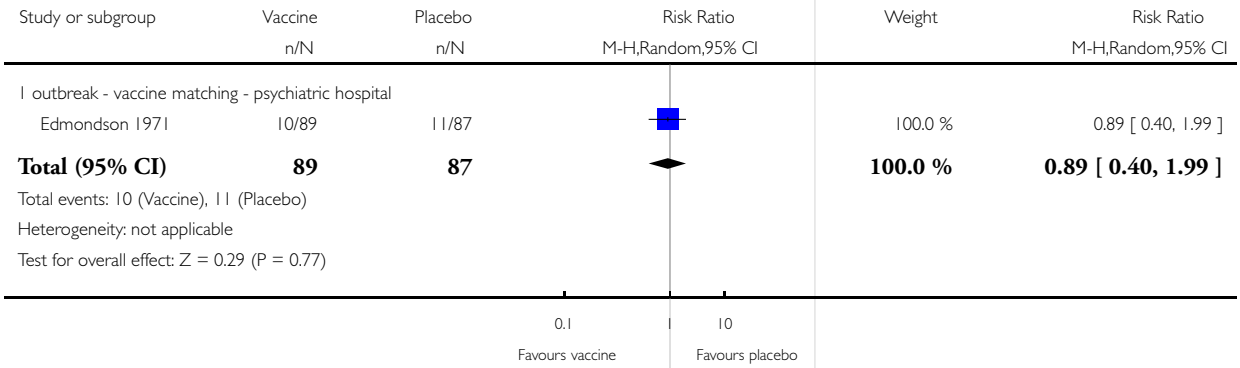


Analysis 14.2. Comparison 14 Vaccine versus placebo - inactivated aerosol vaccine, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 14 Vaccine versus placebo - inactivated aerosol vaccine

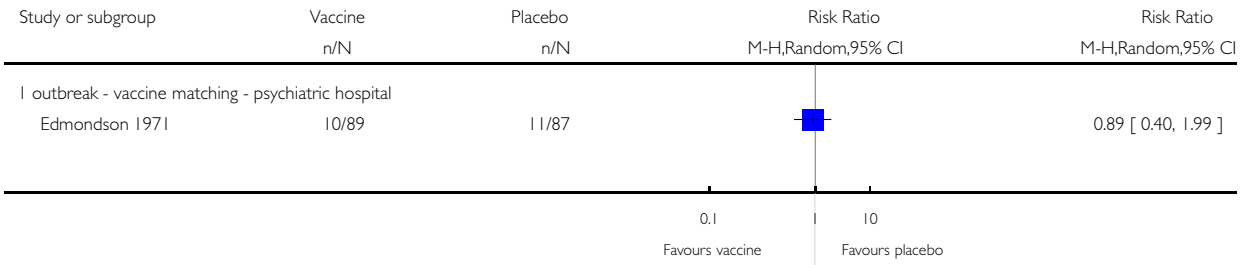
Outcome: 2 Influenza



Review: Vaccines for preventing influenza in the elderly

Comparison: 14 Vaccine versus placebo - inactivated aerosol vaccine

Outcome: 2 Influenza

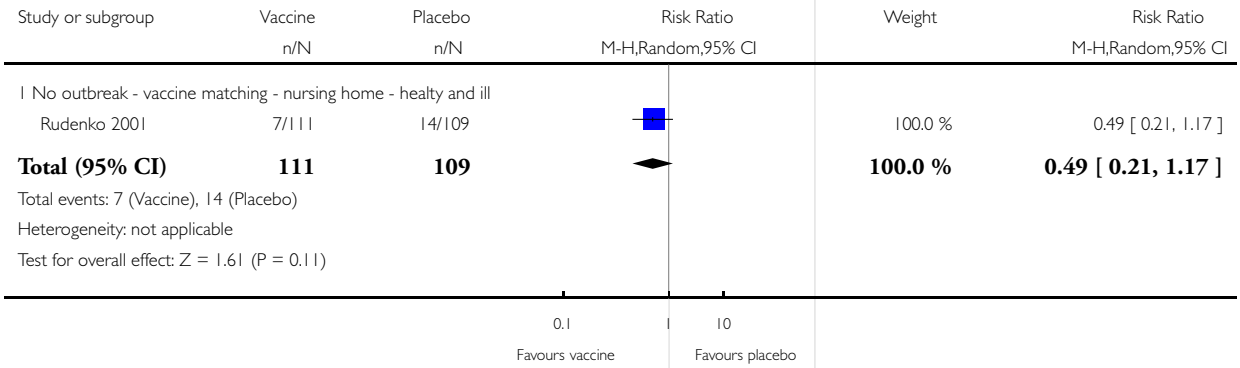


Analysis 15.1. Comparison 15 Vaccine versus placebo - live aerosol vaccine, Outcome 1 Influenza.

Review: Vaccines for preventing influenza in the elderly

Comparison: 15 Vaccine versus placebo - live aerosol vaccine

Outcome: 1 Influenza



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	Risk Ratio M-H,Random,95% CI
1 No outbreak - vaccine matching - nursing home - healty and ill				
Rudenko 2001	7/111	14/109		0.49 [0.21, 1.17]

Analysis 16.1. Comparison 16 Sensitivity analysis Comparison 01: subgoups analysis by study quality, Outcome 1 ILI.

Review: Vaccines for preventing influenza in the elderly

Comparison: 16 Sensitivity analysis Comparison 01: subgoups 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]
Strassburg 1986	34/65	11/19		4.5 %	0.90 [0.58, 1.41]
Patriarca 1985b	37/339	20/119		4.1 %	0.65 [0.39, 1.07]
Coles 1992	34/112	3/12		1.6 %	1.21 [0.44, 3.37]
Taylor 1992	25/45	27/52		5.2 %	1.07 [0.74, 1.55]
Caminiti 1994	12/169	12/73		2.5 %	0.43 [0.20, 0.92]
Monto 2001	247/1728	98/623		6.7 %	0.91 [0.73, 1.13]
Murayama 1999	25/60	38/68		5.3 %	0.75 [0.52, 1.08]
Subtotal (95% CI)	**3066**	**1436**		**36.8 %**	**0.78 [0.65, 0.94]**
Total events: 527 (Vaccine), 364 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 13.17, df = 7 (P = 0.07); I^2 =47%					
Test for overall effect: Z = 2.58 (P = 0.0098)					
2 quality B					
Ruben 1974	38/204	70/192		5.5 %	0.51 [0.36, 0.72]
Goodman 1982	6/36	24/84		2.3 %	0.58 [0.26, 1.30]
Horman 1986	22/100	12/59		3.2 %	1.08 [0.58, 2.02]

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arroyo 1984	10/26	44/90		3.9 %	0.79 [0.46, 1.34]
Fyson 1983a	23/321	29/224		3.9 %	0.55 [0.33, 0.93]
Cartter 1990b	12/30	14/55		3.2 %	1.57 [0.84, 2.95]
Arden 1988	6/31	8/24		1.9 %	0.58 [0.23, 1.45]
Cartter 1990c	75/332	25/126		4.9 %	1.14 [0.76, 1.70]
Cartter 1990a	15/96	3/35		1.3 %	1.82 [0.56, 5.92]
Currier 1988	36/87	15/34		4.5 %	0.94 [0.60, 1.48]
Morens 1995	10/36	1/3		0.7 %	0.83 [0.15, 4.49]
Saito 2002a	58/331	112/368		6.1 %	0.58 [0.44, 0.76]
Saito 2002b	68/743	14/187		3.7 %	1.22 [0.70, 2.12]
Subtotal (95% CI)	**2373**	**1481**		**45.1 %**	**0.82 [0.65, 1.03]**
Total events: 379 (Vaccine), 371 (Control)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 27.13, df = 12 (P = 0.01); I^2 =56%					
Test for overall effect: Z = 1.68 (P = 0.093)					
3 Quality C					
D'Alessio 1969	29/131	7/31		2.7 %	0.98 [0.47, 2.03]
Meiklejohn 1987	14/36	16/19		4.5 %	0.46 [0.29, 0.73]
Isaacs 1997	57/149	12/23		4.6 %	0.73 [0.47, 1.14]
Subtotal (95% CI)	**316**	**73**		**11.7 %**	**0.66 [0.43, 1.00]**
Total events: 100 (Vaccine), 35 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 3.87, df = 2 (P = 0.14); I^2 =48%					
Test for overall effect: Z = 1.97 (P = 0.049)					
4 Quality D					
Mukerjee 1994	62/250	121/216		6.4 %	0.44 [0.35, 0.57]
Subtotal (95% CI)	**250**	**216**		**6.4 %**	**0.44 [0.35, 0.57]**
Total events: 62 (Vaccine), 121 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.49 (P < 0.00001)					
Total (95% CI)	**6005**	**3206**		**100.0 %**	**0.75 [0.65, 0.87]**
Total events: 1068 (Vaccine), 891 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 61.54, df = 24 (P = 0.00004); I^2 =61%					
Test for overall effect: Z = 3.82 (P = 0.00014)					

Review: Vaccines for preventing influenza in the elderly

Comparison: 16 Sensitivity analysis Comparison 01: subgoups analysis by study quality

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 quality A				
Patriarca 1985a	113/548	155/470		0.63 [0.51, 0.77]
Strassburg 1986	34/65	11/19		0.90 [0.58, 1.41]
Patriarca 1985b	37/339	20/119		0.65 [0.39, 1.07]
Coles 1992	34/112	3/12		1.21 [0.44, 3.37]
Taylor 1992	25/45	27/52		1.07 [0.74, 1.55]
Caminiti 1994	12/169	12/73		0.43 [0.20, 0.92]
Monto 2001	247/1728	98/623		0.91 [0.73, 1.13]
Murayama 1999	25/60	38/68		0.75 [0.52, 1.08]
Subtotal (95% CI)	**3066**	**1436**		**0.78 [0.65, 0.94]**
Total events: 527 (Vaccine), 364 (Control)				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 13.17$, df = 7 (P = 0.07); $I^2 = 47\%$				
Test for overall effect: Z = 2.58 (P = 0.0098)				

Review: Vaccines for preventing influenza in the elderly

Comparison: 16 Sensitivity analysis Comparison 01: subgoups analysis by study quality

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
2 quality B				
Ruben 1974	38/204	70/192		0.51 [0.36, 0.72]
Goodman 1982	6/36	24/84		0.58 [0.26, 1.30]
Horman 1986	22/100	12/59		1.08 [0.58, 2.02]
Arroyo 1984	10/26	44/90		0.79 [0.46, 1.34]
Fyson 1983a	23/321	29/224		0.55 [0.33, 0.93]
Cartter 1990b	12/30	14/55		1.57 [0.84, 2.95]
Arden 1988	6/31	8/24		0.58 [0.23, 1.45]
Cartter 1990c	75/332	25/126		1.14 [0.76, 1.70]
Cartter 1990a	15/96	3/35		1.82 [0.56, 5.92]
Currier 1988	36/87	15/34		0.94 [0.60, 1.48]
Morens 1995	10/36	1/3		0.83 [0.15, 4.49]
Saito 2002a	58/331	112/368		0.58 [0.44, 0.76]
Saito 2002b	68/743	14/187		1.22 [0.70, 2.12]
Subtotal (95% CI)	**2373**	**1481**		**0.82 [0.65, 1.03]**
Total events: 379 (Vaccine), 371 (Control)				
Heterogeneity: Tau² = 0.09; Chi² = 27.13, df = 12 (P = 0.01); I² =56%				
Test for overall effect: Z = 1.68 (P = 0.093)				

Review: Vaccines for preventing influenza in the elderly

Comparison: 16 Sensitivity analysis Comparison 01: subgoups analysis by study quality

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
3 Quality C				
D'Alessio 1969	29/131	7/31		0.98 [0.47, 2.03]
Meiklejohn 1987	14/36	16/19		0.46 [0.29, 0.73]
Isaacs 1997	57/149	12/23		0.73 [0.47, 1.14]
Subtotal (95% CI)	**316**	**73**		**0.66 [0.43, 1.00]**
Total events: 100 (Vaccine), 35 (Control)				
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.87$, df = 2 (P = 0.14); $I^2 = 48\%$				
Test for overall effect: Z = 1.97 (P = 0.049)				

Review: Vaccines for preventing influenza in the elderly

Comparison: 16 Sensitivity analysis Comparison 01: subgoups analysis by study quality

Outcome: 1 ILI

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
4 Quality D				
Mukerjee 1994	62/250	121/216		0.44 [0.35, 0.57]
Subtotal (95% CI)	**250**	**216**		**0.44 [0.35, 0.57]**
Total events: 62 (Vaccine), 121 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 6.49 (P < 0.00001)				

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	Weight	Risk Ratio M-H,Random,95% CI
Margolis 1990a	24/336	20/336		28.7 %	1.20 [0.68, 2.13]
Treanor 1994	3/30	0/11		1.1 %	2.71 [0.15, 48.62]
Govaert 1993	58/904	50/902		70.2 %	1.16 [0.80, 1.67]
Keitel 1996	0/21	0/20		0.0 %	Not estimable
Total (95% CI)	**1291**	**1269**		**100.0 %**	**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

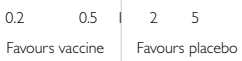
Outcome: 2 Fever

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	11/30	2/11		9.0 %	2.02 [0.53, 7.69]
Total (95% CI)	**366**	**347**		**100.0 %**	**1.35 [0.90, 2.01]**

Total events: 55 (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

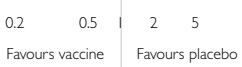
Outcome: 4 Headache

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	Weight	Risk Ratio M-H,Random,95% CI
Govaert 1993	66/904	8/902		100.0 %	8.23 [3.98, 17.05]
Keitel 1996	0/21	0/20		0.0 %	Not estimable
Total (95% CI)	**925**	**922**		**100.0 %**	**8.23 [3.98, 17.05]**

Total events: 66 (Vaccine), 8 (Placebo)

Heterogeneity: not applicable

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

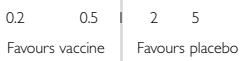
Outcome: 1 General malaise

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

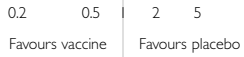
Outcome: 2 Fever

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

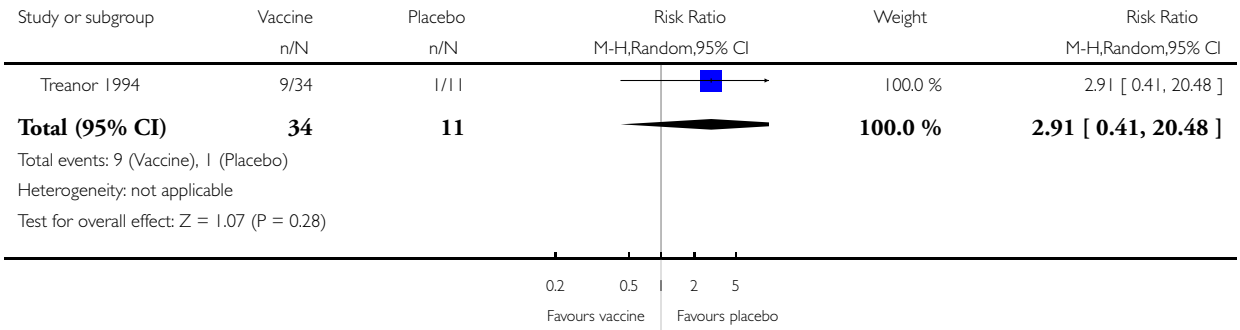
Test for overall effect: Z = 0.69 (P = 0.49)

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



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

b) no description of source
Comparability
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor)
b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)
Exposure
1) Ascertainment of exposure
a) secure record (e.g. surgical records)
b) structured interview where blind to case/control status
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes
b) no
3) Non-Response rate
a) same rate for both groups
b) non respondents described
c) rate different and no designation
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability
Selection
1) Representation of the exposed cohort
a) truly representative of the average _____ (describe) in the community
b) somewhat representative of the average _____ in the community
c) selected group of users e.g. nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (e.g. surgical records)
b) structured interview
c) written self report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor)
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Outcome
1) Assessment of outcome
a) independent blind assessment
b) record linkage
c) self report
d) no description
2) Was follow up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest)

b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Appendix 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 crossover 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)

F E E D B A C K

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.

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Contributors

Keiji Hayashi
Feedback comment and reply added 25/07/07

WHAT'S NEW

Last assessed as up-to-date: 4 May 2006

Date	Event	Description
8 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2006

Date	Event	Description
24 July 2007	Feedback has been incorporated	Feedback comment and reply added to review.

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ) and Daniela Rivetti (DR) wrote the protocol.

Roger E Thomas (RT) participated in the final draft of the protocol and the review.

TOJ, DR and Vittorio Demicheli (VD) designed the review.

Alessandro Rivetti (AR) conducted the searches

TOJ, DR and VD applied inclusion criteria.

TOJ, DR and Melanie Rudin (MR) extracted the data.

VD arbitrated and checked the data extraction.

Carlo Di Pietrantonj (CDP) undertook the meta-analysis and did statistical testing.

TOJ wrote the final review.

All authors contributed to both protocol and final 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

- No sources of support supplied

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