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Vaccines for preventing influenza in healthy adults (Review)

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[Intervention Review]

Vaccines for preventing influenza in healthy adults

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ABSTRACT

Background

Different types of influenza vaccines are currently produced worldwide. Vaccination of pregnant women is recommended internationally, while healthy adults are targeted in North America.

Objectives

To identify, retrieve and assess all studies evaluating the effects (efficacy, effectiveness and harm) of vaccines against influenza in healthy adults, including pregnant women.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2), MEDLINE (January 1966 to May 2013) and EMBASE (1990 to May 2013).

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing influenza vaccines with placebo or no intervention in naturally occurring influenza in healthy individuals aged 16 to 65 years. We also included comparative studies assessing serious and rare harms.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

We included 90 reports containing 116 data sets; among these 69 were clinical trials of over 70,000 people, 27 were comparative cohort studies (about eight million people) and 20 were case-control studies (nearly 25,000 people). We retrieved 23 reports of the effectiveness and safety of vaccine administration in pregnant women (about 1.6 million mother-child couples).

The overall effectiveness of parenteral inactivated vaccine against influenza-like illness (ILI) is limited, corresponding to a number needed to vaccinate (NNV) of 40 (95% confidence interval (CI) 26 to 128). The overall efficacy of inactivated vaccines in preventing confirmed influenza has a NNV of 71 (95% CI 64 to 80). The difference between these two values depends on the different incidence of

ILI and confirmed influenza among the study populations: 15.6% of unvaccinated participants versus 9.9% of vaccinated participants developed ILI symptoms, whilst only 2.4% and 1.1%, respectively, developed laboratory-confirmed influenza.

No RCTs assessing vaccination in pregnant women were found. The only evidence available comes from observational studies with modest methodological quality. On this basis, vaccination shows very limited effects: NNV 92 (95% CI 63 to 201) against ILI in pregnant women and NNV 27 (95% CI 18 to 185) against laboratory-confirmed influenza in newborns from vaccinated women.

Live aerosol vaccines have an overall effectiveness corresponding to a NNV 46 (95% CI 29 to 115).

The performance of one-dose or two-dose whole virion pandemic vaccines was higher, showing a NNV of 16 (95% CI 14 to 20) against ILI and a NNV of 35 (95% CI 33 to 47) against influenza, while a limited impact on hospitalisation was found (NNV 94, 95% CI 70 to 1022).

Vaccination had a modest effect on time off work and had no effect on hospital admissions or complication rates. Inactivated vaccines caused local harms. No evidence of association with serious adverse events was found, but the harms evidence base was limited.

The overall risk of bias in the included trials is unclear because it was not possible to assess the real impact of bias.

Authors' conclusions

Influenza vaccines have a very modest effect in reducing influenza symptoms and working days lost in the general population, including pregnant women. No evidence of association between influenza vaccination and serious adverse events was found in the comparative studies considered in the review. This review includes 90 studies, 24 of which (26.7%) were funded totally or partially by industry. Out of the 48 RCTs, 17 were industry-funded (35.4%).

PLAIN LANGUAGE SUMMARY

Vaccines to prevent influenza in healthy adults

Review question

We evaluated the effect of immunisation with influenza vaccines on preventing influenza A or B infections (efficacy), influenza-like illness (ILI) and its consequences (effectiveness), and determined whether exposure to influenza vaccines is associated with serious or severe harms. The target populations were healthy adults, including pregnant women and newborns.

Background

Over 200 viruses cause influenza and ILI, producing the same symptoms (fever, headache, aches, pains, cough and runny noses). Without laboratory tests, doctors cannot distinguish between them as both last for days and rarely lead to death or serious illness. At best, vaccines may only be effective against influenza A and B, which represent about 10% of all circulating viruses. Annually, the World Health Organization estimates which viral strains should be included in the next season's vaccinations.

Inactivated vaccine is prepared by treating influenza viruses with a specific chemical agent that "kills" the virus. Final preparations can contain either the complete viruses (whole vaccine) or the active part of them (split or subunit vaccines). These kind of vaccines are normally intramuscularly administered (parenteral route)

Live attenuated vaccines is prepared by growing the influenza viruses through a series of cell cultures or animal embryos. With each passage, the viruses lose their ability to replicate in human cells but can still stimulate the immune system. Live attenuated vaccine are administered as aerosol in the nostrils (intranasal route).

The virus strains contained in the vaccine are usually those that are expected to circulate in the following epidemic seasons (two type A and one B strains), accordingly to the recommendations of the World Health Organization (seasonal vaccine).

Pandemic vaccine contains only the virus strain that is responsible of the pandemic (i.e. the type A H1N1 for the 2009/2010 pandemic).

Study characteristics

The evidence is current to May 2013. In this update, 90 reports of 116 studies compared the effect of influenza vaccine with placebo or no intervention. Sixty-nine reports were clinical trials (over 70,000 people), 27 were comparative cohort studies (about eight million people) and 20 were case-control studies (nearly 25,000 people). Of the 116 studies, 23 (three case-control and 20 cohort studies) were performed during pregnancy (about 1.6 million mother-child couples).

Key results

The preventive effect of parenteral inactivated influenza vaccine on healthy adults is small: at least 40 people would need vaccination to avoid one ILI case (95% confidence interval (CI) 26 to 128) and 71 people would need vaccination to prevent one case of influenza (95% CI 64 to 80). Vaccination shows no appreciable effect on working days lost or hospitalisation.

The protection against ILI that is given by the administration of inactivated influenza vaccine to pregnant women is uncertain or at least very limited; the effect on their newborns is not statistically significant.

The effectiveness of live aerosol vaccines on healthy adults is similar to inactivated vaccines: 46 people (95% CI 29 to 115) would need immunisation to avoid one ILI case.

The administration of seasonal inactivated influenza vaccine is not associated with the onset of multiple sclerosis, optic neuritis (inflammation of the optic nerve of the eye) or immune thrombocytopaenic purpura (a disease that affects blood platelets). The administration of pandemic monovalent H1N1 inactivated vaccine is not associated with Guillain-Barré syndrome (a disease that affects the nerves of the limbs and body).

Evidence suggests that the administration of both seasonal and 2009 pandemic vaccines during pregnancy has no significant effect on abortion or neonatal death.

Quality of the evidence

The real impact of biases could not be determined for about 70% of the included studies (e.g. insufficient reporting details, very different scores among the items evaluated). About 20% of the included studies (mainly cohorts) had a high risk of bias. Just under 10% had good methodological quality.

BACKGROUND

Description of the condition

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

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

Description of the intervention

Currently there are three types of influenza vaccines:

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

These vaccines contain both surface and internal antigens. In addition, a variety of non-European manufacturers produce live attenuated vaccines. Traditionally, whole virion vaccines are thought to be the less well tolerated because of the presence of a lipid stratum on the surface of the viral particles (a remnant of the host cell membrane coating the virion, when budding from the host cell). Influenza vaccines are produced worldwide. Periodic antigenic drifts and shifts pose problems for vaccine production and procurement, as a new vaccine closely matching the circulating antigenic

configuration must be produced and procured for the beginning of each new influenza 'season'. To achieve this, the World Health Organization (WHO) has established a worldwide surveillance system, allowing the identification and isolation of viral strains circulating the different parts of the globe. Sentinel practices recover viral particles from the nasopharynx of patients with influenza-like symptoms and the samples are swiftly sent to the laboratories of the national influenza centres (110 laboratories in 79 countries). When new strains are detected the samples are sent to one of the four WHO reference centres (London, Atlanta, Tokyo and Melbourne) for antigenic analysis. Information on the circulating strain is then sent to the WHO, which in February of each year recommends, through a committee, the strains to be included in the vaccine for the forthcoming 'season'. Individual governments may or may not follow the WHO recommendations. Australia, New Zealand and, more recently, South Africa follow their own recommendations for vaccine content. Surveillance and early identification thus play a central part in the composition of the vaccine.

How the intervention might work

Every vaccination campaign has stated aims against which the effects of the campaign must be measured. Perhaps the most detailed document presenting the rationale for a comprehensive preventive programme was that by the US Advisory Committee on Immunization Practice (ACIP), published in 2006 (ACIP 2006). The document identified 11 categories of people at high risk of complications from influenza, among which are healthy adults 50 to 65 years of age and healthcare workers. The rationale for policy choices rests on the heavy burden that influenza imposes on the populations and on the benefits accruing from vaccinating them. Reductions in cases and complications (such as excess hospitalisations, absence from work, mortality and healthcare contacts) and the interruption of transmission are the principal arguments for extending vaccination to healthy adults aged 50 to 65 years (ACIP 2006).

The ACIP 2010 document update recommends routine vaccination for all participants aged six months and older. It underlines the importance of focusing vaccination efforts, when vaccination supplies are limited, on healthy adults who are at increased risk of developing severe complications from influenza, such as:

- people aged 50 years or over;
- women who are or will be pregnant during the influenza season;
- healthcare personnel;
- household contacts and caregivers of children aged below five years and adults aged 50 years or over, with particular emphasis on vaccinating contacts of children younger than six months of age; and
- household contacts and caregivers of persons with medical conditions that put them at higher risk of severe complications from influenza (ACIP 2010).

Pregnant women are included among priority recipients for seasonal influenza immunisation in many countries (AIH 2013; Green Book 2013; NACI 2012; STIKO 2010), because of the risk of influenza-associated morbidity during pregnancy, the possible adverse neonatal outcomes associated with maternal influenza infections, and based on the evidence that vaccination of pregnant women protects their newborns from influenza and influenza-related hospitalisations (NACI 2012).

Inactivated influenza vaccine could be administered at any stage of pregnancy, whereas live vaccine is not licensed for use during pregnancy as the available data about safety and efficacy in mothers and babies are very limited (ACIP 2010; Green Book 2013).

Why it is important to do this review

Given the very high cost of yearly vaccination for large parts of the population, the extreme variability of influenza incidence during each 'season' and the heterogeneity of public health recommendations, we carried out a systematic review of the evidence. To enhance its relevance for decision-makers, in the 2007 update of the review we included comparative non-randomised studies reporting evidence of serious or rare harms (or both) (Jefferson 2007). In the present update (2013), we have also included evidence about influenza vaccination in pregnant women and newborns.

OBJECTIVES

To identify, retrieve and assess all studies evaluating the effects (efficacy, effectiveness and harm) of vaccines against influenza in healthy adults, including pregnant women.

We defined 'effects' as follows:

1. efficacy as the capacity of the vaccines to prevent influenza A or B and its complications;

2. effectiveness as the capacity of the vaccines to prevent influenza-like illness and its consequences; and

3. harm as any harmful event potentially associated with exposure to influenza vaccines.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled trial (RCT) or quasi-RCT comparing influenza vaccines in humans with placebo or no intervention, or comparing types, doses or schedules of influenza vaccine. Only studies assessing protection from exposure to naturally occurring influenza were considered.

Comparative non-randomised studies were included if they reported evidence on the association between influenza vaccines and serious adverse effects, such as Guillain-Barré syndrome or oculo-respiratory syndromes, or if they reported effectiveness or efficacy data for vaccine administration during pregnancy.

We defined as RCTs studies in which it appeared that the individuals (or other experimental units) included in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of healthcare using random allocation. A study was quasi-randomised when it appeared that 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 healthcare using some quasi-random method of allocation (such as by alternation, date of birth or case record number).

Types of participants

Healthy individuals aged 16 to 65 years, irrespective of influenza immune status. Studies considering more than 25% of individuals outside this age range were excluded from the review. Pregnant women together with their newborns were also included.

Types of interventions

Live, attenuated or killed vaccines, or fractions thereof, administered by any route, irrespective of antigenic configuration.

Types of outcome measures

Primary outcomes

Clinical

1. Numbers and seriousness (complications and working days lost) of symptomatic influenza and influenza-like illness (ILI) cases occurring in vaccine and placebo groups.

Harms

1. Number and seriousness of adverse effects (systemic and severe). Systemic adverse effects include cases of malaise, nausea, fever, arthralgia, rash, headache and more generalised and serious signs, such as neurological harms.
2. Maternal outcomes and outcomes related to the course of pregnancy. These include abortion (spontaneous, internal, fetal death, stillbirth), preterm birth (less than 37 weeks), maternal death.
3. Neonatal outcomes: congenital malformations (minor and major), neonatal death.

Secondary outcomes

1. Local adverse effects include induration, soreness and redness at the site of inoculation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (PubMed) (January 1966 to May 2013) and EMBASE.com (1990 to May 2013). Search strategies used for the present version of the review are reported in the appendices (see Appendix 1 for trials and Appendix 2 for observational studies searches).

See Appendix 3 for strategies used in the 2010 update and Appendix 4 for the MEDLINE search strategy used in 2004. There were no language or publication restrictions.

Searching other resources

To identify further trials, we read the bibliographies of retrieved articles and handsearched the journal *Vaccine* from its first issue to the end of 2009. The results of the handsearches are included in CENTRAL. In order to locate unpublished trials for the first edition of this review, we wrote to the following: manufacturers and first or corresponding trial authors of studies in the review.

Data collection and analysis

Selection of studies

Two review authors (AR, CDP) independently excluded all initially identified and retrieved articles not fulfilling the inclusion criteria. In the case of disagreement, one review author (VD) acted as arbitrator.

Data extraction and management

Two review authors (AR, CDP) performed data extraction using a data extraction form (Appendix 5). We checked and entered the data into Review Manager (RevMan 2012) software. We extracted data on the following:

- methodological quality of studies;
- study design (Appendix 6);
- description of setting;
- characteristics of participants;
- description of vaccines (content and antigenic match);
- description of outcomes;
- publication status;
- date of study;
- location of study.

One review author (CDP) carried out statistical analyses.

Assessment of risk of bias in included studies

Experimental studies (trials)

The review authors independently assessed the methodological quality of the included studies using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). One review author (VD) acted as arbitrator in the case of disagreement between the two review authors (CDP, AR) in assigning quality judgements.
We classified studies according to the following key domains for assessing risk of bias (Higgins 2011).

Random sequence generation

- Low risk of bias: if, for example, a table of random numbers or computer-generated random numbers were used.
- High risk of bias: if, for example, alternation, date of birth, day of the week or case record number were used.
- Unclear risk of bias: if insufficient information was provided.

Allocation concealment

- Low risk of bias: if, for example, numbered or coded identical containers were administered sequentially, an on-site computer system that could only be accessed after entering the characteristics of an enrolled participant, or serially numbered, opaque, sealed envelopes, were used, or sealed envelopes that were not sequentially numbered or opaque were used.
- High risk of bias: if, for example, an open table of random numbers was used.
- Unclear risk of bias: if insufficient information was provided.

Blinding

- Low risk of bias: if adequate double-blinding, for example, placebo vaccine, or single-blinding (i.e. blinded outcome assessment) were used.
- High risk of bias: if there was no blinding.
- Unclear risk of bias: if insufficient information was provided.

Incomplete outcome data

Number of losses to follow-up:

- Low risk of bias: no missing data or the proportion of missing data compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.
- High risk of bias: when the proportion of missing data compared with observed event risk was large enough to induce clinically relevant bias in the intervention effect estimate.
- Unclear risk of bias: if insufficient information was provided.

Non-experimental studies

We carried out quality assessment of non-randomised studies in relation to the presence of potential confounders, which could make interpretation of the results difficult. We evaluated the quality of case-control (prospective and retrospective) and cohort studies using the appropriate Newcastle-Ottawa Scales (NOS) (Appendix 7).
Using quality at the analysis stage as a means of interpreting the results, we assigned 'Risk of bias' categories (Higgins 2011):

- Low risk of bias: plausible bias unlikely to seriously alter the results.
- Unclear risk of bias: plausible bias that raises some doubt about the results.
- High risk of bias: plausible bias that seriously weakens confidence in the results.

Measures of treatment effect

We used the risk ratio (RR) and its 95% confidence interval (CI) as the summary measure. We calculated vaccine efficacy (or effectiveness) as VE=1-RR, expressed as a percentage, for cohort and RCT/controlled clinical trial (CCT) studies. For case-control studies we adopted an odds ratio (OR) with 95% CIs.
To enhance relevance to everyday practice, we also expressed the summary measure of the most reliable and significant comparisons (those from RCTs with influenza cases as an outcome by age group) as a risk difference (RD). This is a measure of absolute efficacy of the vaccines, which incorporates significant information such as the incidence in the control arm and allows the calculation of its reciprocal, the number needed to treat (NNT) or in this case the number needed to vaccinate (NNV). The NNV expresses the number of adults needed to be vaccinated to prevent one case of influenza. The NNV can be computed as 1/RD. Since meta-analysis estimates from RD are affected by spurious heterogeneity

we preferred to compute the NNV as 1/((RR-1)*CER), where CER is the proportion of total events in the control group.

Unit of analysis issues

We summarised evidence from non-randomised studies (cohort and case-control) according to Higgins 2011.

We found four different definitions of the 'epidemic period'.

1. The interval between the first and the last virus isolation in the community.
2. The interval during which the influenza virus was recovered from more than a stated percentage of ill participants.
3. The period during which an increase of respiratory illness of more than a stated percentage was recorded.
4. The winter period, taken as a proxy for the epidemic period.

We included data regardless of the definition of epidemic period used in the primary study. When data were presented for the epidemic period and the entire follow-up period, we considered those which occurred during the former.

An ILI case (specific definition) was assumed to be the same as a 'flu-like illness' according to a pre-defined list of symptoms (like that of the Centers for Disease Control and Prevention (CDC) case definition for surveillance), or 'upper respiratory illness' according to a predefined list of symptoms.

The laboratory confirmations of influenza cases we found were:

1. virus isolation from culture;
2. four-fold antibody increase (haemagglutinin) in acute or convalescent phase sera;
3. four-fold antibody increase (haemagglutinin) in post-vaccination or post-epidemic phase sera.

Several trials included more than one active vaccine arm. Where several active arms from the same trial were included in the same analysis, we split the placebo group equally between the different arms, so that the total number of participants in a single analysis did not exceed the actual number in the trials.

Dealing with missing data

For the first publication of this review (Demicheli 1999), we wrote to the trial authors and manufacturers to identify possible unpublished studies and missing data. The response was disappointing and we desisted from any further attempts. Our analysis relies on existing data. Whenever possible we used the intention-to-treat (ITT) population.

Assessment of heterogeneity

We calculated the I^2 statistic for each pooled estimate, to assess the impact on statistical heterogeneity. The I^2 statistic may 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 from the number of studies. When the I^2 value is less than 30% there is little concern about statistical heterogeneity (Higgins 2011). We used random-effects models throughout to take account of the between-study variance in our findings (Higgins 2011). Variance is to be expected in influenza vaccine trials as there are unpredictable systematic differences between trials regarding the circulating strains, degree of antigenic matching of the vaccine, type of vaccine and the levels of immunity presented by different populations in different settings. Not all studies reported sufficient details to enable a full analysis of the sources of heterogeneity, but we were able to take into account vaccine matching and circulating strain.

Assessment of reporting biases

Due to the limited number of studies in each comparison or subgroup, assessment of publication bias was not applicable, since the evidence presented in this review originated mainly from published data. For this reason, our results could be affected by publication bias.

The overall quality of the retrieved studies was poor and was affected by poor reporting or limited descriptions of the studies' designs. A detailed description is provided in the Risk of bias in included studies section of the review.

The main problems with influenza vaccine studies are their poor quality and discrepancies between the data presented, their conclusions and the authors' recommendations.

Data synthesis

We calculated all meta-analyses using a random-effects model.

We constructed the data and analyses tables according to the following criteria.

1. Inactivated parenteral influenza vaccines versus placebo or no intervention (Analysis 01).
2. Live aerosol vaccines (Analysis 02).
3. Inactivated aerosol vaccines (Analysis 03).
4. Inactivated parenteral influenza vaccines versus placebo - cohort studies (Analysis 04).
5. Inactivated parenteral influenza vaccines versus placebo - case-controls (Analysis 05).
6. Serious adverse events - Guillain-Barré syndrome - cohort studies (Analysis 06).
7. Serious adverse events - Guillain-Barré syndrome - case-control (Analysis 07).
8. Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - cohort studies (Analysis 08).
9. Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control (Analysis 09).
10. Serious adverse events - immune thrombocytopaenic purpura - cohort studies (Analysis 10).
11. Serious adverse events - immune thrombocytopaenic purpura - case-control (Analysis 11).

12. 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo (Analysis 12).
13. 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo (Analysis 13).
14. 1968 to 1969 pandemic: inactivated polyvalent aerosol vaccine versus placebo (Analysis 14).
15. 1968 to 1969 pandemic: inactivated monovalent aerosol vaccine versus placebo (Analysis 15).
16. 1968 to 1969 pandemic: live aerosol vaccine versus placebo (Analysis 16).

Since RCT/CCTs on vaccine efficacy/effectiveness in the general population (Analyses 1 to 3) were available, only this type of study design has been included. On the other hand, for vaccine efficacy/effectiveness in pregnancy (Analyses 4 and 5) no eligible RCTs were found, therefore evidence from observational studies was included. Quantitative synthesis of the evidence from observational studies has been conducted using adjusted estimates when these were available, in some cases also original data (unadjusted data) have been used in order to compare meta-analysis results from adjusted and unadjusted estimates.

For Analyses 1 to 3 and 12 to 16, we carried out subgroup analyses according to the degree of matching with that year's WHO recommended content and with circulating viruses ("WHO recommended and matching" when known). WHO recommendations on the content of vaccines have been published since 1973. Different dosages and schedules of the vaccine and the presence of different adjuvants were not compared and we pooled data from the arms of trials comparing only vaccine composition or dosage in the analysis. We checked compliance of the study vaccine with the official antigenic content and potency recommendations by reviewing the WHO records when possible. In case of uncertainty due to ambiguity in the wording used (in the oldest trials), we took the opinion given by the authors into account. We classified the compliance of a live attenuated vaccine with the recommendations according to the antigenic comparability of the wild strains.

The following outcomes were included:

1. Cases of influenza (defined on the basis of a specific list of symptoms and/or signs backed up by laboratory confirmation of infection with influenza A or B viruses): Analyses 1 to 5 and 12 to 16.
2. Cases of ILI (clinically defined on the basis of a specific list of symptoms and/or signs): Analyses 1 to 5 and 12 to 16.
3. Effectiveness (ILI) pregnant women: Analysis 4.
4. Effectiveness (ILI) in newborns: Analyses 4 and 5.
5. Hospital admissions: Analyses 1, 12, 13.
6. Complications: Analyses 2, 12, 13, 16.
7. Working days lost: Analyses 1 and 13.
8. Pregnancy outcome (abortion, congenital malformation, prematurity, infant death): Analyses 4 and 5.
9. Local harms: Analyses 1 to 3.
10. Systemic harms: Analyses 1 to 3.
11. Severe/rare harms (Guillain-Barré syndrome, demyelinating diseases, immune thrombocytopaenic purpura): Analyses 6 to 11.

We calculated hospital admission rates as the proportion of cases hospitalised for respiratory causes. We considered complications as the proportion of cases complicated by bronchitis, pneumonia or otitis. We also considered working days lost due to episodes of sickness absence regardless of cause. Only five trials used working days lost as an outcome measure and four of them measured the work absence in terms of the difference in the average number of days lost in the two arms of the trial (Analysis 1.7). These studies presented a standard error value measured accordingly. The remainder expressed work absence in terms of rate ratio and this does not allow the recalculation of the correct estimate of the standard error (aa Nichol 1999a). Therefore, we excluded this study from the pooled analysis.

We presented local symptoms separately from systemic symptoms. We have considered individual harms in the analysis, as well as a combined endpoint (any or highest symptom). We used all data included in the analysis as presented by the authors in the primary study, regardless of the number of drop-outs. We decided on this approach (complete case scenario) because the majority of the studies did not make any attempt to use an intention-to-treat analysis or mention the reasons for the loss to follow-up, and they did not contain detailed information to allow estimations of the real number of participants.

Studies investigating the association between influenza vaccination and Guillain-Barré syndrome were included in Analysis 6 (cohort on seasonal vaccine) and Analysis 7 (case-control on H1N1 vaccine). In Analysis 7, we have stratified studies according to three different exposure definitions, according to the time between vaccination to onset of symptoms (any time, within seven weeks, over seven weeks). In Analysis 6, evidence for the association between seasonal vaccine and Guillain-Barré syndrome from cohort studies is presented.

Studies investigating the association between influenza vaccination and multiple sclerosis and optic neuritis are included in Analyses 8 and 9 (cohort and case-control studies - demyelinating diseases).

Studies investigating the association between influenza vaccination and immune thrombocytopaenic purpura (ITP) are included in Analyses 10 and 11 (cohort and case-control studies - ITP).

Subgroup analysis and investigation of heterogeneity

Since the degree of matching between vaccine and circulating strains could affect the effectiveness/efficacy of the vaccine, we have analysed the data in separate subgroups according to this parameter. For serious adverse events, when possible, we have analysed data from pregnant women and the general population in separate subgroups. When case-control studies reported safety outcomes, when possible we performed analyses in separate subgroups according to time since exposure. Finally, we carried out a separate analysis of trials carried out during the 1968 to 1969 (H3N2) pandemic and the 2009 to 2010 (H1N1) pandemic.

Sensitivity analysis

As it was not possible to identify all sources of heterogeneity, we decided to carry out a sensitivity analysis on the results by applying fixed-effect and random-effects models to assess the impact of heterogeneity on our results. In order to assess the robustness of our conclusions, we performed a sensitivity analysis by excluding low-quality studies and, in the case of observational studies, by comparing the results from the crude data with those from the adjusted data.

RESULTS

Description of studies

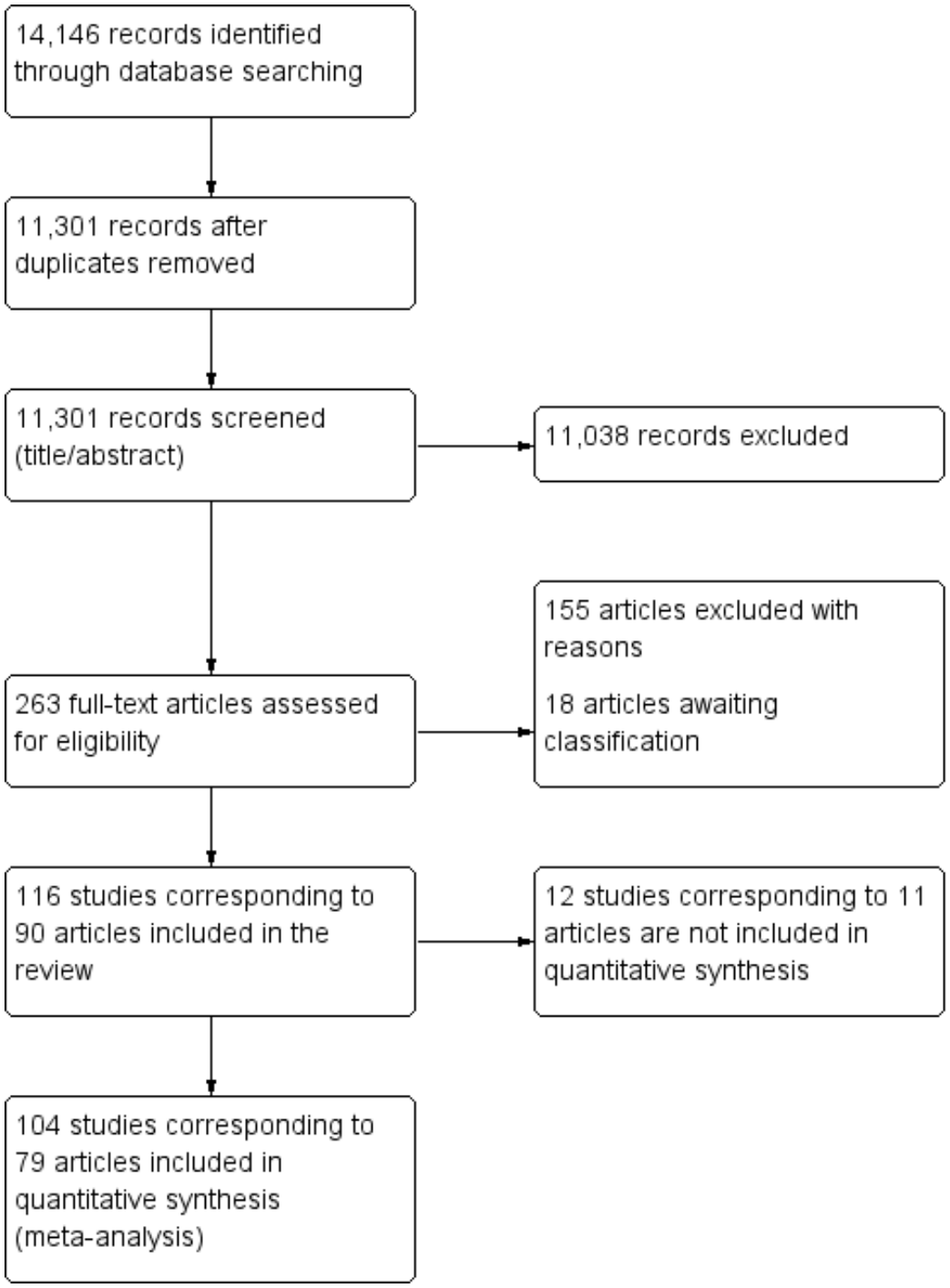
Results of the search

The first publication of this review contained 20 trials (Demicheli 1999). The second publication added five more trials (Demicheli 2004). The third publication included 48 trials in total (Jefferson 2007). The fourth published update (Jefferson 2010) included two new trials (aa Beran 2009a; aa Beran 2009b) and excluded three new trials (Belongia 2009; Chou 2007; Khazeni 2009). In this 2013 update, 41 new study reports have been included and 63 new trials have been excluded.

Some of the included studies had more than two arms, comparing different vaccines, routes of administration, schedules or dosages, or reported data from different settings and epidemic seasons. We split these studies into sub-studies (data sets). For the remainder of this review, the term 'study report' refers to the original study report, while the word 'data set' refers to the sub-study; these sub-studies could refer either to different study arms, to different influenza seasons or to different study designs. Risk of bias can be independently assessed for each sub-study (or data set) study design.

More information about the division of study reports into data sets is given in the Characteristics of included studies table. In this 2013 update, 90 studies (116 data sets) are now included in the review (Figure 1).

Figure 1. Study flow diagram



Included studies

We have coded each trial on the basis of study design and the type of data contributed to the review as follows. The letter preceding the study represents the study design: (a) denotes RCTs, (b) denotes case-control studies and (c) denotes cohort studies. The second letter indicates the contribution to the evidence in the data set: (a) efficacy/effectiveness or (b) harms. So, for example, a case-control study contributing safety or harms data is coded as (bb) and a trial contributing efficacy/effectiveness data is coded as (aa). A (p) code has been added to refer to the studies on vaccination during pregnancy.

Seasonal vaccines: efficacy or effectiveness

1. **RCTs on inactivated parenteral vaccine:** (20 studies/29 data sets) (aa Barrett 2011; aa Beran 2009a; aa Beran 2009b; aa Bridges 2000a; aa Bridges 2000b; aa Eddy 1970; aa Frey 2010; aa Hammond 1978; aa Jackson 2010a; aa Jackson 2010b; aa Keitel 1988a; aa Keitel 1988b; aa Keitel 1997a; aa Keitel 1997b; aa Keitel 1997c; aa Leibovitz 1971; aa Mesa Duque 2001; aa Mixéu 2002; aa Monto 2009; aa Nichol 1995; aa Ohmit 2006; aa Ohmit 2008; aa Powers 1995a; aa Powers 1995b; aa Powers 1995c; aa Tannock 1984; aa Weingarten 1988; aa Zhilova 1986a; aa Zhilova 1986b).
2. **RCTs on live aerosol vaccine:** (eight studies/12 data sets) (aa Edwards 1994a; aa Edwards 1994b; aa Edwards 1994c; aa Edwards 1994d; aa Monto 1982; aa Monto 2009; aa Nichol 1999a; aa Ohmit 2006; aa Ohmit 2008; aa Rytel 1977; aa Zhilova 1986a; aa Zhilova 1986b).
3. **RCTs on inactivated aerosol vaccine:** (one study/one data set) (aa Langley 2011).

Seasonal vaccines: safety (local and systemic harms)

1. **RCTs on inactivated parenteral vaccine:** (20 studies/21 data sets) (aa Barrett 2011; aa Bridges 2000a; aa Bridges 2000b; aa Frey 2010; aa Jackson 2010a; aa Mesa Duque 2001; aa Monto 2009; aa Nichol 1995; aa Ohmit 2006; aa Ohmit 2008; aa Powers 1995a; aa Tannock 1984; aa Weingarten 1988; ab Caplan 1977; ab El'shina 1996; ab Forsyth 1967; ab Goodeve 1983; ab Pyrhönen 1981; ab Rocchi 1979a; ab Saxen 1999; ab Scheifele 2003).
2. **RCTs on live aerosol vaccine:** (13 studies/14 data sets) (ab Atmar 1990; ab Betts 1977a; ab Evans 1976; ab Hrabar 1977; ab Keitel 1993a; ab Keitel 1993b; ab Lauteria 1974; ab Miller 1977; aa Monto 1982; aa Nichol 1999a; aa Ohmit 2006; aa Ohmit 2008; ab Rocchi 1979b; aa Rytel 1977).
3. **RCTs on inactivated aerosol vaccine:** (three studies/three data sets) (ab Boyce 2000; ab Langley 2005; aa Langley 2011).

Two studies with live aerosol vaccine (ab Reeve 1982; ab Spencer 1977) (each one a data set) could not be introduced into the harms analysis (secondary effects) because the data did not allow for quantitative analysis (systemic and local harms were reported given as cumulative in ab Spencer 1977 and data were not clearly reported in ab Reeve 1982).

Administration during pregnancy - efficacy/effectiveness in mothers

1. **Seasonal inactivated vaccine - cohort studies:** (two studies/two data sets) (pca Black 2004; pca Hulka 1964).
2. **2009 to 2010 pandemic: inactivated vaccines - cohort studies:** (one study/one data set) (pca Yamada 2012).

Administration during pregnancy - efficacy/effectiveness in newborns

1. **Seasonal inactivated vaccine - cohort studies on effectiveness (ILI):** (three studies/three data sets) (pca Black 2004; pca Eick 2011; pca France 2006).
2. **Seasonal inactivated vaccine - cohort studies on efficacy (laboratory-confirmed):** (one study/one data set) (pca Eick 2011).
3. **Seasonal inactivated vaccine - case-control on effectiveness (ILI):** (two studies/two data sets) (pba Benowitz 2010; pba Poehling 2011).

Administration during pregnancy - pregnancy-related outcomes (abortion, congenital malformation, prematurity, neonatal death)

1. **Seasonal inactivated vaccine - cohort studies:** (four studies/four data sets) (pca Black 2004; pca Munoz 2005; pcb Omer 2011; pcb Sheffield 2012).
2. **2009 to 2010 pandemic: inactivated vaccine - cohort studies:** (nine studies/nine data sets) (pcb Fell 2012; pcb Håberg 2013; pcb Heikkinen 2012; pcb Källén 2012; pcb Launay 2012; pcb Lin 2012; pcb Oppermann 2012; pcb Pasternak 2012; pcb Richards 2013).
3. **Seasonal inactivated vaccine - case-control:** (one study/one data set) (pbb Irving 2013).

One study has not been introduced in the quantitative synthesis because it is the only study about the A/NJ/8/76 vaccine (pcb Deinard 1981). The retrospective cohort of pcb Toback 2012 was also not included in the analysis because it did not contain useful outcomes.

Administration during pregnancy - severe harms

One cohort study was introduced (pcb Nordin 2013), assessing the association between seasonal vaccine exposure during pregnancy and the following harms within 42 days from administration: Guillain-Barré syndrome, demyelinating diseases and immune thrombocytopenic purpura.

Severe harms - general population

Guillain-Barré syndrome

1. **2009 to 2010 pandemic - case-control:** (two studies/six data sets) (bb Grimaldi Bensouda 2011; bb Dieleman 2011a; bb Dieleman 2011b; bb Dieleman 2011c; bb Dieleman 2011d; bb Dieleman 2011e).
2. **Seasonal inactivated vaccine - case-control:** (one study/one data set) (bb Galeotti 2013).
3. **Seasonal inactivated vaccine - cohort studies:** (two studies/four data sets) (cb Kaplan 1982; cb Lasky 1998).

One cohort study assessing the association between the A/NJ/8/76 vaccine and Guillain-Barré syndrome was not introduced into the analysis (cb Shonberger 1979).

Demyelinating diseases (optic neuritis or multiple sclerosis)

1. **Seasonal inactivated vaccine - case-control:** (four studies/four data sets) (bb DeStefano 2003; bb Hernan 2004; bb Payne 2006; bb Zorzon 2003).
2. **2009 to 2010 pandemic - cohort study:** (one study/one data set) (cb Moro 2013).

Immune thrombocytopenic purpura

1. **Seasonal inactivated vaccine - case-control:** (two studies/two data sets) (bb Garbe 2012; bb Grimaldi-Bensouda 2012).

Other serious adverse events

1. **Oculo-respiratory syndrome:** RCT - cross-over (one study) (ab Scheifele 2003).
2. **Respiratory function**: RCT (ab Atmar 1990).
3. **Cutaneous melanoma:** case-control (bb Mastrangelo 2000).
4. **Bell's palsy:** case-control (bb Mutsch 2004).
5. **Cardiac arrest:** case-control (bb Siscovick 2000).
6. **Rheumatoid arthritis**: case-control (bb Ray 2011).
7. **Neurological and autoimmune disorders**: cohort study (cb Bardage 2011).
8. **Other serious adverse events:** cohort study (cb Baxter 2012).

Pandemic vaccine: efficacy or effectiveness

1. **RCT on inactivated parenteral vaccine:** (four studies/seven data sets) (aa Eddy 1970; aa Mogabgab 1970a; aa Mogabgab 1970b; aa Waldman 1969a; aa Waldman 1969b; aa Waldman 1972b; aa Waldman 1972d).
2. **RCT on inactivated aerosol vaccine:** (two studies/four data sets) (aa Waldman 1969c; aa Waldman 1969d; aa Waldman 1972a; aa Waldman 1972c).
3. **RCT on live aerosol vaccine** (one study/one data set) (aa Sumarokow 1971).

Excluded studies

We excluded 155 studies (see Characteristics of excluded studies table).

Risk of bias in included studies

Out of the 116 included studies (sub-study or data set), we classified 9.5% (11/116) as low risk of bias (nine RCTs, two case-control); 19.8% (23/116) as high risk of bias (six RCTs, 14 cohorts, three case-control) and finally 70.6% (82/116) did not present either sufficient information in one or more key domains or, although presenting a low risk of bias in a specific domain, scored a high risk of bias in one or more items used in the quality evaluation. Table 1 shows the summary quality assessment of all included studies and a graphical display of the quality assessment is presented in Figure 2 and Figure 3. We have highlighted that each 'paper' could include more than one study (data set) and these different studies required separate quality assessment. On the other hand, the funding source can be referred only to a single paper.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

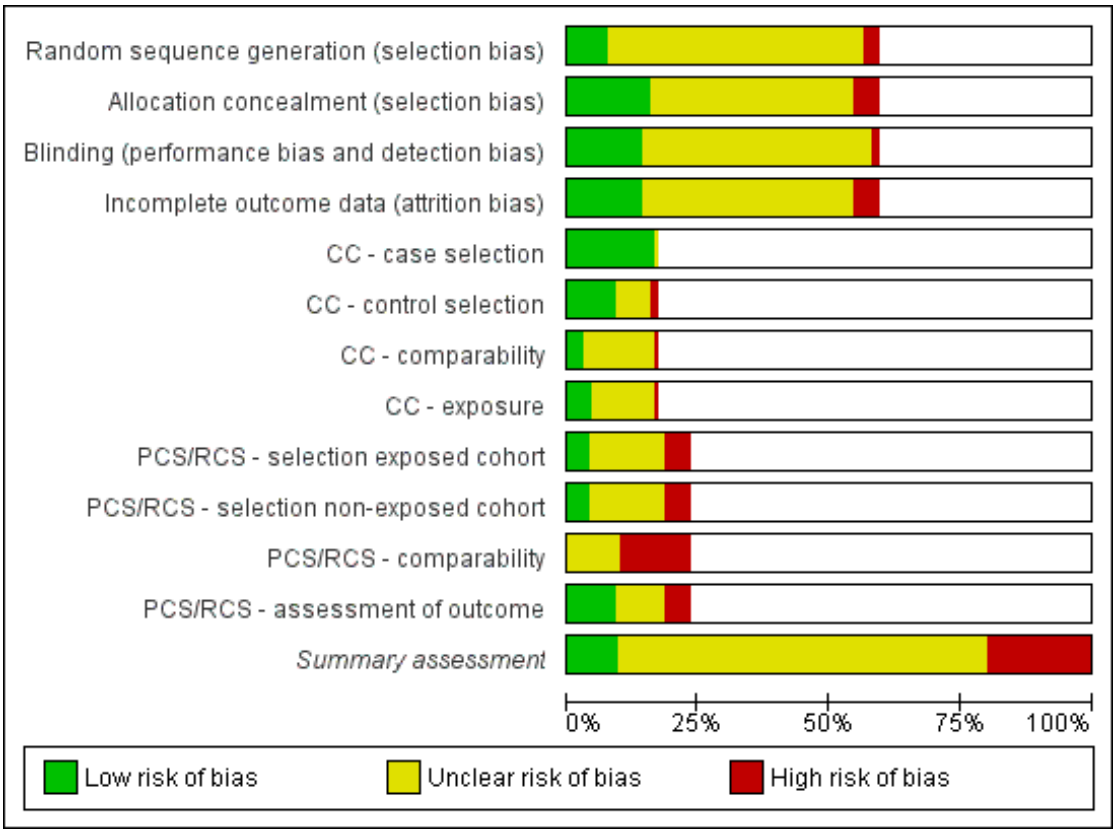
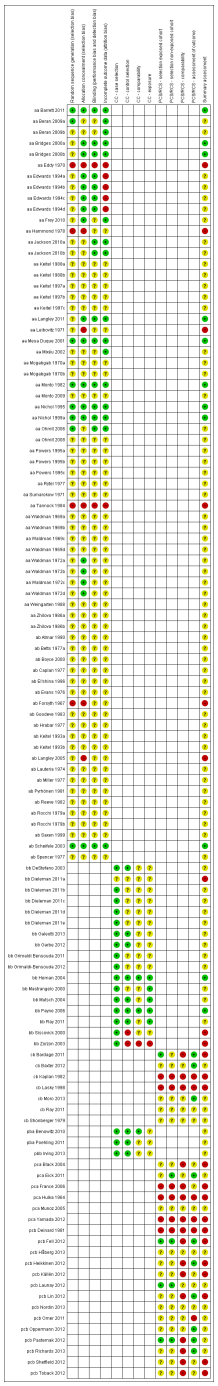


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In the included trials allocation concealment was adequate (low risk of bias) in 18 studies (26.1%), inadequate (high risk of bias) in six (8.7%) and unclear (unclear risk of bias) in 45 (65.2%).

Blinding

We judged blinding as low risk of bias in 16 RCTs (23.2%), as high risk of bias in two studies (2.9%) and as unclear in 51 studies (73.9%).

Incomplete outcome data

The majority of the included RCTs/CCTs did not report sufficient information about loss to follow-up (63 studies; 91.3%).

Selective reporting

The assessment of selective reporting bias presents several difficulties and would require review of the original study protocols for the included studies, which are mainly unavailable.

Other potential sources of bias

Few studies reported information on influenza circulation in the surrounding community, making interpretation of the results and assessment of their generalisability difficult.

It is now known that industry funding of influenza vaccine studies determines publication in high-prestige journals and higher citation rates than other types of funding. In addition, industry funding is associated with optimistic conclusions, but the quality of the majority of influenza vaccine studies is low, irrespective of funding (see Table 2). A previously cited review showed a complex web of interrelationships between these variables (Jefferson 2009a), but how this impacts on policy-making is not known.

Case-control studies - quality assessment

- **Case selection (definition/representativeness)**: case identification is mainly performed by means of registers maintained at several healthcare organisations (HMO, Kaiser Permanente) or by hospital or GP (general practice) registers. A further case ascertainment is conducted by specialists in order to verify the agreement with the chosen case definition. In studies assessing vaccine efficacy, cases were identified by using a laboratory test performed on all participants having symptoms. For 19 out of 20 (95%), we classified case selection and definition as low risk of bias.
- **Control selection (definition):** controls were selected from within the same registers used for case identification or from among participants living in the same catchment area of the hospitals in which the cases were identified. For 10 out of 20 studies (50%), we classified control selection and definition as low risk of bias and for 8 out of 20 (40%) we classified this as unclear risk of bias.
- **Comparability:** the most frequent method used to ensure comparability between cases and controls consisted of matching for age, gender and index date (onset of symptoms for cases and GP visit for controls). Less frequently matching was also done for other possible parameters, such as the number of GP visits within a certain time interval, or by resorting to the use of a propensity score or multivariate models in order to reduce the impact of other possible confounders. Nevertheless many studies (16 out of 20 (80%)) did not provide sufficient information to be able to tell how comparable cases and controls effectively are.
- **Exposure ascertainment (same method of ascertainment for cases and controls/non-response rate):** for studies based on healthcare organisations or insurance registers assessment of vaccine exposure was certified in the same registers. In other studies vaccine exposure was ascertained with a structured interview and less frequently also with the recovering of the vaccination records. In many studies (14 out of 20 (70%)), ascertainment of the vaccine exposure was not fully reliable. For 5 out of 20 (25%), we judged exposure ascertainment as low risk of bias.

Cohort studies - quality assessment

- **Selection exposed cohort (definition/representativeness):** the majority of the studies are retrospective and use a data linkage method to select the exposed cohort. In 17 out of 27 studies (63%) this procedure was insufficiently described.
- **Selection non-exposed cohort (definition/ascertainment):** most of the studies are based on record linkage and the identification of the non-exposed cohort was done by considering the absence of vaccination records. However, insufficient detail was provided and therefore we classified these kinds of studies as unclear risk of bias (17 out of 27 (63%)).
- **Comparability:** in most of the included cohort studies matching procedures for the most probable confounders were applied by using a multivariate model to ensure comparability between exposed and unexposed cohorts. Sometimes a propensity score procedure was also used. Therefore in many studies only a few confounders were used to ensure comparability between exposed and non-exposed cohorts, thus we classified no studies as low risk of bias.
- **Assessment of outcome (demonstration that outcome of interest was not present at the start of the study/whether follow-up was long enough for outcomes to occur/adequacy**

of follow-up of cohorts): outcomes of interest were generally documented in the registries used to identify the study population and consequently were almost always retrospectively assessed, thus we classified 9 out of 27 as low risk of bias.

Effects of interventions

Inactivated parenteral vaccines (Analysis 01)

The overall effectiveness of parenteral inactivated parenteral vaccine against influenza-like illness (ILI) is 16% (95% confidence interval (CI) 5% to 25%), with a corresponding number needed to vaccinate (NNV) of 40 (95% CI 26 to 128). Heterogeneity amongst the studies in this comparison is relatively low (I^2 statistic = 26%) and a sensitivity analysis made by comparing estimates obtained using the random-effects model versus the fixed-effect model does not change the conclusion. The CI of the NNV becomes narrower by applying the fixed-effect model (NNV 38, 95% CI 29 to 49).

Inactivated parenteral vaccines are 16% effective (95% CI 9% to 23%) in preventing ILI symptoms when strains contained in the vaccine antigenically match those circulating (Analysis 1.1.1). The estimated NNV for this comparison is 17 (95% CI 12 to 29). On the other hand, inactivated vaccines are not significantly protective against ILI when the degree of matching between the vaccine and circulating influenza strains is absent or unknown (risk ratio (RR) 0.90, 95% CI 0.69 to 1.18, Analysis 1.1.2). In the subgroup Analysis 1.1.2 heterogeneity is particularly high (I^2 statistic = 82%) and estimates using the fixed-effect model show statistical significance: Vaccine Effectiveness 18% (95% CI 10% to 25%) and NNV 59 (95% CI 43 to 106).

The overall efficacy of inactivated vaccines in preventing confirmed influenza (Analysis 1.2) is 60% (95% CI 53% to 66%) with a NNV of 71 (95% CI 64 to 80). When the vaccine content matches the circulating strain, the efficacy is 62% (95% CI 52% to 69%) and the NNV is 58 (95% CI 52 to 69). The results are very similar when matching is absent or unknown (Vaccine Efficacy 55%, 95% CI 41% to 66% and NNV 60, 95% CI 50 to 80). Since heterogeneity was very low (I^2 statistic = 17% for Analysis 1.2.1; I^2 statistic = 14% for Analysis 1.2.2 and I^2 statistic = 11% overall), there were no differences when comparing the estimates obtained by using a fixed-effect model with those from a random-effects model.

Looking at the NNV in Analysis 1.1 and Analysis 1.2, it seems that effectiveness against ILI is higher than efficacy against laboratory-confirmed influenza (NNV-ILI 40; NNV-influenza 71). These paradoxical results, showing an apparently higher aspecific effectiveness and a lower specific efficacy, are mainly due to the fact that ILI and confirmed influenza have a very different incidence among the study population. We note that 15.6% of unvaccinated participants versus 9.9% of vaccinated participants developed ILI symptoms, whilst the corresponding figures for participants who developed laboratory-confirmed influenza are 2.4% and 1.1% for unvaccinated and vaccinated people, respectively.

Based on the results from a single study (aa Bridges 2000b), physician visits appear 42% less frequent (95% CI 9% to 63%) in participants immunised with vaccines prepared with strains matching circulating viruses (Analysis 1.3.1), whereas there are no significant results when the degree of matching is unknown or absent (RR 1.28, 95% CI 0.90 to 1.83; Analysis 1.3.2). The overall effect is also not significant (RR 0.87, 95% CI 0.40 to 1.89) (Analysis 1.3). Even though the two data sets of aa Bridges 2000b showed very high heterogeneity (I^2 statistic = 87%), no difference arose when comparing the results from the fixed-effect with the random-effects model analysis.

A similar conflicting result is observed when analysing the effect of inactivated vaccine administration on days of illness (Analysis 1.4), when the estimate (mean difference (MD)) obtained in good match conditions was compared with that where there was an unknown or absent degree of matching. As a consequence of the high overall heterogeneity (I^2 statistic = 87%), the result obtained from the fixed-effect model analysis (MD -0.31, 95% CI -0.54 to -0.07) differs substantially from that resulting from the application of a random-effects model (MD -0.21, 95% CI -0.98 to 0.56).

There seems to be no effect on the time an antibiotic or drug was prescribed (Analysis 1.5; Analysis 1.6).

Four trials evaluated time off work, estimating that vaccination saves around 0.04 working days on average. This result is affected by high levels of heterogeneity (I^2 statistic = 82%) and changes depending on whether a fixed-effect (MD -0.04, 95% CI -0.06 to -0.01) or random-effects model (MD -0.04, 95% CI -0.14 to 0.06) is used.

The effect on hospitalisation (Analysis 1.8) was evaluated in two trials (aa Bridges 2000a; aa Leibovitz 1971), but it was not statistically significant. No evidence was found for cases of pneumonia.

Harms

Local tenderness and soreness are more than three times as common among parenteral vaccine recipients than among those in the placebo group (RR 3.13, 95% CI 2.44 to 4.02) (Analysis 1.10.1). There are also increases in erythema (RR 2.59, 95% CI 1.77 to 3.78, Analysis 1.10.2) and induration (RR 4.28, 95% CI 1.25 to 14.67) but not in arm stiffness. The combined local effects endpoint was significantly higher for those receiving the vaccine (RR 2.44, 95% CI 1.82 to 3.28; Analysis 1.10.5).

Myalgia (Analysis 1.11.1) is significantly associated with vaccination (RR 1.77, 95% CI 1.40 to 2.24), as well as systemic fever (RR 1.54, 95% CI 1.22 to 1.95), headache (RR 1.17, 95% CI 1.01 to 1.36), fatigue or indisposition (RR 1.23, 95% CI 1.07 to 1.42) and malaise (RR 1.51, 95% CI 1.18 to 1.92). The combined endpoint was not increased (RR 1.16, 95% CI 0.87 to 1.53; Analysis 1.11.7).

Live aerosol vaccines (Analysis 02)

Live aerosol vaccines have an overall effectiveness of 10% (95% CI 4% to 16%; NNV 46, 95% CI 29 to 115) and content and matching appear not to affect their performance significantly (Analysis 2.1). Overall efficacy (Analysis 2.2) is 53% (95% CI 38% to 65%) and the NNV is 39 (95% CI 32 to 54). Again, neither content nor matching appear to affect their performance significantly.

No evidence is available on complications (e.g. bronchitis, otitis, pneumonia).

The effectiveness of the aerosol vaccines against ILI (with no clear definition) is significant only for vaccines with absent or unknown matching (37%, 95% CI 20% to 51%) and the NNV is 69 (95% CI 23 to 46) (Analysis 2.3).

The conclusions of this comparison were unaffected by analysis using either the fixed-effect or random-effects models.

Harms

Significantly more recipients experienced local symptoms after vaccine administration than after placebo administration (Analysis 2.4).

- Upper respiratory infection (RR 1.66, 95% CI 1.22 to 2.27).
- Cough (RR 1.51, 95% CI 1.08 to 2.10).
- Coryza (RR 1.56, 95% CI 1.26 to 1.94).
- Sore throat (RR 1.66, 95% CI 1.49 to 1.86).
- Combined endpoint (any or highest symptom) (RR 1.56, 95% CI 1.31 to 1.87).

There is no significant increase in systemic harms (combined endpoint: any or highest symptom RR 1.40, 95% CI 0.82 to 2.38), although rates of myalgia (RR 2.47, 95% CI 1.26 to 4.85) and headache (RR 1.54, 95% CI 1.09 to 2.18) are higher in the vaccine than in the placebo groups (Analysis 2.5).

Inactivated aerosol vaccines (Analysis 03)

No RCTs assessing the effectiveness of inactivated aerosol vaccines in preventing ILI could be included; the only available evidence comes from studies carried out during the 1968 to 1969 pandemic (Analyses 12 to 16).

The efficacy of inactivated aerosol vaccine in preventing laboratory-confirmed influenza (Analysis 3.1.1) is assessed in one RCT (aa Langley 2011), whose results do not show a statistically significant protective effect (RR 0.38, 95% CI 0.14 to 1.02).

Harms

None of the trials on inactivated aerosol vaccines reported significant harms.

Inactivated parenteral vaccines - cohort studies (Analysis 04)

In this analysis, we have considered the effects of vaccine administration in pregnant women and their newborns.

Based on unadjusted data from a cohort study (high risk of bias), 2009/2010 H1N1 monovalent pandemic vaccines (Analysis 4.1.1) provide a significant protective effect against ILI in pregnant women (Vaccine Effectiveness 89%, 95% CI 79% to 94%; NNV 54, 95% CI 51 to 61). Seasonal inactivated vaccine is not effective against ILI (RR 0.54, 95% CI 0.22 to 1.32; Analysis 4.1.2). Sensitivity analysis performed using the fixed-effect model showed statistical significance, even for a modest, protective effect (RR 0.76, 95% CI 0.65 to 0.89; NNV 92, 95% CI 63 to 201; VE 24%, 95% CI 11% to 35%).

The effectiveness of vaccination with seasonal inactivated vaccine during pregnancy for preventing ILI in newborns is not statistically significant, as it results from two cohort studies using either hazard ratio (HR) or RR adjusted estimates (Analysis 4.2.1 and Analysis 4.3.1, respectively). Efficacy against confirmed influenza (Analysis 4.3.2) is really modest but has statistical significance (adjusted RR 0.59, 95% CI 0.37 to 0.94; NNV 27, 95% CI 18 to 185; VE 41%, 95% CI 6% to 63%).

It seems that vaccination with the 2009/2010 H1N1 monovalent pandemic vaccine during pregnancy is not associated with a higher risk of abortion (Analysis 4.4.1 and Analysis 4.4.2), congenital malformation (Analysis 4.4.3) or neonatal death (Analysis 4.4.5). Cases of neonatal death and abortion have been observed less frequently among women immunised with seasonal influenza vaccine (Analysis 4.5.1 and Analysis 4.5.4, both unadjusted estimates).

The results of pcb Deinard 1981 are based on the follow-up results of 189 pregnant women immunised with monovalent pandemic A/New Jersey/8/76 (either in split or whole virus formulation) and 517 pregnant women who did not receive vaccination. The time of observation was extended up to the first eight weeks of life of the newborns. No statistically different incidence of maternal pregnancy outcomes and infant deaths was observed between vaccinated and unvaccinated groups. Statistical analysis (Chi^2 test) shows no relation between immunisation history and presence of anomalities at the 8th week of life. This cohort study has not been included in the analysis as the vaccine studied is no longer in use.

Inactivated parenteral vaccines - case-control studies (Analysis 05)

This analysis only includes studies assessing the effect of vaccination against influenza during pregnancy. The incidence of ILI in pregnant women who were immunised with inactivated seasonal vaccine during pregnancy was not statistically different when compared with that observed among unvaccinated pregnant women (Analysis 5.1.1). However, in sensitivity analysis using the fixed-effect model, the results of the analysis become statistically signif-

icant. In conclusion, the results of this comparison were affected by the model used to perform the analysis.
One further case-control study did not find a statistically significant association between exposure to seasonal inactivated vaccine in pregnancy and abortion cases (Analysis 5.2.1).
One retrospective cohort study tried to assess the effect of live attenuated vaccine during pregnancy, based on data from a health insurance database during six subsequent influenza seasons (pcb Toback 2012). A total of 834,999 pregnant women were identified, out of whom 138 received live attenuated vaccine at any time during pregnancy. Claims for hospitalisation or visits to the emergency department within 42 days after immunisation were searched for but all observed events were considered to be related to a normal physiological pregnancy and not to immunisation. The system used (claim data) would be unable to detect birth outcomes.

Serious adverse events - Guillain-Barré syndrome - cohort studies (Analysis 06)

The possible association between exposure to seasonal inactivated vaccine in healthy adults and Guillain-Barré syndrome onset within six weeks following immunisation was investigated by two cohort studies performed during two subsequent epidemic seasons. No significant association was found Analysis 6.1.1). Administration of seasonal inactivated vaccine during pregnancy was not associated with Guillain-Barré syndrome onset within six weeks from immunisation (Analysis 6.1.2).
The cohort of cb Shonberger 1979 was the first study that compared Guillain-Barré syndrome cases by vaccination status and the national incidence in vaccinated and unvaccinated national cohorts after the suspension of the National Influenza Immunisation Program in the winter of 1976 to 1977. At that time the monovalent inactivated swine vaccine A/New Jersey/8/76 had been administered. The attributable risk from vaccination was just below one case of Guillain-Barré syndrome in every 100,000 vaccinations. This cohort study has not been included in the analysis as the vaccine studied is no longer in use.

Serious adverse events - Guillain-Barré syndrome - case-control studies (Analysis 07)

In an analysis performed using the mean of unadjusted data relative to six data sets, exposure to monovalent H1N1 pandemic inactivated vaccine resulted in an apparent statistically significant association with Guillain-Barré syndrome onset when administration took place within six weeks before symptoms occurred (odds ratio (OR) 2.22, 95% CI 1.14 to 4.31, Analysis 7.1.1). Thus, it should be taken into account that only one out of the six data sets showed a statistically significant association between vaccine exposure and Guillain-Barré syndrome onset (bb Dieleman 2011e). When we performed a sensitivity analysis excluding this data set from the pooled estimate, the result was no longer significant. When the analysis was performed considering that vaccine exposure occurred at any time before disease onset, there was no significant association (Analysis 7.1.2).
The analyses performed by pooling authors' estimates adjusted for several confounders (i.e. receipt of other vaccines, family history of autoimmune diseases, physician consultation during the previous year and use of antibiotic, antiviral or antipyretic agents) do not show a statistical association for exposure within six weeks (Analysis 7.2.1) before disease onset or for exposure at any time (Analysis 7.2.2).
Data from one other case-control study confirm that immunisation with seasonal inactivated vaccine is not significantly associated with the onset of Guillain-Barré syndrome within six weeks after inoculation (bb Galeotti 2013) (Analysis 7.3).

Serious adverse events - demyelinating diseases - cohort studies (Analysis 08)

In one cohort study the authors tried to assess whether there is an association between exposure to inactivated trivalent seasonal influenza vaccine during pregnancy and several pathologies (e.g. Guillain-Barré syndrome, demyelinating diseases, immune thrombocytopaenic purpura) within six weeks after immunisation. Unadjusted estimates were calculated for an association with demyelinating diseases by using the number of cases observed among exposed and unexposed hemi-cohorts and indicate that there is no association (Analysis 8.1.2).
One cohort study assessed the safety of the H1N1 vaccine. No statistical association was found between vaccination with H1N1 monovalent pandemic vaccine and demyelinating diseases.

Serious adverse events - demyelinating diseases - case-control studies (Analysis 09)

An association between exposure to seasonal inactivated vaccine and demyelinating diseases (including both multiple sclerosis and optic neuritis case definitions) in a healthy adult population was not statistically significant when we pooled unadjusted data from four case-control studies (OR 0.96, 95% CI 0.79 to 1.17) (Analysis 9.1). Also, when we analysed adjusted data for each of the case definitions separately, the estimates remained non-statistically significant for multiple sclerosis (Analysis 9.2) and for optic neuritis (Analysis 9.3).

Serious adverse events - immune thrombocytopenic purpura - cohort studies (Analysis 10)

One cohort study aimed to assess whether there is an association between exposure to inactivated trivalent seasonal influenza vaccine during pregnancy and several pathologies (e.g. Guillain-Barré syndrome, demyelinating diseases, immune thrombocytopaenic

purpura) within six weeks after immunisation. Neither the unadjusted (Analysis 10.2.2) nor adjusted estimates (Analysis 10.1.2) for an association with immune thrombocytopenic purpura were statistically significant.

Serious adverse events - immune thrombocytopenic purpura - case-control studies (Analysis 11)

Data analysis of two case-control studies (bb Garbe 2012; bb Grimaldi-Bensouda 2012) did not show a statistically significant association between immune thrombocytopaenic purpura and seasonal influenza vaccine in any of the time frames considered (i.e. less than two months, six or 12 months between immunisation and disease onset), or when the data were pooled together (Analysis 11.2). The same conclusions could be drawn when analysis was performed by using estimates adjusted for confounders (Analysis 11.1) and are further confirmed by the fact that a sensitivity analysis carried out by using either a random-effects or fixed-effect model did not change them in any way. It should be observed that no data sets included in this comparison, with the exception of bb Garbe 2012, showed a statistical association between disease and influenza vaccination. It is possible that the ages of the participants (cases and controls) were different in these two studies and that some elderly participants could have been included. Unlike bb Grimaldi-Bensouda 2012, the case-control study (bb Garbe 2012) considered as exposed those cases that were immunised up until 28 days before immune thrombocytopaenic purpura onset.

Serious and rare harms

Oculo-respiratory syndrome

On the basis of one randomised trial in 651 healthy adults aged around 45, trivalent split inactivated vaccine (TIV) caused mild oculo-respiratory syndrome in people with no previous history of oculo-respiratory syndrome (ab Scheifele 2003). Oculo-respiratory syndrome was defined as bilateral conjunctivitis, facial swelling (lip, lid or mouth), difficulty in breathing and chest discomfort (including cough, wheeze, dysphagia or sore throat). Oculo-respiratory syndrome (attributable risk 2.9%, 95% CI 0.6 to 5.2), hoarseness (1.3%, 95% CI 0.3 to 1.3) and coughing (1.2%, 95% CI 0.2 to 1.6) occurred within six days of vaccination. The association did not appear to be specific to any type of TIV.

Bell's palsy

One case-control study and case series, based in the German-speaking regions of Switzerland, assessed the association between an intranasal inactivated virosomal influenza vaccine and Bell's palsy (bb Mutsch 2004). Two hundred and fifty cases that could be evaluated (from an original 773 cases identified) were matched to 722 controls. All were aged around 50. The study reports a massive increase in risk (adjusted OR 84, 95% CI 20.1 to 351.9) within 1 to 91 days from vaccination. Despite its many limitations (case attrition: 187 cases could not be identified; ascertainment bias: physicians picked controls for their own cases; confounding by indication: different vaccine exposure rate between controls and the reference population), it is unlikely that such a large OR could have been affected significantly by systematic error. The authors called for larger pre-licence harms trials, given the rarity of Bell's palsy. On the basis of this study the vaccine was withdrawn from sale.

Rheumatoid arthritis

One case-control study used the register of the Northern California Kaiser Permanente Health Plan (NCKPHP) in order to identify cases of rheumatoid arthritis diagnosed during a three-year period (1 January 1997 to 31 December 1999) among members of NCKPHP for at least two years (i.e. since 1 January 1995) and aged between 15 and 59 (bb Ray 2011). After reviewing clinical cards, 415 cases of definite or probable rheumatoid arthritis were included together with 1245 randomly selected controls matched for age within one year and for a categorical utilisation variable based on the number of clinic visits during the year prior to the rheumatoid arthritis symptom onset date (none, one to two, three to five, six to nine or 10+ visits). The Kaiser Immunisation Tracking System and chart review were used to determine vaccination status of cases and controls. Different time intervals between immunisation and rheumatoid arthritis onset were considered for analysis: 90, 180, 365 and 730 days. No significant association between vaccination and rheumatoid arthritis could be determined for any time interval, even after adjustment for confounders (sex, race and exact number of utilisation visits). The authors of this study performed a data analysis by using a person-time cohort design, in which vaccinated cases contributed to the unexposed follow-up time until they were immunised and to the exposed follow-up time thereafter. Unlike case-control analysis, person-time cohort analysis was performed by excluding cases who showed symptoms in 1996. Even if a significant association for exposure to vaccine occurred within 180 and 365 days before disease onset was found (OR adjusted for race, sex and number of clinic visits 1.36, 95% CI 1.03 to 1.80 and 1.34, 95% CI 1.06 to 1.69, respectively), the authors point out that it is very difficult to estimate with sufficient precision the true onset date of rheumatoid arthritis, as the first symptoms could already be present some time before participants present for medical care. This is the most important limitation of this study and could have affected the estimates in a significant manner.

Neurological and autoimmune disorders

The study of cb Bardage 2011 is a large, prospective cohort study carried out in a Stockholm population (n = 1,945,024) during

the vaccination campaign with monovalent A (H1N1) pandemic vaccine Pandemrix (GlaxoSmithKline, containing adjuvants AS03 and squalene) to evaluate the presence of an association between Pandemrix and neurological and/or autoimmune diseases (Guillain-Barré syndrome, multiple sclerosis, Bell's palsy, narcolepsy, polyneuropathy, an/hypoaesthesia, paraesthesia, rheumatological disease and inflammatory bowel disease). During the first 45 days, participants with high-risk conditions were preferentially vaccinated; vaccination was then offered to the remainder of the population in a second phase of the campaign (see description for more details).

The analysis of the hazard ratio (HR) adjusted for age, sex, socioeconomic status and healthcare consumption (number of hospital admissions and visits to specialist care one year before the pandemic period) showed that in participants immunised during the early phase of the campaign there was a significantly increased risk of Bell's palsy (HR 1.34, 95% CI 1.11 to 1.64), paraesthesia (HR 1.25, 95% CI 1.10 to 1.41) and inflammatory bowel disease (HR 1.25, 95% CI 1.04 to 1.50). For the participants vaccinated in the late phase of the campaign (> 45 days), HR estimates showed that the investigated diseases had been observed with no statistically different incidence between the vaccinated and unvaccinated participants.

A further stratification was performed, considering the time since first vaccination (six weeks or less and more than six weeks). This showed that in participants immunised during the first phase of the campaign, an increased incidence of Bell's palsy and paraesthesia was most pronounced, as well as within six weeks of vaccination (HR 1.74, 95% CI 1.16 to 2.59 for Bell's palsy and HR 1.60, 95% CI 1.25 to 2.05 for paraesthesia) and thereafter (HR 1.26, 95% CI 1.01 to 1.57 for Bell's palsy and 1.17, 95% CI 1.02 to 1.34 for paraesthesia). The increased risk of inflammatory bowel disease among those vaccinated in the early phase was only observed more than six weeks after vaccination (HR 1.29, 95% CI 1.06 to 1.58). Formal tests to determine whether risks further differed between those within and more than six weeks from vaccination were only statistically significant for paraesthesia (P = 0.005). In participants immunised during the second phase of the campaign, polyneuropathy was significantly more common within six weeks of immunisation (HR 1.79, 95% CI 1.16 to 2.77).

Cutaneous melanoma

The association between influenza vaccines and cutaneous melanoma was assessed by a case-control study in 99 cases and 104 controls (bb Mastrangelo 2000). The authors reported a protective effect of repeated influenza vaccination on the risk of cutaneous melanoma (OR 0.43, 95% CI 0.19 to 1.00). The study is at high risk of bias because of the selective nature of cases (all patients in the authors' hospital), attrition bias (four cases and four controls eliminated because of "failure to collaborate"), recall bias (up to five years exposure data were based on patients' recollection) and ascertainment bias (non-blinded exposure survey).

Primary cardiac arrest

The association between influenza vaccination the previous year and the risk of primary cardiac arrest (i.e. occurring in people with no previous history of cardiac disease) was assessed by a case-control study in 360 cases and 418 controls (bb Siscovick 2000). The authors concluded that vaccination is protective against primary cardiac arrest (OR 0.51, 95% CI 0.33 to 0.79). The difficulty of case ascertainment (77% of potential cases had no medical examiner report and/or autopsy) and recall bias (spouses provided exposure data for 304 cases, while 56 survivor cases provided data jointly with their spouses) make the conclusions of this study unreliable. It is impossible to judge the reliability of this study because of a lack of detail on the circulation of influenza in the study areas in the 12 months preceding cardiac arrest (the causal hypothesis is based on the effects of influenza infection on the oxygen supply to the myocardium through lung infection and inflammation).

Pulmonary function

The effects of different types of live attenuated cold recombinant influenza vaccination on pulmonary function were assessed by a double-blind, placebo-controlled randomised trial in 72 healthy volunteers aged around 26 (ab Atmar 1990) (data on 17 asthmatics were not extracted). The authors report several non-significant drops in lung function up to seven days post-inoculation and a higher incidence of influenza-like illness (17/46 versus 4/26) in the vaccinated arms.

Other serious adverse events

The study of cb Baxter 2012 is a large, retrospective cohort performed among members of Kaiser Permanente Health Plans of Northern California, Hawaii and Colorado aged between 18 and 59 years, who were immunised with live attenuated, inactivated influenza vaccine or did not receive vaccination. The study retrospectively investigated the occurrence of adverse events (see description) during five subsequent epidemics, but did not identify any unexpected serious risks when the live attenuated vaccine was used in approved populations.

Vaccines for the 1968 to 1969 (H3N2) influenza pandemic (Analyses 12 to 16)

Five studies yielded 12 data sets (aa Eddy 1970; aa Mogabgab 1970a; aa Mogabgab 1970b; aa Sumarokow 1971; aa Waldman 1969a; aa Waldman 1969b; aa Waldman 1969c; aa Waldman 1969d; aa Waldman 1972a; aa Waldman 1972b; aa Waldman 1972c; aa Waldman 1972d). As one would expect, vaccine performance was poor when the content did not match the pandemic strain (Analysis 12.1; Analysis 12.2). However, one-dose or

two-dose monovalent whole virion (i.e. containing dead complete viruses) vaccines achieved a VE of 65% (95% CI 52% to 75%) protection against ILI (NNV 16, 95% CI 14 to 20), a VE of 93% (95% CI 69% to 98%; NNV 35, 95% CI 33 to 47) protection against influenza and a VE of 65% (95% CI 6% to 87%) with NNV 94 (95% CI 70 to 1022) against hospitalisation (Analysis 13.1; Analysis 13.2; Analysis 13.3).

Approximately half a working day and half a day of illness (Analysis 13.5; Analysis 13.6) were saved but no effect was observed on pneumonia (Analysis 13.4). All comparisons except for ILI are based on a single study (Analysis 13.4). The large effect on ILI is coherent with the high proportion of these illnesses caused by influenza viruses in a pandemic (i.e. the gap between the efficacy and effectiveness of the vaccines is narrow). Aerosol polyvalent or monovalent vaccines had a modest effect.

DISCUSSION

Summary of main results

The overall effectiveness of inactivated parenteral vaccine against influenza-like illness (ILI) is 16% (95% confidence interval (CI) 5% to 25%), with a corresponding number needed to vaccinate (NNV) of 40 (95% CI 26 to 128). The overall efficacy of inactivated vaccines in preventing influenza is 60% (95% CI 53% to 66%) with a NNV of 71 (95% CI 64 to 80). When vaccine content matches the circulating strain the efficacy is 62% (95% CI 52% to 69%) and the NNV is 58 (95% CI 52 to 69). Based on the results from one single study (aa Bridges 2000b), physician visits appear to be 42% less frequent (95% CI 9% to 63%) in participants immunised with vaccines prepared with strains matching circulating viruses, whereas no significant differences are found when the degree of matching is unknown or absent (risk ratio (RR) 1.28, 95% CI 0.90 to 1.83). The overall effect is again not significant (RR 0.87, 95% CI 0.40 to 1.89). There seems to be no effect on the time an antibiotic or a drug is prescribed. Four trials evaluated time off work, estimating that vaccination saves on average around 0.04 working days. This result is affected by high levels of heterogeneity and changes depending on whether a fixed-effect (mean difference (MD) -0.04, 95% CI -0.06 to -0.01) or random-effects model (MD -0.04, 95% CI -0.14 to 0.06) is used. Live aerosol vaccines have an overall effectiveness of 10% (95% CI 4% to 16%) and a NNV of 46 (95% CI 29 to 115), and content and matching appear not to affect their performance significantly. The overall efficacy is 53% (95% CI 38% to 65%) and the NNV is 39 (95% CI 32 to 54). Again, neither content nor matching appear to affect their performance significantly. Many more recipients experienced local symptoms after vaccine administration than placebo administration.

No randomised controlled trials (RCTs) assessing the effectiveness of inactivated aerosol vaccines in preventing ILI could be included. The only available evidence comes from studies carried out during the 1968 to 1969 pandemic. The efficacy of inactivated aerosol vaccine in preventing laboratory-confirmed influenza (Analysis 3.1.1) was assessed in one RCT (aa Langley 2011) whose results did not show a statistically significant protective effect (RR 0.38, 95% CI 0.14 to 1.02).

The effects of influenza vaccine administration in pregnant women and their newborns has been investigated in a RCT (Zaman 2008) in which 23 valent pneumococcal vaccine was administered to the control group. For this reason, the RCT was excluded from the review and the evidence for effectiveness and efficacy is based only on observational studies (case-control and cohort studies).

The effectiveness of vaccination with seasonal inactivated parenteral vaccine during pregnancy for preventing ILI in newborns was not statistically significant. The evidence comes from two cohort studies using either HR or RR adjusted estimates. However, it seems that vaccination has a modest effect against ILI in pregnant women (NNV 92, 95% CI 63 to 201) and against laboratory-confirmed influenza in newborns from vaccinated women (NNV 27, 95% CI 18 to 185).

No evidence of an association was found between seasonal inactivated vaccines and Guillain-Barré syndrome or H1N1 pandemic vaccine and Guillain-Barré syndrome.

There was no evidence of an association between exposure to seasonal inactivated influenza vaccine and other serious adverse events (multiple sclerosis, optic neuritis and immune thrombocytopaenic purpura).

Overall completeness and applicability of evidence

A number of issues should be taken into consideration when interpreting the results of this review.

1. Methods of vaccine standardisation have changed significantly.
2. Recent vaccines present significant differences in purity when compared with older ones.
3. Different doses and schedules were pooled in the analysis.

Taken alone, this review shows that according to randomised evidence, inactivated vaccines have a small effect in preventing the symptoms of influenza and getting people back to work more quickly.

Quality of the evidence

We found evidence from more than 70,000 people in 69 randomised studies. Regardless of quality, all studies failed to report any evidence of an effect on complications. The safety evidence base from randomised trials of inactivated vaccines is very small,

probably indicating less concern with harms. Inactivated vaccines cause rare, major harms that appear to be mostly linked to specific products or lots.

Potential biases in the review process

The conclusions of this review are uncertain regarding the safety profile of inactivated vaccines, which is a reflection of the size of the evidence base.

An earlier review of 274 influenza vaccine studies in all age groups (including most of the studies in this review) showed an inverse relationship between risk of bias and the direction of study conclusions. Conclusions favourable to the use of influenza vaccines were associated with a higher risk of bias. In these studies, the authors made claims and drew conclusions that were unsupported by the data they presented. In addition, industry-funded studies are more likely to have favourable conclusions, to be published in significantly higher-impact factor journals and to have higher citation rates than non-industry-funded studies. This difference is not explained by either their size or methodological quality (Jefferson 2009a). Any interpretation of the body of evidence in this review should be made with these findings in mind.

Agreements and disagreements with other studies or reviews

Systematic reviews estimating the efficacy of influenza vaccination

DiazGranados 2012 performed a meta-analysis that included RCTs on seasonal inactivated or live attenuated influenza vaccines with laboratory-confirmed influenza (with either polymerase chain reaction (PCR) or serological confirmation of infection) as the efficacy outcome. Thirty studies in children and adults were included. The authors provided efficacy estimates (RR with 95% CI) stratified by the degree of matching between the vaccine and circulating strains (good, poor, no matching, matching) and by strain type (A H1N1, A H3N2, B). DiazGranados 2012 estimated that in an adult population the efficacy of inactivated vaccine against laboratory-confirmed influenza is 59% (95% CI 50% to 66%). The efficacy estimate for live attenuated vaccine is 39% (95% CI 16% to 55%).

The systematic review by Osterholm 2012 included evidence of the efficacy of both live attenuated and inactivated vaccines in preventing laboratory-confirmed influenza infection assessed exclusively by either PCR or a positive culture. Considering studies carried out in adults only, the pooled estimate of efficacy from six studies (eight data sets) was 59% (95% CI 51% to 67%). Even though three RCTs estimating the efficacy of live attenuated vaccines were included, the authors did not perform an analysis for the reason that none of the single estimates was statistically significant. Observational studies were also included and discussed.

Systematic reviews assessing the efficacy/effectiveness and/or safety issues of influenza vaccines when administered during pregnancy

The review by Skowronski 2009 is the first comprehensive publication in which the evidence for the effectiveness and safety aspects of vaccination during pregnancy has been exhaustively discussed. In the first part of the paper the authors consider the burden of disease during pregnancy, the risk of death and the influenza-related risk for the fetus and summarise how the US Advisory Committee on Immunization Practice (ACIP) recommendations have changed over the last four decades. The available evidence on protection (in mother and newborns) and vaccination safety issues are descriptively illustrated, discussed and compared with the statements in the current vaccination policies reported. In the authors' opinion, immunisation against influenza at any stage of pregnancy *may* be warranted during pandemics or for women with co-morbidities. Seasonal immunisation with TIV may be warranted in pregnancy, without potential complications during the second half of the pregnancy. Finally, the available evidence is insufficient to recommend standard routine vaccination in the early stages of pregnancy.

Systematic reviews of evidence of severe harms

Farez 2011 evaluates the risk of developing multiple sclerosis or experiencing relapsing multiple sclerosis following immunisation with several vaccinations, including influenza. Meta-analysis performed by pooling the results of four case-control studies (bb DeStefano 2003; bb Hernan 2004; Ramagopalan 2009; bb Zorzon 2003) would exclude an increased risk of developing multiple sclerosis following influenza vaccine administration (odds ratio (OR) 0.97, 95% CI 0.77 to 1.23).

Other issues

In Toback 2012, there is evidence supporting the introduction of a new quadrivalent live attenuated vaccine (Q-LAIV, already licensed in the USA where it will be available for the 2013 to 2014 season) containing two different B strains of different lineage (B/Yamagata/16/88 and B/Victoria/2/87). This evidence comes from two RCTs comparing immunogenicity and local and systemic reactions after administration of either Q-LAIV, trivalent inactivated or trivalent live attenuated vaccines. One of them was performed in adults, the other in a paediatric population. The presence of two B strains would not significantly affect the antibody response against each B strain. Local and systemic adverse events induced by Q-LAIV administration did not differ significantly from those recorded after receiving other vaccines already in use.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review provide no evidence for the utilisation of vaccination against influenza in healthy adults as a routine public health measure. As healthy adults have a low risk of complications due to respiratory disease, the use of the vaccine may only be advised as an individual protective measure.

Implications for research

The major differences in effect sizes between outcomes highlight the need for careful consideration of the best study design to assess the effects of public health measures such as vaccination. Large studies, encompassing several influenza seasons, are required to allow assessment of the effect of the vaccines on rare outcomes such as complications and death.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

aa Barrett 2011

Methods	Double-blind, placebo-controlled, multicentric RCT performed at 36 centres in the USA assessing effectiveness, reactogenicity and antibodies responses of a Vero cell-derived, trivalent, split influenza vaccine
Participants	Healthy adults aged 18 to 48 years recruited at 36 centres throughout USA Individuals were excluded if they belong to a CDC risk category for complications of influenza illness, had a history of surgical or functional asplenia, had been treated with any blood product or immune globulin in the previous 90 days, had a history of allergy to vaccine components, had received a live vaccine within 4 weeks or an inactivated vaccine within 2 weeks of study entry, or had dermatological disorders or tattoos that would obscure the assessment of injection-site reactions. Individuals were not specifically excluded because of egg allergy. Immunisation in previous seasons was not judged to be an exclusion criterion
Interventions	Inactivated, Vero cell-derived, trivalent split influenza vaccine containing 15 µg haemagglutinin of the following strains, which were recommended by WHO for the season 2008 to 2009 in the Northern hemisphere: A-H1N1: A/Brisbane/59/2007 A-H3N2: A/Uruguay/716/2007 (A/Brisbane/10/2007-like) (A/H3N2) B: B/Florida/4/2006 The vaccine was manufactured by Baxter AG, Vienna. Vaccine strains were egg-derived wild type strains provided by the National Institute for Biological Standard and Control (NIBSC). Placebo consisted of phosphate buffered saline Participants were randomly allocated to receive one 0.5 ml dose of either vaccine or placebo into the deltoid muscle Vaccinations were performed between 1 and 15 December 2008
Outcomes	Safety: participants were provided with a diary card, on which they had to record daily the temperature for the first 7 days following immunisation and to report fever and other adverse events for 21 days after immunisation Participants returned for a final study visit 166 to 194 days after vaccination to have a physical examination and final assessment of adverse events Serological: the first serum samples were presumably collected before vaccine administration (it is not well described in any of the 3 reports), the second 18 to 24 days later. HI titres and GMT against vaccine strains was assessed by Focus Diagnostics (Cypress, CA, USA). HI assays were done in triplicate with egg-derived antigen. Titres of less than 1:10 were expressed as 1:5 and judged to be negative Effectiveness: during the visit at day 18 to 24 after immunisation, individuals were instructed to return to the clinic within 48 hours after the onset of symptoms for an influenza-like illness should they have fever with cough, sore throat, muscle ache, headache, fatigue, nausea or bloodshot eyes, or have any 2 of these symptoms without fever. At every visit for an influenza-like illness, until 15 May 2009, nasopharyngeal swabs were

	obtained for culturing and typing viruses Nasopharyngeal swab specimens were sent to BioAnalytical Research, Lake Success, NY, USA, for culture by use of Rapid R-Mix (Diagnostic Hybrids, Athens, OH, USA) and traditional culture methods, and for virus typing with RT-PCR analyses. Influenza type A/H1N1 or A/H3N2 isolates were sent to the laboratory of the Influenza Division, National Center for Immunization and Respiratory Diseases, CDC, Atlanta, GA, USA, for analyses of HI by use of ferret antiserum to assess the antigenic relatedness of the isolate to the vaccine strains
Notes	Industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Individuals were randomly assigned by use of a centralised telephone system" "Randomisation was done in blocks, with block sizes greater than two"
Allocation concealment (selection bias)	Low risk	"The allocation sequence was generated by Baxter, using an interactive voice response system with the random number generator algorithm of Wichmann and Hill, as modified by Mcleod"
Blinding (performance bias and detection bias) All outcomes	Low risk	"At each study site, an investigator, subinvestigator, or study nurse who was masked to treatment allocation was designated to vaccinate participants, and was then prohibited from participation in data collection or the study. To ensure masking, the participants were enrolled by investigators who were not involved in the randomisation process Because the syringes containing the test and the control products were different in appearance both studies employed an observational blinding procedure such that study personnel who administered vaccinations were not involved in recording or reviewing study data"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Both efficacy and safety estimates were calculated on ITT study population. We know that all treated participants (3623 to influenza vaccine and 3620 to placebo) had been included in the safety analysis,

		whereas 3619 and 3617 had been considered for the effectiveness estimate calculation (i.e. those vaccinated and with at least 21 days follow-up after immunisation) . Participants in the per protocol population (completed the study without major protocol deviations) were 3316 and 3318, respectively, in the vaccine and placebo arms Reasons for non-inclusion in the per-protocol population were not specified for 150 vaccine and 135 placebo recipients
Summary assessment	Low risk	Low risk of bias

aa Beran 2009a

Methods	Randomised, double-blind, placebo-controlled study conducted in the Czech Republic during the 2005 to 2006 influenza season. This was defined retrospectively as starting the first week with 2 culture-confirmed cases in the study area and ending the last week with 1 culture-confirmed case in the study area. Randomisation was generated by GSK (sponsor) using the SAS program, in a 2:1 blocking scheme using a minimisation procedure (with no explanation of why such a method or the ratio was used). The allocation concealment method was not explicitly mentioned. However, the authors mentioned that placebo and vaccine treatments were indistinguishable in appearance and that blinding to treatment assignment was maintained until study analysis
Participants	Self referred healthy adults (n = 6203), predominately Caucasian (99.8%), aged between 18 and 64 years (mean 35 + 13 years) of both genders (TIV group: female 55.3%, placebo group: female 54.2%) and with no history of influenza vaccination within the last 3 influenza seasons. A subset of participants who were randomly selected for vaccine safety and reactogenicity were given a calibrated thermometer and a diary card to record symptoms. The method of selection of this subset was not explained. Use of antimicrobial/influenza antiviral therapy seem to be allowed but was not quantified
Interventions	TIV vaccine: 0.5 ml single dose by IM injection or placebo (normal saline) administered intramuscularly. Use of more than one lot was not reported TIV contain haemagglutinin antigens of • A/New Caledonia/20/99 (H1N1) IVR-116 virus as an A/New Caledonia/20/99-like strain • A/New York/55/2004 (H3N2) X-157 virus as an A/California/7/2004-like strain • B/Jiangsu/10/2003 virus as a B/Shanghai/361/2002-like strain 2 modes of surveillance were used: Passive: started on the day of vaccination, participants self report through a toll-free number of ILI symptoms Active: started 2 weeks after vaccination day: a biweekly telephone contact of the participants by someone (not clear who) for ILI symptoms It is not clear if the surveillance included the entire cohort or just a subset, or why the

	authors carried out harms surveillance using the 2 surveillance methods already in place
Outcomes	Serological Blood samples were collected for the specified subset and were tested/analysed at GSK Biologicals SSW Dresden, Germany Blood sample obtained prior to vaccination and at 21 days following vaccination. Serum samples were stored at -20 °C until blinded analyses were conducted An haemagglutination-inhibition test was done using chicken red blood cells with the 3 virus strains present in the TIV used as antigens. The serum titre was expressed as the reciprocal of the highest dilution that showed complete inhibition of haemagglutination Serology was not a primary outcome in this study Effectiveness **Incidence of culture-confirmed ILI (primary outcome, reported as the attack rate in the efficacy cohort)** **Nasal and throat swab collected by a nurse on the same day** Swab samples were stored at 28 °C and transferred within 5 days of the onset of ILI symptoms Sample sent to the National Reference Laboratory for Influenza (NRL, Prague, Czech Republic) for conventional influenza virus culture using Madin Darby canine kidney (MDCK) cells Confirmation of influenza A or B was determined using the following: • haemagglutination assay with turkey and guinea pig erythrocytes • haemagglutination inhibition was used to identify virus type, subtype and drift variant • direct immunoperoxidase assay using anti-influenza A and anti-influenza B nucleoprotein antibodies There were 814 reported ILI episodes, only 46 gave positive culture **Clinical** **Incidence of ILI symptoms (secondary outcome, reported as attack rate in the ATP cohort)** IL was defined as fever (oral temperature greater or equal to 37.8 °C) plus cough and/or sore throat. An ILI episode was defined as the period from the first day of ILI symptoms until the last day of ILI symptoms. A new episode was taken into account only after the complete resolution of the previous one. To count as a separate episode at least 7 days free of any symptoms should pass Number of events was 370 reported events (254 in TIV and 120 in placebo) Number of participants reporting at least one event (240 in TIV and 113 in placebo) was used to calculate the attack rate Reasons to exclude from the ATP cohort include: • protocol violation (inclusion/exclusion criteria): seems that the selected subset have certain criteria but not mentioned by the authors • underlying medical condition: not specified what? Or why not excluded from the efficacy cohort as well since participants are reported to be healthy • forbidden by the protocol: protocol not clear • participants not exposed during the influenza season: not understood what it meant (did the patient travel after getting the study treatment?) **Immunogenicity**: blood sample obtained prior to vaccination and at 21 days following vaccination. Performed only for a subset of patient not all efficacy cohort

	Safety Data on serious adverse events (SAEs) began at the receipt of vaccine/placebo and continued until the end of the study. However safety was solicited from a subset of participants (no mention of method used to randomly select them, no justification for not collecting SAEs from all participants, especially with the presence of 2 surveillance methods) **Reactogenicity**: defined as the presence and intensity of the following symptoms within 4 days of vaccination: pain, redness and swelling (found to occur more in the TIV group) other general symptoms of fatigue, fever, headache, muscle aches, shivering and joint pain (found to occur more in the TIV group) The intensities of adverse events were recorded according to a standard 0 to 3 grade scale: "absent", "easily tolerated", "interferes with normal activity" and "prevents normal activity"
Notes	The authors report that due to the atypical nature of the influenza season during this study we were unable to assess TIV efficacy Industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomisation list was generated by the sponsor by SAS program and used to number the vaccine and placebo treatments"; "A randomization blocking scheme (2:1) was employed to ensure that balance between treatments was maintained."
Allocation concealment (selection bias)	Unclear risk	No explicit description of the method of concealment, authors only mentioned that treatments were numbered and that they were indistinguishable in appearance)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Authors reported that the blinding assignment was maintained until study analysis Authors mentioned the treatments were indistinguishable in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Exclusion of allocated participants from the analysis of the trial** a) Did the report mention explicitly the exclusion of allocated participants from the analysis of trial results? Yes. b) If so did the report mention the reason(s) for exclusion? Yes. Details were reported in the study flow chart
Summary assessment	Unclear risk	Unclear risk of bias

aa Beran 2009b

Methods	A randomised, double-blind, placebo-controlled study conducted during the 2006 to 2007 influenza season at 15 centres located in the Czech Republic and Finland. The protocols and study documents were approved by the ethics committee of each country. Participants were randomised to receive 1 dose of TIV (lot 1 or lot 2 of Fluarix) or placebo (normal saline solution) at the first study visit (day 0) by intramuscular injection. Each 0.5 ml dose of TIV contained 15 mg of each of the haemagglutinin antigens of strains A/New Caledonia/20/99(H1N1) IVR-116, A/Wisconsin/67/2005(H3N2) and B/Malaysia/2506/2004 (from the Victoria lineage) From the day of vaccination, passive and active surveillance (biweekly contact) to detect ILI cases. For each case of suspected ILI, a nasal and throat swab specimen (composed of a swab of both nasal sinuses and a second swab of the throat) was collected for culture (as much as possible on the same day as the ILI report and, at the latest, 5 days after the ILI onset). Each participant was provided with a calibrated thermometer to measure temperature and a diary card to record temperatures and symptoms during the ILI episode. Blinded analysis was carried out at GSK biologicals in Dresden, Germany Blood samples for the evaluation of influenza vaccine immunogenicity were obtained from the randomly selected, planned subset of ? 500 participants just prior to vaccination and 21 to 28 days later. Frozen aliquots of culture supernatants from positive viral cultures were sent to J. Treanor's laboratory University of Rochester Vaccine Evaluation Unit Influenza Serology Laboratory, Rochester, New York) for identification of virus-matching isolates by conventional haemagglutination-inhibition testing (using H1 and H3 antisera from the CDC and B/Malaysia antiserum from the WHO)
Participants	Eligible participants were: • self referred women or men who were: • between 18 and 64 years of age and • had no significant clinical disease at the time of vaccination WHO provided written informed consent
Interventions	**Intervention** 1 dose of TIV (lot 1 or lot 2 of Fluarix), IM injection, at the first day of the study (day 0) Each 0.5 ml dose of TIV contained 15 mg of each of the haemagglutinin antigens of strains A/New/Caledonia/20/99(H1N1) IVR-116, A/Wisconsin/67/2005(H3N2) and B/Malaysia/2506/2004 (from the Victoria lineage) **Comparator** placebo (normal saline solution), IM injection, at the first day of the study (day 0)
Outcomes	Serological (only carried out for the TIV group) Effectiveness Evaluate efficacy of TIV versus placebo in the prevention of culture-confirmed influenza A and/or B due to strains antigenically matched to the vaccine **(their primary objective)** **Secondary objectives** • Evaluation of TIV in the prevention of culture-confirmed influenza due to strains antigenically matched to the vaccine for each of the 2 vaccine lots • Evaluation of TIV in the prevention of culture-confirmed Influenza A and/or B attributable to any influenza A or B strain • Evaluation of TIV in the prevention of ILI which was less stringently defined as at least 1 systemic symptom (fever and/or myalgia) and 1 respiratory symptom (cough and/or sore throat).

aa Beran 2009b (*Continued*)

	Safety vaccine reactogenicity and immunogenicity in a random subset of participants by obtaining blood samples prior to vaccination and 21 to 28 days later. However, no harms data are reported
Notes	The authors conclude that TIV is efficacious against culture-confirmed influenza in healthy adults Industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There is no mention of appearance of the injection content
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reasons for the whole cohort are provided by the patient flow
Summary assessment	Unclear risk	Unclear risk of bias

aa Bridges 2000a

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1997 to 1998 influenza season. Follow-up lasted from November to March. Influenza period was defined as the period during which clinical specimens collected from ill participants yielded influenza viruses: 8 December 1997 through 2 March 1998 and lasted 12 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random number. Pharyngeal swab and paired sera were collected from ill people
Participants	1184 healthy factory employees: 595 treated and 589 placebo. Age of participants was 18 to 64
Interventions	Commercial trivalent, inactivated, intramuscular vaccine. Schedule and dose were not indicated. Vaccine composition was: A/Johannesburg/82/96, A/Nanchang/933/95 and B/Harbin/7/94. Placebo was sterile saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Influenza-like illness, influenza, days ill, physician visits, times any drug was prescribed, times antibiotic was prescribed, working days lost, admissions, adverse effects. They were defined as follow: influenza-like illness: fever = 37.7 °C with cough or sore throat); upper respiratory illness: cough with sore throat or fever = 37.7 °C. Local adverse effects were arm soreness and redness. Systemic adverse effects were: fever, sore throat, coryza,

aa Bridges 2000a (*Continued*)

	myalgia, headache and fatigue, but authors reported no data. Surveillance was passive
Notes	For analysis we chose the influenza-like illness definition. ITT was performed. Systemic adverse effects were not reported. Circulating strain was A/Sidney/5/97-like Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reasons for the whole cohort are provided by the patient flow
Summary assessment	Low risk	Low risk of bias

aa Bridges 2000b

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1998 to 1999 influenza season. Follow-up lasted from November to March. The influenza period was defined as the period during which clinical specimens collected from ill participants yielded influenza viruses: 4 January 1998 through 14 March 1999 and lasted 10 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers. Pharyngeal swabs and paired sera were collected from ill people
Participants	1191 healthy factory employees: 587 treated and 604 placebo. Age of participants was 19 to 64
Interventions	Commercial trivalent, inactivated, intramuscular vaccine. Schedule and dose were not indicated. Vaccine composition was: A/Beijing/262/95, A/Sydney/5/97 and B/Harbin/7/94. Placebo was sterile saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza, days ill, physician visits, times any drug was prescribed, times antibiotic was prescribed, working days lost, admissions, adverse effects. They were defined as follows: influenza-like illness: fever = 37.7 °C with cough or sore throat); upper respiratory illness: cough with sore throat or fever = 37.7 °C. Local adverse effects were arm soreness and redness. Systemic adverse effect were: fever, sore throat, coryza, myalgia, headache and fatigue, but authors reported no data. Surveillance was passive

aa Bridges 2000b (*Continued*)

Notes	For analysis we chose the influenza-like illness definition. ITT was performed. Systemic adverse effects were not reported. Circulating strain was A/Sidney/5/97-like and B/Beijing/184/93-like Government-funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reasons for the whole cohort are provided by the patient flow
Summary assessment	Low risk	Low risk of bias

aa Eddy 1970

Methods	Controlled clinical trial, single-blind, conducted in South Africa during the 1969 influenza season. Follow-up lasted from May to July. The first clinical case of influenza appeared on 21 May 1969 and the last 6 weeks later. The epidemic period lasted 6 weeks. The control participants were selected by drawing a 1-in-4 systematic sample from a ranked list of the personnel numbers
Participants	1758 healthy male black African employees: 1254 treated and 413 placebo. Age of participants was 18 to 65
Interventions	Monovalent inactivated parenteral vaccine. Schedule and dose were single injection, 1 ml. Vaccine composition was: A2/Aichi/2/68 (Hong Kong variant). Placebo was sterile water. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, working days lost, days ill. Influenza-like illness was not defined; case features were generically described in results section. All ill persons were admitted to hospital until recovery. Surveillance was passive
Notes	The word "double blinding" was not used, but the control group received an injection of "dummy vaccine". Poor reporting, poor-quality study. Circulating strain was A2/Hong Kong/68 virus Efficacy data only were extracted Industry-funded

aa Eddy 1970 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Systematic selection
Allocation concealment (selection bias)	High risk	Inadequate
Blinding (performance bias and detection bias) All outcomes	High risk	No descriptions
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient description
Summary assessment	High risk	High risk of bias

aa Edwards 1994a

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1986 to 1987 influenza season. Follow-up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 8 weeks. Participants were recruited from 7 organisations and assigned to 1 of the study groups using a permuted block randomisation scheme that was stratified by treatment centre and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1311 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 872 treated and 439 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live, cold-adapted, aerosol-administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single-dose; cold-adapted 107 to 107.6 pfu/ml; inactivated 15 µg each strain. Vaccine composition was: cold-adapted: Texas/1/85 H1N1 and Bethesda/1/85 H3N2; inactivated: Chile/1/83 H1N1 and Mississippi/1/85 H3N2. Placebo was allantoic fluid. Vaccine was recommended but did not match circulating strain
Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least one of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (only patients who presented for culture were considered); throat culture. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold-adapted and inactivated vaccines were antigenically comparable. Since cold-adapted influenza B vaccines were not sufficiently characterised to include in the study, the authors used monovalent inactivated influenza B

aa Edwards 1994a (*Continued*)

	vaccine in all participants in the cold-adapted arm and as placebo in the control group inactivated arm. Only the cold-adapted comparison was included in the analysis. The circulating strain was Taiwan/1/86. Effectiveness data only were extracted Government-funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description: "permutated block randomization scheme that was stratified by treatment centre and age group"
Allocation concealment (selection bias)	Low risk	Adequate: participants and clinical staff were kept unaware of the assigned vaccine group through the use of sealed randomisation envelopes that contained vaccines codes
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient description

aa Edwards 1994b

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1987 to 1988 influenza season. Follow-up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 14 weeks. Participants were recruited from 7 organisations and assigned to 1 of the study groups using a permuted block randomisation scheme that was stratified by treatment centre and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1561 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 1029 treated and 532 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live, cold-adapted, aerosol-administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single dose; cold-adapted 107 to 107.6 pfu/ml; inactivated 15 µg each strain. Vaccine composition was: cold-adapted: Kawasaki/9/86 H1N1 and Bethesda/1/85 H3N2; inactivated: Taiwan/1/86 H1N1 and Leningrad/360/86 H3N2. Placebo was allantoic fluid. Vaccine was recommended but did not match the circulating strain

aa Edwards 1994b (*Continued*)

Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least 1 of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (ILI retrospectively reported were considered); 4-fold antibody rise between post-vaccination and spring sera. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold-adapted and inactivated vaccines were antigenically comparable. Since cold-adapted influenza B vaccines were not sufficiently characterised to include in the study, the authors used monovalent inactivated influenza B vaccine in all participants in the cold-adapted arm and as placebo in the control group inactivated arm. Only the cold-adapted comparison was included in the analysis. The circulating strain was Sichuan/2/87 (H3N2) (antigen drift from vaccine strain) and B/Victoria/2/87 Effectiveness data only were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient description: "permutated block randomization scheme that was stratified by treatment centre and age group"
Allocation concealment (selection bias)	Low risk	Adequate: participants and clinical staff were kept unaware of the assigned vaccine group through the use of sealed randomisation envelopes that contained vaccines codes
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient description
Summary assessment	Unclear risk	Unclear

aa Edwards 1994c

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1988 to 1989 influenza season. Follow-up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 11 weeks. Participants were recruited from 7 organisations and assigned to 1 of the study groups using a permuted block randomisation scheme that was stratified by treatment centre and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1676 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 1114 treated and 562 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live, cold-adapted, aerosol-administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single dose; cold-adapted 107 to 107.6 pfu/ml; inactivated 15 µg each strain. Vaccine composition was: cold-adapted: Kawasaki/9/86 H1N1 and Los Angeles/2/87 H3N2; inactivated: Taiwan/1/86 H1N1 and Sichuan/2/87 H3N2. Placebo was allantoic fluid. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least 1 of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (ILI retrospectively reported were considered); 4-fold antibody rise between postvaccination and spring sera. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold-adapted and inactivated vaccines were antigenically comparable. Since cold-adapted influenza B vaccines were not sufficiently characterised to include in the study, the authors used monovalent inactivated influenza B vaccine in all participants in the cold-adapted arm and as placebo in the control group inactivated arm. Only the cold-adapted comparison was included in the analysis. The circulating strain was Taiwan/1/86 (H1N1) and B/Yamata/16/88. Effectiveness data only were extracted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description: "permutated block randomization scheme that was stratified by treatment centre and age group"
Allocation concealment (selection bias)	Low risk	Adequate: participants and clinical staff were kept unaware of the assigned vaccine group through the use of sealed randomisation envelopes that contained vaccines codes

aa Edwards 1994c (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient description
Summary assessment	Unclear risk	Unclear

aa Edwards 1994d

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1989 to 1990 influenza season. Follow-up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 11 weeks. Participants were recruited from 7 organisations and assigned to 1 of the study groups using a permuted block randomisation scheme that was stratified by treatment centre and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1507 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 999 treated and 508 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live, cold-adapted, aerosol-administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single-dose; cold-adapted 107 to 107.6 pfu/ml; inactivated 15 µg each strain. Vaccine composition was: Kawasaki/9/86 H1N1 and Los Angeles/2/87 H3N2; inactivated: Taiwan/1/86 H1N1 and Shanghai/11/87 H3N2. Placebo was allantoic fluid. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least 1 of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (ILI retrospectively reported were considered); 4-fold antibody rise between postvaccination and spring sera. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold-adapted and inactivated vaccines were antigenically comparable. Since cold-adapted influenza B vaccines were not sufficiently characterised to include in the study, the authors used monovalent inactivated influenza B vaccine in all participants in the cold-adapted arm and as placebo in the control group inactivated arm. Only the cold-adapted comparison was included in the analysis. The circulating strain was Shanghai/11/87 (H3N2). Effectiveness data only were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

aa Edwards 1994d (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient description: "permutated block randomization scheme that was stratified by treatment centre and age group"
Allocation concealment (selection bias)	Low risk	Adequate: participants and clinical staff were kept unaware of the assigned vaccine group through the use of sealed randomisation envelopes that contained vaccines codes
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient description
Summary assessment	Unclear risk	Unclear

aa Frey 2010

Methods	Randomised, controlled, multicentre, observer-blind trial assessing effectiveness, immunogenicity and safety of both cell culture-derived inactivated flu vaccine (CCIV) and trivalent inactivated flu vaccine (TIV) containing the strain recommended by WHO for the current season (2007 to 2008)
Participants	Participants were recruited at 56 centres in the USA, Finland and Poland Major exclusion criteria: health condition for which inactivated vaccine is recommended, employment prone to influenza transmission, influenza vaccination or laboratory-confirmed influenza within 6 months of enrolment, history of Guillain-Barré syndrome, a temperature of 37.8 °C and/or acute illness within 3 days of enrolment and pregnancy or breast-feeding A total of 11,404 participants were randomised: 11,382 were vaccinated and 10,844 (95%) completed the study
Interventions	Individuals aged 18 to 49 years were randomised equally, with use of an interactive voice response system, to receive a single dose of CCIV, TIV or placebo Both CCIV and TIV (Novartis Vaccines and Diagnostics) contained 15 µg of haemagglutinin per 0.5 ml dose of each of the following virus strains: A/Solomon Islands/3/2006 (H1N1)-like A/Wisconsin/67/2005 (H3N2)-like B/Malaysia/2506/2004-like Preparations were administered in the deltoid muscle of the non-dominant arm. Only the vaccine administrator had access to the randomisation code
Outcomes	**Safety** Study participants were monitored for 30 minutes after vaccination for immediate reactions. Participants recorded the occurrence, duration and severity of local injection

	site and systemic reactions for 7 days after vaccination. Solicited reactions were graded as follows: mild, no limitation of normal daily activities; moderate, some limitation; or severe, unable to perform normal daily activities. Unsolicited reactions were recorded for 21 days after vaccination. Serious adverse events were monitored for the entire study (9 months) **Effectiveness** Influenza surveillance began 21 days after vaccination. Participants had to report to investigators the occurrence of influenza-like illness symptoms (fever 37.8 °C plus sore throat or cough, as well as body aches, chills, headache and runny or stuffy nose). An active survey was also performed by means of weekly phone calls Participants reporting influenza-like illness symptoms underwent clinical evaluations; nasal and throat specimens were obtained for laboratory confirmation of influenza virus. Specimens were targeted for collection within 24 hours after symptom onset, with a window of 120 hours. Specimens were cultured on RhMK and tested by PCR Each study participant was observed during the 6-month study surveillance period or for 6 months after vaccination, whichever was longer. Study duration was around 9 months **Immunogenicity** It was assessed on the first 1045 participants enrolled at USA sites and randomised 8: 25:2 to receive CCIV, TIV or placebo. Serum samples were collected at baseline and 3 weeks after immunisation for seroprotection, seroconversion and GMT determination
Notes	Financial support: "Novartis Vaccines was the funding source and was involved in all stages of the study conduct and analysis" Potential conflicts of interest: "M.L., A.I., N.G., and S.H. are employees of Novartis Vaccines and Diagnostics. T.V. has received consultancy fees from MedImmune and speaker fees from MedImmune, Novartis, and Crucell in relation to meetings on influenza vaccination. S.F. and A.S.-M.: no conflicts"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Low risk	"Individuals...( )..were randomised equally, with use of an interactive voice response system, to receive a single dose of CCIV, TIV, or placebo."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"This randomized, placebo-controlled, observer-blind trial evaluated...." "Only the vaccine administrator had access to the randomization code." No information about the appearance of the preparation is provided in the text

aa Frey 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow of participants during the study is reported and described. Loss to follow-up amounts to about 5% at study end and is balanced through the 3 arms
Summary assessment	Unclear risk	Unclear

aa Hammond 1978

Methods	Controlled clinical trial, double-blinded conducted in Australia during the 1976 influenza season. Follow-up lasted the whole epidemic period. Epidemic influenza was defined by virus isolation and serology tests and lasted from middle of April to middle of August 1976 (17 weeks). Coded identical-looking vials were sequentially administered to enrolled participants. A throat swab was collected from ill people. Serological confirmation was performed on all participants
Participants	225 medical students or staff members: 116 treated and 109 placebo. Age of participants was not indicated
Interventions	Trivalent parenteral subunit vaccine. Schedule and dose were: single dose. Vaccine composition was: 250 IU of A/Victoria/3/75, 250 IU of A/Scotland/840/74 and 300 IU of B/Hong Kong/8/73. Placebo was diphtheria and tetanus toxoids. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza. Clinical illnesses were not defined. Influenza was defined as respiratory illness which was associated with the isolation of influenza virus, a 4-fold or greater rise in antibody titre occurring between post-vaccination and post-epidemic sera, or both. Surveillance was active
Notes	Clinical illness was not defined and data were included in the analysis as "clinical cases without clear definition". Circulating strain was A/Vic/3/75-like. Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate
Allocation concealment (selection bias)	High risk	No description
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description

aa Hammond 1978 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessment	High risk	No description

aa Jackson 2010a

Methods	Randomised, multicentre, double-blind, placebo-controlled trial, assessing the effectiveness and safety of a trivalent inactivated vaccine in preventing confirmed influenza. The study was performed during 2 influenza seasons (2005 to 2006 and 2006 to 2007) in the USA
Participants	Healthy adults aged between 18 and 49 years without significant acute or chronic, or medical or psychiatric illness. Participants with cancer, systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg; belonging to a risk group for which routine influenza vaccination is recommended (chronic pulmonary, cardiovascular, renal, hepatic, haematological or metabolic disorders; immunosuppressive illness, recent/ongoing receipt of immunosuppressive therapy, immunoglobulin, other vaccines, or with human immunodeficiency virus infection were excluded. Participants enrolled for the first season were not included in the second In season I (2005 to 2006), 3514 participants were recruited at 37 centres from 17 September 2005 onwards In season II (2006 to 2007), 4144 participants were recruited at 44 centres from 16 October 2006 onwards
Interventions	Recruited participants were randomised at the beginning of each season in order to receive 1 dose of trivalent inactivated split influenza vaccine TIV (FluLaval™, a trademark of the GlaxoSmithKline group of companies; manufactured by ID Biomedical Corporation of Quebec (IBD-Q), Canada), or saline placebo injection Each 0.5 ml dose of TIV contained 15 μg of haemagglutinin (HA) antigen of each recommended influenza strain For season I (2005 to 2006) were: A/New Caledonia/20/1999 (H1N1) A/New York/55/2004 (H3N2, A/California/7/2004-like) B/Jiangsu/10/2003 (B/Shanghai/361/2002-like)
Outcomes	**Effectiveness** During the influenza seasons, participants were instructed to report symptoms meeting the ILI definition by using a toll-free, study-specific phone number within 48 hours from their onset and to record them together to temperature. ILI symptoms were moreover solicited by weekly outbound phone contact. Visits from nurses were dispatched to participants who filled ILI definition within 24 hours after symptoms onset, nasopharyngeal and oropharyngeal swabs for viral culture were drawn. During season I surveillance for influenza was conducted between 14 November 2005 and 30 April 2006; during season II between 13 November and 30 April. Primary effectiveness study endpoint was: **VMCCI** (vaccine-matched, culture-confirmed influenza). The case definition required the presence of influenza-like illness (ILI), defined as symptoms that interfered with normal daily activities and that included cough and at least 1 additional symptom from

	among fever (oral temperature > 37.7 °C/99.9 °F), headache, myalgia and/or arthralgia, chills, rhinorrhoea/nasal congestion and sore throat. Participants meeting the definition for ILI and with concurrent isolation from a nasopharyngeal swab of an influenza A and/or B virus isolate antigenically matching a vaccine strain for the relevant year were considered to be cases of VMCCI Secondary effectiveness endpoints were: **CCI** (culture-confirmed influenza illness) ILI with any influenza A or B virus isolate by culture **LCI** (laboratory-confirmed influenza illness) one or both of **CCI** or **ILI** with a 4-fold increase in haemagglutination-inhibiting (HI) serum antibody titres to a circulating influenza virus strain between day 21 (± 4 days) postvaccination and final visit specimens obtained after the end of the influenza season **Immunogenicity** Serum samples were collected from study participants at day 0, 21 and about 4 weeks after the end of the surveillance period Immunogenicity was assessed determining GMT, seroconversion and seroprotection rate between samples collected at day 21 and at day 0 on a random selected subset of participants **Safety** Local and systemic reactions (events) occurred within 3 days after immunisation. Participants were observed for the first 30 minutes following immunisation. Participants recorded further reactions occurring no later than 8 days following vaccination by means of an Interactive Voice Response System. Following symptoms were reported (3 days): Fever (at least 37.5 °C) Injection site pain/soreness Injection site redness Injection site swelling Myalgia and/or arthralgia Headache Tiredness Chills Malaise Red eyes Swelling of the face Cough Chest tightness or difficulty in breathing Sore throat, hoarseness or pain on swallowing Participants with at least 1 vaccine reactogenicity event Data were provided pooled for the 2 study seasons Unsolicited spontaneous adverse events (AEs), for which follow-up was extended for at least 135 days following immunisation **Pregnancy outcomes** Pregnancies Spontaneous abortion Full-term birth
Notes	- *Per-protocol* (PP): participants who received the treatment to which they were randomised, responded to ≥ 1 post-vaccination active surveillance telephone call and had no major protocol deviations considered to affect the efficacy or immunogenicity data (determined before unblinding) (for effectiveness estimates)

aa Jackson 2010a (*Continued*)

	- *Intention-to-immunise* (ITI): it was the PP set plus participants with protocol deviations and treatment errors and analysed as randomised The safety set included participants who received any study treatment and had any post-vaccination safety data. If an incorrect treatment was conclusively documented, participants in the safety set were analysed based on the treatment they actually received Funding source was pharmaceutical "GSK Biologicals was the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also took in charge all costs associated with the development and the publishing of this manuscript. The corresponding author had full access to the data, and final responsibility for submission of the manuscript for publication"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Treatment allocation was determined by blocked, stratified randomization with a 1: 1 distribution to TIV or placebo; randomization was stratified by study center, age (18-34 and 35-49 years), and the subject's report of previous recent receipt (within ≤ 2 years) of TIV."
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment "Each study center had a pre-determined sequence of randomization numbers which were allocated sequentially to eligible participants. Participants were allocated equally among 3 different vaccine lots"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Clinic staff (excluding the nurse giving the vaccine), were blinded to the treatment group until the study was complete."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient flow
Summary assessment	Unclear risk	Unclear

aa Jackson 2010b

Methods	See aa Jackson 2010b (the following data refer to the second study season)
Participants	In season II (2006 to 2007), 4144 participants were recruited at 44 centres from 16 October 2006 onwards

aa Jackson 2010b (*Continued*)

Interventions	Recruited participants were randomised at the beginning of each season in order to receive 1 dose of trivalent inactivated split influenza vaccine TIV (FluLaval™, a trademark of the GlaxoSmithKline group of companies; manufactured by ID Biomedical Corporation of Quebec (IBD-Q), Canada), or saline placebo injection Each 0.5 ml dose of TIV contained 15 μg of haemagglutinin (HA) antigen of each recommended influenza strain Antigens for season II (2006 to 2007) were: A/New Caledonia/20/1999 (H1N1) virus A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004
Outcomes	See aa Jackson 2010b
Notes	See aa Jackson 2010b

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See aa Jackson 2010b
Allocation concealment (selection bias)	Unclear risk	See aa Jackson 2010b
Blinding (performance bias and detection bias) All outcomes	Low risk	See aa Jackson 2010b
Incomplete outcome data (attrition bias) All outcomes	Low risk	See aa Jackson 2010b
Summary assessment	Unclear risk	See aa Jackson 2010b

aa Keitel 1988a

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1983 to 1984 influenza season. Follow-up lasted the whole epidemic period. Influenza period was defined as the interval during which community surveillance recovered influenza viruses from 10% or more of persons with febrile respiratory illness per calendar week (from 8 January to 17 March 1984) and lasted 9 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time volunteers were asked to record any illness that occurred during the epidemic period and blood specimens were collected
Participants	598 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 300 treated and 298 placebo. Age of participants was 30 to 60

aa Keitel 1988a (*Continued*)

Interventions	Trivalent, killed, whole, intramuscularly administered vaccine. Schedule and dose were: single dose; 15 µg of haemagglutinin of each influenza strain. Vaccine composition was: A/Philippines/2/82 (H3N2), A/Brazil/11/78 (H1N1) and B/Singapore/222/79. Placebo was sterile saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Outcomes were: ILI, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 °C or higher) . Laboratory confirmation was based on culture and/or 4-fold or greater rise in antibody titre occurring between post-vaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera
Notes	Influenza-like illness and influenza were detected in 3 groups: first vaccinated, multivaccinated and placebo. Febrile illnesses were included in the analysis; the first 2 groups' cases were added up. Circulating strain was A/Victoria/7/83 (H1N1) and B/USSR/100/83. Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessment	Unclear risk	No description

aa Keitel 1988b

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1984 to 1985 influenza season. Follow-up lasted the whole epidemic period. The influenza period was defined as the interval during which community surveillance recovered influenza viruses from 10% or more of persons with febrile respiratory illness per calendar week (from 6 January to 9 March 1985) and lasted 9 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time volunteers were asked to record any illness that occurred during the epidemic period and blood specimens were collected
Participants	697 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 456 treated and 241 placebo. Age of participants was 30 to 60
Interventions	Trivalent, killed, whole, intramuscularly administered vaccine. Schedule and dose were: single dose; 15 µg of haemagglutinin of each influenza strain. Vaccine composition was: A/Philippines/2/82 (H3N2), A/Chile/1/83 (H1N1) and B/USSR/100/83. Placebo was sterile saline for injection
Outcomes	Outcomes were: ILI, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 °C or higher) . Laboratory confirmation was based on culture and/or 4-fold or greater rise in antibody titre occurring between postvaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera. Surveillance was passive
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessment	Unclear risk	No description

aa Keitel 1997a

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1985 to 1986 influenza season. Follow-up lasted the whole epidemic period. The influenza period was defined by viral surveillance. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time, volunteers were asked to record any illness that occurred during the epidemic period and blood specimens were collected
Participants	830 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 577 treated and 253 placebo. Age of participants was 30 to 60
Interventions	Trivalent, killed, whole, intramuscularly administered vaccine. Schedule and dose were: single dose; 15 μg of haemagglutinin of each influenza strain. Vaccine composition was: A/Philippines/2/82 (H3N2), A/Chile/1/83 (H1N1) and B/USSR/100/83. Placebo was sterile saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Influenza-like illness, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 °C or higher) . Laboratory confirmation was based on culture and/or 4-fold or greater rise in antibody titre occurring between post-vaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera. Surveillance was active
Notes	Influenza-like illness and influenza cases were detected in 3 groups: first vaccinated, multi-vaccinated and placebo. Febrile illnesses were included in the analysis; the first 2 groups cases were added up. Circulating strains were B/Ann Arbor/1/86, A/Mississippi/1/85 Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessment	Unclear risk	No description

aa Keitel 1997b

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1986 to 1987 influenza season. Follow-up lasted the whole epidemic period. Influenza period was defined by viral surveillance. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time, volunteers were asked to record any illness that occurred during the epidemic period and blood specimens were collected
Participants	940 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 723 treated and 217 placebo. Age of participants was 30 to 60
Interventions	Trivalent, killed whole, intramuscularly administered vaccine. Schedule and dose were: 2 doses; 15 µg of haemagglutinin of each influenza strains. Vaccine composition was: A/Mississippi/1/85/H3N2), A/Chile/1/83 (H1N1) and B/Ann Arbor/1/86 plus A/Taiwan/1/86 (H1N1). Placebo was sterile saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Influenza-like illness, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 °C or higher). Laboratory confirmation was based on culture and/or 4-fold or greater rise in antibody titre occurred between postvaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera. Surveillance was passive
Notes	Influenza-like illness and influenza cases were detected in 3 groups: first vaccinated, multi-vaccinated and placebo. Febrile illnesses were included in the analysis; the first 2 groups cases were added up. Circulating strain was A/Taiwan/1/86. Effectiveness data only were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessment	Unclear risk	No description

aa Keitel 1997c

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1987 to 1988 influenza season. Follow-up lasted the whole epidemic period. Influenza period was defined by viral surveillance. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time, volunteers were asked to record any illness that occurred during the epidemic period and blood specimens were collected
Participants	934 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 789 treated and 145 placebo. Age of participants was 30 to 60
Interventions	Trivalent, killed, whole, intramuscularly administered vaccine. Schedule and dose were: single dose; 15 μg of haemagglutinin of each influenza strain. Vaccine composition was: A/Leningrad/360/86 (H3N2), A/Taiwan/1/86 (H1N1), B/Ann Arbor/1/86. Placebo was sterile saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Influenza-like illness, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 °C or higher) . Laboratory confirmation was based on culture and/or 4-fold or greater rise in antibody titre occurring between postvaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera. Surveillance was passive
Notes	Influenza-like illness and influenza cases were detected in 3 groups: first vaccinated, multi-vaccinated and placebo. Febrile illnesses were included in the analysis; the first 2 groups' cases were added up. Circulating strains were A/Sichuan/1/87, B/Victoria/2/87. Effectiveness data only were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessment	Unclear risk	No description

aa Langley 2011

Methods	Randomised, placebo-controlled trial assessing the protective efficacy of a nasally administered meningococcal outer membrane protein adjuvanted trivalent influenza vaccine (OMP-TIV) against laboratory-confirmed influenza infection during the 2003 to 2004 influenza season in Canada in healthy adults
Participants	Healthy adults aged 18 to 64 years, who gave informed consent, were eligible to participate (1349 were enrolled at 28 sites in Canada). Exclusion criteria: to belong to groups for which annual influenza vaccination is recommended; presence of significant acute or chronic, uncontrolled medical or psychiatric illness; pregnancy; infection with HIV, hepatitis B or hepatitis C virus; chronic use of any medication or product for symptoms of rhinitis or nasal congestion or any chronic nasopharyngeal complaint or use of such product within 7 days prior to immunisation; asthma; symptoms or diagnosis suggesting gag reflex impairment or predisposition to aspiration; use of systemic glucocorticosteroids or immunosuppressive medications; receipt of investigational drugs in the prior month, presence of febrile or upper respiratory tract illness on the day of immunisation, and known hypersensitivity to mercurials or chicken eggs
Interventions	The vaccine contains equal parts of 3 monovalent egg-grown, formalin-inactivated influenza antigens formulated with OMPs of *N. meningitidis* serogroup B strain 8047 The vaccine tested in this study contained HA from each - A/New Caledonia/20/99 (H1N1) - A/Panama/2007/99 (H3N2) - B/Shangdong/7/97 (H1N1) (recommended for the 2003 to 2004 season) Vaccine was tested in 2 formulations: 1 containing with 75 ± 15 μg/ml of HA from each of the 3 influenza strains and 1 with 150 ± 30 μg HA/ml. Both formulations are sterile, colourless to yellowish opalescent and preserved with 0.01% thimerosal The placebo control was sterile phosphate-buffered isotonic saline with 0.01% thimerosal and was colourless Participants (n = 1348) were randomised to 1 of the following 3 regimens: - Arm 1: meningococcal OMP-adjuvanted TIV with 15 μg of each HA antigen on days 0 and 14 (n = 455) - Arm 2: meningococcal OMP-adjuvanted TIV with 30 μg of each HA antigen on day 0 and saline placebo on day 14 (n = 450) - Control: saline placebo on days 0 and 14 (n = 443) Vaccine and placebo were administered by means of a VP3/100 nasal spray pump (Valois of America, Greenwich, CCCN) with the participant in a sitting position, administering 0.10 ml of preparation in each nostril (0.20 ml in all)
Outcomes	Safety Participants were monitored for 30 minutes after the immunisation on days 0 and 14 for any immediate adverse events and then completed a questionnaire which graded selected complaints as 0 (none), Grade 1 (mild), Grade 2 (moderate) or Grade 3 (severe) . From days 0 to 7 participants self monitored evening oral temperature and completed a written memory aid of reactogenicity. On days 3, 7, 17 and 21 participants reported the maximum oral temperature and severity score in the previous days via an interactive voice response system. A clinic visit for participant assessment was initiated if symptom complaints exceeded Grade 2. Prior to the day 14 dose participants were questioned about interim adverse events and a physical exam was performed. Coding for adverse events was according to Medical Dictionary for Regulatory Activities (MeDRA®, Chantilly,

	VA) version 6.1. The following outcomes were reported: Burning or stinging in the nose Burning or stinging in the throat Itching in the nose, throat or eyes Shortness of breath Lightheadedness or dizziness New rash or a rash becoming itchy Feverishness: temperature (°C) < 37.8; 37.8 to 38.2; 38.3 to 38.9, ≥ 39.0 Immunogenicity Blood and nasal mucus samples were collected on days 0 and 28 for haemagglutinin inhibition (HI) reciprocal titres and salivary secretory IgA (sIgA) measurement, respectively Effectiveness Telephone contacts with participants were made every 2 weeks to solicit adverse events and identify influenza-like illness. Spontaneous illness reports were received via toll-free telephone call centre and reported to investigators. If the participant illness included at least 2 of the illness criteria and was severe enough to impede normal daily activities then a nurse visit was initiated. The nurse verified symptoms, collected nose and throat swabs and recorded the participant's temperature. Samples were cultured on MDCK cells and a multiplex RT-PCR test was used to detect influenza A and B viruses (viruses A were subsequently subtyped by another RT-PCR assay). The primary outcome measure for efficacy was: - CCI (culture confirmed influenza illness) defined as fever (oral temperature > 37.8 °C) and cough and at least 1 of the following: sore throat, runny nose or nasal congestion, muscle or joint ache, headache, fatigue or chills (with symptoms sufficient to impede normal daily activities) and a positive nose and throat swab culture for influenza A or B virus A co-primary endpoint measure was a positive culture, defined as positive nose and throat swab culture for influenza A or B virus and at least 2 of the following 8 symptoms: fever, cough, sore throat, runny nose or nasal congestion, muscle or joint ache, headache, fatigue or chills The secondary outcome measure, influenza-like illness (ILI) with evidence of influenza infection, required laboratory confirmation of influenza by either a positive culture for influenza A or B virus, or positive RT-PCR for influenza A or B virus or a 4-fold rise in reciprocal titre for a circulating influenza strain between days 28 and 180 and fever and cough and at least 1 of sore throat, runny nose or nasal congestion, muscle or joint ache, headache, fatigue or chills
Notes	Safety and primary endpoint estimates (CCI) were calculated on the intention-to-immunise (ITI) population, which included any participant who received at least 1 dose of test article (n = 1348, 455 in Arm 1, 450 in Arm 2, 443 in control arm) For effectiveness estimates of culture positive and ILI evaluable participants (ES) were used, i.e. those who had a complete regimen (i.e. 1 dose of placebo in the placebo group, at least 1 dose of 30 µg, 2 doses of 15µg, n = 1347) A total of 1326 participants completed the study (452 in arm 1, 442 in arm 2, 432 in

	control arm) Industry-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The study was double-blind, randomised and placebo controlled."
Allocation concealment (selection bias)	Low risk	"Subjects were assigned centrally within blocks and stratified within each site by age ≤49 and >49 years, and history of prior influenza immunization within 2 years."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Neither the subject nor the site study team (staff performing clinical safety or efficacy evaluations and investigators) were aware of patient assignment. One research nurse at each site was responsible for randomization, maintenance of the treatment log, test article preparation and administration." "This staff member did not perform any safety or efficacy observations and could not reveal treatment assignment to participants or other study staff." "Both lots are sterile, colorless to yellowish opalescent and preserved with 0.01% thimerosal. The placebo control was sterile phosphate-buffered isotonic saline with 0.01% thimerosal, and was colorless."
Incomplete outcome data (attrition bias) All outcomes	Low risk	About 98% of the initially enrolled participants completed the study
Summary assessment	Low risk	Low risk of bias

aa Leibovitz 1971

Methods	Controlled clinical trial conducted in the USA during the 1969 to 1970 influenza season. The study period was 30 January to 18 May. Follow-up lasted first 7 weeks of training. Influenza was detected from 11 February to 13 May and lasted 6 weeks. Participants were allocated to vaccine or control group according to the last non-zero digit of the social security number. Blinding was not mentioned. Specimens for culture and acute-convalescent blood specimens were obtained from people hospitalised with acute respiratory disease
Participants	9616 military trainees: 1682 treated and 7934 placebo. Age of participants was 18 to 20
Interventions	Monovalent inactivated, experimental, intramuscularly administered vaccine. Schedule and dose were: single dose, 556 CCA. Recombinant virus derived from HK/Aichi/68 and A0/PR8/34 was compared against no vaccination. Vaccine was not recommended but matched circulating strain
Outcomes	Outcomes were: hospitalisation for upper respiratory infection (without definition), hospitalisation for influenza. Laboratory confirmation was based on culture and/or 4-fold or greater rise in antibody titre occurring between acute and convalescent sera. Surveillance was passive
Notes	Recruitment and immunisation period overlapped outbreak period. Most of the illness were due to adenovirus. Illnesses during the first 1 or 2 weeks after vaccination were not excluded, but the authors stated that this fact did not affect the results. Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	High risk	Inadequate
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	High risk	Unclear

aa Mesa Duque 2001

Methods	Randomised controlled trial, double-blind, conducted in Columbia during the 1997 influenza season. Follow-up lasted from 15 March to 31 August. Influenza period was not defined. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers. Double-blinding was ensured by pre-labelled, coded, identical-looking vials. Virological surveillance was not performed
Participants	493 bank employees: 247 treated and 246 placebo. Age of participants was 18 to 60
Interventions	Subunit inactivated, intramuscularly administered vaccine. Schedule and dose were: single dose. Vaccine composition was: A/Wahan/359/95, A/Texas/36/91 and B/Beijing/184/93. Placebo was vitamin C. Vaccine was recommended and matched circulating strain
Outcomes	Episodes of clinical illness, working days lost (WDL) and adverse effects. Clinical disease was defined as upper respiratory illness (fever, sore throat and cough lasting more than 24 hours) according to ICD-IX codes 381, 382, 460, 466, 480 and from 487 to 490. Local adverse effects were oedema, erythema, pain and swelling. Systemic adverse effects were fever, headache and indisposition within 5 days of vaccination. Surveillance was passive
Notes	Circulating strains were not isolated from local cases but by WHO and Columbia surveillance system and matched vaccine components. WDL were detected all the year round, so they were not included in the analysis. Efficacy and safety data were extracted Government-funded

Risk of bias

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

aa Mixéu 2002

Methods	Randomised controlled trial, double-blind, conducted in Brazil during the 1997 influenza season. Follow-up lasted 6 to 7 months. Influenza period was not defined. Authors did not describe the methods used to ensure randomisation and blinding. Virologic surveillance was not performed
Participants	813 flight crews of an airline company: 405 vaccinated and 408 given placebo. Age of participants was 18 to 64
Interventions	Split trivalent, intramuscularly administered vaccine. Schedule and dose were: single dose. Vaccine composition was: A/Nanchang/933/95, A/Texas/36/91 and B/Harbin/7/94. Placebo was vaccine diluent. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, working days lost. Clinical illness was defined as follow: fever > 37.6 °C and cough, headache, myalgia, rhinorrhea, sore throat lasting at least 24 hours. Surveillance was passive
Notes	Local and systemic effects were reported together and therefore not included in the review. Only 294 treated participants and 299 controls completed follow-up. Efficacy data were extracted Industry-funded

Risk of bias

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

aa Mogabgab 1970a

Methods	Randomised study conducted in the USA during the 1968 to 1969 influenza season. Influenza outbreak lasted 9 weeks, from 9 December to 3 February. Randomisation methods were not described. Laboratory confirmation was obtained (by culture or 4-fold antibody titre increase in acute convalescent sera) for 20 men randomly selected each week from among the ill
Participants	1402 airmen previously unvaccinated: 881 vaccinated and 521 given placebo. Age of participants was 18 to 21
Interventions	Monovalent inactivated parenteral influenza A vaccine. Schedule and dose were: single dose. Vaccine composition was: A2/Aichi 2/68 300 CCA. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness and influenza, complications and admissions. All respiratory illnesses were classified as febrile (38.3 °C or greater), afebrile, pharyngitis, bronchitis or pneumonia (complications). Surveillance was passive
Notes	Cases occurring during the first 15 days after vaccination were not included in the analysis. Circulating strain was A2/Hong Kong. Efficacy data were extracted Government-funded

Risk of bias

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

aa Mogabgab 1970b

Methods	Randomised study conducted in the USA during the 1968 to 1969 influenza season. Influenza outbreak lasted 9 weeks, from 9 December to 3 February. Randomisation methods were not described. Laboratory confirmation was obtained (by culture or 4-fold antibody titre increase in acute convalescent sera) for 20 men randomly selected each week from among the ill

aa Mogabgab 1970b (*Continued*)

Participants	1551 airmen previously unvaccinated: 1030 vaccinated and 521 given placebo. Age of participants was 18 to 21
Interventions	Polyvalent inactivated influenza A and B vaccine (the 1967 military formula). Schedule and dose were: single dose. Vaccine composition was: A/Swine/33 100 CCA, A/PR8/34 100 CCA, A1/AA/1/57 100 CCA, A2/Taiwan 1/64 400 CCA, B/Lee/40 100 CCA, B/Mass 3/66 200 CCA. Placebo was saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Influenza-like illness and influenza cases, complications and admissions. All respiratory illnesses were classified as febrile (38.3 °C or greater), afebrile, pharyngitis, bronchitis or pneumonia (complications). Surveillance was passive
Notes	Cases occurring during the first 15 days after vaccination were not included in the analysis. Circulating strain was A2/Hong Kong. Efficacy data were extracted Government-funded

Risk of bias

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

aa Monto 1982

Methods	Randomised, single-blind study conducted in the USA during the 1979 to 1980 influenza season. Follow-up lasted for the whole epidemic period. The epidemic period was defined by first and last isolation (11 February to 18 March) and lasted 5 weeks. Each participant was given a serial number that had previously been assigned randomly by a code to either the vaccine or the placebo group. Specimens for culture were obtained from ill people. At spring time blood specimens were collected
Participants	306 students: 154 vaccinated and 152 given placebo. Age of participants was not reported

aa Monto 1982 (*Continued*)

Interventions	Monovalent, live attenuated, intranasal influenza B. Schedule and dose were: single dose. Vaccine composition was: the vaccine virus, cold recombinant, was produced by recombining the attenuated B/Ann Arbor/1/66 with a wild strain B/Hong Kong/8/73. Placebo was vaccine diluent. Vaccine was not recommended and did not match the circulating strain
Outcomes	Clinical and laboratory confirmed cases and adverse effects. Participants suffered a respiratory illness if they had at least 2 respiratory symptoms. Cases were laboratory-confirmed if they had an increase in antibody titre against 3 influenza B virus antigens, i.e. if there was a 4-fold increase from an initial sample. Side effects were sore throat, coryza, hoarseness, cough, muscle aches, temperature > 100 °F occurring during the first 3 days after vaccination. Surveillance was active
Notes	Vaccine content was not recommended nor matched. Circulating strain was B/Singapore/79-like and B/Buenos Aires/79-like Efficacy and safety data were extracted Government-funded

Risk of bias

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

aa Monto 2009

Methods	Third epidemic season (2007 to 2008) of aa Ohmit 2006 and aa Ohmit 2008
Participants	A total of 1952 healthy adults between 18 and 49 years were enrolled. Some had been also enrolled in the 2 previous seasons
Interventions	Newly enrolled participants were recruited from the community around 4 university campuses in Michigan. Allocation methods are the same as for aa Ohmit 2006 and aa Ohmit 2008 For the 2007 to 2008 season vaccine composition was the following: - Fluzone (Sanofi Pasteur, inactivated trivalent vaccine intramuscular): 15 μg of haemag-

	glutinin from each of the following strains in a 0.5 ml dose: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004 (B/Victoria lineage) - FluMist (MedImmune, live attenuated vaccine, intranasal): $10^{6.5-7.5}$ fluorescent focus units of live attenuated influenza virus reassortants of the same strains as used for the inactivated formulation in a 0.2 ml dose
Outcomes	Same outcomes as aa Ohmit 2008
Notes	Funding source - mixed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Nichol 1995

Methods	Randomised controlled trial conducted in the USA during the 1994 to 1995 influenza season. Follow-up lasted from 1 December 1994 through to 31 March 1995. Influenza period was not defined. Randomisation was performed according to a computer-generated randomisation schedule. Double-blinding was ensured by preloaded, coded, identical-looking syringes. Virological surveillance was not performed
Participants	841 full-time employed: 419 treated and 422 placebo. Age of participants was 18 to 64
Interventions	Subvirion, trivalent, parenteral influenza A and B vaccine. Schedule and dose were: single dose; 15 μg each strain. Vaccine composition was: A/Texas/36/91, A/Shangdong/9/93, B/Panama/45/90. Placebo was vaccine diluent. Vaccine was recommended and matched circulating strain
Outcomes	Cases (symptom-defined), working days lost because of respiratory illness, side effects. Participants were defined as cases if they had at least 1 upper respiratory illness (a sore throat associated with either fever or cough that lasted at least 24 hours). Local adverse effects were defined as arm soreness. Systemic adverse effects were defined as fever, tired-

aa Nichol 1995 (*Continued*)

	ness, "feeling under the weather", muscle ache, headache (within a week after vaccination). Surveillance was active
Notes	Circulating strain was not indicated. Efficacy and safety data were extracted Industry-funded

Risk of bias

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

aa Nichol 1999a

Methods	Randomised controlled trial conducted in the USA during the 1997 to 1998 influenza season. Follow-up lasted from November to March. Site-specific peak outbreak period was defined as weeks including 80% of the isolates of a specific area. Total outbreak period lasted from 14 December 1997 through to 21 March 1998. Total outbreak period was included in the analysis and lasted 14 weeks. Participants were recruited from 7 organisations and assigned to 1 of the study groups using a permuted block randomisation scheme that was stratified by treatment centre and age group. Sealed randomisation envelopes contained vaccine codes. Influenza virus surveillance was carried out in the area
Participants	4561 healthy working adults: 3041 treated and 1520 placebo. Age of participants was 18 to 64
Interventions	Trivalent, live attenuated influenza A and B vaccine in a single dose. Vaccine composition was: A/Shenzhen/227/95, A/Wuhan/395/95, B/Harbin/7/94-like. Placebo was egg allantoic fluid. Vaccine was recommended but did not match the circulating strain
Outcomes	Clinical cases (symptom-defined), working days lost and adverse effects. Case definition had 3 specifications: febrile illness (fever for at least 1 day and 2 or more symptoms for at least 2 days: fever, chills, headache, cough, runny nose, sore throat, muscle aches, tiredness); severe febrile illness (3 days of symptoms and 1 day of fever); febrile upper respiratory tract illness (3 days of upper respiratory tract symptoms and 1 day of fever). We chose the febrile illness outcome for analysis. Systemic adverse effects were defined

aa Nichol 1999a (*Continued*)

	as headache, muscle aches, chills, tiredness and fever. Surveillance was passive
Notes	Complete follow-up data were obtained for 2874 participants in the treatment arm and for 1433 participants in the placebo arm. The outcome working days lost is presented as a rate ratio; the data are presented in a way that allows us to compute the difference in mean days lost but not to compute the standard error. Circulating strain was A/Sidney/ 5/97-like. Efficacy and safety data were extracted Government and industry-funded

Risk of bias

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

aa Ohmit 2006

Methods	Multicentre, randomised, placebo-controlled trial assessing effectiveness of both inactivated and live attenuated vaccines in preventing laboratory-confirmed influenza in healthy adults aged below 50
Participants	For enrolment in the first study year (2004 to 2005), participants were recruited at 4 centres (2 university and 2 community sites) in Michigan. Participants were healthy adults between 18 and 46 years, with exclusion of those for whom influenza vaccination was recommended or contraindicated. In all 1247 were enrolled
Interventions	After informed consent was obtained and a first serum sample drawn, enrolled participants were randomly allocated to receive one dose of the following: - Inactivated trivalent vaccine (Fluzone, Sanofi Pasteur) containing 15 μg of haemagglutinin from each of the following strains: A/New Caledonia/20/99 (H1N1), A/Wyoming/ 3/2003 (H3N2, A/Fujian/411/2002-like strain) and B/Jiangsu/10/2003 (B/Shanghai/ 361/2002-like strain (Yamagata lineage)) in each 0.5 ml dose, as intramuscular injection - Placebo saline administered intramuscularly - Live attenuated trivalent vaccine (FluMist, MedImmune) containing a $10^{6.5-7.5}$ median tissue-culture infective dose of live attenuated influenza virus reassortants of the following strains: A/New Caledonia/20/99 (H1N1), A/Wyoming/ 3/2003 (H3N2 A/Fu-

	jian/411/2002-like strain) and B/Jilin/20/2003 (B/Shanghai/361/2002-like strain (Yamagata lineage)) in each 0.5 ml dose - Placebo saline administered intranasally Identical syringes were filled on site with the inactivated vaccine or matching placebo (physiologic saline) by study nurses who were aware of the intervention assignments. The live attenuated influenza vaccine and matching placebo (physiologic saline) were preloaded in identical nasal spray devices by the manufacturer. Both vaccines were licensed for use in the 2004 to 2005 influenza season Participants were randomised to vaccine or placebo in ratio of 5:1 using 4 site-specific randomisation schedules, generated with the use of a random permuted block design with a block size of 12, in order to assign participants sequentially to receive a vaccine or a placebo as they enrolled Since the trial was double-blind, the participants and the nurses who administered the study vaccine or placebo were unaware of whether the participant was receiving vaccine or placebo but were aware of the route of administration Further serum samples were drawn 3 to 5 weeks after vaccine administration (as participants returned diary cards for local and systemic reactions, preseason sample), and during April to May 2005 (post-season sample)
Outcomes	- Local and systemic reactions within 7 days from immunisation (self filled questionnaires): fever, chills, runny nose or congestion, cough, sore throat, headache, muscle aches, weakness, abdominal pain, trouble breathing, red eyes, arm soreness, arm redness - Laboratory-confirmed influenza. Active surveillance was maintained between November 2004 and April 2005. Participants were contacted by phone or e-mail twice monthly. Symptomatic influenza was described as the presence of at least 1 respiratory symptom (cough or nasal congestion) and at least 1 systemic symptom (fever, feverishness, chills, body aches) occurred during influenza activity and at least 2 weeks after administration. Participants were instructed to contact study staff when 2 at least respiratory and systemic symptoms were observed. Throat swab specimens were collected from all participants with symptomatic influenza Swabs were cultured for identification and all isolates were typed according to strain using the fluorescence antibody assay and evaluated for antigenic relatedness to vaccine strains by the Influenza Branch at the Centers for Disease Control and Prevention (CDC) . In addition, all throat-swab specimens obtained from participants with symptomatic influenza were tested at the University of Michigan by means of real-time PCR assays using the Taqman system (Applied Biosystems) All collected serum samples were tested with the haemagglutination-inhibition assay, with the virus strains present in the vaccines used as antigens and against the circulating type A (H3N2) (A/California/07/2004-like) virus and the circulating type B (B/Hawaii/33/ 2004-like) virus (i.e. Victoria lineage not included in the vaccine) For effectiveness the following endpoints were used: - On ITT population Laboratory-confirmed influenza: culture-positive and/or real-time PCR-positive - On per protocol population Laboratory-confirmed influenza: serologically positive; serologically or culture-positive
Notes	**Intention-to-treat analysis:** includes all enrolled participants who were randomly assigned to a vaccine or placebo group and received a vaccine or a placebo (TIV = 513; placebo IM = 103; LAIV = 519; placebo IN = 103)

aa Ohmit 2006 (*Continued*)

	Per-protocol analyses: limited to participants having the post-intervention (pre-season) blood specimen collected at least 3 weeks after receipt of a vaccine or a placebo and at least 2 weeks before the beginning of local influenza activity (TIV = 367; placebo IM = 73; LAIV = 363; placebo IN = 73) Government-funded

Risk of bias

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

aa Ohmit 2008

Methods	Multicentre, randomised, placebo-controlled trial assessing the effectiveness of both inactivated and live attenuated vaccines in preventing laboratory-confirmed influenza in healthy adults aged below 50. Same methods as aa Ohmit 2006
Participants	For study year 2005 to 2006 healthy men and women, aged 18 to 48 years, were recruited at 6 study sites (4 university sites and 2 community sites) in Michigan. In all 2058 participants were enrolled. Of these, 972 were already enrolled in the 2004 to 2005 season (see aa Ohmit 2006)
Interventions	Participants who were enrolled in the 2005 to 2006 season were randomised (see aa Ohmit 2006) to receive inactivated vaccine (Fluzone; Sanofi Pasteur), live attenuated vaccine (FluMist; MedImmune) or placebo. Participants who had already been enrolled in the 2004 to 2005 season received the same intervention type (i.e. Fluzone, FluMist or placebo) as before - Fluzone (intramuscularly administered) contained 15 g haemagglutinin from each of the following strains: A/New Caledonia/20/99 (H1N1), A/New York/55/2004 (H3N2) (A/California/7/2004-like) and B/Jiangsu/10/2003 (B/Shanghai/361/2002-like) - FluMist (intranasally administered) was formulated to contain a median tissue-culture infective dose of $10^{6.5}$ to $10^{7.5}$ live attenuated influenza virus reassortants of the same strains - Intramuscular or intranasal saline placebo

aa Ohmit 2008 (*Continued*)

Outcomes	- Local and systemic reactions within 7 days from immunisation (see Ohmit 2006) - Symptomatic laboratory-confirmed influenza A or B illness (primary efficacy outcome) . Symptoms were defined as at least 1 respiratory symptom (cough or nasal congestion) plus at least 1 systemic symptom (fever or feverishness, chills or body aches). Laboratory confirmation was assessed by isolation of the influenza virus in cell culture or by comparison of paired post-vaccination (pre-season) and post-season serum with at least a 4-fold increase in haemagglutination-inhibition antibody titre to 1 circulating influenza strain - Illnesses confirmed by identification of the virus in real-time PCR assays was considered as a secondary efficacy outcome
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Powers 1995a

Methods	Randomised controlled trial conducted in the USA during the 1993 to 1994 influenza season. Follow-up was not indicated. Influenza period was not defined. Participants were randomly assigned to receive 1 of the following 5 vaccine preparations in a double-blinded manner: 15 mg of rHA0, 15 mg of rHA0 plus alum, 90 mg of rHA0, licensed and placebo. Spring sera were collected
Participants	34 healthy university students: 26 treated and 8 placebo. Age of participants was: 18 to 45
Interventions	Subvirion licensed trivalent parenteral AB vaccine. Schedule and dose were: single dose; 15 µg each strain. Vaccine composition was: A/Texas/36/91 (H1N1), A/Beijing/32/92 (H3N2) and B/Panama/45/90. Placebo was saline for injection. Vaccine was recommended and matched circulating strain

aa Powers 1995a (*Continued*)

Outcomes	Clinical and laboratory-confirmed cases and adverse effects. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of myalgia or chills. Laboratory evidence of influenza A (H3N2) virus infection was defined as either or both of the isolation of virus from nasopharyngeal secretion and a >= 4-fold increase in serum HAI antibody titre between the 3-week post-vaccination (pre-season) specimen and the corresponding post-season specimen collected in the following spring. Local adverse effects were erythema, pain, tenderness, induration, arm stiffness; systemic adverse effects: were headache, generalised myalgia, diarrhoea, nausea, feverishness, temperature > 37.8 °C
Notes	Efficacy and safety data were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Powers 1995b

Methods	Single-blind randomised controlled trial conducted in the USA during the 1974 to 1975 influenza season. Follow-up lasted from winter to spring. A 'two-month' epidemic period was described by the authors with no reference to a definition and lasted 6 weeks. Study participants were randomly assigned into 3 subgroups to receive either 2 doses of the vaccine (n = 47), 1 dose of vaccine and 1 dose of placebo (n = 48) or 2 doses of placebo (n = 48) at 14 days apart. 6-month sera were collected on all study participants
Participants	34 healthy university students: 26 treated and 8 placebo. Age of participants was 18 to 45
Interventions	Subvirion monovalent parenteral vaccine. Schedule and dose were: single dose; 90 µg rHAO. Vaccine composition was: the recombinant HA vaccine contained full-length uncleaved haemagglutinin (HA0) glycoprotein from the influenza A/Beijing/32/92 (H3N2) virus. Placebo was saline for injection. Vaccine was not recommended but matched circulating strain

aa Powers 1995b (*Continued*)

Outcomes	Clinical and laboratory-confirmed cases. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of myalgia or chills. Laboratory evidence of influenza A (H3N2) virus infection was defined as either or both of the isolation of virus from nasopharyngeal secretion and a >= 4-fold increase in serum HAI antibody titre between the 3-week post-vaccination (pre-season) specimen and the corresponding post-season specimen collected in the following spring
Notes	Safety data were not included; effectiveness data were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Powers 1995c

Methods	Randomised controlled trial conducted in the USA during the 1993 to 1994 influenza season. Follow-up was not indicated. Influenza period was not defined. Participants were randomly assigned to receive 1 of the following 5 vaccine preparations in a double-blinded manner: 15 mg of rHA0, 15 mg of rHA0 plus alum, 90 mg of rHA0, licensed and placebo. Spring sera were collected
Participants	59 healthy university students: 51 treated and 8 placebo. Age of participants was 18 to 45
Interventions	Subvirion monovalent parenteral vaccine. Schedule and dose were: single dose; 15 µg rHAO. Vaccine composition was: the recombinant HA vaccine contained full-length uncleaved haemagglutinin (HA0) glycoprotein from the influenza A/Beijing/32/92 (H3N2) virus. Placebo was saline for injection. Vaccine was not recommended but matched circulating strain
Outcomes	Clinical and laboratory confirmed cases. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of myalgia or chills. Laboratory evidence of influenza A (H3N2) virus infection

aa Powers 1995c (*Continued*)

	was defined as either or both of the isolation of virus from nasopharyngeal secretion and a >= 4-fold increase in serum HAI antibody titre between the 3-week post-vaccination (pre-season) specimen and the corresponding post-season specimen collected in the following spring
Notes	Efficacy data only were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Rytel 1977

Methods	Single-blind randomised controlled trial conducted in the USA during the 1974 to 1975 influenza season. Follow-up lasted from winter to spring. A "two month" epidemic period was described by the authors with no reference to a definition and lasted 6 weeks. Study participants were randomly assigned into 3 subgroups to receive either 2 doses of the vaccine (n = 47), 1 dose of vaccine and 1 dose of placebo (n = 48) or 2 doses of placebo (n = 48) at 14 days apart. 6-month sera were collected on all study participants
Participants	143 young adult female student nurse volunteers: 95 treated and 48 placebo. Age of participants was 18 to 35
Interventions	Live attenuated, bivalent, intranasal influenza A (containing 107,2 EID50) and B (containing 107,8 EID50) vaccines. Schedule and dose were single or double doses. Vaccine composition was: A/England/42/72 (H3N2) and B/Hong Kong/5/72. Placebo was 5% sucrose. Vaccine was not recommended and did not match the circulating strain
Outcomes	Influenza and adverse effects. An influenza case was defined as the presence of an influenza-like illness (3 or more symptoms of acute respiratory disease and temperature greater then 37.2 °C) and virus isolation and/or 4-fold rise in antibody titre in sera obtained at 30 days and 6 months following immunisation. Local adverse effects were upper respiratory symptoms and cough. These were subdivided into moderate and severe. A definition of general adverse effects (again distinguished among moderate and severe)

aa Rytel 1977 (*Continued*)

	was not given
Notes	1 dose and 2 doses were analysed together. Circulating strain was A/PortChalmers/1/73 (H3N2). Efficacy and safety data extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Sumarokow 1971

Methods	Field trial conducted in Russia during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic period was defined as the period of highest influenza morbidity and lasted 11 weeks, from the last 10 days of January to the first 10 days of April. Vaccinations were carried out using coded preparation. Sampling virological and serological survey of ill people was performed
Participants	19,887 population: 9945 treated and 9942 placebo. Age of participants was 13 to 25
Interventions	Live allantoic intranasal vaccine. Schedule and dose were: 3 doses. Vaccine composition was not indicated. Placebo was not described. Vaccine was not recommended and did not match the circulating strain
Outcomes	Clinical cases, deaths, severity of illness. Clinical outcomes were all the acute respiratory infections. Laboratory confirmation was obtained on a sample of ill participants by virus isolation or demonstration of seroconversion. Bronchitis, otitis and pneumonia were considered as complications. Passive surveillance was carried out
Notes	A first study group with children 3 to 12 years old was excluded. A second study group with participants aged 13 to 25 was included in the analysis. The trial compared 2 live vaccines (allantoic intranasal vaccine and tissue vaccine for oral administration) against placebo. Only intranasal vaccine was included in the analysis. Deaths from flu were not recorded. Circulating strain was A2/Hong Kong/68

aa Sumarokow 1971 (*Continued*)

	Effectiveness data only were extracted Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient description
Allocation concealment (selection bias)	Unclear risk	Insufficient description
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient description
Summary assessment	Unclear risk	Insufficient description

aa Tannock 1984

Methods	Controlled clinical trial, double-blind, conducted in Australia during the 1981 influenza season. Follow-up lasted from winter to spring. Influenza period was not defined. Voluntary were alternatively allocated to groups in a double-blind manner. 6-month sera were collected
Participants	88 volunteer staff from Newcastle Hospital and the Commonwealth Steel Corporation: 56 treated and 32 placebo. Age of participants was 16 to 64
Interventions	Trivalent subunit parenteral vaccine. Schedule and dose were: 7 µg each, 1 or 2 doses. Vaccine composition was: A/Brazil/11/78, A/Bangkok/1/79, B/Singapore/222/79. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Influenza and adverse effects. A case of influenza was defined as a respiratory illness, retrospectively reported, associated with a 4-fold antibody titre increase between post-vaccination and post-epidemic sera. Local side effects were redness, swelling, warmth or irritation, pain on contact, pain with pressure, continuous pain, or restriction of arm movement; systemic reactions were fever, chills, sweating, drowsiness or insomnia
Notes	1 dose and 2 doses were analysed together; very high drop-out. Circulating strain was A/Bangkok/1/79. Safety data only were extracted Government-funded
Risk of bias	
Bias	**Authors' judgement**	**Support for judgement**

aa Tannock 1984 (*Continued*)

Random sequence generation (selection bias)	High risk	Inadequate
Allocation concealment (selection bias)	High risk	Inadequate
Blinding (performance bias and detection bias) All outcomes	High risk	Inadequate
Incomplete outcome data (attrition bias) All outcomes	High risk	Inadequate
Summary assessment	High risk	Inadequate

aa Waldman 1969a

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Randomisation methods were not described. One-half of the volunteers gave serial blood and nasal wash samples
Participants	524 school teachers: 465 treated and 118 placebo. Age of participants was not indicated
Interventions	Monovalent inactivated intramuscular vaccine. Schedule and dose were: 1 or 2 doses. Vaccine composition was: A/Hong Kong/68. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical cases and side effects. Clinical case definition was based on the presence of a temperature > 100 °F or a feverish feeling plus any 2 of the following symptoms: sore throat, muscle or joint pain, cough, stuffy or runny nose. Passive surveillance was carried out
Notes	Data concerning adverse effects were only partially reported by graph. Circulating strain was A2/Hong Kong/68. Effectiveness data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear

aa Waldman 1969a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Waldman 1969b

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. Epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Randomisation methods were not described. One-half of the volunteers gave serial blood and nasal wash samples
Participants	590 school teachers: 471 treated and 119 placebo. Age of participants was not indicated
Interventions	Polyvalent inactivated intramuscular vaccine. Schedule and dose were: 1 or 2 doses. Vaccine composition was: A2/Japan/170/62 150 CCA, A2/Taiwan/1/64 150 CCA, B/Massachusetts/3/66 300 CCA. Placebo was saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Clinical cases and side effects. Clinical case definition was based on the presence of a temperature > 100 °F or a feverish feeling plus any 2 of the following symptoms: sore throat, muscle or joint pain, cough, stuffy or runny nose. Passive surveillance was carried out
Notes	Data concerning adverse effects were only partially reported by graph. Circulating strain was A2/Hong Kong/68. Efficacy data only were extracted Government-funded

Risk of bias

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

aa Waldman 1969b (*Continued*)

Summary assessment	Unclear risk	Unclear

aa Waldman 1969c

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Randomisation methods were not described. One-half of the volunteers gave serial blood and nasal wash samples
Participants	597 school teachers: 479 treated and 118 placebo. Age of participants was not indicated
Interventions	Monovalent inactivated aerosol vaccine. Schedule and dose were: 1 or 2 doses. Vaccine composition was: A/Hong Kong/68. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical cases and side effects. Clinical case definition was based on the presence of a temperature > 100 °F or a feverish feeling plus any 2 of the following symptoms: sore throat, muscle or joint pain, cough, stuffy or runny nose. Passive surveillance was carried out
Notes	Data concerning adverse effects were only partially reported by graph. Circulating strain was A2/Hong Kong/68. Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Waldman 1969d

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Randomisation methods were not described. One-half of the volunteers gave serial blood and nasal wash samples
Participants	590 school teachers: 471 treated and 119 placebo. Age of participants was not indicated
Interventions	Polyvalent inactivated aerosol vaccine. Schedule and dose were: 1 or 2 doses. Vaccine composition was: A2/Japan/170/62 150 CCA, A2/Taiwan/1/64 150 CCA, B/Massachusetts/3/66 300 CCA. Placebo was saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Clinical cases and side effects. Clinical case definition was based on the presence of a temperature > 100 °F or a feverish feeling plus any 2 of the following symptoms: sore throat, muscle or joint pain, cough, stuffy or runny nose. Passive surveillance was carried out
Notes	Data concerning adverse effects were only partially reported by graph. Circulating strain was A2/Hong Kong/68. Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Waldman 1972a

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Identical-looking coded vials were used to dispense material. Sampling virological and serological survey of ill people was performed. 2 doses were administered but as the outbreak occurred mostly between them, only the effectiveness of the first dose was assessed
Participants	244 volunteer students and staff members: 195 treated and 49 placebo. Age of participants was not indicated
Interventions	Monovalent A aerosol vaccine. Schedule and dose were: 200 CCA. Vaccine composition was: A2/Aichi/1/68. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 °F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first 1 or 2 weeks after vaccination was not excluded, but the authors stated that this fact did not affect the results. Circulating strain was A2/Aichi/2/68. Efficacy and safety data were extracted Government-funded

Risk of bias

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

aa Waldman 1972b

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Identical-looking coded vials were used to dispense material. Sampling virological and serological survey of ill people was performed. 2 doses were administered but as the outbreak occurred mostly between them, only the effectiveness of the first dose was assessed
Participants	239 volunteer students and staff members: 190 treated and 49 placebo. Age of participants was not indicated
Interventions	Monovalent A subcutaneous vaccine. Schedule and dose were: 200 CCA. Vaccine composition was: A2/Aichi/1/69. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 °F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first 1 or 2 weeks after vaccination was not excluded, but the authors stated that this fact did not affect the results. Circulating strain was A2/Aichi/2/68. Efficacy and safety data were extracted. Government-funded

Risk of bias

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

aa Waldman 1972c

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Identical-looking coded vials were used to dispense material. Sampling virological and serological survey of ill people was performed. 2 doses were administered but as the outbreak occurred mostly between them, only the effectiveness of the first dose was assessed
Participants	243 volunteer students and staff members: 194 treated and 49 placebo. Age of participants was not indicated
Interventions	Bivalent AB aerosol vaccine. Vaccine composition was: A2/Japan/170/62 150 CCA, A2/Taiwan/1/64 150 CCA and B/Massachusetts/3/66 200 CCA. Placebo was saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 °F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first 1 or 2 weeks after vaccination was not excluded but the authors stated that this fact did not affect the results. Circulating strain was A2/Aichi/2/68. Efficacy and safety data were extracted. Government-funded

Risk of bias

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

aa Waldman 1972d

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1968 to 1969 influenza season. Follow-up lasted the whole epidemic period. The epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Identical-looking coded vials were used to dispense material. Sampling virological and serological survey of ill people was performed. 2 doses were administered but as the outbreak occurred mostly between them, only the effectiveness of the first dose was assessed
Participants	236 volunteer students and staff members: 187 treated and 49 placebo. Age of participants was not indicated
Interventions	Bivalent AB subcutaneous vaccine. Vaccine composition was: A2/Japan/170/62 150 CCA, A2/Taiwan/1/64 150 CCA and B/Massachusetts/3/66 200 CCA. Placebo was saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 °F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first 1 or 2 weeks after vaccination was not excluded, but the authors stated that this fact did not affect the results. Circulating strain was A2/Aichi/2/68. Efficacy and safety data were extracted. Government-funded

Risk of bias

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

aa Weingarten 1988

Methods	Randomised controlled trial, double-blind, conducted in the USA during the 1985 to 1986 influenza season. Follow-up was not indicated. Epidemic influenza was defined according to population surveillance data (without better explanation), begun in December 1985 and concluded in February 1986. Participants were assigned using a random number generator to receive either the influenza vaccine or placebo. Virological surveillance was not performed
Participants	179 healthy volunteer hospital employees: 91 treated and 88 placebo. Age of participants was 21 to 65
Interventions	Split trivalent intramuscular vaccine. Schedule and dose were: single dose; 15 µg each strain. Vaccine composition was: A/Chile/1/83 (H1N1), A/Philippines/2/82 (H3N2) and B/USSR/100/83. Placebo was saline for injection. Vaccine was recommended but did not match the circulating strain
Outcomes	Clinical cases symptoms defined, WDL regardless of causes and adverse effects. Influenza illness was defined by the CDC case definition: a documented temperature greater than 100 °F and at least the symptoms of cough or sore throat
Notes	Data regarding WDL and adverse effects were not complete and they were not considered. Most of the influenza infections were caused by type B Efficacy data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Zhilova 1986a

Methods	Semi-randomised, double-blind, placebo-controlled clinical trial that took place in Leningrad, USSR during the 1981 to 1982 influenza season. The study tested the reactogenicity, safety and effectiveness of an inactivated and a live attenuated vaccine, both administered singly or in combination. Allocation was made on the basis of school classes and it is unclear whether this is a cluster-randomised or clinical controlled trial. We have opted for the latter as the text mentions random selection to maintain "equivalence". "Double blind" is mentioned in the text. In January to May 1982 there was a rise in the level of ILI due to influenza and other agents
Participants	3961 participants were enrolled. Participants were healthy "students" aged 18 to 23. Numbers in each of the 4 arms are uneven throughout the trial but no reason is given for this
Interventions	Inactivated vaccine trivalent (Ministry of Health USSR) by subcutaneous injection 0.2 ml once (arm 1), or intranasal live "recombinant" "mono"vaccine 0.5 ml spray 2 to 3 times (Ministry of Health USSR) (arm 2), or combined (arm 3) or subcutaneous and intranasal spray NaCl saline placebo (arm 4). The strains contained were H1N1, H3N2 and B. Vaccine matching was not good
Outcomes	Serological Antibody titres - sub-study on 1221 participants Effectiveness Influenza-like illness (not defined and from the text it is impossible to understand how many influenza-like illness cases were matched to positive laboratory findings) Safety data are not reported in sufficient detail to allow extraction
Notes	The authors conclude that simultaneous inoculation of the vaccines appeared to produce better humoral antibody responses, especially in the last season. However, the correlation between clinical protection and antibody rises is reported as dubious. The authors make the reasonable point that perhaps live attenuated vaccines work better because they stimulate production of secretory antibodies. This is a poorly reported study. No mention is made of how the placebo could have been correctly used in the schedule (i.e. they should have had 6 arms instead of 4 with subcutaneous placebo, spray placebo separately as well combined - maybe this is a problem of translation). Efficacy data only were extracted Government-funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear

aa Zhilova 1986a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

aa Zhilova 1986b

Methods	Semi-randomised, double-blind, placebo-controlled clinical trial that took place in Leningrad, USSR during the 1982 to 1983 influenza season. The study tested the reactogenicity, safety and effectiveness of an inactivated and a live attenuated vaccines both administered singly or in combination. Allocation was made on the basis of school classes and it is unclear whether this is a cluster-randomised or clinical controlled trial. We have opted for the latter as the text mentions random selection to maintain "equivalence". "Double blind" is mentioned in the text. In the season there was an outbreak of A (H3N2) lasting 4 to 5 weeks. However, influenza accounted for only up to 30% of isolates from ill people
Participants	3944 participants were enrolled. Participants were healthy "students" aged 18 to 23. Numbers in each of the 4 arms are uneven throughout the trial but no reason is given for this
Interventions	Inactivated vaccine trivalent (Ministry of Health USSR) by subcutaneous injection 0.2 ml once (arm 1), or intranasal live "recombinant" "mono" vaccine 0.5 ml spray 2 to 3 times (Ministry of Health USSR) (arm 2), or combined (arm 3) or subcutaneous and intranasal spray NaCl saline placebo (arm 4). The strains contained were H1N1, H3N2 and B Vaccine matching was good
Outcomes	Serological Antibody titres - sub-study on 1221 participants Effectiveness Influenza-like illness (not defined and from the text it is impossible to understand how many influenza-like illness cases were matched to positive laboratory findings) Safety data are not reported in sufficient detail to allow extraction Passive surveillance was carried out
Notes	The authors conclude that simultaneous inoculation of the vaccines appeared to produce better humoral antibody responses, especially in the last season. However, the correlation between clinical protection and antibody rises is reported as dubious. The authors make the reasonable point that perhaps live attenuated vaccines work better because they stimulate production of secretory antibodies. This is a poorly reported study. No mention is made of how the placebo could have been correctly used in the schedule (i.e. they should have had 6 arms instead of 4 with subcutaneous placebo, spray placebo separately as well combined - maybe this is a problem of translation). Efficacy data only were extracted. Government-funded

Risk of bias

aa Zhilova 1986b (*Continued*)

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

ab Atmar 1990

Methods	Double-blind, placebo-controlled, randomised trial
Participants	74 healthy volunteers aged 18 to 40 years (data on 17 asthmatics were not extracted)
Interventions	Cold - recombinant vaccine A (H1N1); n = 16 versus cold - recombinant vaccine A (H3N2); n = 13 versus cold - recombinant vaccine B; n = 17 versus placebo; n = 26 Intranasal
Outcomes	Pulmonary function tests (performed on day 0, 3 to 4, 7 after vaccination): - Forced expiratory volume in 1 second (FEV1) - Forced vital capacity (FVC) - FEV1/FVC - Forced expiratory flow rate 25% to 75% (FEF 25 to 75)
Notes	The authors report several non-significant drops in FEV and FVC up to 7 days post-inoculation and a higher incidence of ILI (17/46 versus 4/26) in the vaccinated arms. Safety data only were extracted Government-funded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear

ab Atmar 1990 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Betts 1977a

Methods	Randomised controlled trial carried out from April 1976 at Rochester University. Vaccine and placebo were randomly administered in a double-blind manner, but no description of allocation procedure is given. 36 days after immunisation all participants were challenged with wild type virus (A/Victoria/3/75, H3N2) and antibody response was determined from serum and nasal secretions (before vaccination, 36 hours later and 21 days after challenge, not for analysis)
Participants	47 healthy male and female university students with absent or low HAI titre (i.e. little or no immunity) to both A/Scotland/74 and A/Victoria/3/75
Interventions	Live attenuated A/Scotland/74 (H3N2) versus placebo, one 0.5 ml dose intranasally. On day 37 after immunisation participants were challenged with A/Victoria/3/75
Outcomes	A physician examined the participants 1 day and 4 days after they received vaccine or placebo. Temperature was observed only 1 day after. Observed symptoms were: mild sore throat and rhinorrhoea: vaccine 4/23; placebo 3/24; fever (temperature > 37.50 °C) : none had it
Notes	Safety data only were extracted Industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear

ab Betts 1977a (*Continued*)

Summary assessment	Unclear risk	Unclear

ab Boyce 2000

Methods	Open-label/single-blind randomised controlled trial to assess the safety and immunogenicity of adjuvanted and unadjuvanted subunit influenza vaccine, prepared with the strains recommended for and isolated in the 1997 to 1998 season
Participants	74 healthy adults aged between 10 and 40 years, who did not receive influenza immunisation during the 6 months preceding the trial
Interventions	1) M-59 adjuvanted subunit trivalent flu vaccine (prepared with A/Bayern/795 H1N1, A/Wuhan/359/95 H3N2, B/Beijing/184/93-like strains, each 15 µg/ 0.5 ml dose) 2) Unadjuvanted vaccine (prepared with the same strains at the same concentrations as the adjuvanted preparation) 3) Placebo (consisting of 0.5 ml sterile saline) All preparation were intranasal administered in 2 doses 28 days apart. 24 individuals received their first dose of adjuvanted (n = 12) or unadjuvanted (n = 12) subunit vaccine in an open-label manner. After it was stated that they tolerated the first dose, the randomised phase of the trial (n = 50) was begun. In this phase 18 participants received 2 doses of unadjuvanted vaccine, 19 adjuvanted and 13 placebo
Outcomes	After each immunisation, participants were observed for 30 minutes, were examined after 2 days and then completed a diary card reporting symptoms that occurred within 7 days after. Local reactions: nasal symptoms, unpleasant taste, bloody nasal discharge, sneezing. Systemic reactions: chills, pulmonary, nausea, malaise, myalgia or arthralgia, urticarial rash, headache, oral temperature >= 38 °C, stay at home, use of analgesic or antipyretic. Data were not given separately for the randomised and open-label phase of the study
Notes	It is not possible to consider the safety data separately for the two study phases. Safety data only were extracted Industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear

ab Boyce 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Caplan 1977

Methods	Randomised controlled trial to assess the reactogenicity and safety of monovalent whole virus and split virus vaccines prepared with strain A/Victoria/3/75 from different US manufacturers
Participants	208 healthy adult volunteers aged between 18 and 64 years, recruited from the University of Maryland, USA
Interventions	Monovalent whole-virus vaccine (Merck Sharp & Dohme, Merrell-National Laboratories) or monovalent split virus vaccine (Parke, Davis and Company; Wyeth Laboratories) administered in different antigen concentrations (200, 400 or 800 CCA) versus placebo. All from A/Victoria75. 1 dose intramuscularly
Outcomes	Temperature >= 100 °F (37.8 °C); feverishness; pain or burning; tenderness; malaise or myalgia; nausea or vomiting; headache; other. 21-day follow-up. Safety outcomes are also given as cumulative % for each category: local, systemic, bothersome; febrile; or scores for systemic reactions
Notes	Safety data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab El'shina 1996

Methods	Randomised controlled trial
Participants	432 healthy participants aged between 18 and 22 years who had not received any influenza immunisation during the previous 2 to 3 years
Interventions	Polymer-subunit influenza vaccine "Grippol" prepared with the strains A/Victoria/36/88, Wib - 26, B/Panama 45/90. 2 types containing 5 or 2.5 µg haemagglutinin of each strain respectively were compared with whole-virion inactivated trivalent vaccine (reference preparation, containing 35 µg of haemagglutinin) and placebo (consisting of sterile physiological solution). One 0.5 ml dose was administered subcutaneously
Outcomes	After immunisation participants were placed under medical observation. Fever (48 hours follow-up): weak (37.1 to 37.5 °C), moderate (37.6 to 38.5 °C), severe (> 38.6 °C). Systemic reactions (3 to 4 days follow-up): feeling unwell, sore throat, hyperaemia of nasopharynx, head cold, cough, headache, blocked nose, dizziness, shivering, drowsiness, nausea, hoarseness. Local reaction: all (moderate weak); pain at site of injection
Notes	Safety data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Evans 1976

Methods	Randomised controlled trial
Participants	162 healthy participants aged 18 to 61 years
Interventions	Bivalent live attenuated vaccine WRL 105 (recombinant of A/Okuda/57 and A/Finland/4/74) containing 107.0 EID50 virus/ 0.5 ml dose versus placebo. Both preparations were administered intranasally 3 to 4 weeks apart

ab Evans 1976 (*Continued*)

Outcomes	Reactions to immunisation were observed for 7 days after each dose. Local symptoms (referable to the upper respiratory tract, mainly nasal obstruction, nasal discharge or sore throat) reported as mild moderate or severe. General symptoms (mainly headache fever or myalgia). These 2 are further reported in different intensity classes (mild, moderate, severe, lasting for at least 4 days) reported as mild, moderate or severe. Use of analgesics
Notes	Safety data only were extracted Funding source - mixed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Forsyth 1967

Methods	From this report, only the first phase of the first trial is of interest for the purposes of this review, in which administration of whole virus, oil adjuvanted influenza vaccine Invirin (GSK) was compared with placebo in a semi-randomised allocation. The trial was performed in November to December 1962
Participants	Medical students (n = 380) at the Queen's University of Belfast, UK
Interventions	Trivalent aqueous vaccine (Invirin, Glaxo) one 0.25 ml dose IM containing strains A/Singapore/1/57, A/England/1/61, B/England/939/59. Placebo (phosphate-buffered saline) was administered as control. Participants born on odd days were given placebo (n = 186) ; those born on even days received the vaccine (n = 194)
Outcomes	Local reactions: pain, erythema, tenderness, bruises. Stratified by means of scores ranging from 0 to 3 depending on their severity. Systemic reactions: coryza, migraine, paroxysmal tachycardia. All assessed at day 0, 1, 3, 7, 21 after inoculation. Data refer to a 3-day follow-up

ab Forsyth 1967 (*Continued*)

Notes	Safety data only were extracted Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	High risk	Unclear

ab Goodeve 1983

Methods	Randomised controlled trial, double-blind	
Participants	119 healthy young adults from the Medical and Science Faculties of Sheffield University, UK, aged 18 to 19 years without egg allergy	
Interventions	Purified subunit monovalent B/Hong Kong/73 flu vaccine prepared in 4 antigen concentration 40, 20, 10, 5 µg of HA per each 0.5 ml dose versus saline placebo (0.5 ml dose) subcutaneously administered. Participants were divided in 5 groups of equal dimensions (no further description), each group received one of the tested coded preparations. Artificial challenge 1 month later with live attenuated RB77 virus	
Outcomes	Local and systemic reactions were assessed by means of questionnaires completed by participants 24 hours after immunisation. Local reactions (including redness, swelling, itching), local pain (including pain on pressure, pain on contact, continuous pain)	
Notes	Safety data only were extracted Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear

ab Goodeve 1983 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Hrabar 1977

Methods	Randomised controlled trial, double-blind, carried out during the season 1976 to 1977
Participants	167 students at the technical school in Zagreb, former Republic of Yugoslavia, without sensitivity to egg proteins, pregnancy, acute or chronic diseases
Interventions	Cold-adapted recombinant A/Victoria/3/75 vaccine administered in 3 different antigen concentrations (107.5, 106.5, 105.5 EID50/0.5 ml) versus placebo. 1 0.5 ml dose intranasal
Outcomes	Participants were medically examined on each of the successive 5 days after immunisation (lasting for at least 1 day). Throat infection, granular palate, oedematous uvula, fever (no cases) as cases and subject-days. For the following outcomes, authors give the total number of observed cases, without indication of the corresponding arm: malaise, swollen tonsils, fever (1), rhinorrhoea (1), conjunctivitis (7), laryngitis or hoarseness (3), cough (1), swollen tonsils (1), malaise (1). Surveillance was active
Notes	Safety data only were extracted Government-funded

Risk of bias

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

ab Hrabar 1977 (*Continued*)

Summary assessment	Unclear risk	Unclear

ab Keitel 1993a

Methods	This paper reports the results of 2 randomised controlled trials carried out in the USA
Participants	Healthy volunteers recruited at Texas A&M University and Texas Medical Center, aged between 18 and 40 years
Interventions	2 0.5 ml doses of cold-adapted recombinant influenza vaccines, 1 month apart, containing 107.1 TCID50 of each strain/dose. 2 studies were carried out in which 4 groups were formed: 1) placebo 1st and 2nd dose. 2) 1st: A/Kawasaki/9/86 (H1N1, CR 125) + A/Bethesda/1/85 (H3N2, CR90) + B/Ann Arbor/1/86 (B, CRB117)
Outcomes	Mild upper respiratory symptoms. Fever >= 37.8 °C within 1 week after each inoculation
Notes	Safety data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Keitel 1993b

Methods	This paper reports the results of 2 randomised controlled trials carried out in the USA
Participants	Healthy volunteers recruited at Texas A&M University and Texas Medical Center, aged between 18 and 40 years
Interventions	A/Kawasaki/9/86 (H1N1, CR 125, but different lot from 1st) + A/Los Angeles/2/87 (H3N2, CR149) + B/Ann Arbor/1/86 (B, CRB117 but different lot from 1st) 3) 1st: A/Kawasaki/9/86 (H1N1, CR125) + A/Bethesda/1/85 (H3N2, CR90) 2nd: B/Ann

ab Keitel 1993b (*Continued*)

	Arbor/1/86 (B, CRB117) 4) 1st: B/Ann Arbor/1/86 (B, CRB117) 2nd: A/Kawasaki/9/86 (H1N1, CR125) + A/Los Angeles/2/87 (H3N2, CR149)
Outcomes	Mild upper respiratory symptoms. Fever >= 37.8 °C Within 1 week after each inoculation
Notes	See Keitel 1993a. Safety data only were extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Langley 2005

Methods	Randomised controlled trial
Participants	Healthy adults aged 18 to 50 years
Interventions	Inactivated A/New Caledonia/20/99 (H1N1) + A/Panama/2007/99 (H3N2) + B/Guangdong/120/2000 non-covalent associated with outer membrane protein of *N. meningitidis*. Single nasal dose containing 15, 30, 45 µg versus placebo (phosphate buffered saline) intranasal administered
Outcomes	Local: within 7 days, graphic - rhinorrhoea, congestion, itch/burn, nosebleed, red/puffy eyes, sneezing, sore throat. Systemic: within 7 days - cough, shortness of breath, headache, muscle/joint aches, poor appetite, fatigue within 48 hours, nasal mucosa inflammation, nasal discharge, pharyngeal inflammation, sinusitis, enlarged cervical/post-auricular nodes
Notes	Safety data only were extracted Government and industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

ab Langley 2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	High risk	Inadequate
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	High risk	High risk

ab Lauteria 1974

Methods	Controlled trial. Randomisation procedure was neither described nor mentioned. Participants were paired according to age and sex, in each pair 1 individual received vaccine, the other placebo. Double-blind
Participants	37 volunteers aged 18 to 24 years, with titre of serum neutralising antibodies to A/Hong Kong/8/68 ? 1:16
Interventions	Live attenuated A/England/ 8/68 grown in presence of heated equine serum. 2 0.5 ml doses containing 104 TCID50 of this strain or placebo (0.85% NaCl) were administered intranasally 2 to 3 weeks apart
Outcomes	Individual observed for 4 days, beginning 24 hours after immunisation. Fever, myalgia, rhinitis, cough, pharyngitis
Notes	Safety data only were extracted Government and industry-funded

Risk of bias

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

ab Lauteria 1974 (*Continued*)

Summary assessment	Unclear risk	Unclear

ab Miller 1977

Methods	Randomised controlled trial
Participants	43 seronegative healthy adults aged between 22 and 50 years
Interventions	Live attenuated serum inhibitor resistant flu B vaccine R75 (a recombinant of B/Hong Kong/5/72 with B/Russia/69) containing 107.2 EID50 of R75/0.5 ml dose versus placebo (sucrose 5%). Intranasal, 2 doses, 2 weeks apart
Outcomes	Participants were interviewed during the 5 days following each immunisation. Local reaction (defined as immediate complains and comprising bad taste or burning, lasting for a few moments). Systemic reaction (consisting essentially of headache and rhinorrhoea)
Notes	Safety data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Pyrhönen 1981

Methods	Randomised controlled trial carried out in the 1976 to 1977 season in Finland
Participants	307 healthy adults
Interventions	1 of the following 4 preparations were administered to 1 of the 4 groups of participants: live attenuated A/Victoria/3/75; 2 2 ml doses (2 104.5 bivalent subunit vaccine containing 1200 IU of A/Victoria/3/75 (H3N2) and 800 IU of B/Hong Kong/8/73 per dose (0.5 ml) B versus placebo (phosphate buffered saline). Participant received 1 dose

ab Pyrhönen 1981 (*Continued*)

	administered subcutaneously. Vaccinations were performed between 15 to 23 December 1976; epidemics occurred February to June 1977
Outcomes	Harms assessed by questionnaires filled out by each participant within 3 days after immunisation. Fever: vaccine 11/151; placebo 9/154 - muscle ache; vaccine 26/151; placebo 12/154 - redness: vaccine 53/151; placebo 3/154 - tenderness at vaccination site: vaccine 89/151; placebo 12/154 - tenderness of axillary glands: vaccine 6/151; placebo 2/154
Notes	Safety data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Reeve 1982

Methods	Randomised controlled trial carried out in Wien
Participants	20 university students aged 20 to 24 years
Interventions	First phase: cold-recombinant, live flu vaccine II RB-77 (B/Ann Arbor/1/66 and B/Tecumse/10/77) containing 107.2 EID50 per 0.5 ml dose versus placebo. 1 dose intranasally. During this phase, participants lived under sequestered condition and close contact between vaccine and placebo recipients was possible. 2nd phase: 3 weeks after the 1st dose all participants were immunised with 1 dose of the same vaccine
Outcomes	During the 5 days following immunisation, participants were medically observed and temperature recorded morning and evening. Occurring symptoms were attributed scores (0 to 3) depending on their severity (no, light, moderate, severe). Fever (oral temperature > 38 °C): 0/10; 0/10 sneezing: 1/10; 0/10 stuffy nose: 7/10; 1/10 running nose: 3/10; 0/10 afebrile subjective symptoms: 8/10; 2/10

ab Reeve 1982 (*Continued*)

Notes	Safety data only were extracted Industry-funded

Risk of bias

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

ab Rocchi 1979a

Methods	Cluster-randomised controlled trial carried out during the 1976 to 1977 season
Participants	496 healthy military recruits (aged 18 to 20 years) belonging to 4 different companies from "Scuola Allievi Sottoufficiali" in Viterbo, Italy
Interventions	1 of the following 4 preparations were administered to 1 of the 4 groups of participants: live attenuated A/Victoria/3/75; 2 2 ml doses (2 104.5 EID50/dose) oral. Live attenuated recombinant A/Puerto Rico/8/34, A/Victoria/3/75; 2 0.5 ml doses intranasally (107 EID50/dose). Inactivated A/Victoria/3/75 (600 IU), B/Hong Kong/5/72 (300 IU) and AlPO4, intramuscular placebo (vaccine diluent) administered intranasally. The 2 doses were administered 2 to 3 weeks apart
Outcomes	Within 15 days after administration of the 1st dose. Malaise, myalgia, headache, sore throat, cough, fever equal to or more than 38.5 °C, fever equal to or more than 37.5 °C, 3 or more symptoms, any symptoms. Surveillance was passive
Notes	Units of randomisation appear to be companies. No description of allocation manner is mentioned. Blind (only for the cases of intranasal administration). Influenza outbreak occurred when the immunisation began (intraepidermic study) Safety data only were extracted Government-funded

Risk of bias

ab Rocchi 1979a (*Continued*)

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

ab Rocchi 1979b

Methods	As above
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Saxen 1999

Methods	Randomised controlled trial, double-blind, conducted in Finland during the 1996 to 1997 influenza season. Randomisation methods were not described
Participants	216 healthcare workers: 211 treated and 427 placebo
Interventions	Trivalent inactivated intramuscular vaccine. Schedule and dose were: single dose; 15 µg each strain. Vaccine composition was: A/Wahan/359/95, A/Singapore/6/86 and B/Beijing/184/93. Placebo was saline for injection. Vaccine was recommended
Outcomes	Working days lost because of respiratory infections, episodes of respiratory infections, days ill and antimicrobial prescriptions. Respiratory infection was a common cold; febrile influenza-like illnesses were not detected. Local adverse effects were defined as local pain. Systemic adverse effects were defined as fever and fatigue
Notes	Efficacy data were not extracted because episodes of respiratory infections were unclearly defined. Safety data only were extracted Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

ab Scheifele 2003

Methods	Randomised, double-blind, placebo-controlled, cross-over trial assessing the association between exposure to the vaccine and onset of oculo-respiratory syndrome (ORS) in healthy adults with no previous history of ORS. The trial took place in 5 centres in Canada in September 2001 and was one of the conditions of registration of the vaccine, given the high incidence of ORS in the previous season. Centralised randomisation and allocation of centrally prepared, coded, opaque syringes took place. Cross-over to either vaccine or placebo took place 5 to 7 days after the initial injection
Participants	651 adults with a mean age of 45 took part. 17 participants are unaccounted for

ab Scheifele 2003 (*Continued*)

Interventions	Fluviral (Shire) split trivalent containing A/New Caledonia/20/99 (H1N1); A/Panama/2007/99 (H3N2); B/Victoria/504/2000 with additional splitting with Triton X-100 splitting agent or saline placebo 0.5 ml. Additional splitting was necessary to test the hypothesis that large clumps of virions were responsible for the ORS seen the previous season
Outcomes	ORS (bilateral conjunctivitis, facial swelling - lip, lid or mouth, difficulty in breathing and chest discomfort, including cough, wheeze, dysphagia or sore throat). Local signs/symptoms (redness, swelling, pain). Follow-up was by phone interview at 24 hours and 6 days after vaccination
Notes	The authors conclude that (mild) ORS is significantly associated with split TIV immunisation (attributable risk 2.9%, 0.6 to 5.2). Other adverse effects associated with TIV are hoarseness (1.3%, 0.3 to 1.3) and coughing 1.2%, 0.2 to 1.6). The study is good quality and the authors conclusions are robust. It is extraordinary that no one has looked for these symptoms before but it may be that the relatively young age of participants and the hypothesis contributed to this. Safety-only study Government-funded

Risk of bias

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

ab Spencer 1977

Methods	Controlled trial, single-blind
Participants	21 pairs of students and employers at the University of California, aged between 24 and 50 years who lived together or worked in close proximity
Interventions	Recombinant, live attenuated R 75 vaccine (B/Hong Kong/5/72 and B/Russia/69) containing 107.5 EID/dose versus placebo (allantoic fluid). Lyophilised vaccine was supplied by Smith, Kline and French Laboratories and diluted with 2.5 ml of a 5% sucrose solution just before administration. Both preparations were administered intranasally

ab Spencer 1977 (*Continued*)

	(5 drops/nostril). In each pair 1 individual received vaccine and the other 1 placebo. A second dose was administered 14 days apart
Outcomes	Any clinical symptoms within 7 days after each immunisation (rhinitis, cough, pharyngitis, headache, malaise and myalgia were the prominent observed symptoms, but given as aggregates)
Notes	Reported safety data do not allow quantitative analysis Industry-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

bb DeStefano 2003

Methods	Case-control study
Participants	Data from Vaccine Safety Datalink (large database of cases of disease following vaccination) in the USA
Interventions	Immunisation with influenza and other vaccines assessed by means of medical records
Outcomes	Cases: physician diagnosis of multiple sclerosis or optic neuritis in medical record Controls: up to 3 controls per case were selected from automated HMO member files, at least 1 year of HMO enrolment, matched on age (within 1 year) and gender
Notes	Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

bb DeStefano 2003 (*Continued*)

CC - case selection All outcomes	Low risk	From HMO registry
CC - control selection All outcomes	Low risk	From HMO registry
CC - comparability All outcomes	Unclear risk	Poor matching
CC - exposure All outcomes	Unclear risk	From registry and from telephone interview
Summary assessment	Unclear risk	Unclear

bb Dieleman 2011a

Methods	Case-control study
Participants	Cases = 145 Guillain-Barre syndrome (GBS) cases (defined accordingly to the Brighton Collaboration definition) diagnosed in France between 2007 and 2010 Controls (1080) = the dates for control recruitment were matched (by calendar month) to the index date of the associated case. Additional matching criteria included gender, age (65 years for cases aged 18 years or more and 61 year for cases younger than 18 years) and place of residence (southern or northern France)
Interventions	Exposure to influenza vaccine. Data about pandemic vaccine has been analysed separately Exposure to virus and occurrence of ILI has been also tested as risk factor
Outcomes	Association between Guillain-Barré syndrome and influenza vaccine exposure
Notes	The study has been financial supported by LA-SER, GSK Biologicals, and Sanofi-Pasteur

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Unclear risk	From different countries
CC - control selection All outcomes	Unclear risk	Not same population, not sufficient description
CC - comparability All outcomes	Unclear risk	Matching
CC - exposure All outcomes	Unclear risk	Interview

bb Dieleman 2011a (*Continued*)

Summary assessment	High risk	High risk of bias

bb Dieleman 2011b

Methods	Case-control study
Participants	Cases = 145 Guillain-Barré syndrome (GBS) cases (defined accordingly to the Brighton Collaboration definition) diagnosed in France between 2007 and 2010 Controls (1080) = the dates for control recruitment were matched (by calendar month) to the index date of the associated case. Additional matching criteria included gender, age (65 years for cases aged 18 years or more and 61 year for cases younger than 18 years) and place of residence (southern or northern France)
Interventions	Exposure to influenza vaccine. Data about pandemic vaccine has been analysed separately Exposure to virus and occurrence of ILI has been also tested as risk factor
Outcomes	Association between Guillain-Barré syndrome and influenza vaccine exposure
Notes	The study has been financial supported by LA-SER, GSK Biologicals and Sanofi-Pasteur

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Low
CC - control selection All outcomes	Unclear risk	Not same population
CC - comparability All outcomes	Unclear risk	Matching
CC - exposure All outcomes	Unclear risk	Interview
Summary assessment	Unclear risk	Unclear

bb Dieleman 2011c

Methods	Case-control study
Participants	Cases = 145 Guillain-Barré syndrome (GBS) cases (defined accordingly to the Brighton Collaboration definition) diagnosed in France between 2007 and 2010 Controls (1080) = the dates for control recruitment were matched (by calendar month) to the index date of the associated case. Additional matching criteria included gender, age (65 years for cases aged 18 years or more and 61 year for cases younger than 18 years) and place

bb Dieleman 2011c (*Continued*)

	of residence (southern or northern France)	
Interventions	Exposure to influenza vaccine. Data about pandemic vaccine has been analysed separately Exposure to virus and occurrence of ILI has been also tested as risk factor	
Outcomes	Association between Guillain-Barré syndrome and influenza vaccine exposure	
Notes	The study has been financial supported by LA-SER, GSK Biologicals and Sanofi-Pasteur	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Low
CC - control selection All outcomes	Unclear risk	Not same population
CC - comparability All outcomes	Unclear risk	Matching
CC - exposure All outcomes	Unclear risk	Interview
Summary assessment	Unclear risk	Unclear

bb Dieleman 2011d

Methods	Case-control study	
Participants	Cases = 145 Guillain-Barré syndrome (GBS) cases (defined accordingly to the Brighton Collaboration definition) diagnosed in France between 2007 and 2010 Controls (1080) = the dates for control recruitment were matched (by calendar month) to the index date of the associated case. Additional matching criteria included gender, age (65 years for cases aged 18 years or more and 61 year for cases younger than 18 years) and place of residence (southern or northern France)	
Interventions	Exposure to influenza vaccine. Data about pandemic vaccine has been analysed separately Exposure to virus and occurrence of ILI has been also tested as risk factor	
Outcomes	Association between Guillain-Barré syndrome and influenza vaccine exposure	
Notes	The study has been financial supported by LA-SER, GSK Biologicals and Sanofi-Pasteur	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

bb Dieleman 2011d (*Continued*)

CC - case selection All outcomes	Low risk	Low
CC - control selection All outcomes	Unclear risk	Not same population
CC - comparability All outcomes	Unclear risk	Matching
CC - exposure All outcomes	Unclear risk	Interview
Summary assessment	Unclear risk	Unclear

bb Dieleman 2011e

Methods	Case-control study
Participants	Cases = 145 Guillain-Barré syndrome (GBS) cases (defined accordingly to the Brighton Collaboration definition) diagnosed in France between 2007 and 2010 Controls (1080) = the dates for control recruitment were matched (by calendar month) to the index date of the associated case. Additional matching criteria included gender, age (65 years for cases aged 18 years or more and 61 year for cases younger than 18 years) and place of residence (southern or northern France)
Interventions	Exposure to influenza vaccine. Data about pandemic vaccine has been analysed separately Exposure to virus and occurrence of ILI has been also tested as risk factor
Outcomes	Association between Guillain-Barré syndrome and influenza vaccine exposure
Notes	The study has been financial supported by LA-SER, GSK Biologicals and Sanofi-Pasteur

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Low
CC - control selection All outcomes	Unclear risk	Not same population
CC - comparability All outcomes	Unclear risk	Matching
CC - exposure All outcomes	Unclear risk	Interview

bb Dieleman 2011e (*Continued*)

Summary assessment	Unclear risk	Unclear

bb Galeotti 2013

Methods	Case-control study testing the association between influenza vaccination and GBS
Participants	Cases (n = 140): adults with Guillain-Barré syndrome (GBS) defined accordingly to the Brighton Collaboration definition (levels 1 to 3) recruited at 121 neurological centres in 7 Italian regions and having symptoms onset between 1 October 2010 and 15 May 2011 Controls (n = 308): were selected from among patients admitted to the Emergency Department of the same hospital as the cases for acute conditions unrelated to chronic diseases (e. g. trauma). Each control was individually matched to a case for admission date (i.e. the same date as the case or up to 30 days afterwards), sex, age (± 5 years) and region of residence
Interventions	Exposure to influenza vaccination (date and brand of vaccine) was verified by contacting patients' general practitioners (GPs) by telephone. A neurologist (FG) closely verified and queried data quality
Outcomes	Guillain-Barré syndrome
Notes	The authors also performed data analysis with a controlled case-series design, considering the 6 weeks following exposure as the risk time Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Consecutive series of cases
CC - control selection All outcomes	Low risk	Hospital control
CC - comparability All outcomes	Unclear risk	Matched analysis only for sex, age, region, admission date
CC - exposure All outcomes	Unclear risk	Unclear if interviewers were blinded to case-control status
Summary assessment	Unclear risk	Unclear risk of bias

bb Garbe 2012

Methods	Case-control surveillance study
Participants	Cases (n = 169): patients 18 years of age or older with a diagnosis of certain or probable immune thrombocytopaenia (ITP). Out of the 169 cases included, 130 were outpatients and 39 inpatients Controls (n = 770): 731 outpatients and 39 inpatients selected from the same hospitals as the cases. The index date for outpatient controls was defined as the date of hospitalisation or the date of initiation of the control disease episode if this preceded hospitalisation. The index date for inpatient controls was the date of the interview
Interventions	Exposure to influenza vaccination during the 28 days preceding the index date. Exposure to other vaccines and drugs has also been considered
Outcomes	Immune thrombocytopaenia (ITP)
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Hospital population
CC - control selection All outcomes	Low risk	Hospital control
CC - comparability All outcomes	Unclear risk	No matching
CC - exposure All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

bb Grimaldi Bensouda 2011

Methods	Multicentre, case-control study
Participants	Cases (n = 104): Guillain-Barré syndrome (GBS) cases (Brighton Collaboration definition, levels 1 to 3) Controls (n = 1198): each case was matched to up to 25 controls on age (plus or minus 1 year), sex, index date and country. Matched controls recruited in the Netherlands, Sweden, the UK, France and Denmark
Interventions	Exposure to monovalent pandemic H1N1 2009 to 2010 influenza vaccine during the 6 months preceding the index date. Vaccination data were obtained from vaccine registries (Denmark and France), from general practitioner records in the (UK and Netherlands) and from structured interviews (Sweden)

bb Grimaldi Bensouda 2011 (*Continued*)

Outcomes	Guillain-Barré syndrome	
Notes	This study was funded by the European Centre for Disease Prevention and Control	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Neurological clinic registry
CC - control selection All outcomes	Unclear risk	From the same population using only GP registry
CC - comparability All outcomes	Unclear risk	Poor matching
CC - exposure All outcomes	Unclear risk	Interview and record linkage
Summary assessment	Unclear risk	Unclear

bb Grimaldi-Bensouda 2012

Methods	Case-control study	
Participants	Cases (n = 198) were participants with an immune thrombocytopenia (ITP) diagnosis (American Society of Hematology diagnostic criteria) identified with the collaboration of 22 university and major regional hospitals in France participating in the Pharmacoepidemiological General Research on ITP (PGRx-ITP) registry project Controls (n = 878) matched on age (2 years), sex, region of residence (northern or southern France), index date (date of first symptoms for the cases and date of consultation for the referents 2 months) from a random sample	
Interventions	Exposure to influenza vaccine. Assessed by structured interview and confirmed by vaccination records	
Outcomes	Immune thrombocytopenia (ITP)	
Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Multicentre registry consecutive series of cases

bb Grimaldi-Bensouda 2012 (*Continued*)

CC - control selection All outcomes	Unclear risk	Same population using registry from a sample of GPs
CC - comparability All outcomes	Unclear risk	Matching 1:5
CC - exposure All outcomes	Unclear risk	Structured interview - confirmation by GPs
Summary assessment	Unclear risk	Unclear

bb Hernan 2004

Methods	Case-control study based on the General Practice Research Database (GPRD)
Participants	Cases (n = 163): patients with confirmed diagnosis of multiple sclerosis between 1 January 1993 and 31 December 2000 Controls (n = 1604): subjects from the GPRD matched to the cases for age, sex, practice, date of joining the practice
Interventions	Exposure to vaccinations (also influenza) as shown from medical records
Outcomes	Association between exposure to influenza vaccine and onset of multiple sclerosis
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Nested case-control from GPRD registry
CC - control selection All outcomes	Low risk	GPRD registry
CC - comparability All outcomes	Low risk	Matched
CC - exposure All outcomes	Low risk	Registry
Summary assessment	Low risk	Low

bb Mastrangelo 2000

Methods	Case-control study assessing the association between influenza vaccines and cutaneous melanoma
Participants	99 cases and 104 controls
Interventions	Influenza vaccine exposure is not described
Outcomes	
Notes	The authors report a protective effect of repeated influenza vaccination on the risk cutaneous melanoma (OR 0.43, 95% CI 0.19 to 1.00). The study is at high risk of bias because of the selective nature of cases (all patients in the authors' hospital), attrition bias (4 cases and 4 controls eliminated because of "failure to collaborate", recall bias (up to 5 years exposure data were based on patients' recollection) and ascertainment bias (non-blinded exposure survey) Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Low
CC - control selection All outcomes	Unclear risk	Not sufficient information
CC - comparability All outcomes	Unclear risk	Not sufficient information
CC - exposure All outcomes	Low risk	Low
Summary assessment	Unclear risk	Unclear

bb Mutsch 2004

Methods	1 case-control study and case series based in the German-speaking regions of Switzerland, which assessed the association between an intranasal inactivated virosomal influenza vaccine and Bell's palsy
Participants	250 cases that could be evaluated (from an original 773 cases identified) were matched to 722 controls for age and date of clinic visit. All were aged around 50
Interventions	Immunisation with influenza vaccine took place within 91 days before disease onset
Outcomes	Bells' palsy.

Notes	The study reports a massive increase in risk (adjusted OR 84, 95% CI 20.1 to 351.9) within 1 to 91 days since vaccination. Despite its many limitations (case attrition: 187 cases could not be identified; ascertainment bias: physicians picked controls for their own cases; confounding by indication: different vaccine exposure rate between controls and the reference population) it is unlikely that such a large OR could have been affected significantly by systematic error. The authors called for larger pre-licence safety trials, given the rarity of Bell's palsy. On the basis of this study the vaccine was withdrawn commercially Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	"All 4891 primary care physicians, ear, nose, and throat specialists, and neurologists in the study area were invited twice to report cases of Bell's palsy first diagnosed between October 1, 2000, and April 30, 2001."
CC - control selection All outcomes	Low risk	Subsequently, the physicians who had reported cases of Bell's palsy were asked to document the date of the visit and information pertinent to the study's inclusion and exclusion criteria and to select, from among their patients without Bell's palsy, 3 controls sequentially from their registration log Trained study monitors contacted the physicians and reviewed the selection forms regularly to ensure consistency in the selection of controls. At this point, participating physicians had not been made aware of the exposure to be investigated (influenza vaccination)
CC - comparability All outcomes	Unclear risk	The controls were matched with the case patients according to age (within 5 years), date of the clinic visit (within 4 days) and physician
CC - exposure All outcomes	Low risk	Physicians were asked to document the dates of administration and the brand name and type of influenza vaccine (parenteral or intranasal) used during the study period. Other vaccine exposures during the study period and the preceding 2 months were also documented. Since in all 43 sentinel cases reported in the study area the onset of Bell's palsy occurred within 91 days after intranasal vacci-

bb Mutsch 2004 (*Continued*)

		nation, we defined the period of 1 to 91 days as the postexposure risk period
Summary assessment	Unclear risk	Unclear

bb Payne 2006

Methods	Case-control study assessing the association between influenza and other vaccines (data not extracted for this review) and optic neuritis "A matched case-control study design was used with each optic neuritis case matched to 3 controls based on sex, deployment during the 18 weeks preceding the diagnosis date, and the military component in which the individual served (eg, active or reserve/National Guard). The protocol for this vaccine postmarketing surveillance investigation was approved by the Centers for Disease Control and Prevention (CDC) Institutional Review Board and reviewed by the Food and Drug Administration and Department of Defense"
Participants	US military personnel aged at least 18 years
Interventions	Cases (n = 1131) were participants with a diagnosis of optic neuritis between 1 January 1998 and 31 December 2003. The following ICD-9 codes were considered: 377.30-32, 377.39 Controls (n = 4524): participants were matched to the cases on the basis of sex, deployment during the 18 weeks before diagnosis, military component. The study was carried out by using data from the Defense Medical Surveillance System, a longitudinal surveillance database
Outcomes	Date of case diagnosis was ascertained and immunisation status (Anthrax, smallpox, Hepatitis B, influenza) verified by means of electronic records in respect of 3 time intervals: 6, 12 and 18 weeks before onset. For controls, vaccination status was determined for the 3 intervals before the index date. Results were focused on the 18-week time interval
Notes	Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	We defined optic neuritis cases as those having a first-time diagnosis of the following ICD-9-CM codes: optic neuritis, unspecified (377.30); optic papillitis (377.31); retrobulbar neuritis, acute (377.32); and optic neuritis, other (377.39) during the period between 1 January 1998 and 31 December 2003
CC - control selection All outcomes	Low risk	Controls were selected if their DMSS diagnostic records indicated no history of an optic neuropathy, if they served in the military on the same date of diagnosis as their matched

bb Payne 2006 (*Continued*)

		case, and if they had at least 18 weeks of military service preceding this index date
CC - comparability All outcomes	Low risk	Matching
CC - exposure All outcomes	Low risk	We ascertained the date of each case's first diagnosis of optic neuritis and determined all vaccinations received during each of the following 3 prior study intervals from the electronic record; 6 weeks (42 days), 12 weeks (84 days) and 18 weeks (126 days). For each of the 3 matched controls, we determined all vaccinations during the 3 intervals predating their index date
Summary assessment	Low risk	low

bb Ray 2011

Methods	Case-control study
Participants	Cases (n = 415): participants with diagnosis of definite rheumatoid arthritis based on American College of Rheumatology (ACR) criteria Controls (n = 1245) matched for age and number of medical visits before index date
Interventions	Exposure to influenza vaccine. Different times intervals before symptom onset were considered (90, 180, 365 and 730 days). Vaccine exposure status was determined from Kaiser Immunization Tracking System (KITS) and supplemented by chart reviews. Risk of association was, moreover, also determined for tetanus and hepatitis B vaccines
Outcomes	
Notes	This study was funded by the Centers for Disease Control and Prevention Vaccine Safety Datalink Project

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Included as cases the incident cases from the cohort analysis and additional new onset cases identified from the study population whose symptoms began during 1996
CC - control selection All outcomes	Low risk	Same population

bb Ray 2011 (*Continued*)

CC - comparability All outcomes	Unclear risk	Poor matching
CC - exposure All outcomes	Low risk	NCKPHP databases
Summary assessment	Unclear risk	Unclear

bb Siscovick 2000

Methods	Study assessing the association between influenza vaccination the previous year and the risk of primary (i.e. occurring in people with no previous history of cardiac disease) cardiac arrest. Case-control study on 360 cases and 418 controls
Participants	Cases: participants who experienced primary cardiac arrest, aged between 25 to 74 years Controls: healthy participants selected randomly from the community, who were matched to the cases for age and sex
Interventions	Immunisation with influenza vaccine, assessed by means of questionnaires
Outcomes	Cardiac arrest
Notes	The authors concluded that vaccination is protective against primary cardiac arrest (OR 0. 51, 95% CI 0.33 to 0.79). The difficulty of case ascertainment (77% of potential cases had no medical report and/or autopsy), recall bias (spouses provided exposure data for 304 cases, while 56 survivor cases provided data jointly with their spouses) make the conclusions of this study unreliable. It is impossible to judge the reliability of this study because of a lack of detail on the circulation of influenza in the study areas in the 12 months preceding cardiac arrest (the causal hypothesis is based on the effects of influenza infection on the oxygen supply to the myocardium through lung infection and inflammation). Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	From paramedic incident reports, cases of out-of-hospital PCA attended by paramedics in King County, Washington, from October 1988 to July 1994 were identified. PCA cases were defined by the occurrence of a sudden pulseless condition and the absence of evidence of a non-cardiac condition as the cause of cardiac arrest
CC - control selection All outcomes	High risk	Selected from the community by using random digit dialling

bb Siscovick 2000 (*Continued*)

CC - comparability All outcomes	Unclear risk	For each PCA case, 1 to 2 controls, matched for age (within 7 years) and sex
CC - exposure All outcomes	Unclear risk	Data on the participants' vaccination status were collected from both case and control spouses by using a standardised questionnaire. For each participant, information was collected on whether they had received an influenza vaccination during the previous 12 months and, if so, when the vaccination had been given. We did not collect information on whether they had received influenza vaccination during the years prior to that period
Summary assessment	High risk	

bb Zorzon 2003

Methods	Case-control study
Participants	Cases (n = 140): participants affected by multiple sclerosis (MS) as defined by the International Panel on MS Diagnosis Controls (n = 131): sex- and age-matched to the cases
Interventions	Exposure to influenza vaccination (unspecified). Exposure to many other factors was assessed by means of face-to-face structured questionnaires. Time of onset after exposure is probably not mentioned in the text
Outcomes	Multiple sclerosis
Notes	"The study was supported by a grant of the University of Trieste, Italy: MPI 60%, 2001"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Hospital population
CC - control selection All outcomes	High risk	Blood donor population
CC - comparability All outcomes	High risk	Poor matching
CC - exposure All outcomes	High risk	Interview

bb Zorzon 2003 (*Continued*)

Summary assessment	High risk	High risk

cb Bardage 2011

Methods	Large, prospective, cohort study assessing the possible association between monovalent, pandemic, H1N1 flu vaccine Pandemrix (GSK) and neurological and/or autoimmune disease
Participants	The study population comprised 1,945,024 people and corresponds to all people registered in Stockholm county on 1 October 2009 and who had lived in the region since 1 January 1998
Interventions	Monovalent A (H1N1) pandemic vaccine Pandemrix (GlaxoSmithKline, Middlesex, UK) containing adjuvants AS03 and squalene. H1N1 vaccination campaign was initially targeted to healthcare workers and groups considered to be at high risk of complications from influenza (children with multifunctional disorders; pregnant women; patients with chronic heart or lung disease, diabetes mellitus, chronic liver failure, chronic renal failure or immunosuppression; people with body mass index > 40, patients with neuromuscular disease affecting breathing capacity) For the campaign an apposite register was established (Vaccinera) in which information on the dates of a first and second dose of vaccine, batch number, medical contraindications against vaccination and chronic conditions defining high-risk patients were recorded The vaccination campaign began on 13 October 2009 and within it 2 phases could be distinguished. During the first 6 weeks (from 13 October through November 2009), participants with a high-risk condition were preferentially vaccinated, whereas during the second phase (from December 2009 onwards), vaccination was offered to the remainder of the population In total, 1,024,019 participants received at least 1 vaccine dose (446,770 during phase I, 577,249 during phase II)
Outcomes	Data on vaccination (Vaccinera database) were linked to data on utilisation of inpatient and specialist healthcare (admissions to hospital and visits to specialist care in the county, dates, diagnoses, responsible medical departments and length of hospital stay) contained in the common healthcare registers for Stockholm County Council (GVR) from 1 January 1998 to 31 August 2010 Neurological and autoimmune diagnoses to consider for follow-up were selected based on indication of the European Medicines Agency and defined by the ICD-10 (International Classification of Diseases, 10th revision) classification for hospital admissions and visits to specialist care: Guillain-Barré syndrome (GBS): G61 Multiple sclerosis (MS) (demyelinating disease): G35 (G36.0 + G37.9) Bell's paralysis: G51 Narcolepsy: G47.4 Polyneuropathy, unspecified: G62.9 An/hypoaesthesia: R20.0 + R20.1 Paraesthesia: R20.2

	Rheumatological disease (RA): M05-M06 + M08 Inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis): K50-K51 Insulin-dependent diabetes among individuals born 1990 and later: E10 Entering diagnoses into the county healthcare database is part of the doctor's routine diagnostic work and therefore depends on patients seeking health care. An active search for adverse events during the study period was not performed For each investigated pathology, the prevalent diagnoses were considered (i.e. those registered between 1 January 1998 and 30 September 2009) and the incident diagnoses (i.e. those during or after the pandemic period for unvaccinated people and after a first vaccination for vaccinated people between 1 October 2009 and 31 August 2010) Since risk groups were prioritised for vaccination, for risk estimates analysis data were stratified for the first and second phase of the vaccination campaign (the cut-off point was 45 days from 1 October 2009), considering vaccination as a time-varying covariate and also time since first vaccination (6 weeks)
Notes	- Preliminary assessment (prevalence in vaccination phase I and II): All but 1 (narcolepsy) of the investigated neurological and autoimmune disorders were significantly more prevalent in those vaccinated in the early phase of the campaign (first 45 days) than in the unvaccinated cohort. Comparing the vaccinated in the late phase (> 45 days) with the unvaccinated cohort, the prevalence of the investigated diseases was not statistically relevant, except for inflammatory bowel disease (prevalence odds ratio 1.17, 95% confidence interval 1.12 to 1.22) and also Guillain-Barré syndrome (OR 0. 79, 0.67 to 0.95) and type 1 diabetes (OR 0.77, 0.64 to 0.92, for those born in 1990 and later) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Low risk	Selected group of users
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Drawn from the same community as the exposed cohort
PCS/RCS - comparability All outcomes	High risk	Not assessed
PCS/RCS - assessment of outcome All outcomes	Low risk	Record linkage
Summary assessment	High risk	Unclear

cb Baxter 2012

Methods	Retrospective cohort study in which the incidence of medical attended events (MAEs) that occurred in participants immunised with live attenuated influenza vaccine (LAIV) through several seasons were compared with that observed in 2 matched control groups (unvaccinated and immunised with inactivated vaccine). Data for the LAIV exposed population were also analysed with a self controlled case series method
Participants	Participants were members of the Kaiser Permanente (KP) Health Plans in Northern California, Hawaii and Colorado. Through KP immunisation registries, approximately 20,000 individuals of 18 to 49 years of age who were immunised from the 2003 to 2004 to 2007 to 2008 influenza seasons with LAIV as part of routine clinical practice were identified
Interventions	Intervention hemi-cohort: LAIV vaccine provided by MedImmune. Each annual formulation of the vaccines contained the strains recommended for inclusion by the US Public Health Service. Study participants with high-risk underlying medical conditions such as cancer, organ transplantation, diabetes, endocrine and metabolic disorders, blood disorders, liver disorders, kidney disorders and cardiopulmonary disorders were identified via automated extraction of healthcare databases and excluded from all analysis cohorts. A total of 21,340 participants 18 to 49 years of age were vaccinated with the Ann Arbor strain LAIV during the 5 study seasons Control hemi-cohort 1: unvaccinated (n = 21,340). Participants were KP members who participated in the health plan during the same month as the reference LAIV recipients; for the unvaccinated population, the effective vaccination date was the date on which the matched LAIV recipient was vaccinated Control hemi-cohort 2: trivalent inactivated vaccine purchased by KP for immunisation practices (n = 18,316). Participants were KP members vaccinated during the same month as the reference LAIV recipient Both controls were matched for region (Northern California, Hawaii, Colorado), birth date (within one year), sex and prior healthcare utilisation (≤ 1 or > 1 clinic visits during the 180 days before vaccination) 1:1 to the participants of the intervention hemi-cohort. For northern California only, participants were also matched on their specific medical clinic. In the case that a match could not be found within a specific control group, the LAIV recipient was excluded from the cohort comparison For self controlled case series analysis intervals of 3 and 21 days postvaccination were compared with control intervals from 4 to 42 days postvaccination (for the 3-day risk interval) and 22 to 42 days postvaccination (for a 0 to 21-day risk interval)
Outcomes	**Medical attended adverse events** (MAEs) Based on medical diagnoses found in KP database records and collected from outpatient clinics, emergency departments (ED) and hospital admissions, MAEs were occurred in 5 main categories and include events considered to be vaccine associated: 1) Acute respiratory tract (ART) events: acute laryngitis, acute laryngotracheitis, acute respiratory failure, acute tracheitis, acute respiratory distress syndrome, asthma, bronchitis, cough, epiglottitis, influenza, influenza with pneumonia, mastoiditis, otitis media, pharyngitis, pneumococcal pneumonia, pneumonia, pulmonary congestion and hypostasis, shortness of breath, sinusitis, tachypnoea, tonsillitis, urinary tract infection, viral pneumonia. Follow-up 42 days 2) Acute gastrointestinal tract (AGI) events: abdominal pain, acute gastritis, acute gastroenteritis, appendicitis, intestinal obstruction, intussusception, irritable bowel syndrome, mesenteric adenitis, nausea and vomiting, pancreatitis, paralytic ileus, perfora-

	tion of intestine, peritonitis, persistent vomiting, small bowel obstruction, ulceration of intestine and volvulus. Follow-up 42 days 3) Asthma and wheezing (AW) events: asthma/reactive airway disease, wheezing/shortness of breath. Follow-up 180 days 4) Systemic bacterial infections (SBI) events: bacteraemia, bacterial meningitis, intracranial and intraspinal abscess, septicaemia, shock: unspecified, shock: endotoxic, and gram-negative shock. Follow-up 42 days 5) Rare diagnoses: potentially related to wild-type influenza infection: encephalitis/encephalopathy, Guillain-Barré syndrome, meningitis, myocarditis, other paralytic syndromes, pericarditis, polymyositis, Reye syndrome and viral meningitis. Follow-up 42 days **Severe adverse events** (SAEs) Death, inpatient hospitalisation, persistent or significant disability or incapacity, congenital anomaly/birth defect (in the offspring of a participant) or any life-threatening event. Follow-up from 0 to 42 days postvaccination
Notes	Sources of support: "This study was sponsored by MedImmune, LLC. Authors employed by MedImmune were involved in the study design, analysis, and interpretation of data, and in the preparation of the manuscript. Authors employed by Kaiser Permanente were involved in the study design, collection, analysis, and interpretation of data, and in the preparation of the manuscript. The Kaiser Permanente Vaccine Study Center was paid for their services in data collection and analysis but authors were not compensated for their work on this manuscript"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Selected group of users Participants were screened for underlying medical conditions and provided the appropriate vaccine based on the eligibility criteria in each vaccine's package insert, physician discretion and patient choice
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	No description of the derivation of the non-exposed cohort
PCS/RCS - comparability All outcomes	Unclear risk	Matched but not very relevant*:* *"*TIV-vaccinated and unvaccinated participants were matched to LAIV recipients on region (Northern California, Hawaii, Colorado), birth date (within one year), sex, and prior healthcare utilization. Prior utilization was calculated based on the number of clinic visits during the 180 days before vaccination and classified as low (≤ 1 visit) and high (> 1 visit) for matching. In Northern California, participants also were

cb Baxter 2012 (*Continued*)

		matched on their specific medical clinic, of which there were 48"
PCS/RCS - assessment of outcome All outcomes	Low risk	Record linkage
Summary assessment	Unclear risk	Unclear

cb Kaplan 1982

Methods	Surveillance population-based study conducted in the USA during the 1979 to 1980 and 1980 to 1981 influenza seasons. The study tested the association between influenza vaccination and Guillain-Barré syndrome. Reports from each case were obtained from neurologists. All case reports were included. The follow-up period was 1 September 1979 to 31 March 1980 and 1 September 1980 to 31 March 1981
Participants	USA (minus Maryland), adult population, 18 years or older
Interventions	Seasonal parenteral vaccine
Outcomes	Cases of Guillain-Barré syndrome. Vaccine-associated cases were defined as those with onset within the 8-week period after influenza vaccination
Notes	Vaccination rates in the population were obtained from a national immunisation survey Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	High risk	High risk
PCS/RCS - selection non-exposed cohort All outcomes	High risk	High risk
PCS/RCS - comparability All outcomes	High risk	High risk
PCS/RCS - assessment of outcome All outcomes	High risk	High risk
Summary assessment	High risk	High risk

cb Lasky 1998

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	High risk	High risk
PCS/RCS - selection non-exposed cohort All outcomes	High risk	High risk
PCS/RCS - comparability All outcomes	High risk	High risk
PCS/RCS - assessment of outcome All outcomes	High risk	High risk
Summary assessment	High risk	High risk

cb Moro 2013

Methods	Retrospective cohort study evaluating the association between the administration of monovalent pandemic inactivated vaccine H1N1 and severe adverse events
Participants	Participants were identified within several administrative and medical databases of the Italian region Emilia Romagna (about 4.4 million individuals). By data linkage participants immunised with Focetria® in the 2009 to 2010 season (n = 103,642) were identified. From the unvaccinated population (n = 3,967,917) a matched unexposed cohort was selected by using a propensity score
Interventions	Immunisation with MF59-adjuvanted, monovalent H1N1 vaccine Focetria® (Novartis Vaccines and Diagnostics, Siena, Italy)

cb Moro 2013 (*Continued*)

Outcomes	Guillain Barré syndrome, paralytic syndromes, encephalitis and encephalomyelitis, Bell's palsy, demyelinating disease, convulsion, autoimmune hepatitis, vasculitis, immune thrombocytopenia	
Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear description of the vaccinated population
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Using administrative databases
PCS/RCS - comparability All outcomes	Unclear risk	Propensity score
PCS/RCS - assessment of outcome All outcomes	Low risk	Blind validation process throughout
Summary assessment	Unclear risk	Unclear

cb Ray 2011

Methods	See bb Ray 2011. Study data were analysed using a cohort design	
Participants		
Interventions		
Outcomes		
Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	Unclear risk	Unclear

cb Ray 2011 (*Continued*)

PCS/RCS - assessment of outcome All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

cb Shonberger 1979

Methods	Surveillance, population-based study conducted in the USA during the 1976 to 1977 influenza season. The study tested the association between influenza vaccination and Guillain-Barré syndrome. Neurologists were directly contacted; physician and hospital records were reviewed. Suspected cases were reported to the CDC directly by patients or medical personnel were included only if accepted by a state health department. Follow-up period was 1 October 1976 to 31 January 1977
Participants	USA population
Interventions	Monovalent A/New Jersey/76 or bivalent A/New Jersey/76 and A/Victoria/75 parenteral vaccine
Outcomes	Cases of Guillain-Barré syndrome
Notes	Results were stratified by age group and vaccine type. Vaccination rates in the population were obtained from a national immunisation survey Rare events (safety) Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	High risk
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	High risk
PCS/RCS - comparability All outcomes	Unclear risk	High risk
PCS/RCS - assessment of outcome All outcomes	Unclear risk	High risk
Summary assessment	Unclear risk	High risk

pba Benowitz 2010

Methods	Case-control study assessing the effectiveness of influenza vaccination of pregnant women in preventing hospitalisation for influenza in their newborns. Study period ranged from October 2000 to April 2009
Participants	Cases (n = 113): infants below 12 months hospitalised for influenza between October 2000 and April 2009 who tested positive for influenza with direct fluorescent antibody (DFA) Controls (n = 192): participants hospitalised for influenza during the same time interval as the cases but negative with the DFA test. For each case 1 or 2 controls matched for birth date and date of hospitalisation were randomly selected
Interventions	Immunisation with influenza vaccine during pregnancy (until 14 days before delivery)
Outcomes	DFA confirmed influenza
Notes	This study was supported by the National Center for Research Resources, a component of the National Institutes of Health (NIH)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Infants hospitalised with DFA positive
CC - control selection All outcomes	Low risk	Infant hospitalised with DFA negative
CC - comparability All outcomes	Low risk	Matching
CC - exposure All outcomes	Unclear risk	Structured interview
Summary assessment	Unclear risk	Unclear

pba Poehling 2011

Methods	Case-control study assessing the effectiveness of influenza vaccine administered during pregnancy in preventing influenza in newborns under 6 months
Participants	Children (n = 1510) aged below 6 months, who were hospitalised for fever and/or acute respiratory illness during 7 consecutive epidemic seasons (between 2002 and 2003 and 2008 and 2009). Those with positive laboratory confirmation of influenza were enrolled as cases (n = 151); those whose result was negative were enrolled as controls (n = 1359)
Interventions	Influenza vaccination during pregnancy
Outcomes	Influenza

pba Poehling 2011 (*Continued*)

Notes	This project was supported the Centers for Disease Control and Prevention, National Institute of Allergy and Infectious Diseases,and Wachovia Research Fund. 3 authors had received funding from industry in the past (of these one was on the MedImmune Advisory Board and another was a NexBio consultant Funding source - mixed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
CC - case selection All outcomes	Low risk	Laboratory-confirmed
CC - control selection All outcomes	Low risk	Infants without laboratory-confirmed influenza
CC - comparability All outcomes	Unclear risk	No matching, unclear information
CC - exposure All outcomes	Unclear risk	Structured interview
Summary assessment	Unclear risk	Unclear

pbb Irving 2013

Methods	Case-control study investigating the association between influenza immunisation during pregnancy and spontaneous abortion
Participants	Cases (n = 243) were identified from among the members of 6 Vaccine Safety Datalink organisations. Diagnoses of spontaneous abortion (ICD-9 code 634) and unspecified abortion (ICD-9 codes 637) assigned during the 2005 to 2006 and 2006 to 2007 seasons were reviewed and different diagnoses excluded Controls (n = 243) were selected from among women who had confirmed intrauterine pregnancy and delivery after the 20th gestational week by frequency-matching of last menstrual period (within 2 weeks) and healthcare organisation
Interventions	Immunisation with influenza vaccine. Participants were considered exposed if they were immunised within 28 days before index date. Analysis considering whether vaccine exposure occurred during or before pregnancy was also performed
Outcomes	Spontaneous abortion cases
Notes	Government-funded

Risk of bias

pbb Irving 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
CC - case selection All outcomes	Low risk	Consecutive series of cases from electronic databases
CC - control selection All outcomes	Low risk	From the same population
CC - comparability All outcomes	Unclear risk	Matched by LMP - confounders
CC - exposure All outcomes	Unclear risk	Medical record
Summary assessment	Unclear risk	Unclear

pca Black 2004

Methods	Retrospective cohort study assessing the effectiveness of flu vaccination for the prevention of ILI or pneumonia in pregnant women and their newborns
Participants	- All women with live births in Kaiser Permanente Northern California (KPNC) between the November and February of 5 subsequent seasons (1997 to 1998 and 2001 to 2002, n = 49,585) excluding cases lacking birth date information and women who were discharged after the end of the flu season - All live births in Kaiser Permanente Northern California that occurred during the same time periods as for the mothers (n = 48,639), again cases lacking gestational age or gender information and infants discharged after the end of the flu season were excluded
Interventions	Immunisation with flu vaccine (no details about type and composition). Data about immunisation were obtained from the KPNC database. In all, 3707 out of the 49,585 pregnant women included in the study were vaccinated, whereas this was 3652 out of the 48,639 live births
Outcomes	- Hospitalisation for Pneumonia or Influenza: At least 1 inpatient stay during the same flu season as delivery or birth with a principal (first) diagnosis of either influenza or pneumonia. To identify these outcomes the following ICD (9th revision) codes were used to identify inpatient cases: influenza 487 and pneumonia 480, 481, 482, 483, 484, 485 and 486 - Outpatient visits: at least 1 physician visit during the same flu season as delivery or birth with 1 of the following diagnoses: upper respiratory infection, pharyngitis, otitis media, asthma, bronchial asthma, viral infection, pneumonia, fever, cough or wheezing associated with respiratory illness This information was available from the KPNC databases, which include laboratory, hospitalisation and outpatient utilisation information for their members The effect measure (hazard ratio and corresponding 95% confidence interval) was calculated for ILI visits (including and excluding asthma diagnoses) for the mother and hospitalisation for pneumonia or influenza, ILI visits (excluding otitis media) and otitis

pca Black 2004 (*Continued*)

	media visits in newborns - Caesarean section - Preterm delivery (< 37 weeks)	
Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	From KPNC databases: the influenza vaccination status of women in the cohort was determined through review of the Kaiser Immunization Tracking System database
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	From KPNC databases
PCS/RCS - comparability All outcomes	High risk	No matching
PCS/RCS - assessment of outcome All outcomes	Unclear risk	KPNC maintains administrative databases that include laboratory, hospitalisation and outpatient utilisation information for their members
Summary assessment	High risk	High

pca Eick 2011

Methods	Prospective cohort study carried out in 6 hospitals located in the Navajo and White Mountain Apache reservation during 3 subsequent epidemic seasons (2002 to 2005)
Participants	Mother-infant pairs recruited after delivery at Indian Health Service hospitals on the Navajo or White Mountain Apache reservation, either at the hospital or by home visit The study was conducted during 3 influenza seasons from November 2002 to September 2005 The enrolment periods for each year were - 1 December 2002 to 15 March 2003 - 1 November 2003 to 8 March 2004 - 1 November 2004 to 15 March 2005 Inclusion was restricted to mothers who delivered a healthy infant at 36 weeks or later gestation during the enrolment periods. Eligible infants were aged 2 weeks or younger at enrolment. Overall, 1169 mother-infant pairs were enrolled in the study (241 in 2002 to 2003; 574 in 2003 to 2004; and 354 in 2004 to 2005). Of these, 1160 had at least 1 serum sample and were included

Interventions	Immunisation of the mother with influenza vaccine. Assessed by reviewing of medical record (also in order to obtain information about prenatal visits, illnesses and birth information, in addition to administration and timing of influenza vaccine) or, if missing, by maternal report at enrolment The decision for influenza vaccination was made by the treating clinician and the pregnant woman; personnel had no role in these decisions. Altogether 587 children were born from an unvaccinated mother and 573 from a vaccinated mother during the 3 study seasons
Outcomes	Surveillance for all medically attended illnesses in *enrolled infants* was conducted at Indian Health Service and nearby private facilities through the influenza season, or until the child reached 6 months of age (whichever came first). It also included review of the clinic, emergency department and inpatient paediatric ward logs. A nasopharyngeal aspirate specimen for viral culture was obtained from infants with ILI within 72 hours of the medical visit - Medically attended influenza-like illness (ILI): defined as a medical visit with at least 1 of the following signs or symptoms reported: fever of 38.0 ºC or higher, diarrhoea or respiratory symptoms (including cough, runny nose or difficulty breathing) - Laboratory-confirmed influenza: the first ILI episode with either: a) isolation of influenza virus from the nasopharyngeal aspirate specimen b) a 4-fold or greater rise in HI antibody in serum collected at 2 to 3 or 6 months compared with the previous serum specimen, indicating influenza virus infection during the time interval c) a positive rapid influenza diagnostic test result with a medical diagnosis of influenza
Notes	”Funding/support: “The study was funded by the National Vaccine Program Office, Department of Health and Human Services, the Office of Minority Women’s Health, Centers for Disease Control and Prevention, Aventis-Pasteur, and Evans-Powderject.” Funding source - mixed

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	The study was carried out within Indian reservations
PCS/RCS - selection non-exposed cohort All outcomes	Low risk	Derived from the same community as the exposed cohort
PCS/RCS - comparability All outcomes	Unclear risk	Reported for some parameters only: sex, presence of household smokers, having wood or coal stove in the house (more frequent among vaccinated), presence of other children in day care, infant breast fed (more frequent among vaccinated), gestational age, mean birthweight

pca Eick 2011 (*Continued*)

PCS/RCS - assessment of outcome All outcomes	Low risk	Active surveillance and testing for laboratory confirmation for symptomatic ILI cases
Summary assessment	Unclear risk	Unclear

pca France 2006

Methods	Retrospective cohort study based on Vaccine Safety Datalink, assessing the effect of influenza vaccination in pregnant women in preventing respiratory illness in newborns. 6 epidemic seasons were considered
Participants	Infants who were born before or during the influenza season at 4 managed care organisations (MCOs) (Kaiser Permanente Colorado, Denver; Kaiser Permanente Northern California, Oakland; Kaiser Permanente Northwest, Portland, Oregon; and Group Health Cooperative, Seattle, Washington) between 1 October 1995 and 30 September 2001 were eligible for study inclusion Mother-infant pairs were included in the final study population if: (1) the mothers were aged 18 to 45 years and enrolled in the MCO for longer than 1 year (2) the infants' gestational age was at least 30 weeks at birth (3) the infants were continuous MCO members for at least 14 days during the influenza season (4) the infants had a least 1 outpatient visit during the first 3 months of life
Interventions	An infant was considered exposed if the mother was vaccinated against influenza during the pregnancy and there were at least 28 days from the vaccination date of the mother to the birth date of the infant. Infants of mothers vaccinated within 27 days of birth were excluded from the primary analysis
Outcomes	Medically attended ARI
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	High risk	From MCO databases
PCS/RCS - selection non-exposed cohort All outcomes	High risk	From MCO databases
PCS/RCS - comparability All outcomes	High risk	Poor matching

pca France 2006 (*Continued*)

PCS/RCS - assessment of outcome All outcomes	Unclear risk	Data link
Summary assessment	High risk	High risk

pca Hulka 1964

Methods	Prospective cohort study assessing the effectiveness of flu vaccination in pregnancy
Participants	Pregnant women (n = 544) recruited from the "hill" district of Pittsburgh
Interventions	- Polyvalent flu vaccine containing 200 units of A2 antigen - Placebo 2 1 ml doses were administered 1 month apart
Outcomes	- Adverse effects following immunisation (pain, malaise) - Influenza-like illness - Days in bed Assessed by means of questionnaires/phone interviews after epidemic
Notes	Effectiveness follow-up was available for 59% and 100% of participants in the intervention and placebo arm, respectively Funding source - mixed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	High risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	High risk	Unclear
PCS/RCS - comparability All outcomes	High risk	Unclear - high attrition
PCS/RCS - assessment of outcome All outcomes	High risk	Interview
Summary assessment	High risk	Unclear

pca Munoz 2005

Methods	Retrospective cohort study based on the electronic database of Kelsey-Seybold Clinic (KSC), a large multispecialty clinic in the metropolitan area of Houston (USA). For the study 5 subsequent flu seasons were taken in account, from 1998 to 2003, considering the time between 1 July and 30 June each year. Approximately 25 obstetricians and 60 paediatricians provided medical care in KSC locations and about 2500 deliveries occurred every year during the time considered for the study
Participants	Exposed cohort (n = 225): women who were immunised with inactivated influenza vaccine within 6 months before delivery and who had an uncomplicated singleton pregnancy, were healthy, had at least 1 prenatal care visit at KSC, and their offspring had at least 1 clinic visit at KSC in their first year of life Comparison (n = 826): for each vaccinated woman a comparison group was selected by matching (KSC database) 3 to 5 women for maternal age at delivery, month of delivery and type of insurance (with the exclusion of both Medicaid or self insurance because of small numbers in this clinic population), who had not received influenza vaccine during pregnancy
Interventions	Influenza vaccines that were used during the study period were Aventis Pasteur or Wyeth products. For the control group the index date ("pseudo vaccination date") corresponds to the same number of days before delivery as the real vaccination date for a matching vaccinated woman
Outcomes	Women - ARI (acute respiratory illness): cases recorded at any time, during each flu season and during each epidemic peak of that season diagnosed with the following ICD-9 codes: 079, 460-466, 470-478, 480-487. The peak of influenza activity was the period during which the number of laboratory-confirmed cases included at least 85% of influenza cases for that season - Serious adverse events: hospitalisation (death, cause for hospitalisation and permanently disabling conditions are also included) within 42 days from immunisation identified by ICD-9 codes - Medical diagnoses occurred between vaccination and delivery with an incidence $\geq$ 2% among vaccinated women) Newborns - Diagnoses different from a "normal newborn infant" given at discharge and within 2 days from delivery - Reason for at least 3 days hospitalisation within 1 week, between 8 and 180 days, and between 6 months and 1 years after delivery - Diagnoses reported during ambulatory medical visits during the first 6 months of life In the last 2 categories URTI and respiratory infections are also included
Notes	Little information about characteristics and comparability of the exposed and unexposed cohorts. Outcomes used to assess the effectiveness of vaccination are in some way 'surrogate' and include only hospitalisation and ambulatory diagnoses. For the assessment of effectiveness in mothers, the first 2 weeks after vaccination should have been excluded from follow-up Government-funded
Risk of bias	

pca Munoz 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Women were included in the study sample if they had received inactivated influenza vaccine within 6 months before delivery of an uncomplicated singleton pregnancy and were otherwise healthy, had at least 1 prenatal care visit at KSC and their offspring had at least 1 clinic visit at KSC in their first year of life
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	A comparison group was selected by matching of maternal age at delivery, month of delivery and type of insurance (patients with Medicaid or self insurance were excluded because of the small numbers in this clinic population). For each vaccinated woman, they selected 3 to 5 (ratio, 1:3.5) matching healthy women who met all the inclusion criteria but who had not received influenza vaccine during pregnancy
PCS/RCS - comparability All outcomes	Unclear risk	Matching
PCS/RCS - assessment of outcome All outcomes	Unclear risk	The potential protective effect of the vaccine was estimated by recording the occurrence of acute respiratory tract illnesses in vaccinated women from the time of receipt of influenza vaccine to delivery and in unvaccinated women for the equivalent period of time. Specifically, the occurrence of acute respiratory illnesses (ARIs) during the peak of the influenza season was compared between the groups. Diagnostic codes for ARI included 079, 460-466, 470-478, 480-487
Summary assessment	Unclear risk	Unclear

pca Yamada 2012

Methods	Questionnaire-based, retrospective cohort study performed at the 121 obstetrical facilities of Hokkaido (Japan)
Participants	All 121 obstetric facilities in Hokkaido were requested to deliver a 12-item questionnaire to all postpartum women who gave birth between 1 December 2009 and 31 May 2010 during their stay in obstetric facilities. About 1/3 of the women who delivered in

pca Yamada 2012 (*Continued*)

	Hokkaido during this time answered the questionnaire (n = 7535)
Interventions	Influenza vaccination during pregnancy. Out of the 7535 women who answered the questionnaire, 4921 received pandemic influenza vaccine. Among them, 2212 were also reported to have been vaccinated with seasonal vaccine. A further 270 (considered as unvaccinated) received seasonal vaccine only
Outcomes	Influenza. Definition was not provided. All information was collected by means of a questionnaire, on which items about admission to the intensive care unit, intubation or ventilation, and diagnosis of influenza encephalopathy were also present
Notes	Strongly biased Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	High risk	By interview
PCS/RCS - selection non-exposed cohort All outcomes	High risk	By interview
PCS/RCS - comparability All outcomes	High risk	No matching
PCS/RCS - assessment of outcome All outcomes	High risk	By interview
Summary assessment	High risk	High

pcb Deinard 1981

Methods	Prospective cohort study assessing the safety of monovalent A/NJ/8/76 vaccine administration during pregnancy
Participants	Pregnant women enrolled at several obstetric clinics (Minneapolis) on the occasion of a prenatal visit (n = 706)
Interventions	Flu vaccine containing A/NewJersey/8/76 (split or whole virus formulation) administered during the first, second or third pregnancy semester. Vaccine was administered to 189 women, whereas 517 acted as unvaccinated controls
Outcomes	- Local and systemic reactions observed and reported after vaccine administration (only the vaccinated assessed by questionnaire) - Pregnancy outcomes: maternal mortality, elective abortion, spontaneous abortion, stillbirth, premature live birth

pcb Deinard 1981 (*Continued*)

	- Infant outcomes: deaths, major or minor congenital anomalies, abnormalities during the first 8 days of life
Notes	This study should have been performed without external/private/industry funding Government-funded

Risk of bias

Bias	Authors' judgement	Support for judgement
PCS/RCS - selection exposed cohort All outcomes	High risk	
PCS/RCS - selection non-exposed cohort All outcomes	High risk	
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	High risk	
Summary assessment	High risk	

pcb Fell 2012

Methods	Retrospective cohort assessing the safety of pandemic, monovalent H1N1 vaccine in pregnant women, by using Ontario's birth record database
Participants	Women with singleton birth in 2009 to 2010 season (n = 55,570)
Interventions	Monovalent pandemic H1N1 influenza vaccine. In all, 23,340 pregnant women were also immunised with seasonal vaccine
Outcomes	Frequency of neonatal outcomes in newborns: - Preterm birth (< 37 weeks or < 32 weeks) - Small for gestational age (below 10th or 3rd percentile) - 5-minute Apgar score below 7 - Fetal death
Notes	"This study was funded by the Canadian Institutes of Health Research (grant 218653)"

Risk of bias

Bias	Authors' judgement	Support for judgement
PCS/RCS - selection exposed cohort All outcomes	Low risk	

pcb Fell 2012 (*Continued*)

PCS/RCS - selection non-exposed cohort All outcomes	Low risk	
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Low risk	
Summary assessment	High risk	

pcb Heikkinen 2012

Methods	Prospective cohort study assessing the safety of pandemic MF-59 adjuvanted influenza vaccine (Focetria) during pregnancy
Participants	Pregnant women recruited in midwife practices and hospitals in the Netherlands (n = 4281), Argentina (n = 239) and Italy (n = 9). Altogether 4508 pregnant women were included: 2295 were vaccinated and 2213 were not immunised. There were 4522 live births and 18 intrauterine deaths (2310 born from vaccinated and 2213 from unvaccinated mothers). For 4385 babies 3 months follow-up data were available
Interventions	Monovalent, pandemic, H1N1, MF-59 adjuvanted flu vaccine Focetria (Novartis Vaccine and Diagnostic, Cambridge, MA). Among the 2295 vaccinated pregnant women, 1724 received 2 doses, 571 received 1 dose
Outcomes	Gestational diabetes Pre-eclampsia Spontaneous abortion Stillbirth Live birth Low birthweight Preterm birth Neonatal death Congenital malformation
Notes	"This study was supported by Novartis Vaccines and Diagnostics"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear

pcb Heikkinen 2012 (*Continued*)

PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Low risk	
Summary assessment	High risk	Unclear

pcb Håberg 2013

Methods	Cohort study assessing the risk of neonatal death following exposure to pandemic monovalent H1N1 influenza vaccine or influenza virus during pregnancy	
Participants	A total of 113,331 pregnant women	
Interventions	Immunisation with pandemic monovalent H1N1 adjuvanted influenza vaccine Pandemrix (GSK) or Cavaplan (not adjuvanted)	
Outcomes	Fetal death	
Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Data link
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Data link
PCS/RCS - comparability All outcomes	Unclear risk	Multivariate model
PCS/RCS - assessment of outcome All outcomes	Unclear risk	Data link
Summary assessment	Unclear risk	Unclear risk of bias

pcb Källén 2012

Methods	Retrospective cohort study assessing the effect on newborn outcomes of pandemic squalene adjuvanted H1N1 vaccine

pcb Källén 2012 (*Continued*)

Participants	The total number of vaccinated women was 18,612 having 18,844 infants (vaccination group, pandemic H1N1 Pandemrix). These women were compared with 136,914 women having 138,931 infants who gave birth after September 2009 and before the end of 2010 (non-vaccinated group) and with 83,298 women having 84,484 infants who gave birth in the year 2009 before October (pre-vaccination group)
Interventions	Pandemrix (GlaxoSmithKline; Brentford, Middlesex, UK) containing inactivated split influenza virus A/California/07/2009), squalene adjuvant and thiomersal preservative
Outcomes	Stillbirth Preterm birth Low birthweight SGA (small for gestational age) Congenital malformations
Notes	"No specific funding was obtained for this study"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Unclear risk	Unclear
Summary assessment	High risk	

pcb Launay 2012

Methods	Prospective cohort study assessing the effect of immunisation with pandemic monovalent vaccine during pregnancy
Participants	Pregnant women (n = 877) between 12 and 35 weeks of gestation, aged at least 18 years, who were not vaccinated or infected
Interventions	Immunisation with pandemic monovalent influenza vaccine
Outcomes	Delivery before the 37th gestational week, birthweight, death before or during labour

pcb Launay 2012 (*Continued*)

Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Low risk	Low
PCS/RCS - selection non-exposed cohort All outcomes	Low risk	Low
PCS/RCS - comparability All outcomes	Unclear risk	No information was given about possible confounders
PCS/RCS - assessment of outcome All outcomes	Unclear risk	Unclear
Summary assessment	Unclear risk	Unclear

pcb Lin 2012

Methods	Retrospective cohort study	
Participants	A total of 396 pregnant Taiwanese women were included in the study. Among them 198 received influenza vaccine during pregnancy	
Interventions	Monovalent H1N1 unadjuvanted, inactivated, split-virus vaccine AdimFlu-S® (Adimmune Corporation; Taichung, Taiwan)containing 15 g of New York Medical College X-179A reassortant of the A/California/7/2009 (H1N1)-like strain in 0.5 ml dose	
Outcomes	Systemic and local adverse events in vaccinated mothers In newborns: Hyperbilirubinaemia Contact dermatitis Upper respiratory tract infection Seborrhoeic dermatitis Respiratory distress	
Notes	Government-funded	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear

pcb Lin 2012 (*Continued*)

PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Low risk	Medical records
Summary assessment	High risk	

pcb Nordin 2013

Methods	Retrospective cohort study based on data from Vaccine Safety Datalink (VSD)
Participants	Pregnant women aged between 14 and 49 years (n = 223,898) identified in the VSD, who were pregnant between 1 June 2002 and 31 July 2009
Interventions	Immunisation with inactivated trivalent influenza vaccine
Outcomes	Demyelinating diseases, neurological events, thrombocytopenia within 42 days after immunisation
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	KP registry
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	KP registry
PCS/RCS - comparability All outcomes	Unclear risk	Matched analysis
PCS/RCS - assessment of outcome All outcomes	Unclear risk	KP registry
Summary assessment	Unclear risk	Unclear

pcb Omer 2011

Methods	Retrospective cohort study based on data from the Georgia Pregnancy Risk Assessment Monitoring System (PRAMS)
Participants	In all 4168 pregnant women were included during 2 consecutive epidemic seasons (2004 to 2005 and 2005 to 2006), 578 received influenza vaccination
Interventions	Influenza vaccination during pregnancy
Outcomes	Small for gestational age (SGA) and preterm births. Periods with different viral circulation were considered in the analysis
Notes	"The study was partially funded through the Emory University, Global Health Institute Faculty of Distinction Fund award (recipient: SBO). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript" Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	Unclear risk	Unclear
PCS/RCS - assessment of outcome All outcomes	High risk	Interview
Summary assessment	Unclear risk	Unclear

pcb Oppermann 2012

Methods	Prospective cohort study based data from the Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy (D) carried out during the 2009 to 2010 pandemic
Participants	Pregnant women who received consultation regarding reproductive safety of medical products, planned pregnancy and lactation from the Institute for Clinical Teratology and Drug Risk Assessment. Out of the initial population (n = 16,788), 323 participants received influenza vaccine and completed the follow-up. A randomly selected control group of 1329 non-vaccinated women was the control group
Interventions	- Non-adjuvanted split-virion vaccine CSL H1N1 Pandemic Influenza Vaccine® (CSL Biotherapies) approved by the responsible national authority (Paul-Ehrlich-Institut) in November 2009 exclusively for the vaccination of pregnant women (216/323)

pcb Oppermann 2012 (*Continued*)

	- MF59-adjuvanted monovalent H1N1 vaccine (2/32) - Pandemrix® (GlaxoSmithKline) AS03-adjuvanted monovalent split-virion influenza vaccine (90/323) - Unknown vaccine (15/323)
Outcomes	Abortion, preterm birth, malformations
Notes	"This study was supported by the German Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut), Langen, Germany"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	Unclear risk	Unclear
PCS/RCS - assessment of outcome All outcomes	Low risk	Low
Summary assessment	Unclear risk	Unclear

pcb Pasternak 2012

Methods	Retrospective cohort study assessing the safety of pandemic H1N1 vaccination
Participants	Danish women who were pregnant during the time interval between November 2009 and September 2010 (n = 58,585). Of these, 7062 received influenza vaccine
Interventions	Monovalent, inactivated, AS03-adjuvanted split virion influenza A (H1N1) pdm09 vaccine (Pandemrix, GlaxoSmithKline Biologicals)
Outcomes	Abortion cases (retained or spontaneous)
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Low risk	

pcb Pasternak 2012 (*Continued*)

PCS/RCS - selection non-exposed cohort All outcomes	Low risk	
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Low risk	
Summary assessment	Unclear risk	Unclear

pcb Richards 2013

Methods	Retrospective cohort study assessing the effect of pandemic H1N1 immunisation during pregnancy on neonatal outcomes
Participants	Eligible pregnant women were identified by means of electronic medical records from Kaiser Permanente (KP) managed care organisation sites in Georgia and Mid-Atlantic States. A total of 3327 third-trimester live births to 3236 mothers between 25 May 2009 and 17 April 2010 were included
Interventions	Immunisation with H1N1 pandemic vaccine
Outcomes	Preterm birth (27 to 36 weeks), low birthweight
Notes	Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	KP registry
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	KP registry
PCS/RCS - comparability All outcomes	High risk	Possible residual confounding
PCS/RCS - assessment of outcome All outcomes	Low risk	Low
Summary assessment	Unclear risk	Unclear

pcb Sheffield 2012

Methods	Retrospective cohort study assessing the safety of seasonal influenza vaccination administered during pregnancy, covering 5 subsequent epidemic seasons (from 2003 to 2004 to 2007 to 2008)
Participants	Women who delivered and received prenatal care at the Southwestern Medical Center of University of Texas and Parkland Health & Hospital System, Dallas, Texas. In all 8690 were vaccinated and 76,153 acted as unvaccinated controls
Interventions	Seasonal influenza vaccination was offered to pregnant women between October through March in each season
Outcomes	- Estimated gestational age - Birthweight - Major malformations* - Stillbirth* - NICU admission* - Neonatal death - Neonatal pneumonia* - Hyperbilirubinaemia *For these outcomes the authors provided effect estimates considering the trimester of administration
Notes	This study should have been performed without external/private/industry funding Government-funded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Unclear risk	Unclear
Summary assessment	High risk	

pcb Toback 2012

Methods	Retrospective cohort study testing the safety of live attenuated influenza vaccine when administered during pregnancy
Participants	Pregnant women (n = 834,999) identified by means of a safety database (LifeLink Health Plan Claims Database, Norwalk, USA) between October 2003 and September 2009. Of these, 138 received immunisation with live attenuated influenza vaccine during their pregnancy
Interventions	Live attenuated influenza vaccine
Outcomes	Hospitalisation and emergency department visits within 42 days after immunisation
Notes	"This research was funded by MedImmune, LLC, Gaithersburg, MD. As part of a consulting agreement with RTI Health Solutions, MedImmune provided funding to support protocol development, data collection, analysis, and manuscript development activities associated with this manuscript. Editorial assistance in formatting the manuscript for submission was provided by Sue Myers, MSc, and Gerard P. Johnson, PhD, of Complete Healthcare Communications, Inc. (Chadds Ford, PA) and was funded by MedImmune, LLC"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS - selection exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - selection non-exposed cohort All outcomes	Unclear risk	Unclear
PCS/RCS - comparability All outcomes	High risk	
PCS/RCS - assessment of outcome All outcomes	Unclear risk	Unclear
Summary assessment	High risk	

AE = adverse event
ARI = acute respiratory illness
ATP = according to protocol
CDC = Centers for Disease Control and Prevention
CCI = culture-confirmed influenza illness
CCIV = cell culture-derived inactivated flu vaccine
CI = confidence interval
DFA = direct fluorescent antibody
FEF = forced expiratory flow
FEV1 = forced respiratory volume in one second

FVC = forced expiratory vital capacity
GBS = Guillain-Barré syndrome
GMT = geometrical mean titre
GSK = Glaxo-Smith-Kline
HA = haemagglutinin
HAO = full-length uncleaved haemagglutinin
HI = haemagglutination-inhibiting
HMO = health maintenance organisation
ICD = International Classification of Diseases
ILI = influenza-like illness
ITI = intention-to-immunise
ITT = intention-to-treat
IM = intramuscular
IN = intranasal
IU = international units
KP = Kaiser Permanente
KSC = Kelsey-Seybold Clinic
LAIV = live attenuated influenza vaccine
LCI = laboratory-confirmed influenza illness
LMP = last menstrual period
MAE = medical attended event
MCO = managed care organisation
MDCK = Madin Darby canine kidney cells
mmHg = millimetres of mercury
NaCl = sodium chloride
NCKPHP = Northern California Kaiser Permanente Health Plan
NICU = neonatal intensive care unit
OMP = outer membrane protein
OR = odds ratio
ORS = oculo-respiratory syndrome
PCA = primary cardiac arrest
PCR = polymerase chain reaction
PCS/RCS = prospective/retrospective cohort study
PP = per-protocol
RCT = randomised controlled trial
rHAO = recombinant uncleaved haemagglutinin glycoprotein
RhMK = rhesus macaque kidney cells
RT-PCR = reverse transcription polymerase chain reaction
SAE = serious adverse event
SAS = statistical analysis systems
TIV = trivalent inactivated vaccine
URTI = upper respiratory tract infection
VMCCI = vaccine matched, culture-confirmed influenza
WDL = working days lost
WHO = World Health Organization
WRL = Wellcome Research Laboratories (Beckenham, Kent)

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

Study	Reason for exclusion
Al-Dabbagh 2013	No outcomes of interest, differences in cytokine levels between ORS cases and controls after vaccination
Ambrosch 1976	Data tables and figure missing
Ambrose 2012	No original data
Aoki 1986	Randomised controlled trial, single-blind. Outcomes were clinical cases and adverse effects. Follow-up data were not reported by arms
Arnou 2010	Intradermal administration (3 different lots of the same vaccine) versus intramuscular administration. Serologic response and AE at day 21. No adequate placebo/no intervention control
Atmar 1995	No outcomes of interest
Atmar 2011	Absence of an adequate control
Ausseil 1999	No design (average days of sick leave in vaccinated and non-vaccinated subjects during 1996 and 1997 from staff of an international banking institution)
Banzhoff 2001	No design (cohort), no safety outcomes
Baxter 2010	No design: cohort study for effectiveness
Baxter 2011	A 'head to head trial': "FluBlok (purified HA proteins manufactured in expresSF+® insect cells under serum free conditions using a baculovirus expression system (BEVS). Uncleaved HA produced by this method is referred to as rHA0. Vaccine formulation consisted of 135g total HA protein (45g each) as determined by single radial immunodiffusion assay (SRID) and included rHA0 derived from the following influenza strains A/Solomon Islands/03/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 VS. The same CDC-derived vaccine seed viruses were used for the licensed trivalent inactivated vaccine (TIV; Fluzone [2007-2008 formulation; Sanofi Pasteur, Swiftwater, PA), which contained 15g of each HA [45g total])"
Baxter 2012	No design: controlled case series
Belongia 2009	Case-control study, no harm assessment
Belshe 2001	No original data
Benke 2004	Questionnaire survey; non-comparative analysis
Beran 2013	Absence of an adequate control group (quadrivalent versus trivalent inactivated vaccine; low versus normal adjuvant content)
Betts 1977b	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)

(*Continued*)

Beyer 1996	Review
Carlson 1979	No adequate control, no outcome of interest
Cate 1977	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Chlibek 2002	Not a randomised controlled trial
Choe 2011a	No design: cross-sectional study
Choe 2011b	No design: case series
Choe 2011c	No design: case series
Chou 2007	Case report
Clover 1991	Randomised controlled trial. More than 75% of the study population was out of the age range stated in the protocol
Confavreux 2001	Participants are MS cases
Conlin 2013	Inadequate comparison and study design: cohort study with pandemic versus seasonal (not exposed) vaccines in women and newborns
Das Gupta 2002	Does not contain effectiveness data
Davidson 2011	Inadequate comparison: all enrolled subjects received LAIV, then they were randomised to either placebo or Lactobacillus GG
Davies 1972	Cohort with efficacy outcomes. Experimental and control group were selected separately
Davies 1973	Not randomised. Subjects volunteered for immunisation and comparison was made with a randomly selected non-immunised control group
De Serres 2003a	No comparison, absence of adequate control group
De Serres 2003b	No control
De Serres 2004	Population at risk of further oculo-respiratory syndrome episodes
De Wals 2012	No design: self controlled case series for association between H1N1 and GBS
Dolin 1977	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Dominguez 2012	No design: case-control study assessing effectiveness in general population
Eames 2012	No design: effectiveness cohort study in general population

(*Continued*)

Edmonson 1970	Influenza B vaccine was used as control
Eick-Cost 2012	No design: case-control study assessing effectiveness in general population
El'shina 1998	Major inconsistencies in the study text
Englund 1993	Inadequate comparison (Tetanus Toxoid vaccine)
Finklea 1969	Randomised controlled trial, double-blind. 2 bivalent inactivated influenza vaccines, with the same viral composition, differing in purification procedures, were compared Outcomes were clinical cases and adverse effects Raw data about clinical cases were not reported by arm Circulating virus showed significant antigenic differences from the A2 vaccine strain
Fisher 2012	No outcomes of interest (antibody titres only)
Foy 1981	Absence of adequate control
Frank 1981	No usable safety data (scores)
Freestone 1976	Conference proceedings
Gerstoft 2001	Not a randomised controlled trial
Greenbaum 2002	No outcome of interest
Gross 1999	Outcome measures outside inclusion criteria
Grotto 1998	Not a randomised controlled trial
Gruber 1994	Randomised controlled trial conducted in the USA on 41 cystic fibrosis (CF) patients and 89 family members, recruited through a clinic. Participants were randomly assigned in a double-blinded fashion by family to receive either intranasal, live, cold-adapted influenza A vaccine or the recommended intramuscular trivalent inactivated influenza vaccine The study lasted 3 years (from 1989 to 1991). Participants were immunised each fall, staying in the same assigned vaccine group. The live vaccine arm counted 20 CF and 33 family members; the trivalent vaccine arm 21 and 56 respectively 69 of them (17 CF patients and 52 family members) dropped out. The reasons were stated in the article The live vaccine was the same throughout the period: A/Kawasaki/9/86 (H1N1) 107.3 pfu, A/Los Angeles/2/87 107.3 pfu The viral strains used in the inactivated vaccines were: - 1989 to 1990: A/Taiwan/1/86 (H1N1), A/Shanghai/11/87 (H3N2), B/Yagamata/16/88, 15 mg/dose of each - 1990 to 1991: A/Taiwan/1/86 (H1N1), A/Shanghai/16/89 (H3N2), B/Yagamata/16/88, 15 mg/dose of each - 1991 to 1992: A/Taiwan/1/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90, 15 mg/dose of each Live vaccine recipients also received monovalent inactivated influenza B vaccine (identical to that contained

(*Continued*)

	in the trivalent vaccine) as an intramuscular placebo. Allantoic fluid was the placebo for aerosol administration Data were extracted and loaded for family members only Outcomes were clinical and laboratory confirmed cases, working days lost (WDL), admissions, deaths and adverse effects Clinical cases were classified as "respiratory illness" or "febrile respiratory illness". Laboratory-confirmed cases were defined by an influenza virus isolation from a throat swab. Adverse effects were defined as temperature > 38 °C, rhinorrhoea, sore throat, cough, increasing sputum, redness, swelling, chills. Results are expressed as % of subject-days with symptoms Participants were followed throughout the period. Owing to the drop-outs, the vaccinated were counted as subject-years: 54 in the live vaccine arm; 56 in the trivalent vaccine arm The influenza illness surveillance period for study subjects was defined as the interval from the date of the first influenza isolate from the population under routine surveillance to 2 weeks after the last isolate for each year Viral strains circulating during the outbreaks were: - 1989-1990: A/Shanghai/11/87 (H3N2) - 1990-1991: A/Beijing/353/89 (H3N2), B/Panama/45/90-like - 1991-1992: A/Beijing/353/89 (H3N2) This trial was excluded since it was not placebo-controlled and the authors did not specify if the strains used to develop cold-adapted and inactivated vaccines were antigenically comparable or not
Gwini 2011	No design: self controlled case series
Haber 2004	Analysis of temporal trends of Guillain Barré syndrome (GBS) 1990 to 2003, comparison with temporal trends of non-GBS adverse event reports from the Vaccine Adverse Event Reporting System (VAERS)
Haigh 1973	Not randomised: all the volunteers were immunised on a single day and the intention to allocate patients randomly was not strictly adhered to
Halperin 2002	Outcome measures outside inclusion criteria
Hambidge 2011	Participants affected by sickle cell crisis
Hellenbrand 2012	No design: case-control study assessing effectiveness in general population
Hobson 1970	Polyvalent influenza vaccine was used as control
Hobson 1973	Randomised controlled trial. Clinical outcomes were side effects only
Hoskins 1973	Influenza B vaccine was used as control
Hoskins 1976	Not placebo or 'do nothing' controlled
Hoskins 1979	No control group
Howell 1967	Not prospective: appears to be an historical cohort
Hurwitz 1983	Report of GBS surveillance 1978 to 1979, non-comparative study

(*Continued*)

Jackson 2011	No adequate control (the same vaccine prepared with different antigenic concentrations was administered to each group)
Janjua 2012	No design: case-control study assessing effectiveness in general population
Jianping 1999	Not a randomised controlled trial
Jimenez-Jorge 2012	No design: case-control study assessing effectiveness in general population
Keitel 2001	Efficacy outcome measures outside inclusion criteria. The safety data are presented in a non-analysable way
Kelly 2012	No design: case-control study assessing effectiveness in general population
Khazeni 2009	Review and cost-effectiveness analysis
Kiderman 2001	Tables and text show inconsistencies that do not allow data extraction
Kim 2012	Surveillance for adverse events
Kissling 2012	No design: case-control study assessing effectiveness in general population
Kunz 1977	No adequate control
Langley 2004	Review
Lee 2011	No design: self controlled case series
Leeb 2011	No design: case series
Leroux-Roels 2010a	Absence of an adequate control, serological outcomes only
Leroux-Roels 2010b	Absence of an adequate control, serological outcomes only
Liem 1973	Reported the results of 9 placebo-controlled clinical trials and 2 field studies, involving a total of about 10,000 participants, carried out in several countries to assess the efficacy of killed influenza spray vaccines. Studies were conducted during the years 1969 to 1971 Allocation of the participants to the arms of the trials was done according to a pre-determined randomisation scheme. 8 of them were double-blind. The field studies were not randomised. The attack rate for influenza among the population study was very low and in 2 of the trials the vaccination procedure started too late, when the outbreak was ongoing. The attack rates, exclusively based on the serologically confirmed cases, are only reported by a graph and it is impossible to derive the crude data
Louik 2013	Methods for assessing flu vaccine exposure during pregnancy
Mackenzie 1975	No design: allocation is arbitrary and groups with different characteristics were formed
Mackenzie 2012	Non-comparative design

(*Continued*)

Mair 1974	Influenza B vaccine was used as control
Maynard 1968	Influenza B vaccine was used as control
McCarthy 2004	Review
Mendelman 2001	Does not report original results
Merelli 2000	Review
Meyers 2003a	Review
Meyers 2003b	Review
Micheletti 2011	Total number of AEs observed after administration of each vaccine type
Monto 2000	Not a randomised controlled trial
Moro 2011	Non-comparative study
Morris 1975	Design is unclear: no standard random allocation. Only 25 out of 30 seem to have been immunised but in the method description 30 were considered for exposure to natural influenza A/Scotland/840/74. One of these was excluded prior because they had tonsillitis
Mostow 1977	Outcomes were safety only. Absence of adequate control
Muennig 2001	Not a randomised controlled trial
Murray 1979	Not adequate comparison (pregnant versus non-pregnant women)
Nazareth 2013	Absence of control group, non-comparative
Nichol 1996	Same data as Nichol 1995 (included)
Nichol 1999b	Review
Nichol 2001	Not a randomised controlled trial
Nichol 2003	Contains data from previous studies
Nichol 2004	Re-analysis of Nichol 1999 (included)
Omon 2011	Non-comparative study
Petrie 2011	No new data: reports data from already published and included studies (aa Ohmit 2006, aa Ohmit 2008, aa Monto 2009)
Phillips 2013	Absence of adequate control group

(*Continued*)

Puig-Barbera 2012	No design: case-control study assessing effectiveness in general population (also children and elderly)
Puleston 2010	Not outcomes of interest
Pyhala 2001	Not a randomised controlled trial
Reynales 2012	Safety survey after Celtura (H1N1) administration. Absence of control group
Rimmelzwaan 2000	Outcome measures outside inclusion criteria
Rocchi 1979c	Very poor reporting, unclear definition, no description of methods
Rowhani-Rahbar 2012	Participants are children
Ruben 1972	Absence of adequate control
Ruben 1973	Both arms contained the same vaccine strains
Safranek 1991	Re-assessment of Schonberger 1979 (included)
Sarateanu 1980	Absence of adequate control
Schonberger 1981	Review of the evidence of the aetiology of GBS, no original data presented
Schwartz 1996	Report about Nichol 1995 (included)
Simpson 2012	No design: cohort and case-control study assessing effectiveness in general population
Skowronski 2002	Non-comparative (survey)
Skowronski 2003	Population at risk of further ORS episodes
Smith 1977a	Reports a small part of the Hoskins trial. It compared illness occurring among a group of vaccinated boys against non-vaccinated controls that had no part in the trial
Smith 1977b	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Song 2011	One trial is a 'head to head' (Gc501 versus Fluarix) with serological outcomes only, the other one (safety) has no control
Souayah 2011	Compares the incidence of GBS cases after tetravalent HPV vaccine with that observed after pneumococcal and flu vaccine administration
Spencer 1975	Authors did not report crude data on the clinical outcomes
Spencer 1979	Reporting does not allow one to understand the methods used to allocate subjects and to conceal allocation. Clinical outcome data are not reported

(*Continued*)

Steinhoff 2012	Inadequate control (23v pneumococcal vaccine administered to the control group). Re-analysis of Zaman 2008 data (excluded)
Sumaya 1979	No outcomes of interest
Talaat 2010	Data on AEs are not provided in a useful form (bar graphs or cumulatively in the text)
Tavares 2011	Non-comparative
Taylor 1969	No outcomes of interest, rhinovirus vaccine as control
Tokars 2012	No design: controlled case series
Treanor 2001	Outcome measures outside inclusion criteria
Treanor 2002	Outcome measures outside inclusion criteria
Treanor 2012	No design: case-control study
Tsai 2010	Non-comparative
Tsatsaris 2011	Same vaccine administered in different pregnancy weeks (inadequate comparison)
Tyrrell 1970	None of the 3 studies reported in this paper are includible for the following reasons 1. No design, no comparison, no outcomes 2. Probable controlled clinical trial, but subjects' ages probably out of range (schools) 3. No design, even if an unvaccinated control group for school 3 and for the employees of the Imperial Chemical Industries is present
Vesikari 2012	Safety data after dose I (seasonal versus placebo) are not extract (bar graph)
Warshauer 1976	Not randomised. Data reporting was not complete
Wilde 1999	Pneumococcal vaccine was used as control
Williams 1973	No placebo or 'do nothing' control
Williams 2011	No design: case series
Wise 2012	No design
Wood 1999	Not a randomised controlled trial
Wood 2000	Not a randomised controlled trial
Yang 2012	No safety data

(*Continued*)

Yeager 1999	Non-comparative study: absence of a control arm
Yih 2012	No design: controlled case series
Zaman 2008	Inadequate control (23v pneumococcal vaccine administered to the control group)

AEs = adverse events
CDC = Centers for Disease Control and Prevention
CF = cystic fibrosis
GBS =Guillain-Barré syndrome
HA = haemagglutinin
HPV = human papillomavirus
LAIV = live attenuated influenza vaccine
MS = multiple sclerosis
ORS = oculo-respiratory syndrome
rHAO = recombinant uncleaved haemagglutinin glycoprotein

Characteristics of studies awaiting assessment *[ordered by study ID]*

ab Wacheck 2010

Methods	Randomised, dose-escalation study
Participants	Healthy adults (n = 48)
Interventions	ΔNS1-H1N1 A/New/Caledonia vaccine (6.4, 6.7, 7.0, 7.4 and 7.7 $\log_{10}$ MTCID) versus placebo
Outcomes	Local and systemic reactions, immunogenicity
Notes	

ab López-Macías 2011a

Methods	Phase 2, randomised, double-blind, placebo-controlled trial (part A)
Participants	Healthy adults between 18 and 64 (n = 1013)
Interventions	Monovalent, H1N1, pandemic virus-like particles (VLP) influenza vaccine (5, 15, 45 μg of VLP/dose or saline placebo, 2 doses administered 21 days apart)
Outcomes	Adverse events, immunogenicity
Notes	

ab López-Macías 2011b

Methods	Randomised, placebo-controlled, cross-over trial (part B)
Participants	Healthy adults between 18 and 64 (n = 3547)
Interventions	Monovalent, H1N1, pandemic virus-like particles (VLP) influenza vaccine (15 μg of VLP/dose) versus saline placebo
Outcomes	Adverse events
Notes	

ab Mallory 2010

Methods	Randomised, placebo-controlled trial
Participants	Healthy adults aged between 18 and 49 (n = 300)
Interventions	Monovalent, pandemic, H1N1 live attenuated vaccine versus placebo. 2 doses administered 28 days apart
Outcomes	Local and systemic reactions, immunogenicity
Notes	

ab Plennevaux 2010

Methods	Randomised controlled trial
Participants	Healthy adults aged 18 to 64 (n = 849)
Interventions	Monovalent, pandemic H1N1, inactivates, split virion vaccine (1 dose 7.5, 15 or 30 μg HA/dose) versus placebo
Outcomes	Local and systemic reactions, immunogenicity
Notes	

ab Precioso 2011

Methods	Phase 1, multicentre, randomised, double-blind trial
Participants	Healthy adults between 18 and 50 years (n = 266)
Interventions	Monovalent, H1N1, inactivated, split vaccine with different antigenic content, with or without adjuvants and placebo (10 arms)
Outcomes	Local and systemic reaction, immunogenicity
Notes	

ab Treanor 2010

Methods	Dose-escalation study
Participants	Healthy adults aged 18 to 49 (n = 128)
Interventions	Recombinant, haemagglutinin influenza-flagellin fusion vaccine (VAX 125, 0.1, 0.3, 1, 2, 3, 5, 8 μg/dose, placebo)
Outcomes	Local and systemic reactions, C-reactive protein response
Notes	

ab Treanor 2011

Methods	Randomised, placebo-controlled trial
Participants	Healthy adults between 18 and 49 (n = 4648)
Interventions	Recombinant HA protein vaccine versus placebo
Outcomes	Local and systemic reactions, protective efficacy, antibody response
Notes	

ab Turley 2011

Methods	Phase 1, randomised, multicentre trial
Participants	Adults aged between 18 to 49 (n = 60)
Interventions	Recombinant M2e-flagellin influenza vaccine (STF2.4xM2e). Different dosages (0.03, 0.1, 0.3, 1, 3, 10 μg/dose) versus placebo
Outcomes	Local and systemic reactions, immunogenicity
Notes	

Atsmon 2012

Methods	Randomised, single-blind, controlled trial
Participants	Healthy adults aged between 18 and 49 (n = 60)
Interventions	Multimeric-001 influenza vaccine
Outcomes	Local and systemic reactions, immunogenicity
Notes	

Chichester 2012

Methods	Phase 1, randomised, double-blind, placebo-controlled clinical trial
Participants	Healthy adults (n = 100)
Interventions	Recombinant adjuvanted haemagglutinin-based influenza vaccine (HAI-05) administered in 15 μg, 45 μg or 90 μg/dose versus non-adjuvanted vaccine versus placebo. 2 doses were administered
Outcomes	Local and systemic reactions. antibody response.
Notes	

Couch 2012

Methods	Randomised controlled trial
Participants	Healthy adults aged between 18 and 40 (n = 125)
Interventions	Inactivated avian influenza A (H7N7) vaccine containing 7.5, 15, 45 or 90 mg of HA/dose versus placebo. 2 doses were administered 28 days apart
Outcomes	Local and systemic reactions, serum antibody response
Notes	NCT00546585

Heinonen 1973

Methods	Follow-up study
Participants	Pregnant women (n = 50,897) and newborns (years 1958 to 1966)
Interventions	Influenza or polio vaccine during pregnancy
Outcomes	Malignancies
Notes	

Huang 2011

Methods	Follow-up study
Participants	Pregnant women (n = 14,475) immunised with H1N1 pandemic vaccine in Taiwan (season 2009/2010)
Interventions	Administration of adjuvanted or non-adjuvanted pandemic vaccine during pregnancy
Outcomes	Maternal death, gestational age, abortion, neonatal death

Huang 2011 (*Continued*)

Notes	

Phonrat 2013

Methods	Randomised controlled trial
Participants	Healthy adults aged between 12 and 75 (n = 363)
Interventions	Live attenuated, cold-adapted, monovalent H1N1 (A/17/CA/2009/38) versus saline placebo, intranasally administered
Outcomes	Local and systemic reactions, antibody response
Notes	

Pleguezuelos 2012

Methods	Single-centre, randomised, double blind trial
Participants	Healthy males aged 18 to 40 (n = 48), with body mass index between 18.5 and 28.5 kg/m^2, low or non-smoker
Interventions	Administration of synthetic polypeptide vaccine (Flu-v) containing 250 μg or 500 μg of protein/dose (either with or without adjuvant) versus placebo
Outcomes	Local and systemic reactions, antibody response
Notes	

Scheifele 2013

Methods	Randomised controlled trial
Participants	Healthy adults (n = 326) who were immunised with pandemic, monovalent H1N1, AS03 adjuvanted influenza vaccine during the 2009-2010 season in Canada (Arepanrix vaccine)
Interventions	Non-adjuvanted pandemic H1N1 vaccine versus placebo
Outcomes	Local and systemic events, antibody response
Notes	

Taylor 2012

Methods	Randomised, dose-escalation trial
Participants	Healthy adults aged 18 to 49 (n = 112)
Interventions	Recombinant haemagglutinin influenza-flagellin fusion vaccine (VAX128) administered in different antigen concentrations (0.5 to 20 μg/dose) versus buffer placebo
Outcomes	Local and systemic reactions, antibody response
Notes	

Xu 2012

Methods	Cohort study based on data from the North American Organization of Teratology Information Specialists (OTIS)
Participants	Pregnant women (n = 198)
Interventions	Exposure to influenza vaccine at different times of gestation
Outcomes	Spontaneous abortion
Notes	

HA = haemagglutinin
VLP = virus-like particles
MTCID = median tissue culture infective dose

DATA AND ANALYSES

Comparison 1. Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	16	25795	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.78, 0.87]
1.1 WHO recommended - matching vaccine	7	4760	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.77, 0.89]
1.2 WHO recommended - vaccine matching absent or unknown	7	20942	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.75, 0.90]
1.3 Monovalent not WHO recommended - vaccine matching	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.28, 3.70]
1.4 Monovalent not WHO recommended - vaccine matching - high dose	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.09, 2.30]
2 Influenza	22	51724	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.33, 0.44]
2.1 WHO recommended - matching vaccine	12	26947	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.31, 0.45]
2.2 WHO recommended - vaccine matching absent or unknown	7	15068	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.35, 0.56]
2.3 Monovalent not WHO recommended - vaccine matching	2	9675	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.10, 0.54]
2.4 Monovalent not WHO recommended - vaccine matching - high dose	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.00, 2.49]
3 Physician visits	2	2308	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.40, 1.89]
3.1 WHO recommended - matching vaccine	1	1178	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.37, 0.91]
3.2 WHO recommended - vaccine matching absent or unknown	1	1130	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.90, 1.83]
4 Days ill	3	3133	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.98, 0.56]
4.1 WHO recommended - matching vaccine	2	2003	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.85, -0.32]
4.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	0.66 [0.16, 1.16]
5 Times any drugs were prescribed	2	2308	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
5.1 WHO recommended - matching vaccine	1	1178	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.04, -0.00]
5.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	0.0 [-0.00, 0.00]
6 Times antibiotic was prescribed	2	2308	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.03, -0.01]

6.1 WHO recommended - matching vaccine	1	1178	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.03, -0.01]
6.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
7 Working days lost	4	3726	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.14, 0.06]
7.1 WHO recommended - matching vaccine	3	2596	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.19, 0.02]
7.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	0.09 [0.00, 0.18]
8 Hospitalisations	3	11924	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.08]
8.1 WHO recommended - matching vaccine	1	1178	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 WHO recommended - vaccine matching absent or unknown	1	1130	Risk Ratio (M-H, Random, 95% CI)	2.89 [0.12, 70.68]
8.3 Monovalent not WHO recommended - vaccine matching	1	9616	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.08]
9 Clinical cases (clinically defined without clear definition)	3	4259	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.05]
9.1 WHO recommended - matching vaccine	2	2056	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.25]
9.2 WHO recommended - vaccine matching absent or unknown	1	2203	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 0.99]
10 Local harms	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Local - tenderness/soreness	20	35655	Risk Ratio (M-H, Random, 95% CI)	3.13 [2.44, 4.02]
10.2 Local - erythema	9	29499	Risk Ratio (M-H, Random, 95% CI)	2.59 [1.77, 3.78]
10.3 Local - induration	3	7786	Risk Ratio (M-H, Random, 95% CI)	4.28 [1.25, 14.67]
10.4 Local - arm stiffness	1	50	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.54, 4.83]
10.5 Local - combined endpoint (any or highest symptom)	11	12307	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.82, 3.28]
11 Systemic harms	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Systemic - myalgia	10	30360	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.40, 2.24]
11.2 Systemic - fever	12	19202	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.22, 1.95]
11.3 Systemic - headache	13	31351	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.01, 1.36]
11.4 Systemic - fatigue or indisposition	11	31140	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.07, 1.42]
11.5 Systemic - nausea/vomiting	3	1667	Risk Ratio (M-H, Random, 95% CI)	2.68 [0.55, 13.08]
11.6 Systemic - malaise	3	26111	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.18, 1.92]
11.7 Systemic - combined endpoint (any or highest symptom)	6	2128	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.87, 1.53]

Comparison 2. Live aerosol vaccine versus placebo or 'do nothing'

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	6	12688	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.84, 0.96]
1.1 WHO recommended - matching vaccine	2	4254	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.12]
1.2 WHO recommended - vaccine matching absent or unknown	3	8150	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.97]
1.3 Non WHO recommended - vaccine matching absent or unknown	1	284	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
2 Influenza	9	11579	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.35, 0.62]
2.1 WHO recommended - matching vaccine	4	6584	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.82]
2.2 WHO recommended - vaccine matching absent or unknown	3	4568	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.68]
2.3 Non WHO recommended - vaccine matching absent or unknown	2	427	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.08, 0.56]
3 Influenza cases (clinically defined without clear definition)	3	23900	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.71, 1.11]
3.1 WHO recommended - matching vaccine	1	1931	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.80]
3.2 WHO recommended - vaccine matching absent or unknown	1	2082	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.25]
3.3 Non WHO recommended - vaccine matching absent or unknown	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
4 Local harms	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Local - upper respiratory infection symptoms	6	496	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.22, 2.27]
4.2 Local - cough	6	2401	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.08, 2.10]
4.3 Local - coryza	2	4782	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.26, 1.94]
4.4 Local - sore throat	7	6940	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.49, 1.86]
4.5 Local - hoarseness	1	306	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.51, 2.83]
4.6 Local - combined endpoint (any or highest symptom)	3	4921	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.31, 1.87]
5 Systemic harms	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Systemic - myalgia	4	1318	Risk Ratio (M-H, Random, 95% CI)	2.47 [1.26, 4.85]
5.2 Systemic - fever	4	1318	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.54, 1.92]
5.3 Systemic - fatigue or indisposition	3	1018	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.93, 2.07]
5.4 Systemic - headache	2	975	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.09, 2.18]

5.5 Systemic - combined endpoint (any or highest symptom)	5	1018	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.82, 2.38]

Comparison 3. Inactivated aerosol vaccine versus placebo or 'do nothing'

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	1	1348	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.14, 1.02]
1.1 WHO recommended - vaccine matching absent or unknown	1	1348	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.14, 1.02]
1.2 WHO recommended - matching vaccine	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Local harms	3	1578	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.71, 1.27]
2.1 Local - sore throat	3	1500	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.54, 1.33]
2.2 Local - combined endpoint (any or highest symptom)	1	78	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.71, 1.48]
3 Systemic harms	3	1880	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.71, 1.62]
3.1 Systemic - myalgia	2	151	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.36, 2.25]
3.2 Systemic - fatigue or indisposition	2	151	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.52, 3.75]
3.3 Systemic - headache	2	151	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.85, 2.72]
3.4 Systemic - fever	1	1349	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.03, 7.80]
3.5 Systemic - combined endpoint (any or highest symptom)	1	78	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.12, 1.04]

Comparison 4. Inactivated parenteral vaccine versus placebo - cohort studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seasonal inactivated vaccine effectiveness in mothers - pregnant women	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 H1N1 - vaccine - effectiveness ILI (unadjusted data)	1	7328	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.06, 0.21]
1.2 Seasonal - vaccine - effectiveness ILI - (unadjusted data)	2	50129	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.22, 1.32]
2 Seasonal inactivated vaccine effectiveness in newborns - pregnant women	2		Hazard Ratio (Random, 95% CI)	Subtotals only

2.1 Seasonal vaccine effectiveness ILI (HR adjusted data)	2	Hazard Ratio (Random, 95% CI)	0.96 [0.90, 1.03]
3 Seasonal inactivated vaccine effectiveness in newborns - pregnant women	1	Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Seasonal vaccine effectiveness ILI (RR adjusted data)	1	Risk Ratio (Random, 95% CI)	0.92 [0.73, 1.16]
3.2 Seasonal vaccine efficacy influenza - laboratory-confirmed	1	Risk Ratio (Random, 95% CI)	0.59 [0.37, 0.94]
4 H1N1 vaccine - safety - pregnancy-related outcomes - pregnant women	9	Odds Ratio (Random, 95% CI)	Subtotals only
4.1 Abortion (OR - adjusted data)	5	Odds Ratio (Random, 95% CI)	0.75 [0.62, 0.90]
4.2 Abortion (HR - adjusted data)	2	Odds Ratio (Random, 95% CI)	0.88 [0.67, 1.16]
4.3 Congenital malformation (OR - adjusted data)	5	Odds Ratio (Random, 95% CI)	1.06 [0.90, 1.25]
4.4 Prematurity (< 37 weeks) (OR adjusted data)	8	Odds Ratio (Random, 95% CI)	0.86 [0.76, 0.97]
4.5 Neonatal death (OR adjusted data)	1	Odds Ratio (Random, 95% CI)	1.81 [0.16, 20.35]
5 Seasonal vaccine - safety - pregnancy-related outcomes - pregnant women	4	Odds Ratio (Random, 95% CI)	Subtotals only
5.1 Abortion (OR - unadjusted data)	1	Odds Ratio (Random, 95% CI)	0.60 [0.41, 0.86]
5.2 Congenital malformation (OR unadjusted data)	2	Odds Ratio (Random, 95% CI)	0.55 [0.08, 3.73]
5.3 Prematurity (OR unadjusted data)	4	Odds Ratio (Random, 95% CI)	0.96 [0.79, 1.17]
5.4 Neonatal death (OR unadjusted data)	1	Odds Ratio (Random, 95% CI)	0.55 [0.35, 0.88]

Comparison 5. Inactivated parenteral vaccine versus placebo - case-control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Effectiveness in newborns - pregnant women (adjusted data)	2		Odds Ratio (Random, 95% CI)	0.24 [0.04, 1.40]
1.1 Seasonal vaccine - effectiveness - ILI - pregnant women	2		Odds Ratio (Random, 95% CI)	0.24 [0.04, 1.40]

2 Seasonal vaccine safety - pregnancy-related outcomes (adjusted data)	1	Odds Ratio (Random, 95% CI)	0.80 [0.36, 1.78]
2.1 Abortion	1	Odds Ratio (Random, 95% CI)	0.80 [0.36, 1.78]

Comparison 6. Serious adverse events - Guillain-Barré syndrome - cohort studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seasonal influenza vaccination and Guillain-Barré syndrome	3		Risk Ratio (Random, 95% CI)	1.28 [0.85, 1.93]
1.1 General population (adjusted data)	2		Risk Ratio (Random, 95% CI)	1.29 [0.83, 2.02]
1.2 Pregnant women (unadjusted data)	1		Risk Ratio (Random, 95% CI)	0.65 [0.03, 15.95]

Comparison 7. Serious adverse events - Guillain-Barré syndrome - case-control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 2009 to 2010 A/H1N1 - general population (unadjusted data)	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 < 7 weeks	6	1528	Odds Ratio (M-H, Random, 95% CI)	2.22 [1.14, 4.31]
1.2 At any time	6	1656	Odds Ratio (M-H, Random, 95% CI)	1.69 [0.87, 3.29]
2 2009 to 2010 A/H1N1 - general population (adjusted data)	4		Odds Ratio (Random, 95% CI)	0.83 [0.39, 1.75]
2.1 < 7 weeks	4		Odds Ratio (Random, 95% CI)	0.92 [0.35, 2.40]
2.2 > 6 weeks	3		Odds Ratio (Random, 95% CI)	0.71 [0.22, 2.32]
3 Seasonal influenza vaccination general population (adjusted data)	1		Odds Ratio (Random, 95% CI)	1.38 [0.18, 10.43]

Comparison 8. Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - cohort studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza vaccination (seasonal) - demyelinating diseases (unadjusted data)	1	223898	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.25]
1.1 General population	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Pregnant women	1	223898	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.25]

2 Influenza vaccination (H1N1) - demyelinating diseases (unadjusted)	1	144252	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.51, 8.22]

Comparison 9. Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza vaccination (seasonal) - general population - demyelinating diseases (unadjusted data)	4	8009	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.17]
2 Influenza vaccination (seasonal) - general population - multiple sclerosis (adjusted data)	2		(Random, 95% CI)	0.76 [0.54, 1.08]
3 Influenza vaccination (seasonal) - general population - optic neuritis (adjusted data)	2		Odds Ratio (Random, 95% CI)	1.03 [0.82, 1.30]

Comparison 10. Serious adverse events - immune thrombocytopaenic purpura - cohort studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seasonal influenza vaccine - HR (adjusted data)	1		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 General population	0		Hazard Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Pregnant women	1		Hazard Ratio (Random, 95% CI)	0.90 [0.68, 1.19]
2 Seasonal influenza vaccine (unadjusted data)	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 General population	0	0	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Pregnant women	1	223898	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.70, 1.20]

Comparison 11. Serious adverse events - immune thrombocytopaenic purpura - case-control studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seasonal influenza vaccine - general population (adjusted data)	2		Odds Ratio (Random, 95% CI)	Subtotals only
1.1 < 2 months	2		Odds Ratio (Random, 95% CI)	1.87 [0.43, 8.06]
1.2 < 6 months	1		Odds Ratio (Random, 95% CI)	0.90 [0.55, 1.47]

1.3 < 12 months	1		Odds Ratio (Random, 95% CI)	0.70 [0.47, 1.04]
2 Seasonal influenza vaccine - general population (unadjusted data)	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 < 2 months	2	1926	Odds Ratio (M-H, Random, 95% CI)	1.72 [0.48, 6.15]
2.2 < 6 months	1	1065	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.59, 1.43]
2.3 < 12 months	1	1066	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.50, 1.05]

Comparison 12. 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	3	3065	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.57, 0.88]
1.1 Standard recommended parenteral - non-matching - 1 dose	3	2715	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.95]
1.2 Standard recommended parenteral - non-matching - 2 doses	1	350	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.44, 0.98]
2 Influenza	1	2072	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.26, 0.87]
2.1 Standard recommended parenteral - non-matching	1	2072	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.26, 0.87]
3 Hospitalisations	1	2072	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.68]
3.1 Standard recommended parenteral - non-matching	1	2072	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.68]
4 Pneumonia	1	2072	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.14, 7.17]
4.1 Standard recommended parenteral - non-matching	1	2072	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.14, 7.17]

Comparison 13. 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	4	4580	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.48]
1.1 WHO recommended parenteral - matching vaccine - 1 dose	4	4226	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.23, 0.53]
1.2 WHO recommended parenteral - matching vaccine - 2 doses	1	354	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.22, 0.57]
2 Influenza	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.02, 0.31]
2.1 WHO recommended parenteral - matching vaccine	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.02, 0.31]
3 Hospitalisations	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.94]

3.1 WHO recommended parenteral - matching vaccine	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.94]
4 Pneumonia	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.05, 6.51]
4.1 WHO recommended parenteral - matching vaccine	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.05, 6.51]
5 Working days lost	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]
5.1 WHO recommended parenteral - matching vaccine	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]
6 Days ill	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]
6.1 WHO recommended - matching vaccine	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]

Comparison 14. 1968 to 1969 pandemic: inactivated polyvalent aerosol vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	2	1000	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.46, 0.95]
1.1 Inactivated polyvalent aerosol vaccine versus placebo - non-matching - 1 dose	2	644	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.32, 1.27]
1.2 Inactivated polyvalent aerosol vaccine versus placebo - non-matching - 2 doses	1	356	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.97]

Comparison 15. 1968 to 1969 pandemic: inactivated monovalent aerosol vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	2	1009	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.32, 0.91]
1.1 Inactivated monovalent aerosol vaccine versus placebo - matching - 1 dose	2	650	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.17, 1.41]
1.2 Inactivated monovalent aerosol vaccine versus placebo - matching - 2 doses	1	359	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.86]

Comparison 16. 1968 to 1969 pandemic: live aerosol vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza cases (clinically defined without clear definition)	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
1.1 Non-matching	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
2 Complications (bronchitis, otitis, pneumonia)	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.24]
2.1 Non-matching	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.24]

Analysis 1.1. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 1 Influenza-like illness

Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 WHO recommended - matching vaccine					
aa Bridges 2000b	82/582	128/596		7.8 %	0.66 [0.51, 0.84]
aa Mix u 2002	86/294	98/299		6.0 %	0.89 [0.70, 1.14]
aa Keitel 1997b	25/723	14/217		1.3 %	0.54 [0.28, 1.01]
aa Powers 1995a	4/26	2/8		0.2 %	0.62 [0.14, 2.76]
aa Keitel 1988b	13/456	9/241		0.7 %	0.76 [0.33, 1.76]
aa Mesa Duque 2001	194/247	225/246		13.9 %	0.86 [0.80, 0.93]
aa Nichol 1995	249/409	287/416		17.5 %	0.88 [0.80, 0.98]
Subtotal (95% CI)	**2737**	**2023**		**47.4 %**	**0.83 [0.77, 0.89]**
Total events: 653 (Vaccine), 763 (placebo / do nothing)					
Heterogeneity: Chi² = 8.12, df = 6 (P = 0.23); I² =26%					
Test for overall effect: Z = 5.41 (P < 0.00001)					
2 WHO recommended - vaccine matching absent or unknown					
aa Bridges 2000a	161/576	132/554		8.3 %	1.17 [0.96, 1.43]
aa Keitel 1988a	15/300	14/298		0.9 %	1.06 [0.52, 2.17]
aa Keitel 1997c	53/789	14/145		1.5 %	0.70 [0.40, 1.22]
aa Frey 2010	432/7414	353/3843		28.6 %	0.63 [0.55, 0.73]

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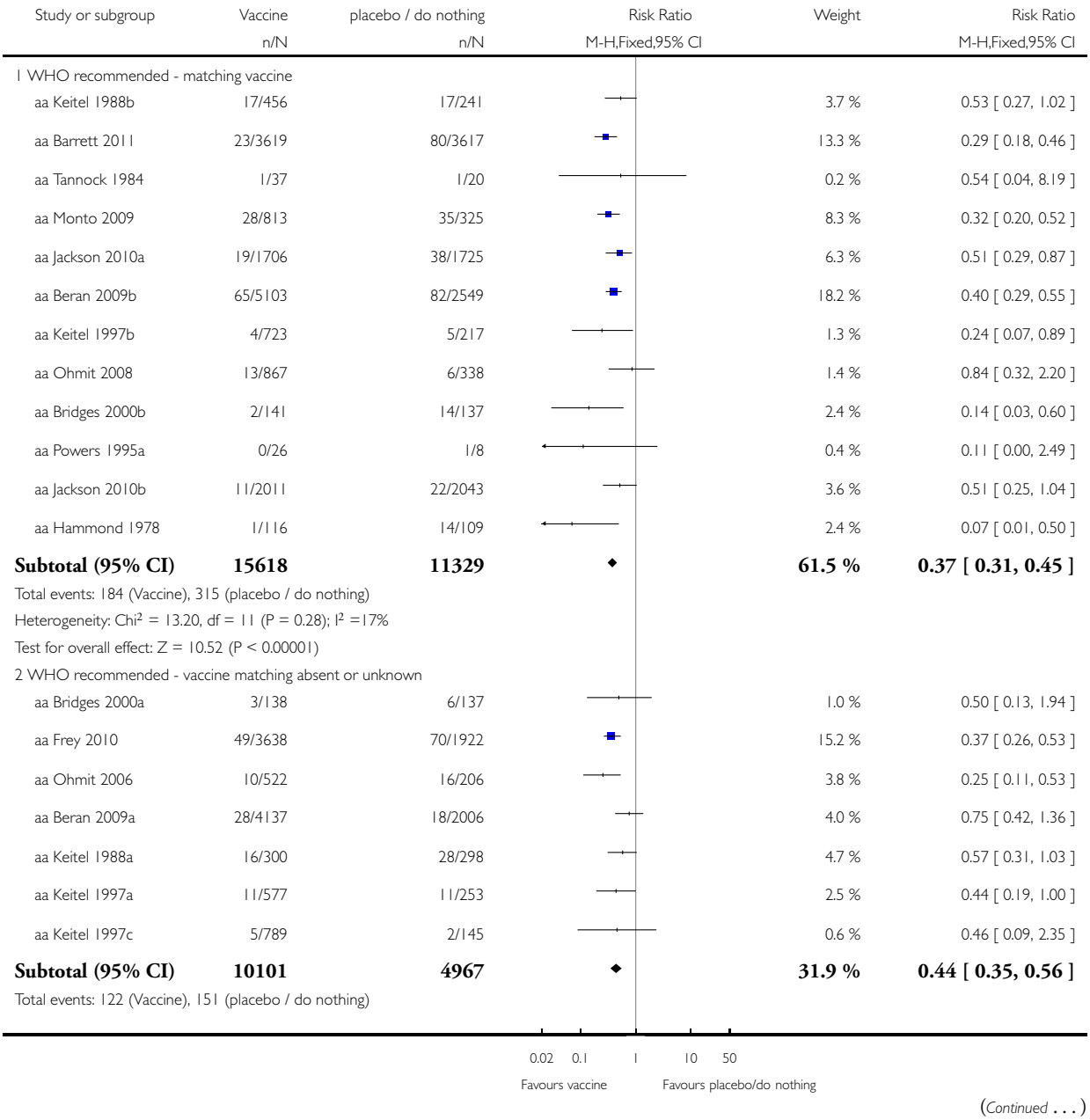
Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
aa Keitel 1997a	41/577	23/253		2.0 %	0.78 [0.48, 1.27]
aa Weingarten 1988	21/91	19/88		1.2 %	1.07 [0.62, 1.85]
aa Beran 2009a	254/4011	120/2003		9.8 %	1.06 [0.86, 1.30]
Subtotal (95% CI)	**13758**	**7184**		**52.2 %**	**0.82 [0.75, 0.90]**
Total events: 977 (Vaccine), 675 (placebo / do nothing)					
Heterogeneity: Chi^2 = 33.72, df = 6 (P<0.00001); I^2 =82%					
Test for overall effect: Z = 4.11 (P = 0.000040)					
3 Monovalent not WHO recommended - vaccine matching					
aa Powers 1995c	13/51	2/8		0.2 %	1.02 [0.28, 3.70]
Subtotal (95% CI)	**51**	**8**		**0.2 %**	**1.02 [0.28, 3.70]**
Total events: 13 (Vaccine), 2 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
4 Monovalent not WHO recommended - vaccine matching - high dose					
aa Powers 1995b	3/26	2/8		0.2 %	0.46 [0.09, 2.30]
Subtotal (95% CI)	**26**	**8**		**0.2 %**	**0.46 [0.09, 2.30]**
Total events: 3 (Vaccine), 2 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.34)					
Total (95% CI)	**16572**	**9223**		**100.0 %**	**0.83 [0.78, 0.87]**
Total events: 1646 (Vaccine), 1442 (placebo / do nothing)					
Heterogeneity: Chi^2 = 42.62, df = 15 (P = 0.00018); I^2 =65%					
Test for overall effect: Z = 6.45 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.61, df = 3 (P = 0.89), I^2 =0.0%					

Analysis 1.2. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 2 Influenza



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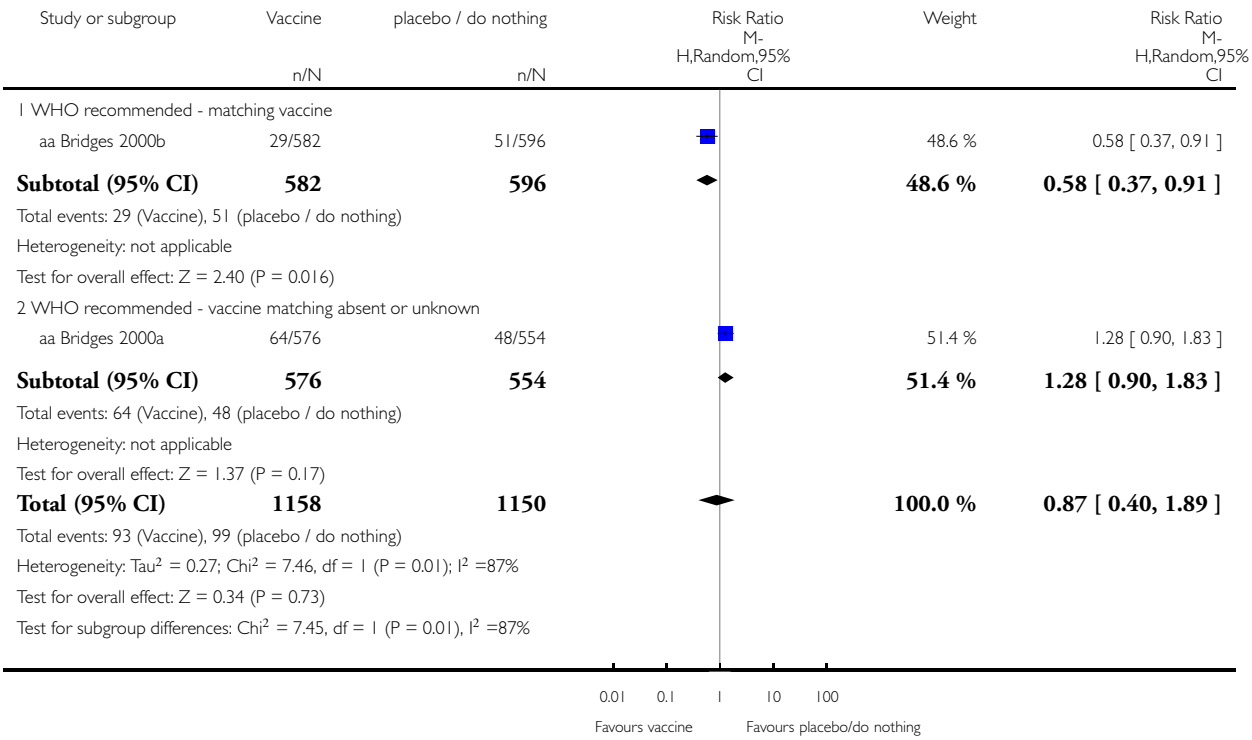
Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 6.99, df = 6 (P = 0.32); I² =14%					
Test for overall effect: Z = 6.74 (P < 0.00001)					
3 Monovalent not WHO recommended - vaccine matching					
aa Leibovitz 1971	5/1682	102/7934		5.9 %	0.23 [0.09, 0.57]
aa Powers 1995c	1/51	1/8		0.3 %	0.16 [0.01, 2.26]
Subtotal (95% CI)	**1733**	**7942**		**6.2 %**	**0.23 [0.10, 0.54]**
Total events: 6 (Vaccine), 103 (placebo / do nothing)					
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² =0.0%					
Test for overall effect: Z = 3.34 (P = 0.00083)					
4 Monovalent not WHO recommended - vaccine matching - high dose					
aa Powers 1995b	0/26	1/8		0.4 %	0.11 [0.00, 2.49]
Subtotal (95% CI)	**26**	**8**		**0.4 %**	**0.11 [0.00, 2.49]**
Total events: 0 (Vaccine), 1 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
Total (95% CI)	**27478**	**24246**		**100.0 %**	**0.38 [0.33, 0.44]**
Total events: 312 (Vaccine), 570 (placebo / do nothing)					
Heterogeneity: Chi² = 23.63, df = 21 (P = 0.31); I² =11%					
Test for overall effect: Z = 12.99 (P < 0.00001)					
Test for subgroup differences: Chi² = 3.52, df = 3 (P = 0.32), I² =15%					

Analysis 1.3. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 3 Physician visits.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 3 Physician visits

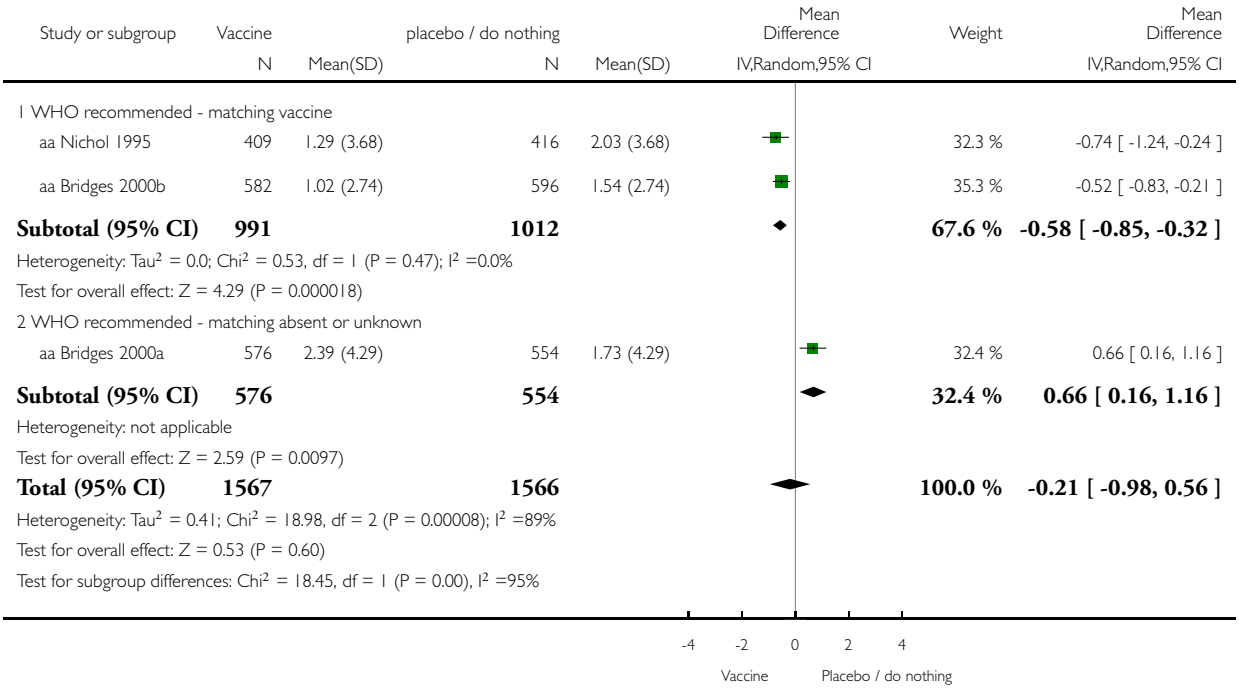


Analysis 1.4. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 4 Days ill.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 4 Days ill



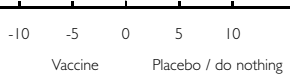
Analysis 1.5. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 5 Times any drugs were prescribed.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 5 Times any drugs were prescribed

Study or subgroup	Vaccine N	Mean(SD)	placebo / do nothing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
aa Bridges 2000b	582	0.05 (0.14)	596	0.07 (0.14)		41.7 %	-0.02 [-0.04, 0.00]
Subtotal (95% CI)	**582**		**596**			**41.7 %**	**-0.02 [-0.04, 0.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.45 (P = 0.014)							
2 WHO recommended - matching absent or unknown							
aa Bridges 2000a	576	0.08 (0.01)	554	0.08 (0.01)		58.3 %	0.0 [0.00, 0.00]
Subtotal (95% CI)	**576**		**554**			**58.3 %**	**0.0 [0.00, 0.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**1158**		**1150**			**100.0 %**	**-0.01 [-0.03, 0.01]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.98, df = 1 (P = 0.01); I^2 =83%							
Test for overall effect: Z = 0.85 (P = 0.40)							
Test for subgroup differences: Chi^2 = 5.98, df = 1 (P = 0.01), I^2 =83%							



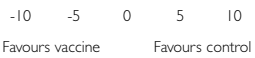
Analysis 1.6. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 6 Times antibiotic was prescribed.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 6 Times antibiotic was prescribed

Study or subgroup	Vaccine N	Mean(SD)	placebo / do nothing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
aa Bridges 2000b	582	0.04 (0.12)	596	0.06 (0.12)		55.0 %	-0.02 [-0.03, -0.01]
Subtotal (95% CI)	**582**		**596**			**55.0 %**	**-0.02 [-0.03, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.86 (P = 0.0042)							
2 WHO recommended - matching absent or unknown							
aa Bridges 2000a	576	0.06 (0.13)	554	0.07 (0.13)		45.0 %	-0.01 [-0.03, 0.01]
Subtotal (95% CI)	**576**		**554**			**45.0 %**	**-0.01 [-0.03, 0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.29 (P = 0.20)							
Total (95% CI)	**1158**		**1150**			**100.0 %**	**-0.02 [-0.03, -0.01]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.92, df = 1 (P = 0.34); I^2 =0.0%							
Test for overall effect: Z = 2.99 (P = 0.0028)							
Test for subgroup differences: Chi^2 = 0.92, df = 1 (P = 0.34), I^2 =0.0%							



Analysis 1.7. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 7 Working days lost.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 7 Working days lost

Study or subgroup	Vaccine N	Mean(SD)	placebo / do nothing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
aa Bridges 2000b	582	0.08 (0.21)	596	0.12 (0.21)		37.0 %	-0.04 [-0.06, -0.02]
aa Nichol 1995	409	1.29 (3.69)	416	2.03 (3.68)		3.5 %	-0.74 [-1.24, -0.24]
aa Mix u 2002	294	0.26 (0.48)	299	0.34 (0.48)		30.6 %	-0.08 [-0.16, 0.00]
Subtotal (95% CI)	**1285**		**1311**			**71.1 %**	**-0.09 [-0.19, 0.02]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.29$, df = 2 (P = 0.02); $I^2 = 76\%$							
Test for overall effect: Z = 1.59 (P = 0.11)							
2 WHO recommended - matching absent or unknown							
aa Bridges 2000a	576	0.29 (0.76)	554	0.2 (0.76)		28.9 %	0.09 [0.00, 0.18]
Subtotal (95% CI)	**576**		**554**			**28.9 %**	**0.09 [0.00, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.99 (P = 0.047)							
Total (95% CI)	**1861**		**1865**			**100.0 %**	**-0.04 [-0.14, 0.06]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 16.64$, df = 3 (P = 0.00084); $I^2 = 82\%$							
Test for overall effect: Z = 0.78 (P = 0.44)							
Test for subgroup differences: $Chi^2 = 6.24$, df = 1 (P = 0.01), $I^2 = 84\%$							

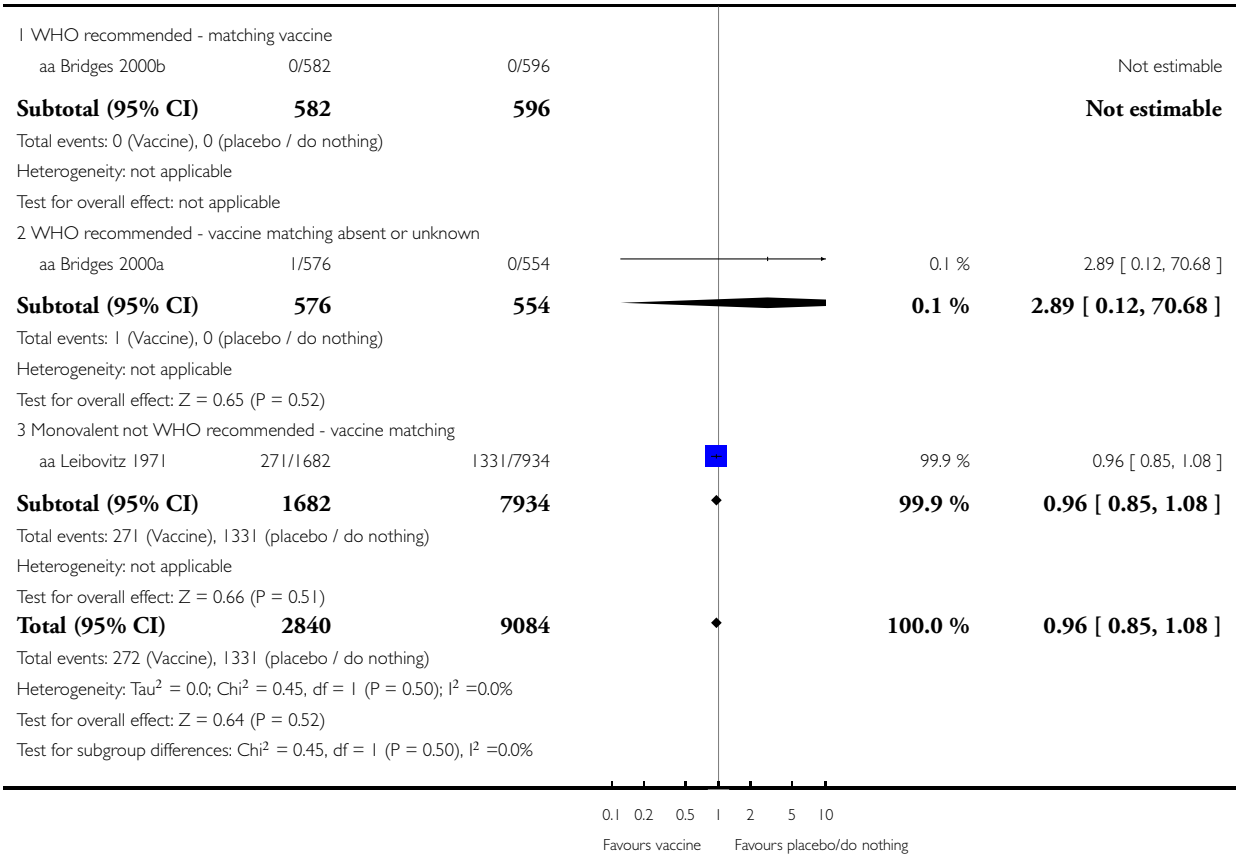
Analysis 1.8. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 8 Hospitalisations.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 8 Hospitalisations

Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
aa Bridges 2000b	0/582	0/596			Not estimable
Subtotal (95% CI)	**582**	**596**			**Not estimable**
Total events: 0 (Vaccine), 0 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 WHO recommended - vaccine matching absent or unknown					
aa Bridges 2000a	1/576	0/554		0.1 %	2.89 [0.12, 70.68]
Subtotal (95% CI)	**576**	**554**		**0.1 %**	**2.89 [0.12, 70.68]**
Total events: 1 (Vaccine), 0 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
3 Monovalent not WHO recommended - vaccine matching					
aa Leibovitz 1971	271/1682	1331/7934		99.9 %	0.96 [0.85, 1.08]
Subtotal (95% CI)	**1682**	**7934**		**99.9 %**	**0.96 [0.85, 1.08]**
Total events: 271 (Vaccine), 1331 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Total (95% CI)	**2840**	**9084**		**100.0 %**	**0.96 [0.85, 1.08]**
Total events: 272 (Vaccine), 1331 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%					

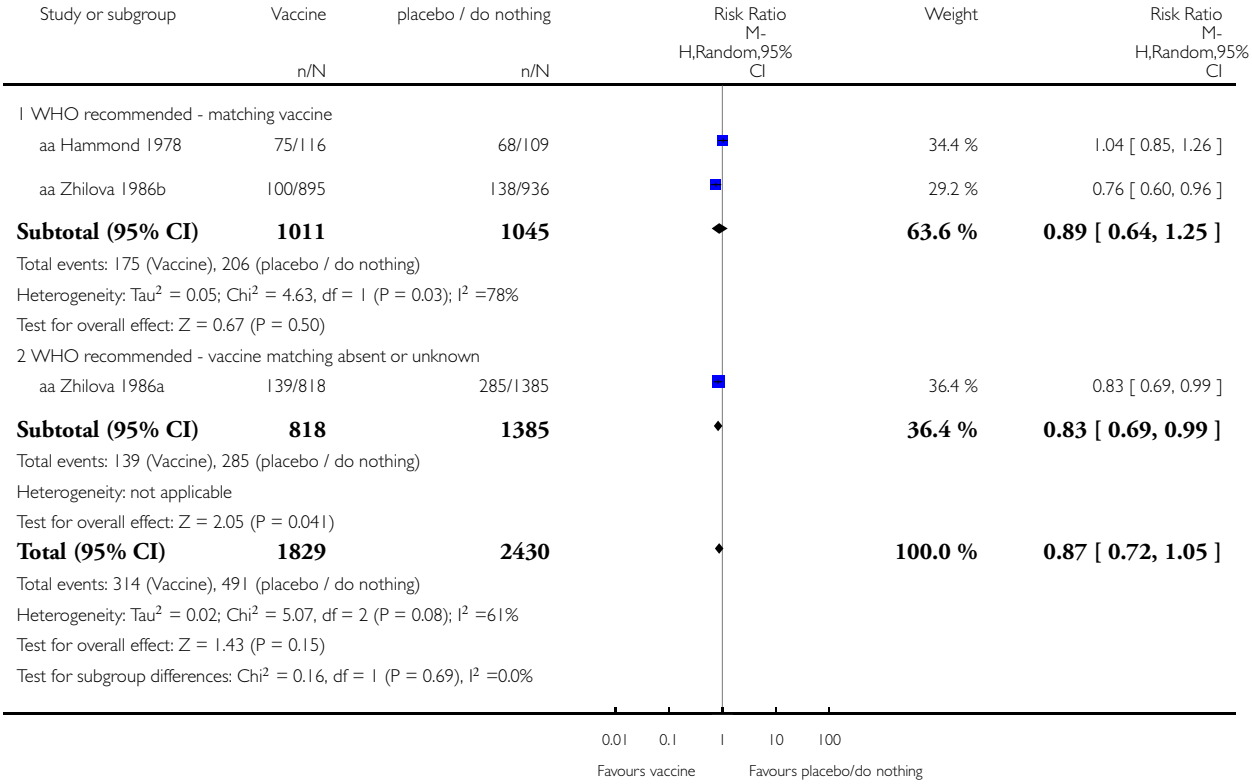


Analysis 1.9. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 9 Clinical cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 9 Clinical cases (clinically defined without clear definition)



Analysis 1.10. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 10 Local harms.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 10 Local harms

Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Local - tenderness/soreness					
aa Monto 2009	428/813	69/325		5.9 %	2.48 [1.99, 3.09]
aa Weingarten 1988	28/55	4/53		3.2 %	6.75 [2.54, 17.93]
ab El'shina 1996	21/108	3/107		2.6 %	6.94 [2.13, 22.57]
aa Ohmit 2008	412/818	22/155		5.4 %	3.55 [2.40, 5.26]
aa Barrett 2011	1571/3623	274/3620		6.1 %	5.73 [5.08, 6.46]
ab Forsyth 1967	81/194	13/186		4.8 %	5.97 [3.45, 10.35]
aa Ohmit 2006	270/501	20/99		5.3 %	2.67 [1.79, 3.98]
aa Jackson 2010a	1933/3783	530/3828		6.2 %	3.69 [3.39, 4.02]
ab Saxen 1999	60/216	15/211		4.8 %	3.91 [2.29, 6.66]
aa Nichol 1995	267/419	101/422		6.0 %	2.66 [2.21, 3.20]
aa Tannock 1984	31/55	11/31		4.8 %	1.59 [0.94, 2.69]
aa Powers 1995a	21/26	5/24		3.8 %	3.88 [1.74, 8.65]
ab Scheifele 2003	323/620	45/624		5.7 %	7.22 [5.40, 9.67]
ab Pyrhönen 1981	89/151	12/154		4.7 %	7.56 [4.32, 13.23]
aa Bridges 2000a	315/594	106/586		6.0 %	2.93 [2.43, 3.54]
aa Mesa Duque 2001	128/247	133/246		6.0 %	0.96 [0.81, 1.13]
ab Caplan 1977	89/193	9/15		5.2 %	0.77 [0.49, 1.19]
aa Frey 2010	2006/7414	384/3843		6.1 %	2.71 [2.45, 3.00]
aa Bridges 2000b	309/582	130/595		6.0 %	2.43 [2.05, 2.88]
ab Goodeve 1983	13/96	1/23		1.3 %	3.11 [0.43, 22.61]
Subtotal (95% CI)	**20508**	**15147**		**100.0 %**	**3.13 [2.44, 4.02]**
Total events: 8395 (Vaccine), 1887 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.26; Chi^2 = 443.11, df = 19 (P<0.00001); I^2 =96%					
Test for overall effect: Z = 8.98 (P < 0.00001)					
2 Local - erythema					

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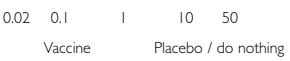
Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Weingarten 1988	6/55	0/53		1.6 %	12.54 [0.72, 217.16]
aa Bridges 2000a	86/594	34/586		17.2 %	2.50 [1.71, 3.65]
ab Forsyth 1967	61/194	0/186		1.7 %	117.95 [7.35, 1893.36]
aa Bridges 2000b	92/582	45/595		17.8 %	2.09 [1.49, 2.93]
aa Mesa Duque 2001	8/247	1/246		2.9 %	7.97 [1.00, 63.23]
aa Jackson 2010a	475/3783	234/3828		20.1 %	2.05 [1.77, 2.39]
aa Powers 1995a	7/26	0/24		1.7 %	13.89 [0.84, 230.82]
aa Frey 2010	964/7414	384/3843		20.4 %	1.30 [1.16, 1.45]
aa Barrett 2011	114/3623	27/3620		16.6 %	4.22 [2.78, 6.40]
Subtotal (95% CI)	**16518**	**12981**		**100.0 %**	**2.59 [1.77, 3.78]**
Total events: 1813 (Vaccine), 725 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 68.86, df = 8 (P<0.00001); I^2 =88%					
Test for overall effect: Z = 4.93 (P < 0.00001)					
3 Local - induration					
aa Mesa Duque 2001	9/247	2/246		29.1 %	4.48 [0.98, 20.53]
aa Barrett 2011	125/3623	14/3620		47.3 %	8.92 [5.14, 15.47]
aa Powers 1995a	2/26	2/24		23.6 %	0.92 [0.14, 6.05]
Subtotal (95% CI)	**3896**	**3890**		**100.0 %**	**4.28 [1.25, 14.67]**
Total events: 136 (Vaccine), 18 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.76; Chi^2 = 5.59, df = 2 (P = 0.06); I^2 =64%					
Test for overall effect: Z = 2.31 (P = 0.021)					
4 Local - arm stiffness					
aa Powers 1995a	7/26	4/24		100.0 %	1.62 [0.54, 4.83]
Subtotal (95% CI)	**26**	**24**		**100.0 %**	**1.62 [0.54, 4.83]**
Total events: 7 (Vaccine), 4 (placebo / do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
5 Local - combined endpoint (any or highest symptom)					
aa Jackson 2010a	2487/3783	1675/3828		12.7 %	1.50 [1.44, 1.57]
aa Tannock 1984	31/55	11/31		9.0 %	1.59 [0.94, 2.69]
ab Goodeve 1983	16/96	1/23		1.9 %	3.83 [0.54, 27.44]
aa Nichol 1995	267/419	101/422		12.1 %	2.66 [2.21, 3.20]
ab Saxen 1999	60/216	15/211		9.0 %	3.91 [2.29, 6.66]
aa Bridges 2000a	315/594	106/586		12.1 %	2.93 [2.43, 3.54]
aa Mesa Duque 2001	128/247	133/246		12.2 %	0.96 [0.81, 1.13]



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Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Bridges 2000b	309/582	130/595		12.2 %	2.43 [2.05, 2.88]
aa Weingarten 1988	28/55	4/53		5.3 %	6.75 [2.54, 17.93]
ab El'shina 1996	35/108	7/107		6.8 %	4.95 [2.30, 10.66]
aa Powers 1995a	21/26	5/24		6.6 %	3.88 [1.74, 8.65]
Subtotal (95% CI)	**6181**	**6126**		**100.0 %**	**2.44 [1.82, 3.28]**
Total events: 3697 (Vaccine), 2188 (placebo / do nothing)					
Heterogeneity: Tau² = 0.18; Chi² = 177.54, df = 10 (P<0.00001); I² =94%					
Test for overall effect: Z = 5.94 (P < 0.00001)					

Analysis 1.11. Comparison 1 Inactivated parenteral vaccine versus placebo or 'do nothing', Outcome 11 Systemic harms.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 1 Inactivated parenteral vaccine versus placebo or 'do nothing'

Outcome: 11 Systemic harms

Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Systemic - myalgia					
ab Rocchi 1979a	2/126	2/110		1.3 %	0.87 [0.13, 6.09]
ab Pyrhönen 1981	26/151	12/154		7.7 %	2.21 [1.16, 4.22]
aa Powers 1995a	5/26	4/24		3.2 %	1.15 [0.35, 3.80]
aa Ohmit 2006	74/501	13/99		9.2 %	1.12 [0.65, 1.95]
ab Scheifele 2003	34/620	18/624		9.0 %	1.90 [1.09, 3.33]
aa Ohmit 2008	110/818	9/155		7.5 %	2.32 [1.20, 4.47]
aa Frey 2010	817/7414	269/3843		17.6 %	1.57 [1.38, 1.80]

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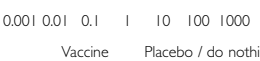
Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Barrett 2011	652/3623	227/3620		17.4 %	2.87 [2.49, 3.31]
aa Nichol 1995	26/419	24/422		9.4 %	1.09 [0.64, 1.87]
aa Jackson 2010a	692/3783	389/3828		17.8 %	1.80 [1.60, 2.02]
Subtotal (95% CI)	**17481**	**12879**		**100.0 %**	**1.77 [1.40, 2.24]**
Total events: 2438 (Vaccine), 967 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 49.61, df = 9 (P<0.00001); I^2 =82%					
Test for overall effect: Z = 4.79 (P < 0.00001)					
2 Systemic - fever					
ab Pyrhönen 1981	11/151	9/154		6.8 %	1.25 [0.53, 2.92]
aa Barrett 2011	83/3623	37/3620		23.2 %	2.24 [1.53, 3.29]
aa Powers 1995a	0/26	0/24			Not estimable
aa Mesa Duque 2001	8/247	4/246		3.7 %	1.99 [0.61, 6.53]
ab Caplan 1977	8/193	1/15		1.3 %	0.62 [0.08, 4.65]
aa Ohmit 2006	37/501	5/99		6.0 %	1.46 [0.59, 3.63]
aa Nichol 1995	26/419	26/422		15.0 %	1.01 [0.59, 1.71]
ab El'shina 1996	3/108	2/107		1.7 %	1.49 [0.25, 8.72]
aa Ohmit 2008	62/818	11/155		11.7 %	1.07 [0.58, 1.98]
ab Rocchi 1979a	0/126	2/110		0.6 %	0.17 [0.01, 3.60]
aa Jackson 2010a	96/3783	55/3828		27.8 %	1.77 [1.27, 2.45]
ab Saxen 1999	6/216	2/211		2.1 %	2.93 [0.60, 14.36]
Subtotal (95% CI)	**10211**	**8991**		**100.0 %**	**1.54 [1.22, 1.95]**
Total events: 340 (Vaccine), 154 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 11.89, df = 10 (P = 0.29); I^2 =16%					
Test for overall effect: Z = 3.58 (P = 0.00034)					
3 Systemic - headache					
aa Ohmit 2006	171/501	25/99		9.0 %	1.35 [0.94, 1.94]
aa Frey 2010	1112/7414	576/3843		17.2 %	1.00 [0.91, 1.10]
aa Jackson 2010a	683/3783	716/3828		17.2 %	0.97 [0.88, 1.06]
ab Caplan 1977	23/193	2/15		1.2 %	0.89 [0.23, 3.43]
ab El'shina 1996	12/108	4/107		1.7 %	2.97 [0.99, 8.93]
ab Scheifele 2003	68/620	34/624		8.1 %	2.01 [1.35, 2.99]
aa Nichol 1995	45/419	61/422		9.0 %	0.74 [0.52, 1.07]
aa Ohmit 2008	225/818	34/155		10.2 %	1.25 [0.91, 1.72]
ab Rocchi 1979a	3/126	2/110		0.7 %	1.31 [0.22, 7.69]



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Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Mesa Duque 2001	32/247	29/246		6.6 %	1.10 [0.69, 1.76]
ab Forsyth 1967	0/194	2/186		0.2 %	0.19 [0.01, 3.97]
aa Powers 1995a	9/26	4/24		1.9 %	2.08 [0.73, 5.87]
aa Barrett 2011	646/3623	487/3620		16.9 %	1.33 [1.19, 1.48]
Subtotal (95% CI)	**18072**	**13279**		**100.0 %**	**1.17 [1.01, 1.36]**
Total events: 3029 (Vaccine), 1976 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 43.84, df = 12 (P = 0.00002); I^2 =73%					
Test for overall effect: Z = 2.04 (P = 0.042)					
4 Systemic - fatigue or indisposition					
aa Jackson 2010a	761/3783	678/3828		19.0 %	1.14 [1.03, 1.25]
aa Ohmit 2008	180/818	27/155		8.8 %	1.26 [0.88, 1.82]
aa Frey 2010	778/7414	384/3843		18.2 %	1.05 [0.94, 1.18]
ab El'shina 1996	6/108	1/107		0.5 %	5.94 [0.73, 48.55]
aa Barrett 2011	635/3623	430/3620		18.3 %	1.48 [1.32, 1.65]
aa Ohmit 2006	102/501	14/99		5.6 %	1.44 [0.86, 2.41]
ab Saxen 1999	14/216	5/211		1.8 %	2.74 [1.00, 7.46]
ab Rocchi 1979a	5/126	3/110		1.0 %	1.46 [0.36, 5.95]
ab Scheifele 2003	43/620	22/624		5.8 %	1.97 [1.19, 3.25]
aa Nichol 1995	79/419	82/422		11.6 %	0.97 [0.73, 1.28]
aa Mesa Duque 2001	50/247	51/246		9.3 %	0.98 [0.69, 1.38]
Subtotal (95% CI)	**17875**	**13265**		**100.0 %**	**1.23 [1.07, 1.42]**
Total events: 2653 (Vaccine), 1697 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 31.98, df = 10 (P = 0.00040); I^2 =69%					
Test for overall effect: Z = 2.87 (P = 0.0041)					
5 Systemic - nausea/vomiting					
ab Scheifele 2003	14/620	2/624		46.5 %	7.05 [1.61, 30.87]
ab El'shina 1996	1/108	0/107		18.7 %	2.97 [0.12, 72.16]
ab Caplan 1977	9/193	1/15		34.8 %	0.70 [0.09, 5.16]
Subtotal (95% CI)	**921**	**746**		**100.0 %**	**2.68 [0.55, 13.08]**
Total events: 24 (Vaccine), 3 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.84; Chi^2 = 3.47, df = 2 (P = 0.18); I^2 =42%					
Test for overall effect: Z = 1.22 (P = 0.22)					
6 Systemic - malaise					
aa Barrett 2011	522/3623	278/3620		33.9 %	1.88 [1.63, 2.15]
aa Frey 2010	557/7414	231/3843		33.4 %	1.25 [1.08, 1.45]

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Study or subgroup	Vaccine n/N	placebo / do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Jackson 2010a	338/3783	236/3828		32.7 %	1.45 [1.23, 1.70]
Subtotal (95% CI)	**14820**	**11291**		**100.0 %**	**1.51 [1.18, 1.92]**
Total events: 1417 (Vaccine), 745 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 15.96, df = 2 (P = 0.00034); I^2 =87%					
Test for overall effect: Z = 3.31 (P = 0.00093)					
7 Systemic - combined endpoint (any or highest symptom)					
ab Rocchi 1979a	8/126	4/110		5.4 %	1.75 [0.54, 5.64]
ab Saxen 1999	14/216	5/211		7.2 %	2.74 [1.00, 7.46]
aa Nichol 1995	79/419	82/422		42.8 %	0.97 [0.73, 1.28]
aa Mesa Duque 2001	50/247	51/246		34.7 %	0.98 [0.69, 1.38]
aa Tannock 1984	5/50	2/31		3.1 %	1.55 [0.32, 7.51]
aa Powers 1995a	9/26	4/24		6.8 %	2.08 [0.73, 5.87]
Subtotal (95% CI)	**1084**	**1044**		**100.0 %**	**1.16 [0.87, 1.53]**
Total events: 165 (Vaccine), 148 (placebo / do nothing)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 6.60, df = 5 (P = 0.25); I^2 =24%					
Test for overall effect: Z = 1.00 (P = 0.32)					

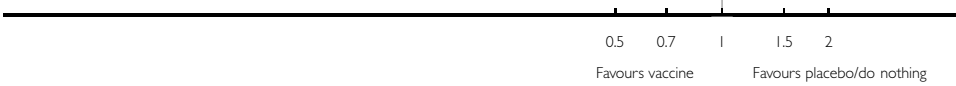
Analysis 2.1. Comparison 2 Live aerosol vaccine versus placebo or 'do nothing', Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 2 Live aerosol vaccine versus placebo or 'do nothing'

Outcome: 1 Influenza-like illness

Study or subgroup	Vaccine n/N	Placebo/do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
aa Edwards 1994c	201/1114	240/1125		15.8 %	0.85 [0.71, 1.00]
aa Edwards 1994d	148/999	146/1016		10.0 %	1.03 [0.83, 1.27]
Subtotal (95% CI)	**2113**	**2141**		**25.7 %**	**0.92 [0.76, 1.12]**
Total events: 349 (Vaccine), 386 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.07$, df = 1 (P = 0.15); $I^2 = 52\%$					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 WHO recommended - vaccine matching absent or unknown					
aa Edwards 1994a	89/872	92/878		5.8 %	0.97 [0.74, 1.28]
aa Edwards 1994b	208/1029	262/1064		17.3 %	0.82 [0.70, 0.96]
aa Nichol 1999a	751/2874	412/1433		42.7 %	0.91 [0.82, 1.01]
Subtotal (95% CI)	**4775**	**3375**		**65.8 %**	**0.89 [0.82, 0.97]**
Total events: 1048 (Vaccine), 766 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.55$, df = 2 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.77 (P = 0.0057)					
3 Non WHO recommended - vaccine matching absent or unknown					
aa Monto 1982	70/144	74/140		8.5 %	0.92 [0.73, 1.16]
Subtotal (95% CI)	**144**	**140**		**8.5 %**	**0.92 [0.73, 1.16]**
Total events: 70 (Vaccine), 74 (Placebo/do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	**7032**	**5656**		**100.0 %**	**0.90 [0.84, 0.96]**
Total events: 1467 (Vaccine), 1226 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.76$, df = 5 (P = 0.58); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.14 (P = 0.0017)					
Test for subgroup differences: $Chi^2 = 0.17$, df = 2 (P = 0.92), $I^2 = 0.0\%$					

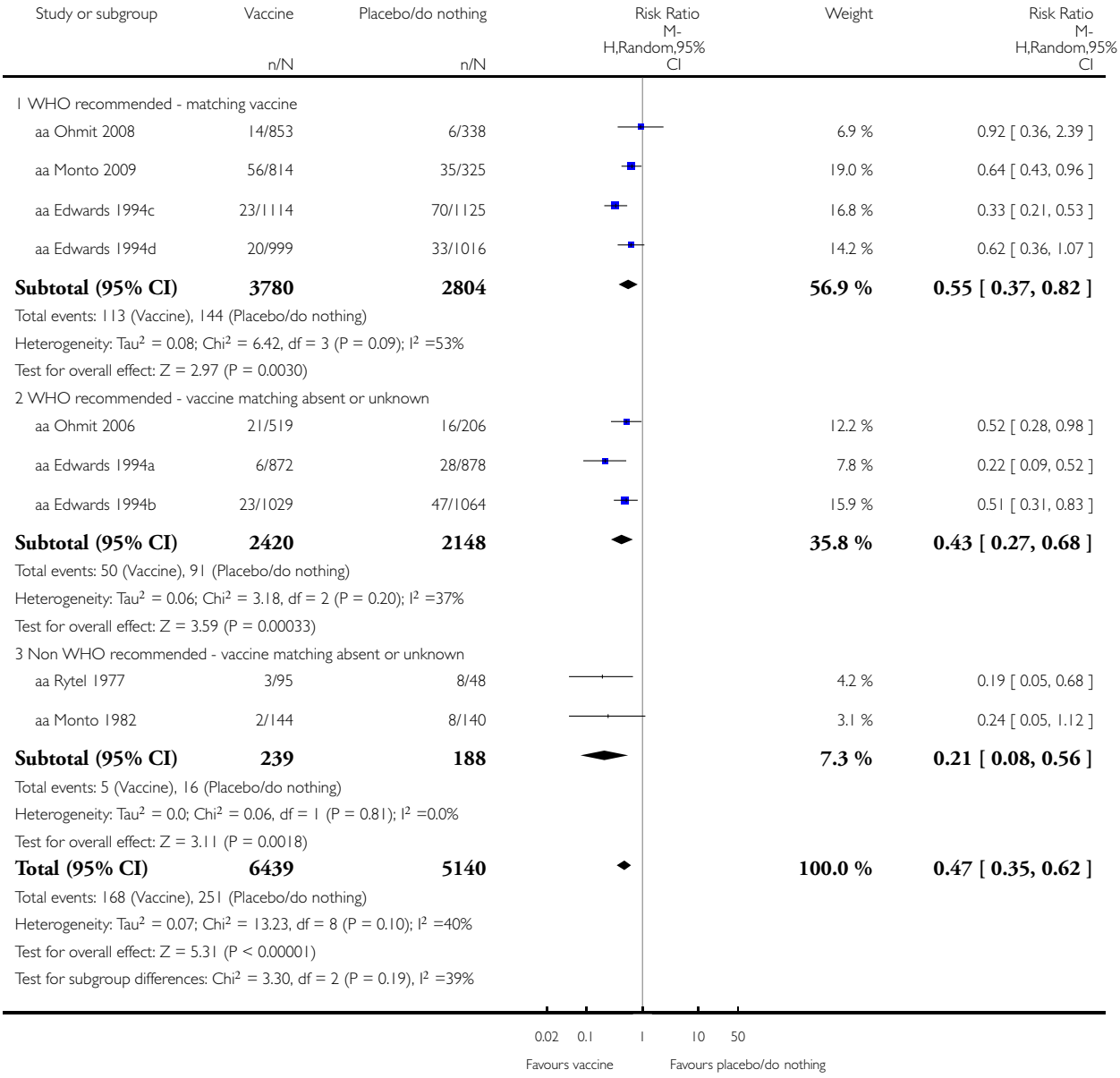


Analysis 2.2. Comparison 2 Live aerosol vaccine versus placebo or 'do nothing', Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 2 Live aerosol vaccine versus placebo or 'do nothing'

Outcome: 2 Influenza

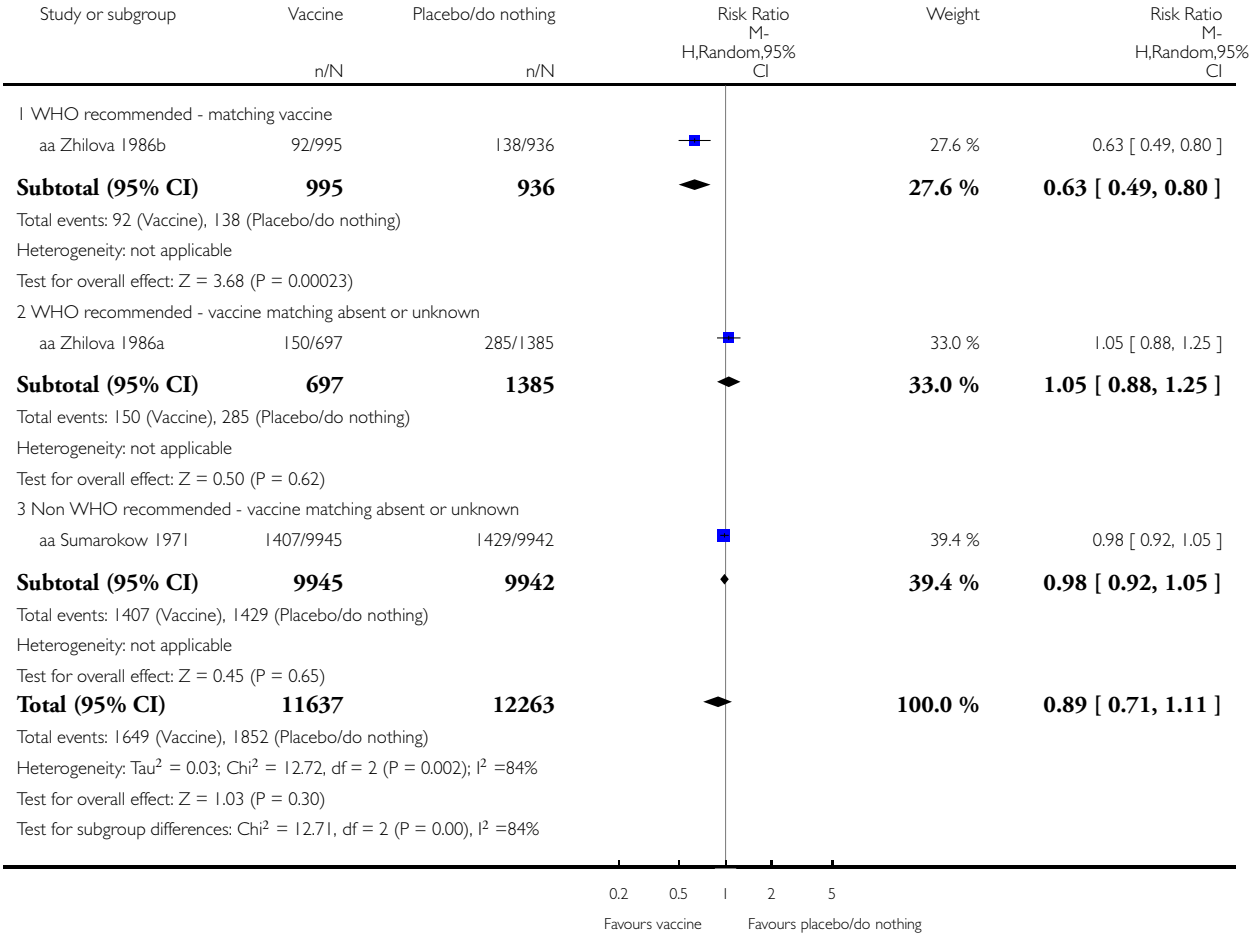


Analysis 2.3. Comparison 2 Live aerosol vaccine versus placebo or 'do nothing', Outcome 3 Influenza cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 2 Live aerosol vaccine versus placebo or 'do nothing'

Outcome: 3 Influenza cases (clinically defined without clear definition)

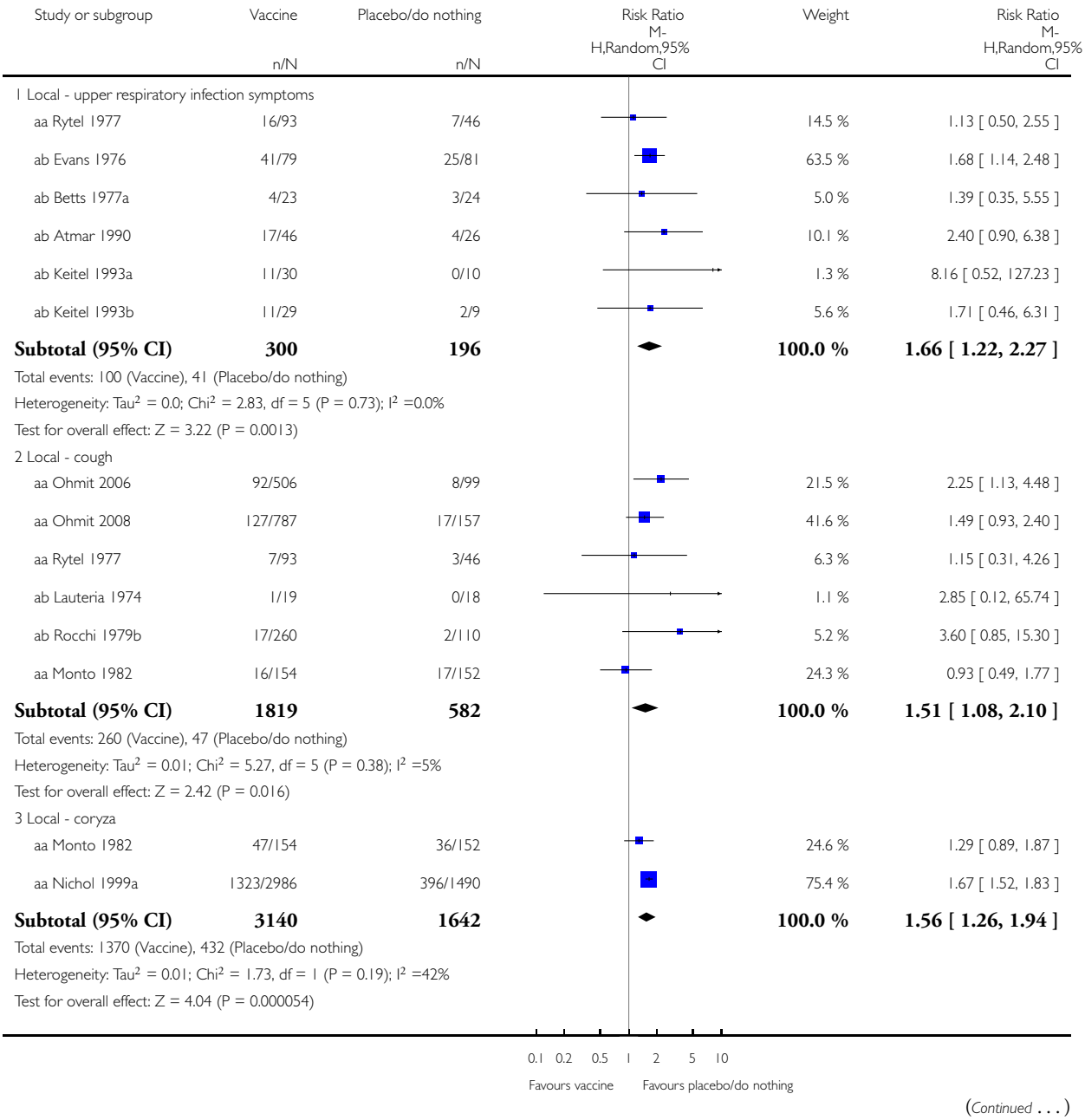


Analysis 2.4. Comparison 2 Live aerosol vaccine versus placebo or 'do nothing', Outcome 4 Local harms.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 2 Live aerosol vaccine versus placebo or 'do nothing'

Outcome: 4 Local harms



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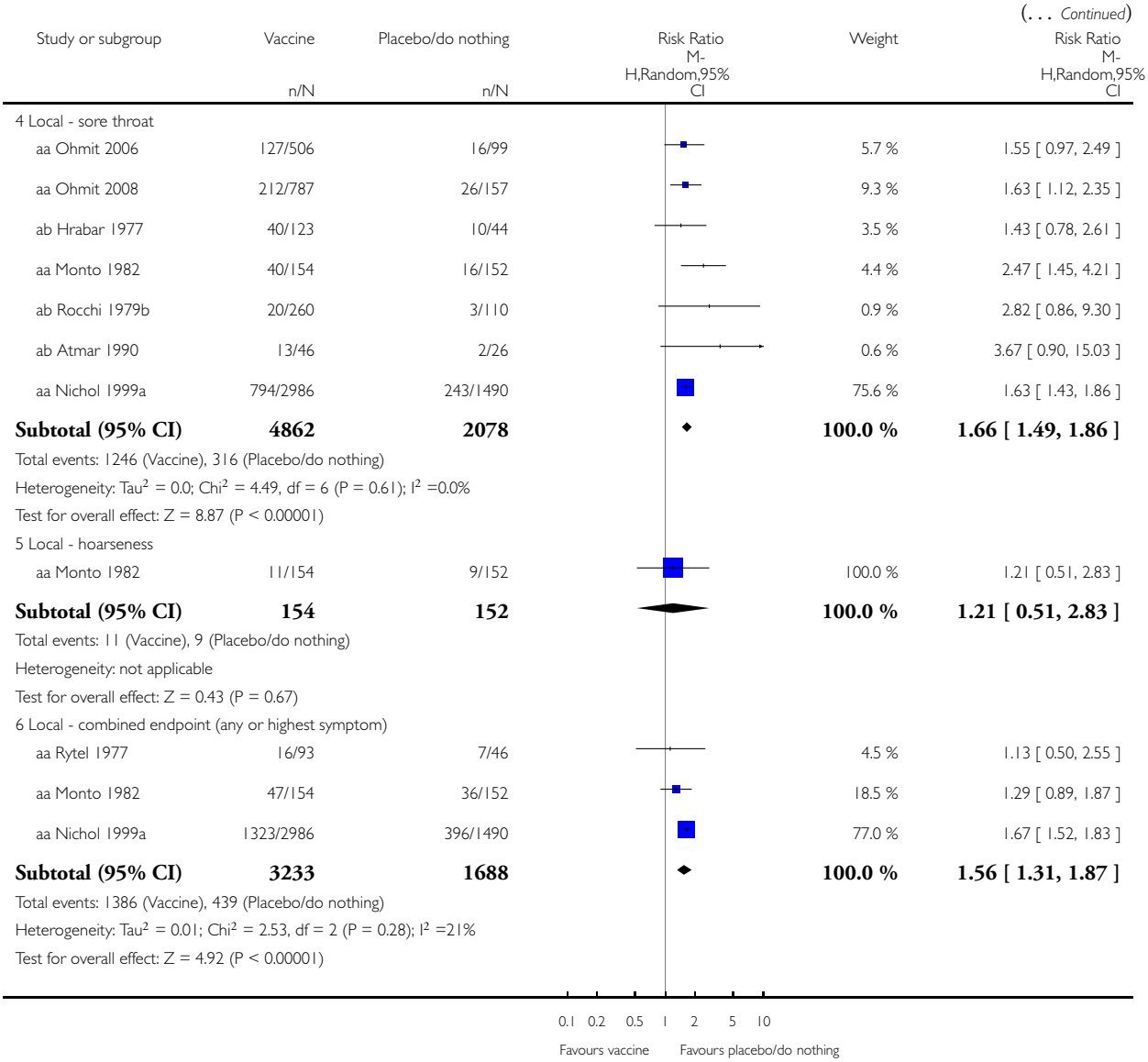
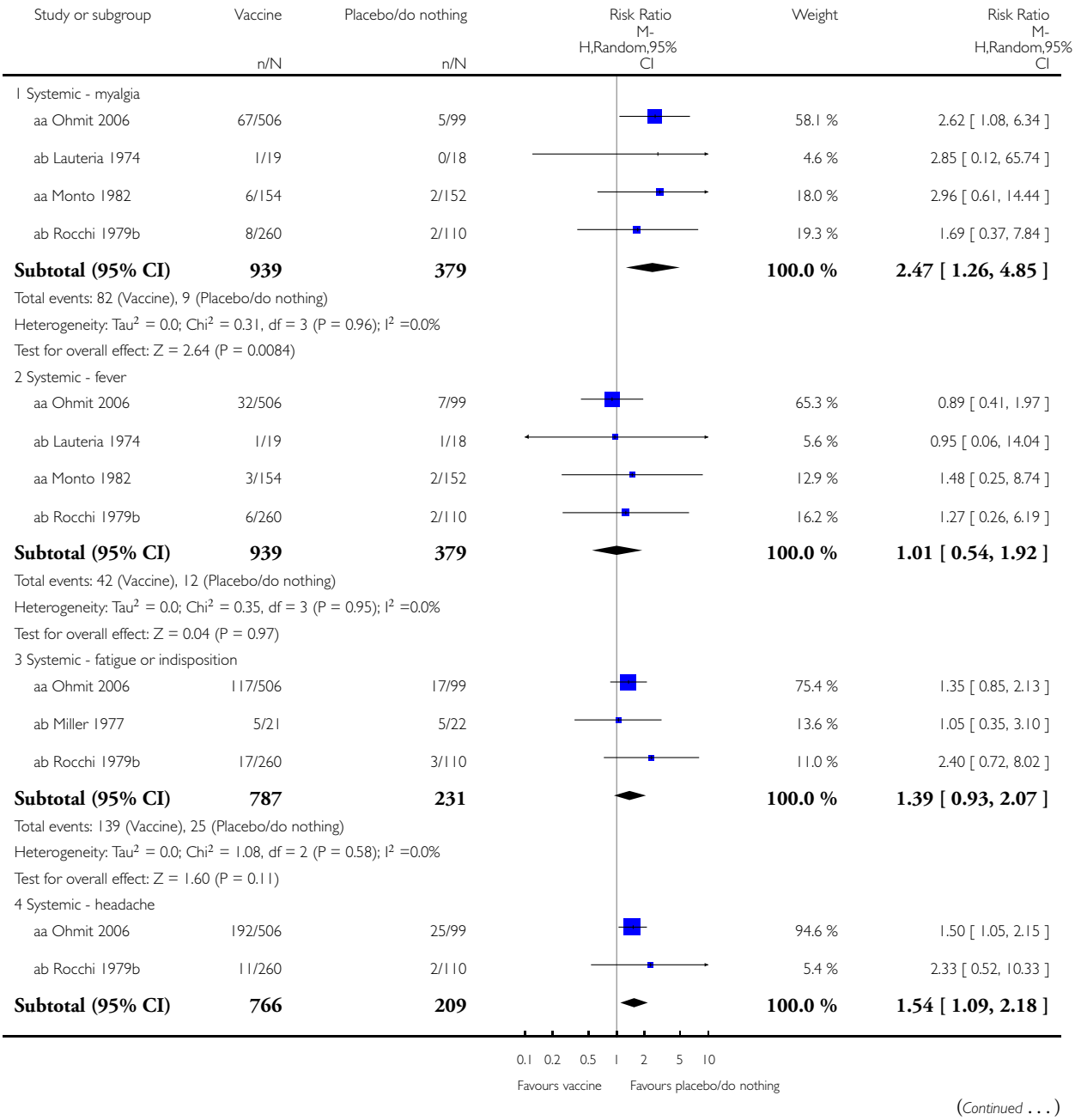


Analysis 2.5. Comparison 2 Live aerosol vaccine versus placebo or 'do nothing', Outcome 5 Systemic harms.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 2 Live aerosol vaccine versus placebo or 'do nothing'

Outcome: 5 Systemic harms



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Study or subgroup	Vaccine n/N	Placebo/do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 203 (Vaccine), 27 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.43 (P = 0.015)					
5 Systemic - combined endpoint (any or highest symptom)					
aa Rytel 1977	13/93	4/46		15.6 %	1.61 [0.55, 4.66]
ab Evans 1976	9/21	14/22		27.7 %	0.67 [0.37, 1.21]
ab Miller 1977	31/79	21/81		31.8 %	1.51 [0.96, 2.40]
ab Rocchi 1979b	23/260	4/110		16.1 %	2.43 [0.86, 6.87]
aa Monto 1982	6/154	2/152		8.8 %	2.96 [0.61, 14.44]
Subtotal (95% CI)	**607**	**411**		**100.0 %**	**1.40 [0.82, 2.38]**
Total events: 82 (Vaccine), 45 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 8.39$, df = 4 (P = 0.08); $I^2 = 52\%$					
Test for overall effect: Z = 1.24 (P = 0.22)					

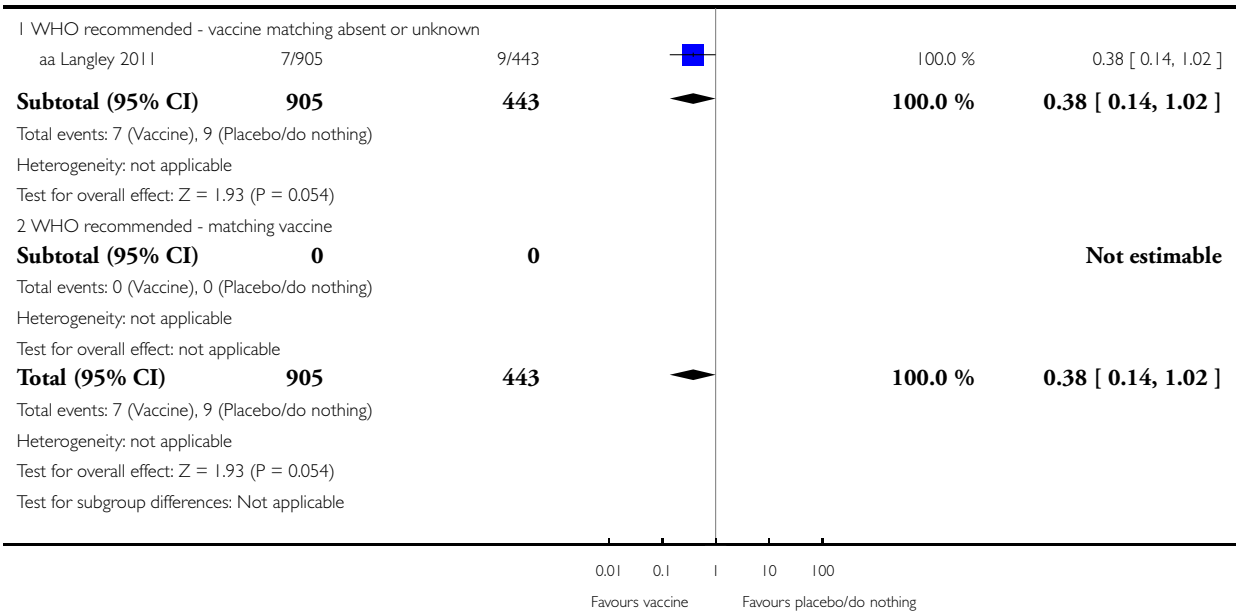
Analysis 3.1. Comparison 3 Inactivated aerosol vaccine versus placebo or 'do nothing', Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 3 Inactivated aerosol vaccine versus placebo or 'do nothing'

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Placebo/do nothing n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 WHO recommended - vaccine matching absent or unknown					
aa Langley 2011	7/905	9/443		100.0 %	0.38 [0.14, 1.02]
Subtotal (95% CI)	**905**	**443**		**100.0 %**	**0.38 [0.14, 1.02]**
Total events: 7 (Vaccine), 9 (Placebo/do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.054)					
2 WHO recommended - matching vaccine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo/do nothing)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**905**	**443**		**100.0 %**	**0.38 [0.14, 1.02]**
Total events: 7 (Vaccine), 9 (Placebo/do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.054)					
Test for subgroup differences: Not applicable					

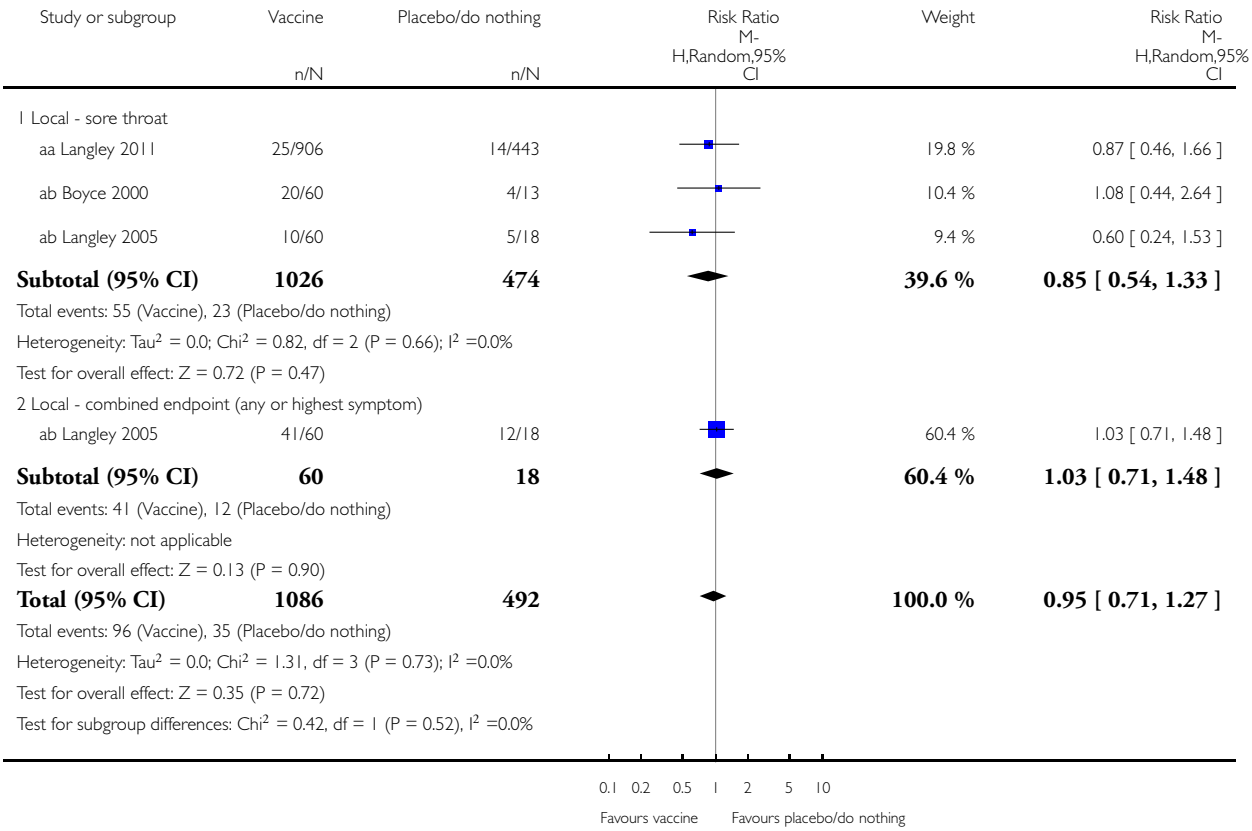


Analysis 3.2. Comparison 3 Inactivated aerosol vaccine versus placebo or 'do nothing', Outcome 2 Local harms.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 3 Inactivated aerosol vaccine versus placebo or 'do nothing'

Outcome: 2 Local harms



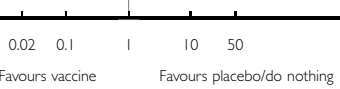
Analysis 3.3. Comparison 3 Inactivated aerosol vaccine versus placebo or 'do nothing', Outcome 3 Systemic harms.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 3 Inactivated aerosol vaccine versus placebo or 'do nothing'

Outcome: 3 Systemic harms

Study or subgroup	Vaccine n/N	Placebo/do nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Systemic - myalgia					
ab Boyce 2000	5/60	2/13		7.2 %	0.54 [0.12, 2.49]
ab Langley 2005	12/60	3/18		12.5 %	1.20 [0.38, 3.79]
Subtotal (95% CI)	**120**	**31**		**19.7 %**	**0.90 [0.36, 2.25]**
Total events: 17 (Vaccine), 5 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.23 (P = 0.82)					
2 Systemic - fatigue or indisposition					
ab Boyce 2000	4/60	1/13		3.8 %	0.87 [0.11, 7.13]
ab Langley 2005	16/60	3/18		13.3 %	1.60 [0.52, 4.88]
Subtotal (95% CI)	**120**	**31**		**17.1 %**	**1.40 [0.52, 3.75]**
Total events: 20 (Vaccine), 4 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.25$, df = 1 (P = 0.61); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.67 (P = 0.50)					
3 Systemic - headache					
ab Boyce 2000	25/60	3/13		15.2 %	1.81 [0.64, 5.09]
ab Langley 2005	28/60	6/18		31.3 %	1.40 [0.69, 2.84]
Subtotal (95% CI)	**120**	**31**		**46.5 %**	**1.52 [0.85, 2.72]**
Total events: 53 (Vaccine), 9 (Placebo/do nothing)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.40 (P = 0.16)					
4 Systemic - fever					
aa Langley 2011	1/906	1/443		2.2 %	0.49 [0.03, 7.80]
Subtotal (95% CI)	**906**	**443**		**2.2 %**	**0.49 [0.03, 7.80]**
Total events: 1 (Vaccine), 1 (Placebo/do nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
5 Systemic - combined endpoint (any or highest symptom)					
ab Langley 2005	6/60	5/18		14.5 %	0.36 [0.12, 1.04]
Subtotal (95% CI)	**60**	**18**		**14.5 %**	**0.36 [0.12, 1.04]**
Total events: 6 (Vaccine), 5 (Placebo/do nothing)					



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Study or subgroup	Vaccine n/N	Placebo/do nothing 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 = 1.88 (P = 0.060)					
Total (95% CI)	**1326**	**554**		**100.0 %**	**1.07 [0.71, 1.62]**
Total events: 97 (Vaccine), 24 (Placebo/do nothing)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 7.23, df = 7 (P = 0.41); I^2 =3%					
Test for overall effect: Z = 0.32 (P = 0.75)					
Test for subgroup differences: Chi^2 = 6.13, df = 4 (P = 0.19), I^2 =35%					

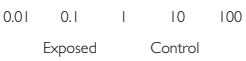
Analysis 4.1. Comparison 4 Inactivated parenteral vaccine versus placebo - cohort studies, Outcome 1 Seasonal inactivated vaccine effectiveness in mothers - pregnant women.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 4 Inactivated parenteral vaccine versus placebo - cohort studies

Outcome: 1 Seasonal inactivated vaccine effectiveness in mothers - pregnant women

Study or subgroup	Exposed n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 H1N1 - vaccine - effectiveness ILI (unadjusted data)					
pca Yamada 2012	11/4921	50/2407		100.0 %	0.11 [0.06, 0.21]
Subtotal (95% CI)	**4921**	**2407**		**100.0 %**	**0.11 [0.06, 0.21]**
Total events: 11 (Exposed), 50 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.71 (P < 0.00001)					
2 Seasonal - vaccine - effectiveness ILI - (unadjusted data)					
pca Black 2004	134/3707	2004/45878		53.2 %	0.83 [0.70, 0.98]
pca Hulka 1964	24/363	36/181		46.8 %	0.33 [0.20, 0.54]
Subtotal (95% CI)	**4070**	**46059**		**100.0 %**	**0.54 [0.22, 1.32]**
Total events: 158 (Exposed), 2040 (Control)					
Heterogeneity: Tau^2 = 0.38; Chi^2 = 12.12, df = 1 (P = 0.00050); I^2 =92%					
Test for overall effect: Z = 1.35 (P = 0.18)					

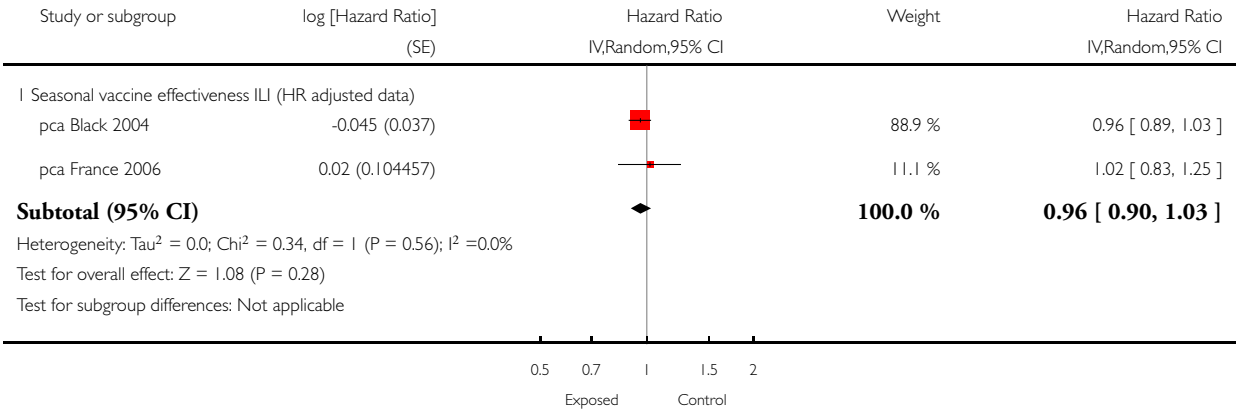


Analysis 4.2. Comparison 4 Inactivated parenteral vaccine versus placebo - cohort studies, Outcome 2 Seasonal inactivated vaccine effectiveness in newborns - pregnant women.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 4 Inactivated parenteral vaccine versus placebo - cohort studies

Outcome: 2 Seasonal inactivated vaccine effectiveness in newborns - pregnant women

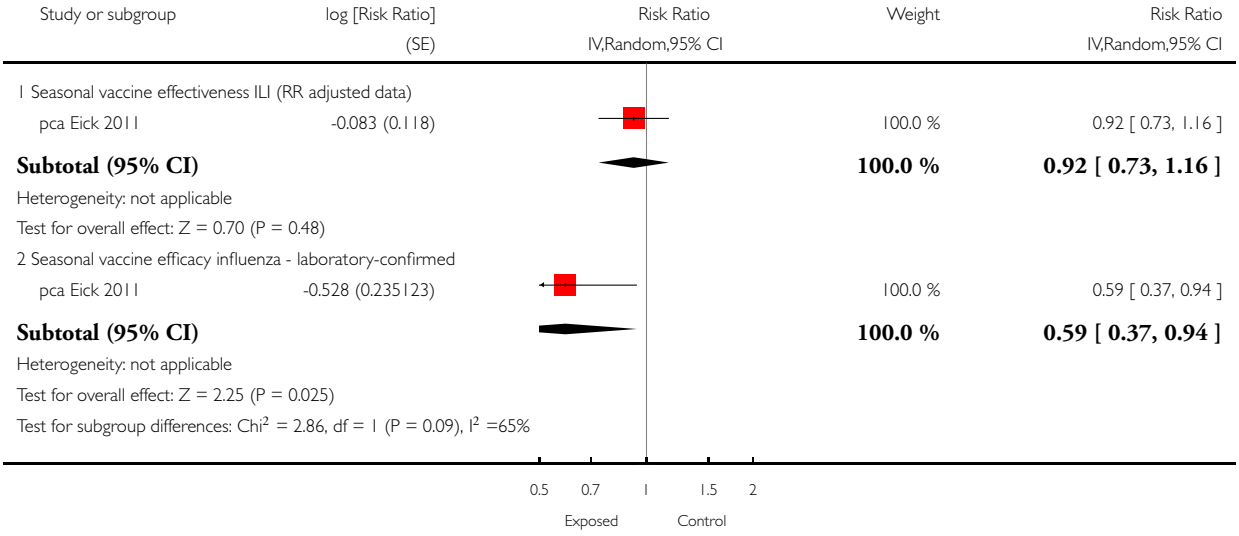


Analysis 4.3. Comparison 4 Inactivated parenteral vaccine versus placebo - cohort studies, Outcome 3 Seasonal inactivated vaccine effectiveness in newborns - pregnant women.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 4 Inactivated parenteral vaccine versus placebo - cohort studies

Outcome: 3 Seasonal inactivated vaccine effectiveness in newborns - pregnant women

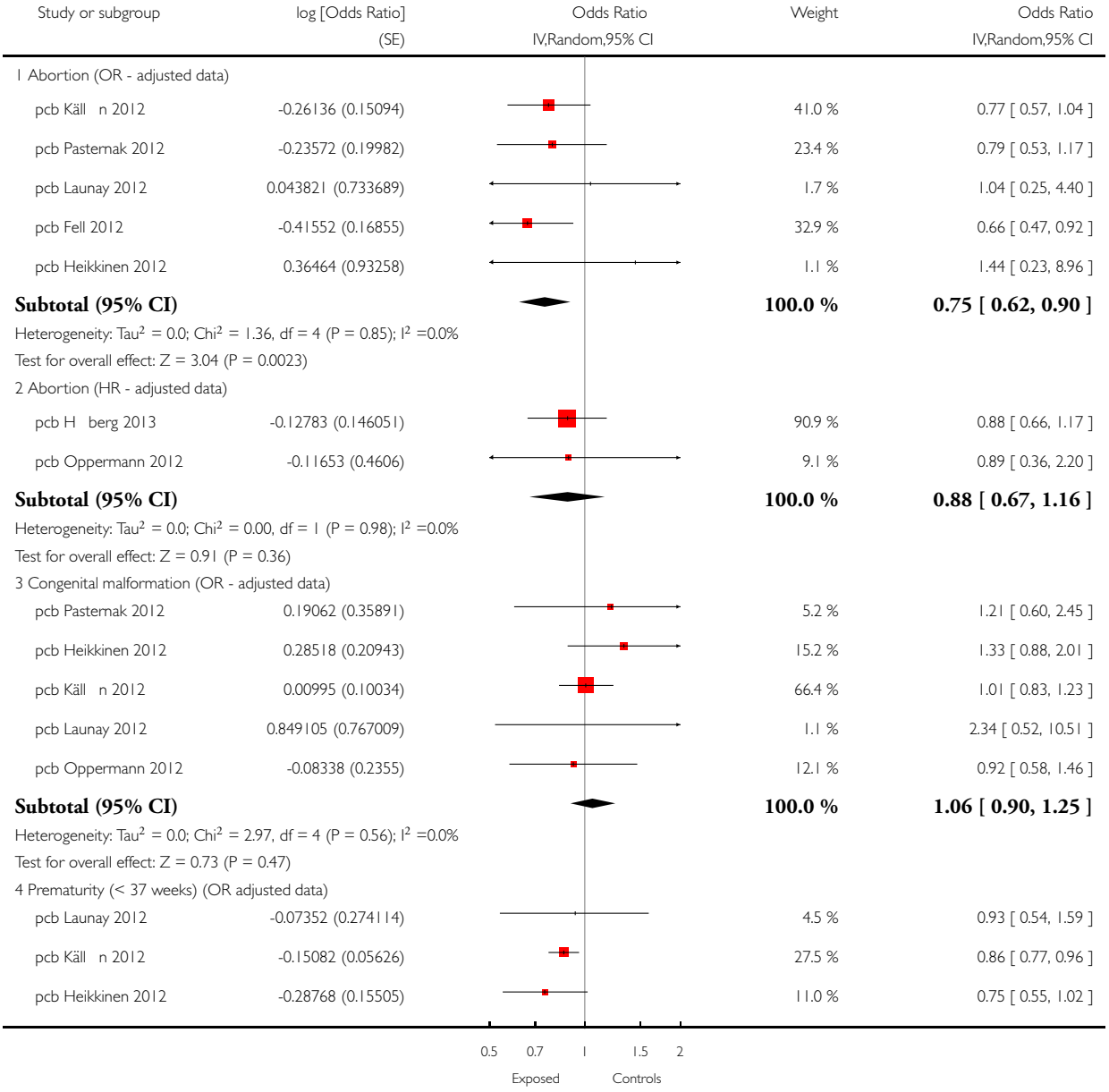


Analysis 4.4. Comparison 4 Inactivated parenteral vaccine versus placebo - cohort studies, Outcome 4 H1N1 vaccine - safety - pregnancy-related outcomes - pregnant women.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 4 Inactivated parenteral vaccine versus placebo - cohort studies

Outcome: 4 H1N1 vaccine - safety - pregnancy-related outcomes - pregnant women



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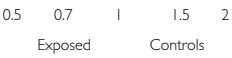
Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
pcb Fell 2012	-0.05129 (0.03766)		31.4 %	0.95 [0.88, 1.02]
pcb Richards 2013	-0.46204 (0.14813)		11.8 %	0.63 [0.47, 0.84]
pcb Lin 2012	-0.61776 (0.34967)		2.9 %	0.54 [0.27, 1.07]
pcb Oppermann 2012	-0.02441 (0.21659)		6.7 %	0.98 [0.64, 1.49]
pcb Pasternak 2012	0.27763 (0.28359)		4.2 %	1.32 [0.76, 2.30]
Subtotal (95% CI)			**100.0 %**	**0.86 [0.76, 0.97]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 14.01$, df = 7 (P = 0.05); $I^2 = 50\%$				
Test for overall effect: Z = 2.49 (P = 0.013)				
5 Neonatal death (OR adjusted data)				
pcb Heikkinen 2012	0.59333 (1.23463)		100.0 %	1.81 [0.16, 20.35]
Subtotal (95% CI)			**100.0 %**	**1.81 [0.16, 20.35]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.48 (P = 0.63)				
Test for subgroup differences: $Chi^2 = 8.72$, df = 4 (P = 0.07), $I^2 = 54\%$				

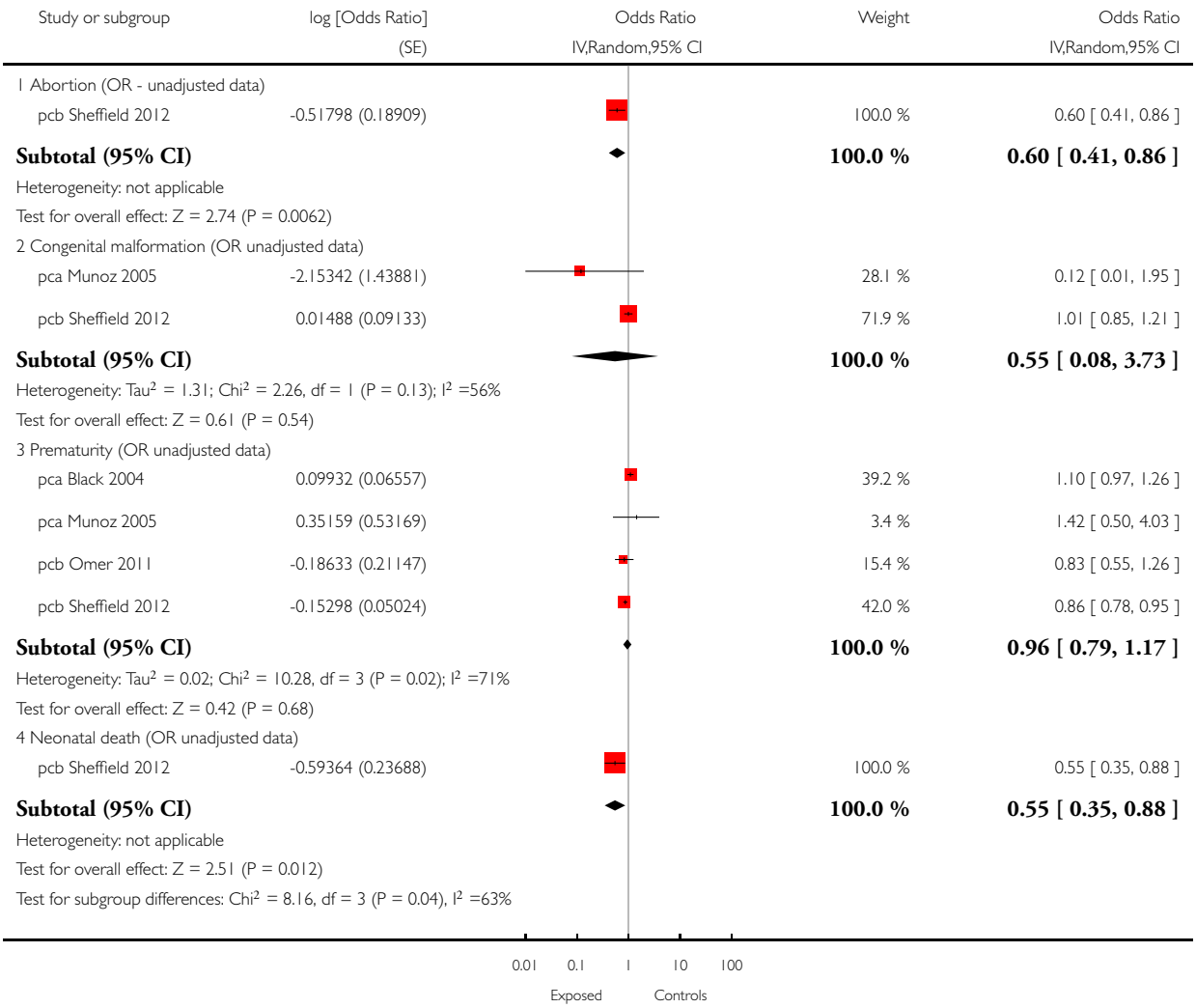


Analysis 4.5. Comparison 4 Inactivated parenteral vaccine versus placebo - cohort studies, Outcome 5 Seasonal vaccine - safety - pregnancy-related outcomes - pregnant women.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 4 Inactivated parenteral vaccine versus placebo - cohort studies

Outcome: 5 Seasonal vaccine - safety - pregnancy-related outcomes - pregnant women

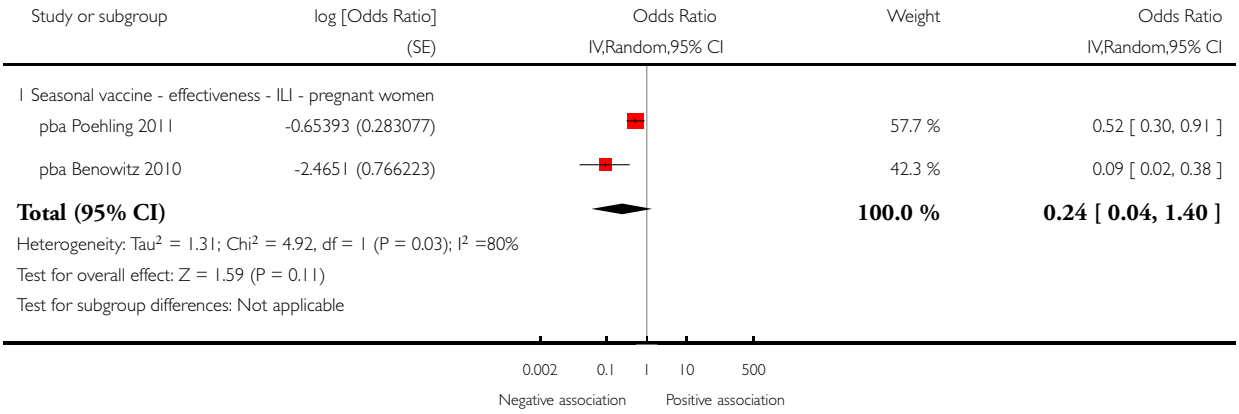


Analysis 5.1. Comparison 5 Inactivated parenteral vaccine versus placebo - case-control, Outcome 1 Effectiveness in newborns - pregnant women (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 5 Inactivated parenteral vaccine versus placebo - case-control

Outcome: 1 Effectiveness in newborns - pregnant women (adjusted data)

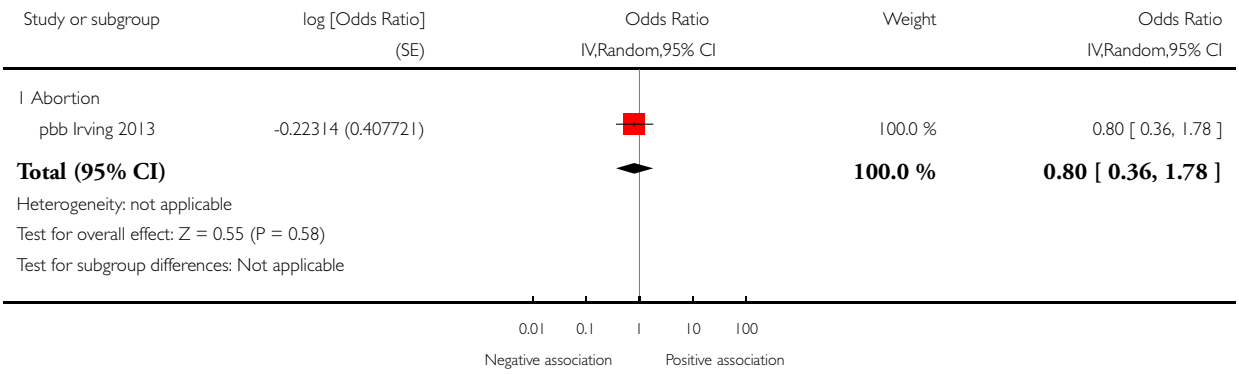


Analysis 5.2. Comparison 5 Inactivated parenteral vaccine versus placebo - case-control, Outcome 2 Seasonal vaccine safety - pregnancy-related outcomes (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 5 Inactivated parenteral vaccine versus placebo - case-control

Outcome: 2 Seasonal vaccine safety - pregnancy-related outcomes (adjusted data)

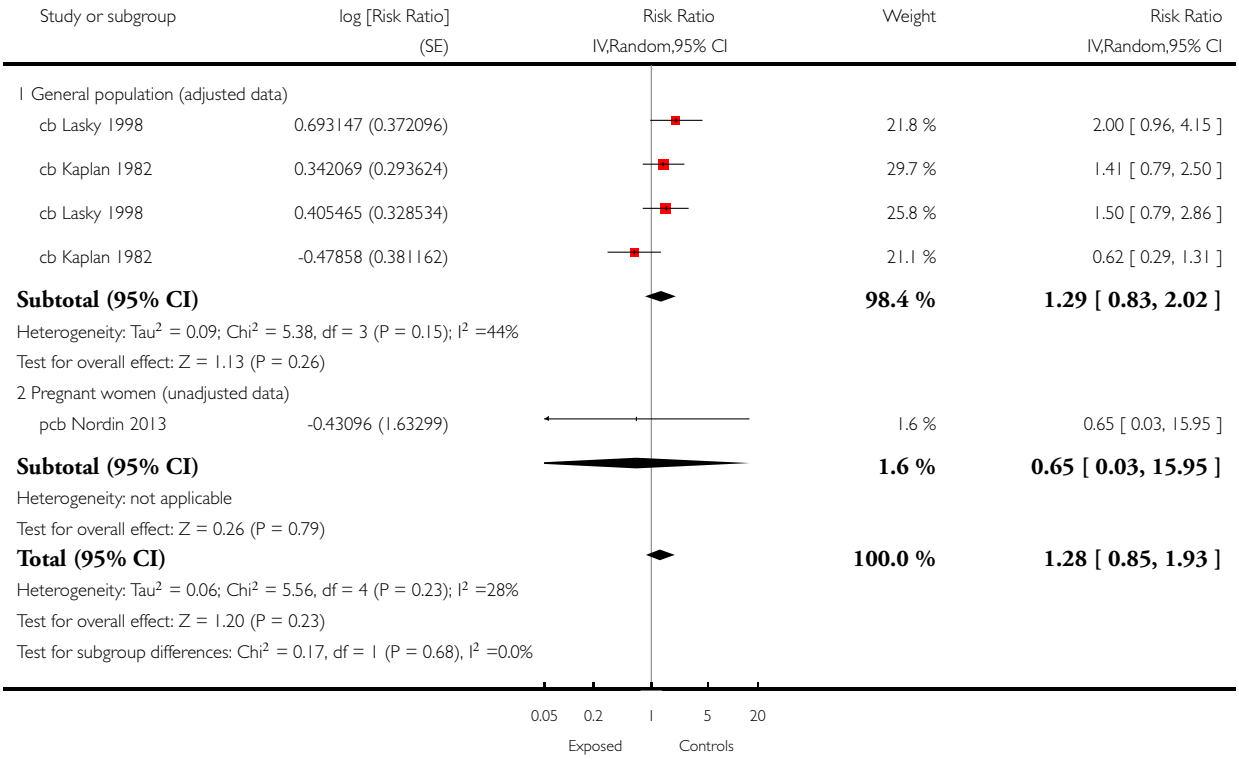


Analysis 6.1. Comparison 6 Serious adverse events - Guillain-Barré syndrome - cohort studies, Outcome 1 Seasonal influenza vaccination and Guillain-Barré syndrome.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 6 Serious adverse events - Guillain-Barr syndrome - cohort studies

Outcome: 1 Seasonal influenza vaccination and Guillain-Barr syndrome

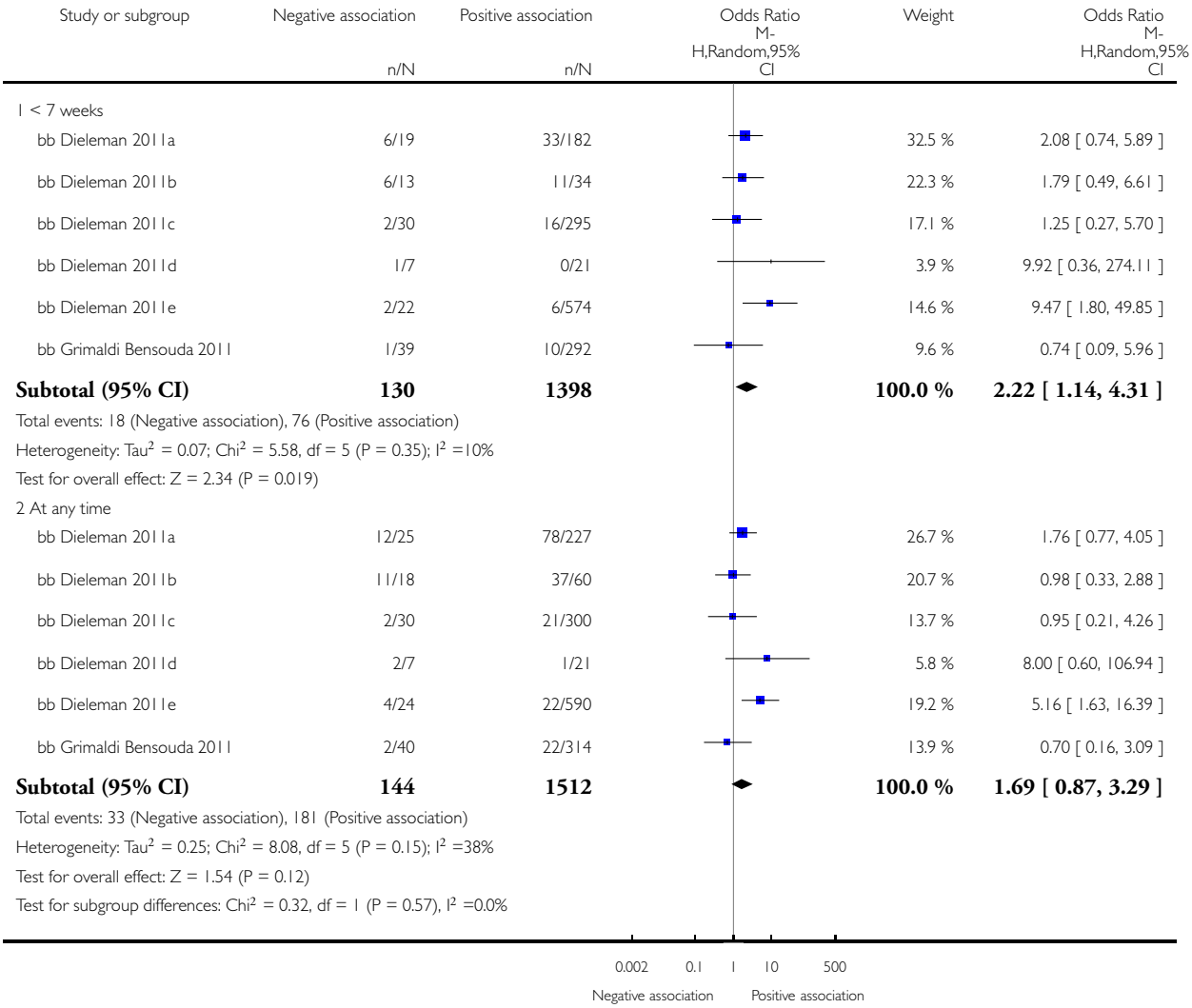


Analysis 7.1. Comparison 7 Serious adverse events - Guillain-Barré syndrome - case-control, Outcome 1 2009 to 2010 A/H1N1 - general population (unadjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 7 Serious adverse events - Guillain-Barr syndrome - case-control

Outcome: 1 2009 to 2010 A/H1N1 - general population (unadjusted data)

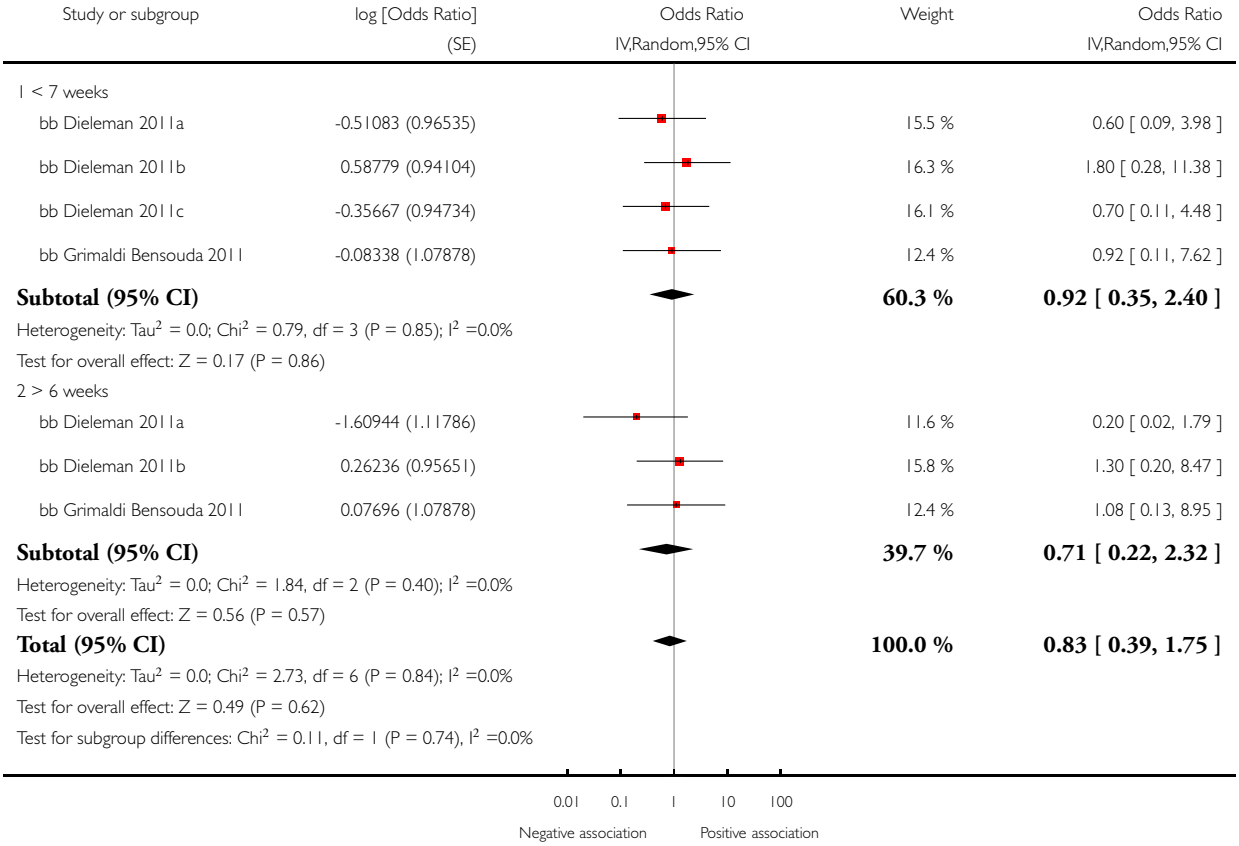


Analysis 7.2. Comparison 7 Serious adverse events - Guillain-Barré syndrome - case-control, Outcome 2 2009 to 2010 A/H1N1 - general population (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 7 Serious adverse events - Guillain-Barr syndrome - case-control

Outcome: 2 2009 to 2010 A/H1N1 - general population (adjusted data)

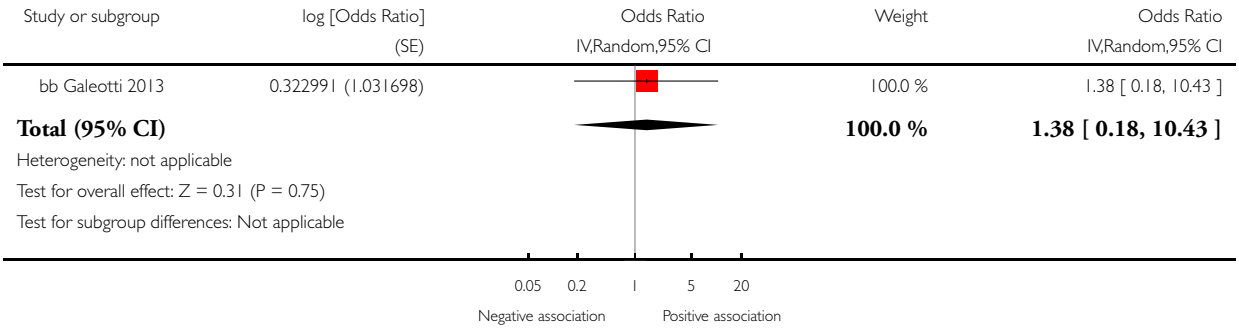


Analysis 7.3. Comparison 7 Serious adverse events - Guillain-Barré syndrome - case-control, Outcome 3 Seasonal influenza vaccination general population (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 7 Serious adverse events - Guillain-Barr syndrome - case-control

Outcome: 3 Seasonal influenza vaccination general population (adjusted data)



Analysis 8.1. Comparison 8 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - cohort studies, Outcome 1 Influenza vaccination (seasonal) - demyelinating diseases (unadjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 8 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - cohort studies

Outcome: 1 Influenza vaccination (seasonal) - demyelinating diseases (unadjusted data)

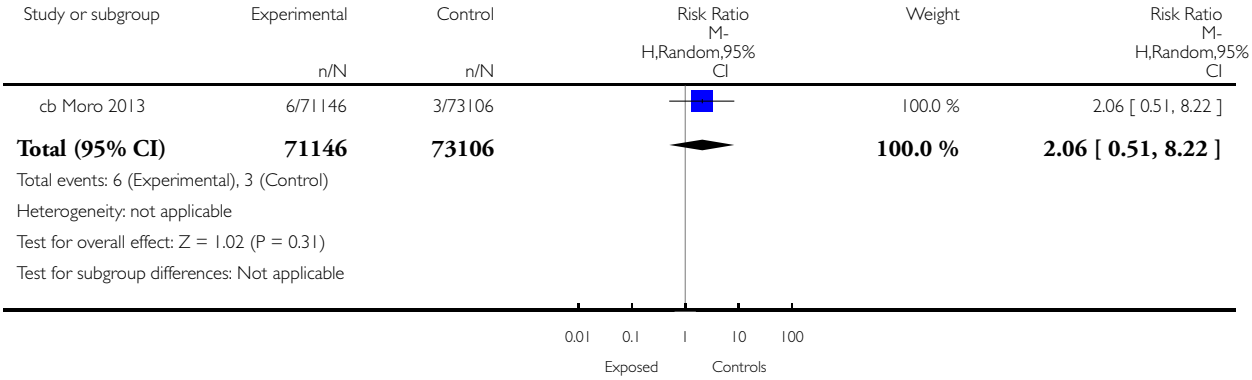
Study or subgroup	Exposed n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 General population					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Exposed), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Pregnant women					
pcb Nordin 2013	1/75906	12/147992		100.0 %	0.16 [0.02, 1.25]
Subtotal (95% CI)	**75906**	**147992**		**100.0 %**	**0.16 [0.02, 1.25]**
Total events: 1 (Exposed), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.081)					
Total (95% CI)	**75906**	**147992**		**100.0 %**	**0.16 [0.02, 1.25]**
Total events: 1 (Exposed), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.081)					
Test for subgroup differences: Not applicable					

Analysis 8.2. Comparison 8 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - cohort studies, Outcome 2 Influenza vaccination (H1N1) - demyelinating diseases (unadjusted).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 8 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - cohort studies

Outcome: 2 Influenza vaccination (H1N1) - demyelinating diseases (unadjusted)



Analysis 9.1. Comparison 9 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies, Outcome 1 Influenza vaccination (seasonal) - general population - demyelinating diseases (unadjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 9 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies

Outcome: 1 Influenza vaccination (seasonal) - general population - demyelinating diseases (unadjusted data)

Study or subgroup	Negative association n/N	Positive association n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
bb DeStefano 2003	73/440	177/950		30.7 %	0.87 [0.64, 1.17]
bb Hernan 2004	10/163	153/1661		8.1 %	0.64 [0.33, 1.25]
bb Payne 2006	173/1131	510/3393		55.0 %	1.02 [0.85, 1.23]
bb Zorzon 2003	19/140	12/131		6.1 %	1.56 [0.72, 3.35]
Total (95% CI)	**1874**	**6135**		**100.0 %**	**0.96 [0.79, 1.17]**

Total events: 275 (Negative association), 852 (Positive association)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.75$, df = 3 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 0.40 (P = 0.69)

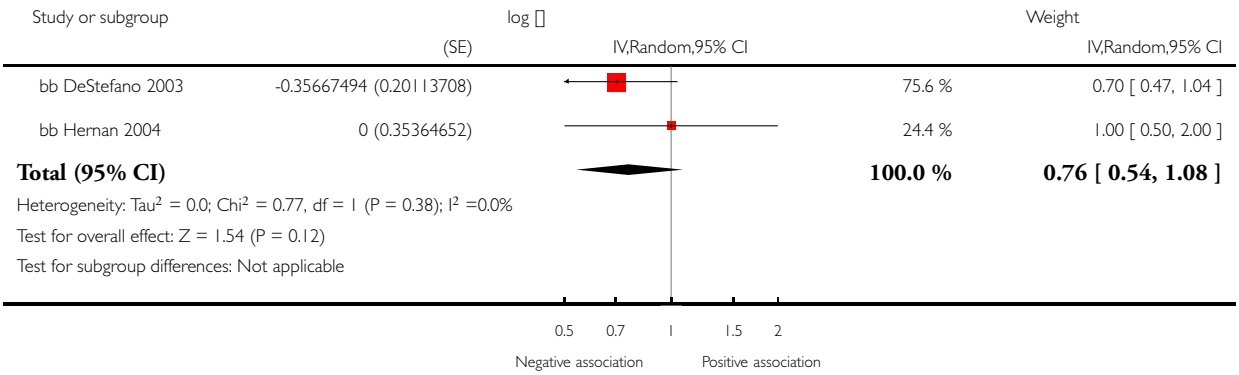
Test for subgroup differences: Not applicable

Analysis 9.2. Comparison 9 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies, Outcome 2 Influenza vaccination (seasonal) - general population - multiple sclerosis (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 9 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies

Outcome: 2 Influenza vaccination (seasonal) - general population - multiple sclerosis (adjusted data)

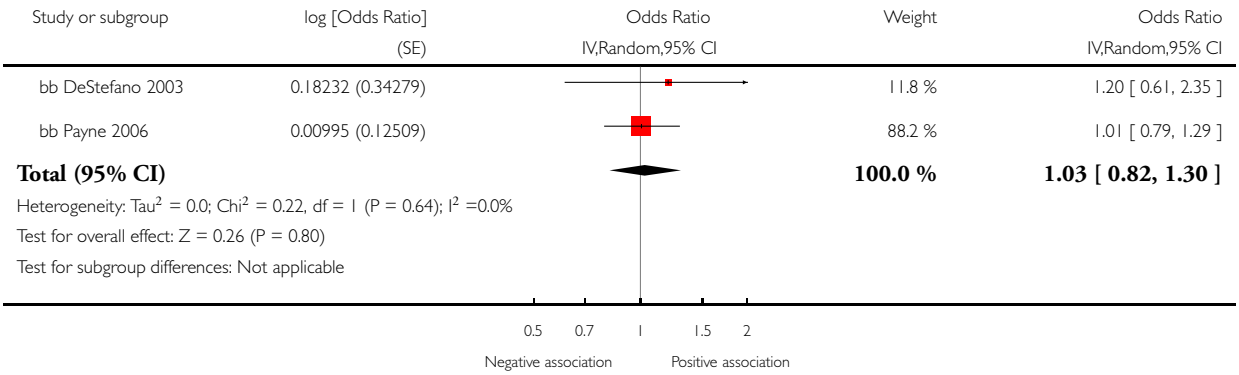


Analysis 9.3. Comparison 9 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies, Outcome 3 Influenza vaccination (seasonal) - general population - optic neuritis (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 9 Serious adverse events - demyelinating diseases (multiple sclerosis, optic neuritis) - case-control studies

Outcome: 3 Influenza vaccination (seasonal) - general population - optic neuritis (adjusted data)

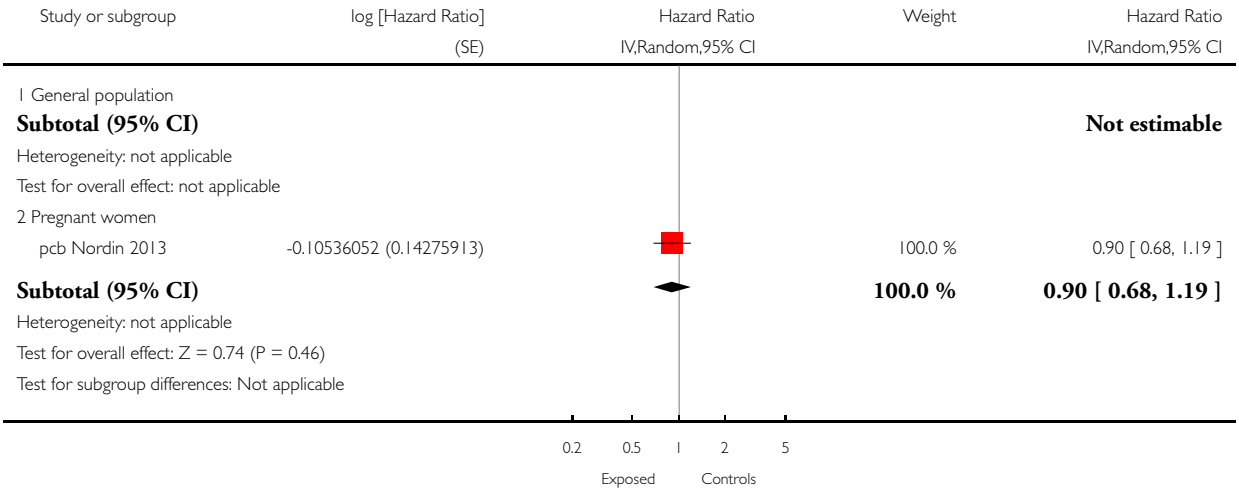


Analysis 10.1. Comparison 10 Serious adverse events - immune thrombocytopaenic purpura - cohort studies, Outcome 1 Seasonal influenza vaccine - HR (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 10 Serious adverse events - immune thrombocytopaenic purpura - cohort studies

Outcome: 1 Seasonal influenza vaccine - HR (adjusted data)



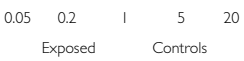
Analysis 10.2. Comparison 10 Serious adverse events - immune thrombocytopaenic purpura - cohort studies, Outcome 2 Seasonal influenza vaccine (unadjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 10 Serious adverse events - immune thrombocytopaenic purpura - cohort studies

Outcome: 2 Seasonal influenza vaccine (unadjusted data)

Study or subgroup	Exposed n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 General population					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Exposed), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Pregnant women					
pcb Nordin 2013	80/75906	170/147992		100.0 %	0.92 [0.70, 1.20]
Subtotal (95% CI)	**75906**	**147992**		**100.0 %**	**0.92 [0.70, 1.20]**
Total events: 80 (Exposed), 170 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.53)					
Test for subgroup differences: Not applicable					

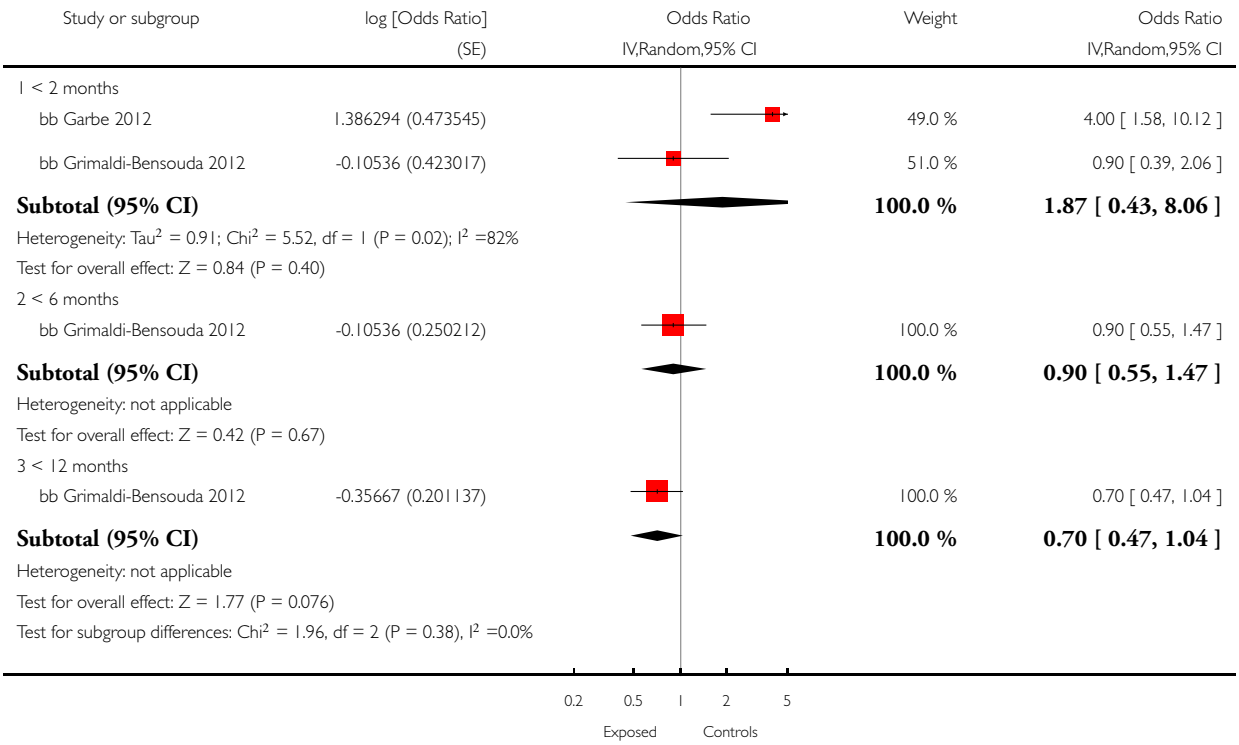


Analysis 11.1. Comparison 11 Serious adverse events - immune thrombocytopaenic purpura - case-control studies, Outcome 1 Seasonal influenza vaccine - general population (adjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 11 Serious adverse events - immune thrombocytopaenic purpura - case-control studies

Outcome: 1 Seasonal influenza vaccine - general population (adjusted data)

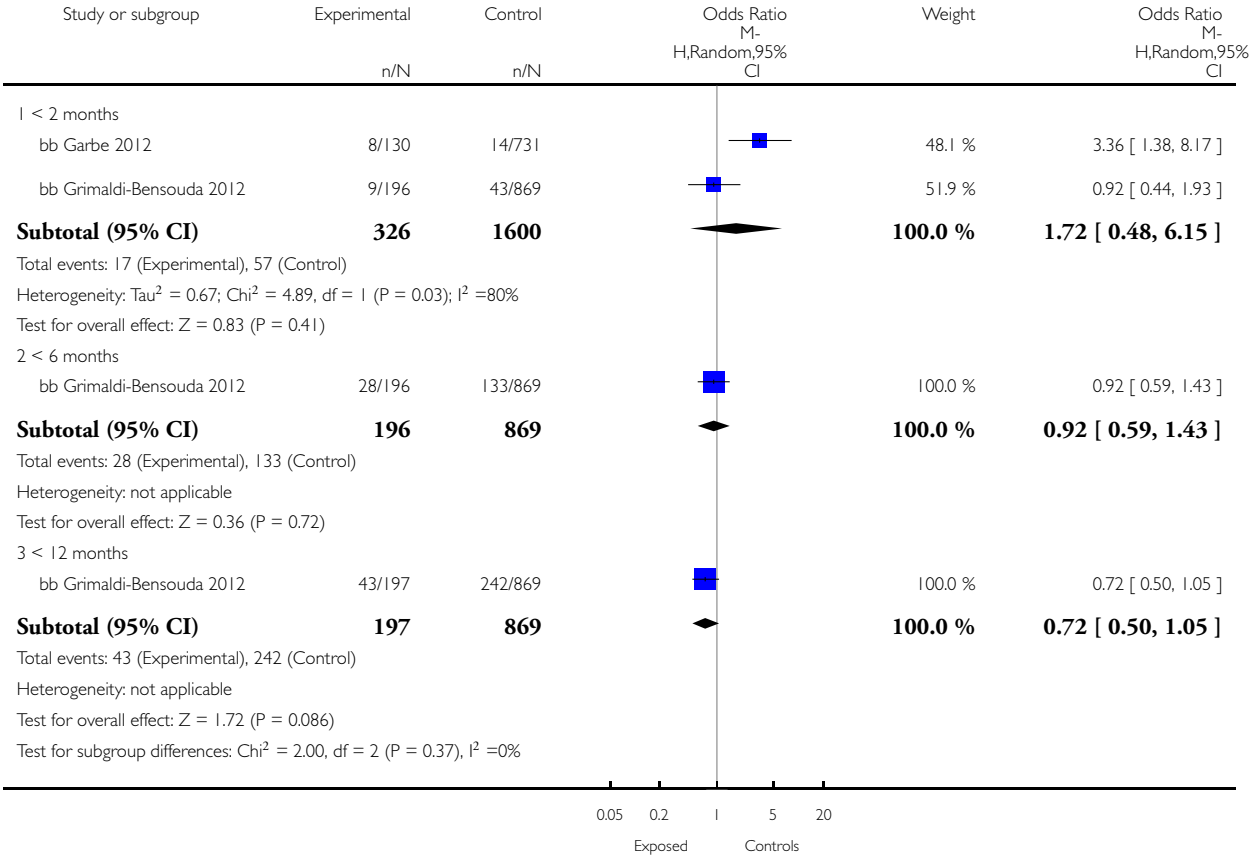


Analysis 11.2. Comparison 11 Serious adverse events - immune thrombocytopaenic purpura - case-control studies, Outcome 2 Seasonal influenza vaccine - general population (unadjusted data).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 11 Serious adverse events - immune thrombocytopaenic purpura - case-control studies

Outcome: 2 Seasonal influenza vaccine - general population (unadjusted data)



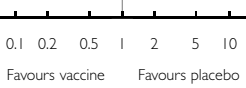
Analysis 12.1. Comparison 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo

Outcome: 1 Influenza-like illness

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 Standard recommended parenteral - non-matching - 1 dose					
aa Mogabgab 1970b	31/1030	41/1042		22.1 %	0.76 [0.48, 1.21]
aa Waldman 1969b	49/240	33/118		31.8 %	0.73 [0.50, 1.07]
aa Waldman 1972d	27/187	20/98		16.9 %	0.71 [0.42, 1.19]
Subtotal (95% CI)	**1457**	**1258**		**70.8 %**	**0.74 [0.57, 0.95]**
Total events: 107 (Vaccine), 94 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.05, df = 2 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 2.35 (P = 0.019)					
2 Standard recommended parenteral - non-matching - 2 doses					
aa Waldman 1969b	42/231	33/119		29.2 %	0.66 [0.44, 0.98]
Subtotal (95% CI)	**231**	**119**		**29.2 %**	**0.66 [0.44, 0.98]**
Total events: 42 (Vaccine), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.08 (P = 0.038)					
Total (95% CI)	**1688**	**1377**		**100.0 %**	**0.71 [0.57, 0.88]**
Total events: 149 (Vaccine), 127 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.28, df = 3 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 3.10 (P = 0.0019)					
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%					



Analysis 12.2. Comparison 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo

Outcome: 2 Influenza

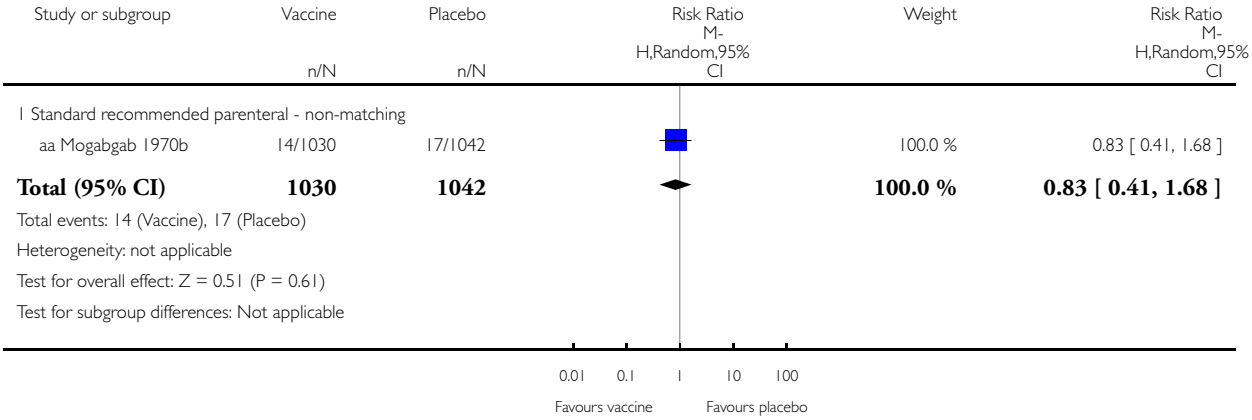
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Standard recommended parenteral - non-matching					
aa Mogabgab 1970b	15/1030	32/1042		100.0 %	0.47 [0.26, 0.87]
Total (95% CI)	**1030**	**1042**		**100.0 %**	**0.47 [0.26, 0.87]**
Total events: 15 (Vaccine), 32 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
Test for subgroup differences: Not applicable					

Analysis 12.3. Comparison 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo, Outcome 3 Hospitalisations.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo

Outcome: 3 Hospitalisations

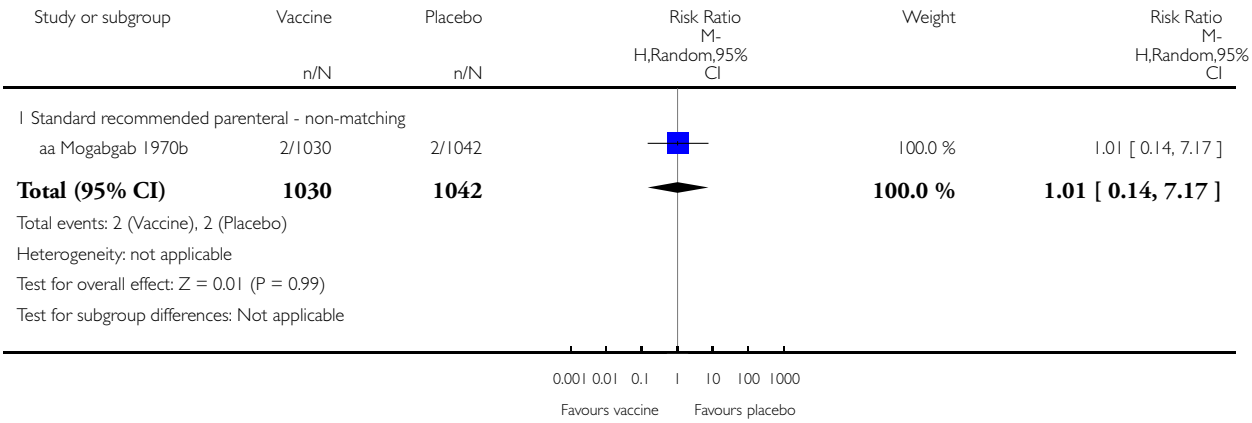


Analysis 12.4. Comparison 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo, Outcome 4 Pneumonia.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 12 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo

Outcome: 4 Pneumonia



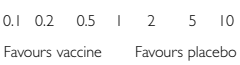
Analysis 13.1. Comparison 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome: 1 Influenza-like illness

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 WHO recommended parenteral - matching vaccine - 1 dose					
aa Mogabgab 1970a	16/881	41/1042		18.0 %	0.46 [0.26, 0.82]
aa Eddy 1970	25/1254	42/413		21.6 %	0.20 [0.12, 0.32]
aa Waldman 1969a	29/230	33/118		23.2 %	0.45 [0.29, 0.70]
aa Waldman 1972b	14/190	20/98		15.8 %	0.36 [0.19, 0.68]
Subtotal (95% CI)	**2555**	**1671**		**78.5 %**	**0.35 [0.23, 0.53]**
Total events: 84 (Vaccine), 136 (Placebo)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 7.67$, df = 3 (P = 0.05); $I^2 = 61\%$					
Test for overall effect: Z = 4.93 (P < 0.00001)					
2 WHO recommended parenteral - matching vaccine - 2 doses					
aa Waldman 1969a	23/235	33/119		21.5 %	0.35 [0.22, 0.57]
Subtotal (95% CI)	**235**	**119**		**21.5 %**	**0.35 [0.22, 0.57]**
Total events: 23 (Vaccine), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.21 (P = 0.000025)					
Total (95% CI)	**2790**	**1790**		**100.0 %**	**0.35 [0.25, 0.48]**
Total events: 107 (Vaccine), 169 (Placebo)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.68$, df = 4 (P = 0.10); $I^2 = 48\%$					
Test for overall effect: Z = 6.47 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.95), $I^2 = 0.0\%$					

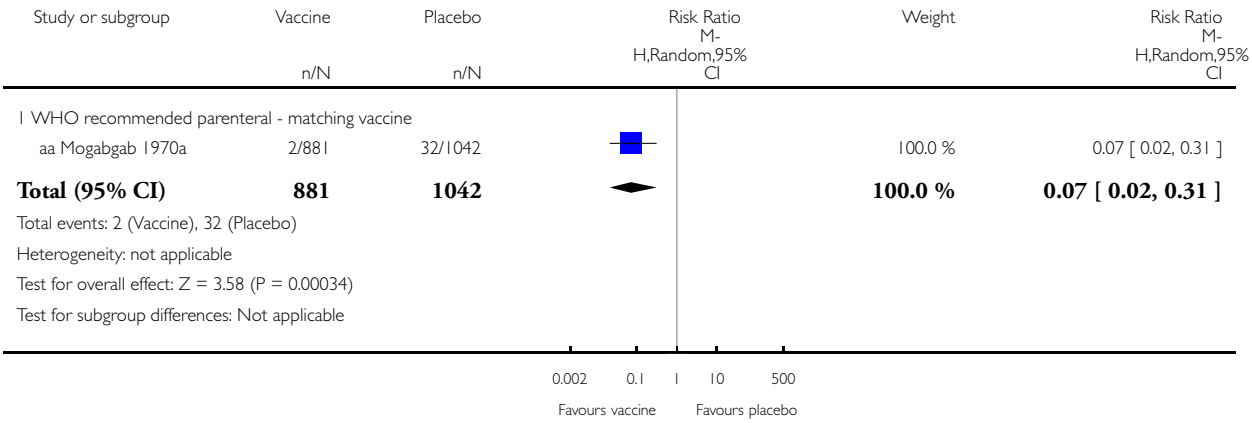


Analysis 13.2. Comparison 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome: 2 Influenza

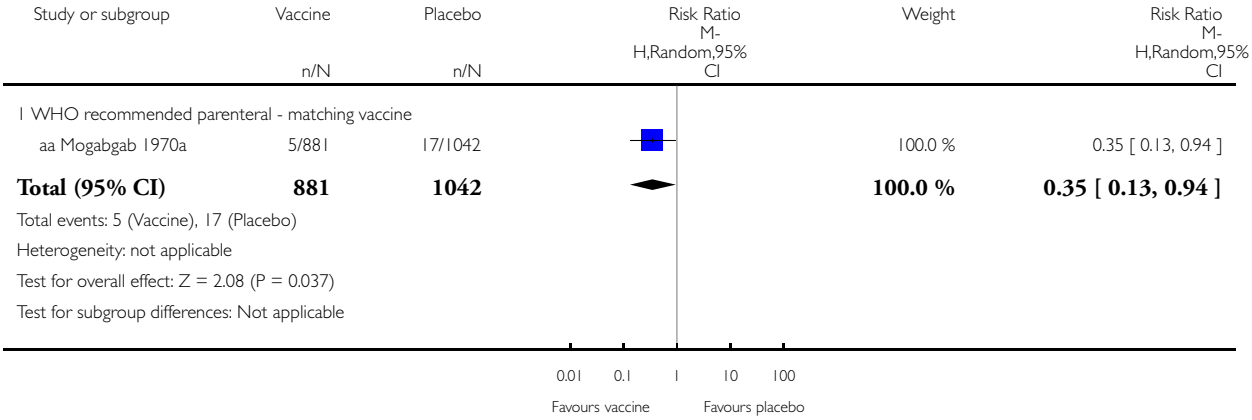


Analysis 13.3. Comparison 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo, Outcome 3 Hospitalisations.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome: 3 Hospitalisations

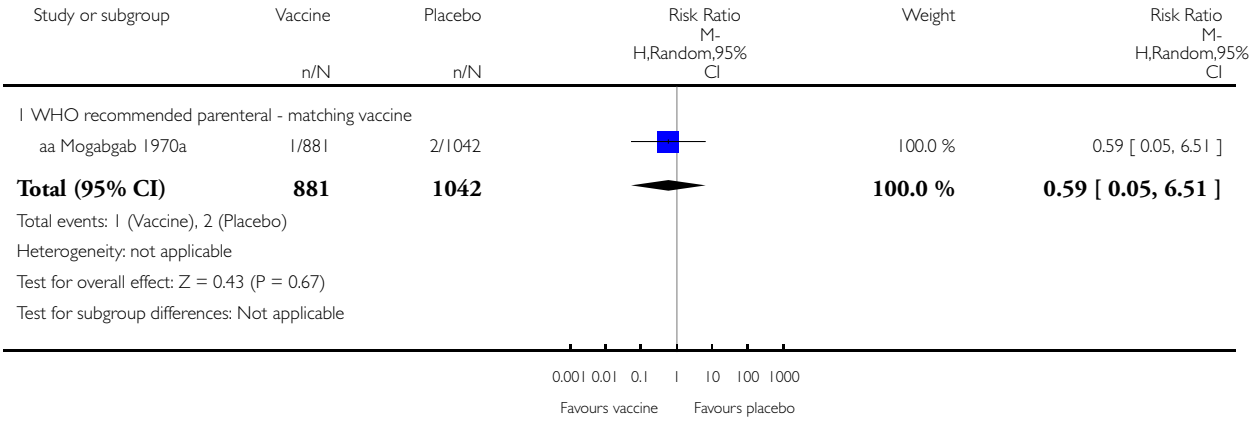


Analysis 13.4. Comparison 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo, Outcome 4 Pneumonia.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome: 4 Pneumonia

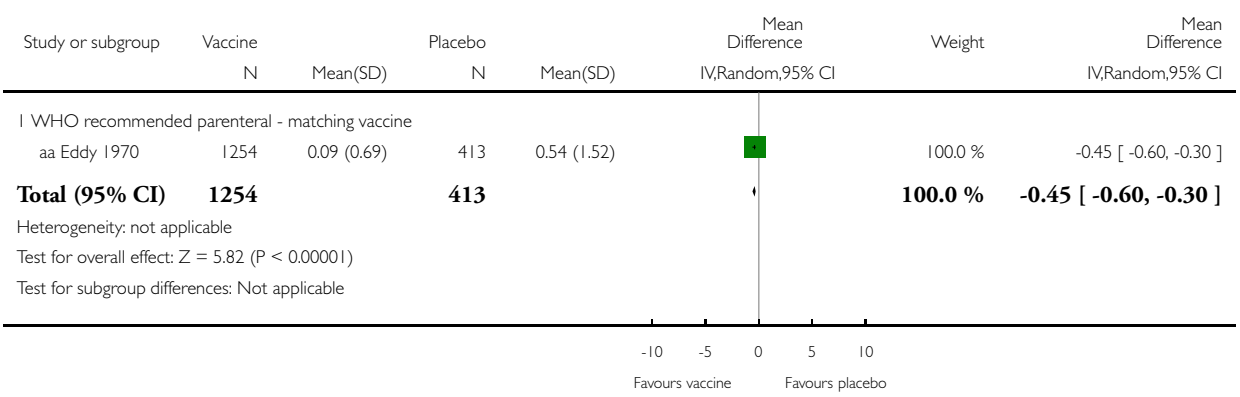


Analysis 13.5. Comparison 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo, Outcome 5 Working days lost.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome: 5 Working days lost



Analysis 13.6. Comparison 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo, Outcome 6 Days ill.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 13 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome: 6 Days ill

Study or subgroup	Vaccine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
aa Eddy 1970	1254	0.09 (0.69)	413	0.54 (1.52)		100.0 %	-0.45 [-0.60, -0.30]
Total (95% CI)	**1254**		**413**			**100.0 %**	**-0.45 [-0.60, -0.30]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.82 (P < 0.00001)

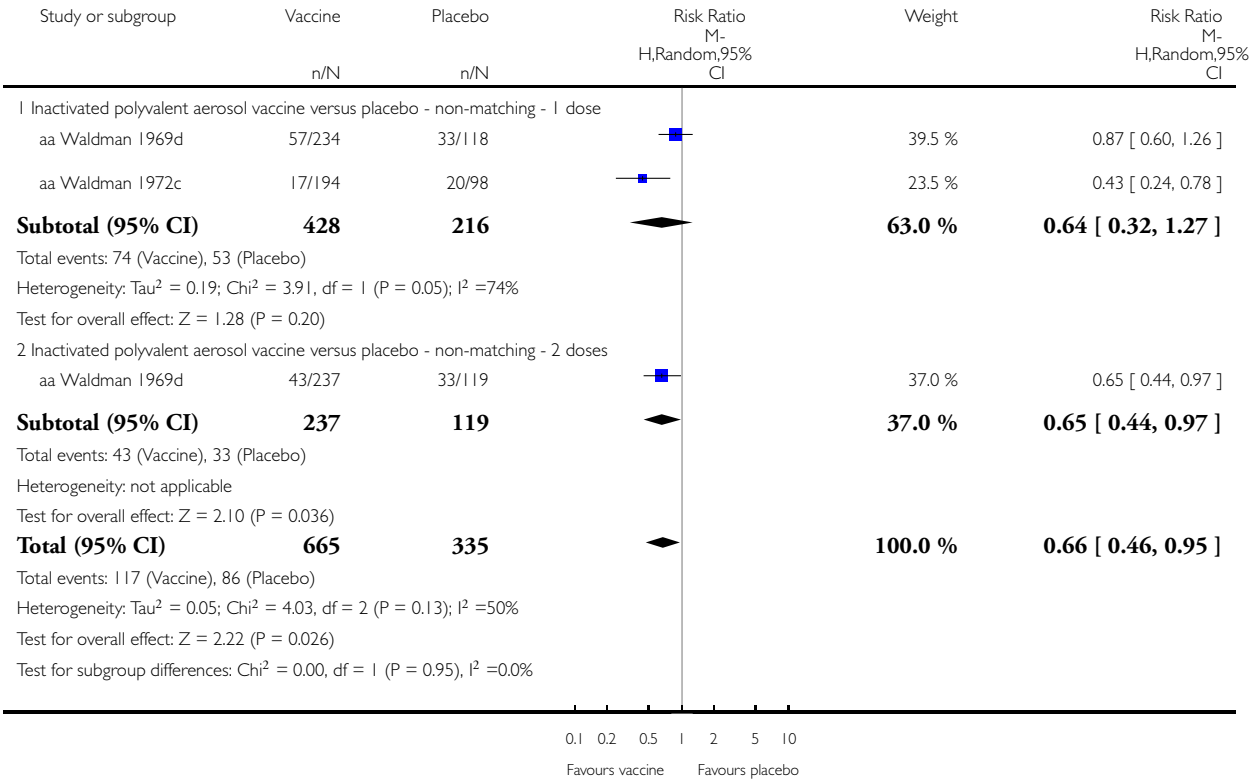
Test for subgroup differences: Not applicable

Analysis 14.1. Comparison 14 1968 to 1969 pandemic: inactivated polyvalent aerosol vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 14 1968 to 1969 pandemic: inactivated polyvalent aerosol vaccine versus placebo

Outcome: 1 Influenza-like illness

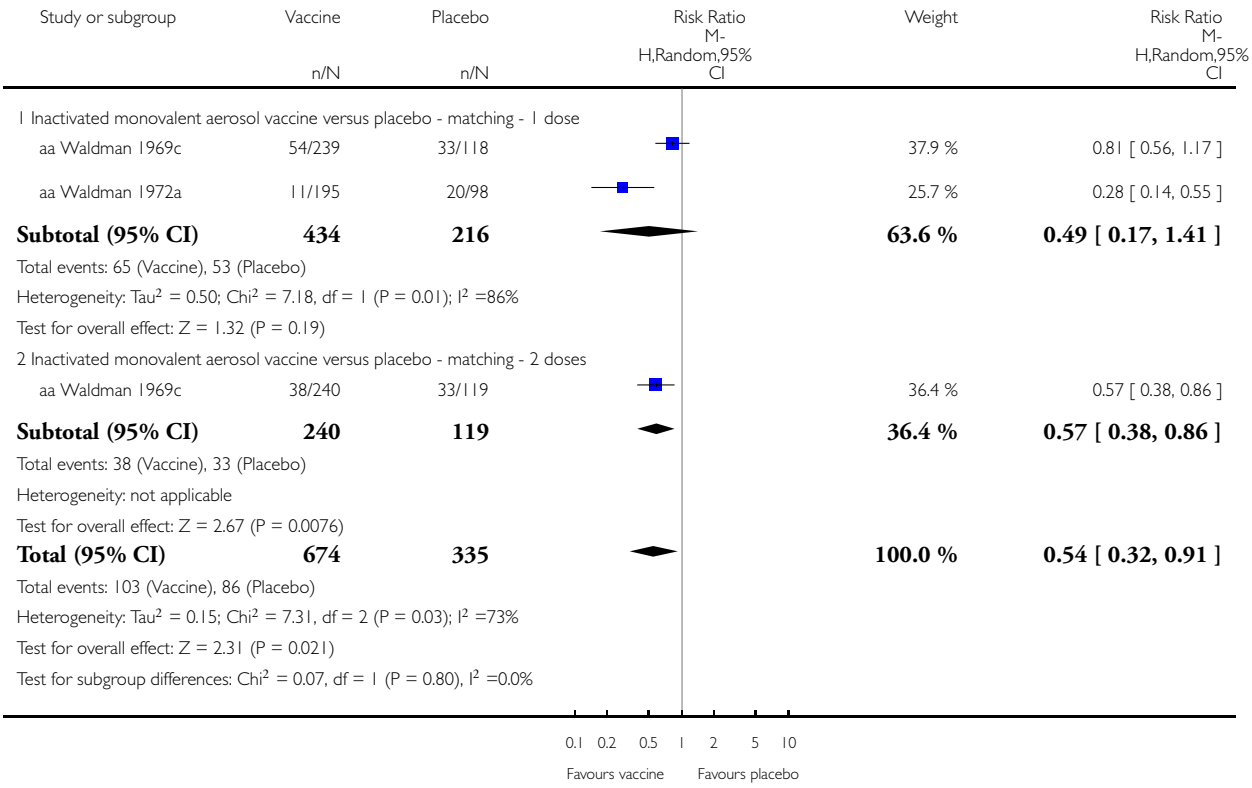


Analysis 15.1. Comparison 15 1968 to 1969 pandemic: inactivated monovalent aerosol vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 15 1968 to 1969 pandemic: inactivated monovalent aerosol vaccine versus placebo

Outcome: 1 Influenza-like illness

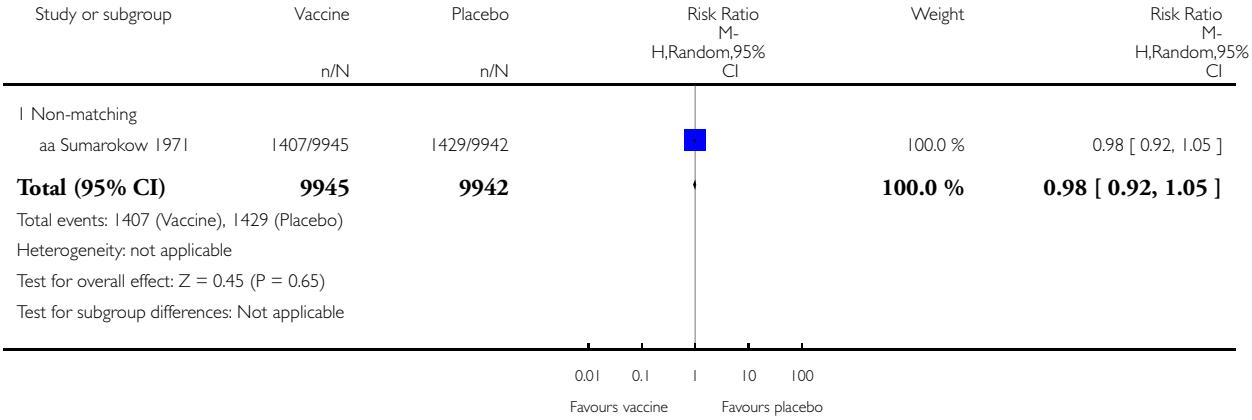


Analysis 16.1. Comparison 16 1968 to 1969 pandemic: live aerosol vaccine versus placebo, Outcome 1 Influenza cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 16 1968 to 1969 pandemic: live aerosol vaccine versus placebo

Outcome: 1 Influenza cases (clinically defined without clear definition)

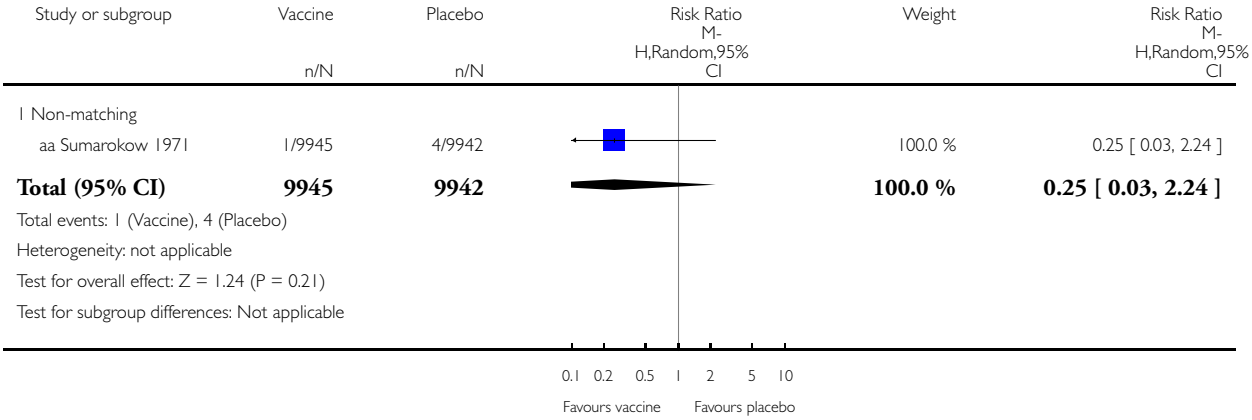


Analysis 16.2. Comparison 16 1968 to 1969 pandemic: live aerosol vaccine versus placebo, Outcome 2 Complications (bronchitis, otitis, pneumonia).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 16 1968 to 1969 pandemic: live aerosol vaccine versus placebo

Outcome: 2 Complications (bronchitis, otitis, pneumonia)



ADDITIONAL TABLES

Table 1. Risk of bias in included studies

Study design	High risk	Low risk	Unclear risk	Total
Case-control	3	2	15	20
Cohort	14	0	13	27
RCT/CCT	6	9	54	69
Total	23	11	82	116

Table 1 dispalys the overall methodological quality assessment of the included studies described in the text and represented in extended form (with all items of the tools) in Figure 1.

Table 2. Funding source of included studies

Study design	Government, institutional or public	Industry	Mixed	Total
Case-control	13	1	1	15
Cohort	22	3	2	27
RCT/CCT	31	12	5	48
Total	66	16	8	90

APPENDICES

Appendix 1. PubMed and EMBASE search strategies (trials)

MEDLINE (PubMed)
#1 "Influenza, Human"[MeSH]
#2 "Influenzavirus A"[MeSH]
#3 "Influenzavirus B"[MeSH]
#4 influenza*[Text Word] OR flu[Text Word]
#5 #1 OR #2 OR #3 OR #4
#6 "Vaccines"[MeSH]
#7 "Immunization"[MeSH]
#8 (vaccin*[Text Word] OR immuni*[Text Word] OR inocula*[Text Word])
#9 #6 OR #7 OR #8
#10 #5 AND #10
#11 "Influenza Vaccines"[MeSH]
#12 #10 OR #11
#13 "Randomized Controlled Trial" [Publication Type]
#14 "Controlled Clinical Trial" [Publication Type]
#15 randomized[Title/Abstract]
#16 placebo[Title/Abstract]
#17 "drug therapy" [Subheading]
#18 randomly[Title/Abstract]
#19 trial[Title/Abstract]
#20 groups[Title/Abstract]
#21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22 ("Animals"[MeSH]) NOT "Humans"[MeSH]
#23 #21 NOT #22
#24 #12 AND #23
EMBASE
#1 'influenza vaccine'/de
#2 'influenza'/exp
#3 'influenza virus a'/exp OR 'influenza virus b'/exp
#4 flu:ab,ti OR influenza*:ab,ti

#5 #2 OR #3 OR #4
#6 'vaccine'/de OR 'acellular vaccine'/de OR 'dna vaccine'/de OR 'inactivated vaccine'/de OR 'live vaccine'/de OR 'subunit vaccine'/de OR 'virus vaccine'/de OR 'virosome vaccine'/de OR 'recombinant vaccine'/de
#7 'immunization'/de OR 'vaccination'/de OR 'active immunization'/de OR 'immunoprophylaxis'/de OR 'mass immunization'/de
#8 vaccin*:ab,ti OR immuni*:ab,ti OR inocul*:ab,ti
#9 #6 OR #7 OR #8
#10 #5 AND #9
#11 #1 OR #10
#12 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#13 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl*) NEAR/3 (blind* OR mask*)):ab,ti
#14 #12 OR #13
#15 #11 AND #14

Appendix 2. PubMed and EMBASE search strategies (observational studies)

MEDLINE (PubMed)
#1 "Influenza Vaccines"[MeSH] OR "Influenza, Human"[MeSH]
#2 (influenza* [Text Word] OR flu[Text Word]) AND (vaccin*[Text Word] OR immuni*[Text Word] OR inocula*[Text Word])
#3 #1 OR #2
#4 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])
#5 ("cross over" OR "crossover" OR "Follow Up") OR ("Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Prospective Studies"[MeSH]) OR ("time series" OR "interrupted time series") OR ("Case-Control Studies"[MeSH] OR (cases[Title/Abstract] AND controls[Title/Abstract])) OR ("Cohort Studies"[MeSH] OR cohort*) OR ("Comparative Study"[Publication Type]) OR ("before after"[Title/Abstract] OR "before-after"[Title/Abstract] OR "before/after"[Title/Abstract] OR "before and after"[Title/Abstract]) OR (volunteer*[Title/Abstract]) OR (control*[Text Word] AND evaluation[Text Word]) OR (longitudinal[Text Word]) OR (retrospective*[Text Word])
#6 #4 OR #5
#7 #3 OR #6
EMBASE
#1 'influenza vaccine' OR (influenza OR flu AND (vaccin* OR immuni* OR inoculat*)) OR 'influenza vaccine' /syn OR ('influenza' /exp AND 'vaccine' /exp)
#2 'case control study' /syn OR 'case control' :de,ab,ti OR (cases :ab,ti AND controls :ab,ti) OR 'cohort analysis' /syn OR 'cohort study' :de,ab,ti OR 'study cohort' :de,ab,ti OR prospectiv* :ab,ti OR volunteer* :ab,ti OR observational :ab,ti OR 'clinical trial' :it OR 'randomized controlled trial' :it OR 'drug therapy' /exp OR 'drug therapy' :de OR randomized :ab,ti OR randomised :ab,ti OR placebo :ab,ti OR randomly :ab,ti OR trial :ab,ti OR groups :ab,ti
#3 'clinical trial' :it OR 'randomized controlled trial' :it OR 'randomized controlled trial' /exp OR 'randomization' /exp OR 'single blind procedure' /exp OR 'double blind procedure' /exp OR 'clinical trial' /exp OR 'clinical' NEAR/0 'trial' OR 'clinical trial' OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR 'placebo' /exp OR placebo* OR random* OR 'control group' /exp OR 'experimental design' /exp OR 'comparative study' /exp OR 'evaluation study' OR 'evaluation studies' /exp OR 'follow up' /exp OR 'prospective study' /exp OR control* OR prospectiv* OR volunteer*
#4 #2 OR #3
#5 #1 AND #4
#6 #1 AND #4 AND [embase]/lim

Appendix 3. Search strategies for 2010 update

MEDLINE (PubMed)

#1 "Influenza Vaccines"[MeSH] OR ("Influenza, Human/complications"[MeSH] OR "Influenza, Human/epidemiology"[MeSH] OR "Influenza, Human/immunology"[MeSH] OR "Influenza, Human/mortality"[MeSH] OR "Influenza, Human/prevention and control"[MeSH] OR "Influenza, Human/transmission"[MeSH])

#2 ((influenza vaccin*[Text Word]) OR ((influenza [Text Word] OR flu[Text Word]) AND (vaccin*[Text Word] OR immuni*[Text Word] OR inoculation*[Text Word] OR efficacy[Text Word] OR effectiveness[Text Word])))

#3 #1 OR #2

#4 randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) AND humans [mh]

#5 ("cross over" OR "crossover" OR "Follow Up") OR ("Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Prospective Studies"[MeSH]) OR ("time series" OR "interrupted time series") OR (placebo* OR random* OR "double blind" OR "single blind" OR clinical trial* OR trial design) OR ("Case-Control Studies"[MeSH] OR (cases[Title/Abstract] AND controls[Title/Abstract])) OR ("Cohort Studies"[MeSH] OR cohort*) OR ("Comparative Study"[Publication Type]) OR ("before after"[Title/Abstract] OR "before-after"[Title/Abstract] OR "before/after"[Title/Abstract] OR "before and after"[Title/Abstract]) OR (volunteer*[Title/Abstract]) OR (control*[Text Word] AND evaluation[Text Word])

#6 #4 OR #5

#7 #3 AND #6

EMBASE

#1 'influenza vaccine' /exp OR 'influenza vaccine' OR (influenza OR flu AND (vaccin* OR immuni* OR inoculat*)) OR 'influenza vaccine' /syn OR ('influenza' /exp AND 'vaccine' /exp)

#2 'case control study' /syn OR 'case control' :de,ab,ti OR (cases :ab,ti AND controls :ab,ti) OR 'cohort analysis' /syn OR 'cohort study' :de,ab,ti OR 'study cohort' :de,ab,ti OR prospectiv* :ab,ti OR volunteer* :ab,ti OR observational :ab,ti OR 'clinical trial' :it OR 'randomized controlled trial' :it OR 'drug therapy' /exp OR 'drug therapy' :de OR randomized :ab,ti OR randomised :ab,ti OR placebo :ab,ti OR randomly :ab,ti OR trial :ab,ti OR groups :ab,ti

#3 'clinical trial' :it OR 'randomized controlled trial' :it OR 'drug therapy' /exp OR 'drug therapy' :de OR randomized :ab,ti OR randomised :ab,ti OR placebo :ab,ti OR randomly :ab,ti OR trial :ab,ti OR groups :ab,ti

#4 'clinical trial' :it OR 'randomized controlled trial' :it OR 'randomized controlled trial' /exp OR 'randomization' /exp OR 'single blind procedure' /exp OR 'double blind procedure' /exp OR 'clinical trial' /exp OR 'clinical' NEAR/0 'trial' OR 'clinical trial' OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR 'placebo' /exp OR placebo* OR random* OR 'control group' /exp OR 'experimental design' /exp OR 'comparative study' /exp OR 'evaluation study' OR 'evaluation studies' /exp OR 'follow up' /exp OR 'prospective study' /exp OR control* OR prospectiv* OR volunteer* AND [humans]/lim

#5 #2 OR #3 OR #4

#6 #1 AND #5

#7 #1 AND #5 AND [humans]/lim AND [embase]/lim

Appendix 4. MEDLINE search strategy for 2004 update

MEDLINE

#1 ("Influenza Vaccine/administration and dosage"[MeSH] OR "Influenza Vaccine/adverse effects"[MeSH] OR "Influenza Vaccine/contraindications"[MeSH] OR "Influenza Vaccine/immunology"[MeSH] OR "Influenza Vaccine/metabolism"[MeSH] OR "Influenza Vaccine/radiation effects"[MeSH] OR "Influenza Vaccine/therapeutic use"[MeSH] OR "Influenza Vaccine/toxicity"[MeSH]) OR ("Influenza/epidemiology"[MeSH] OR "Influenza/immunology"[MeSH] OR "Influenza/mortality"[MeSH] OR "Influenza/prevention and control"[MeSH] OR "Influenza/transmission"[MeSH])

#2 (influenza vaccin*[Title/Abstract]) OR ((influenza [Title/Abstract] OR flu[Title/Abstract]) AND (vaccin*[Title/Abstract] OR immuni*[Title/Abstract] OR inoculati*[Title/Abstract] OR efficacy[Title/Abstract] OR effectiveness[Title/Abstract])

#3 #1 OR #2

#4 "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH] OR "Controlled Clinical Trial"[Publication Type] OR "Controlled Clinical Trials"[MeSH] OR "Random Allocation"[MeSH] OR "Double-Blind Method"[MeSH] OR "Single-Blind Method"[MeSH]

#5 controlled clinical trial*[Title/Abstract] OR randomised controlled trial*[Title/Abstract] OR clinical trial*[Title/Abstract] OR random allocation[Title/Abstract] OR random*[Title/Abstract] OR placebo[Title/Abstract] OR double - blind[Title/Abstract] OR

single - blind[Title/Abstract] OR RCT[Title/Abstract] OR CCT[Title/Abstract] OR allocation[Title/Abstract] OR follow - up[Title/Abstract]
#6 #4 OR #5
#7 #3 AND #6

Appendix 5. 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	Cross-over RCT
Non-randomised analytical (specifically designed to assess association)	Prospective/retrospective cohort	Case-control	Cross-sectional
Non-randomised comparative (not specifically designed to assess association)	Case cross-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?

	Subgroup distribution	
	Yes	No
Age group		
Occupation		
Health status		
Gender		
Risk group		

Description of study

Methods

Participants

Interventions/exposure

Outcomes

Notes

PART 2a

Methodological quality assessment

RCTs and CCTs only

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgement of 'Low risk' of bias	The investigators describe a random component in the sequence generation process such as: - Referring to a random number table

(*Continued*)

	- Using a computer random number generator - Coin tossing - Shuffling cards or envelopes - Throwing dice - Drawing of lots - Minimisation* *Minimisation may be implemented without a random element and this is considered to be equivalent to being random
Criteria for the judgement of 'High risk' of bias	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: - Sequence generated by odd or even date of birth - Sequence generated by some rule based on date (or day) of admission - Sequence generated by some rule based on hospital or clinic record number Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example: - Allocation by judgement of the clinician - Allocation by preference of the participant - Allocation based on the results of a laboratory test or a series of tests - Allocation by availability of the intervention
Criteria for the judgement of 'Unclear risk' of bias	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment**	
Criteria for a judgement of 'Low risk' of bias	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: - Central allocation (including telephone, web-based and pharmacy-controlled randomisation) - Sequentially numbered drug containers of identical appearance - Sequentially numbered, opaque, sealed envelopes
Criteria for the judgement of 'High risk' of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: - Using an open random allocation schedule (e.g. a list of random numbers) - Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered)

(*Continued*)

	- Alternation or rotation - Date of birth - Case record number - Any other explicitly unconcealed procedure
Criteria for the judgement of 'Unclear risk' of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement - for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study**	
Criteria for a judgement of 'Low risk' of bias	Any one of the following: - No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding - Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Criteria for the judgement of 'High risk' of bias	Any one of the following: - No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding - Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
Criteria for the judgement of 'Unclear risk' of bias	Any one of the following: - Insufficient information to permit judgement of 'Low risk' or 'High risk' - The study did not address this outcome
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors**	
Criteria for a judgement of 'Low risk' of bias	Any one of the following: - No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding - Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
Criteria for the judgement of 'High risk' of bias	Any one of the following: - No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding - Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely

(*Continued*)

	to be influenced by lack of blinding
Criteria for the judgement of 'Unclear risk' of bias	Any one of the following: - Insufficient information to permit judgement of 'Low risk' or 'High risk' - The study did not address this outcome
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data**	
Criteria for a judgement of 'Low risk' of bias	Any one of the following: - No missing outcome data - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate - For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size - Missing data have been imputed using appropriate methods
Criteria for the judgement of 'High risk' of bias	Any one of the following: - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate - For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size - 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation - Potentially inappropriate application of simple imputation
Criteria for the judgement of 'Unclear risk' of bias	Any one of the following: - Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomised not stated, no reasons for missing data provided) - The study did not address this outcome
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting**	

(*Continued*)

Criteria for a judgement of 'Low risk' of bias	Any of the following: - The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way - The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Criteria for the judgement of 'High risk' of bias	Any one of the following: - Not all of the study's pre-specified primary outcomes have been reported - One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified - One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) - One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis - The study report fails to include results for a key outcome that would be expected to have been reported for such a study
Criteria for the judgement of 'Unclear risk' of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category
OTHER BIAS **Bias due to problems not covered elsewhere in the table**	
Criteria for a judgement of 'Low risk' of bias	The study appears to be free of other sources of bias
Criteria for the judgement of 'High risk' of bias	There is at least one important risk of bias. For example, the study: - Had a potential source of bias related to the specific study design used or - Has been claimed to have been fraudulent or - Had some other problem
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: - Insufficient information to assess whether an important risk of bias exists or - Insufficient rationale or evidence that an identified problem will introduce bias

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 - 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

Notes (for statistical use only)

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
Group1					
Group 2					
Group 3					
Group 4					
Comparator					

Outcomes list - effectiveness

Outcome	How defined (including length of follow-up)	Description/follow-up/notes

Outcomes list - safety

Outcome	How defined (including length of follow-up)	Description/follow-up/notes

Investigators to be contacted for more information? Yes/No
Contact details (principal investigator, fill in only if further contact is necessary):

PART 3c

Data extraction and manipulation

(To be used for dichotomous outcomes)
Non-randomised longitudinal studies only

Comparison

Outcomes	n/N index group	n/N comparator

Notes (for statistical use only)

PART 3d

Description of studies

Case-control studies only

Event 1

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

Exposure

	How defined	How ascertained	Notes
Vaccine exposure 1			
Vaccine exposure 2			

Event 2

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

Exposure

	How defined	How ascertained	Notes
Vaccine exposure 1			
Vaccine exposure 2			

Notes (for statistical use only)

Part 3e

Data extraction and manipulation

Case-control studies only

Status	Numerator	Denominator
Cases		
Control		

Notes (for statistical use only)

Appendix 6. Included studies design

A case-control study is a prospective or retrospective epidemiological study usually used to investigate the causes of disease. Study participants who have experienced an adverse outcome or disease are compared with participants who have not. Any differences in the presence or absence of hypothesised risk factors are noted.
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 7. Methodological quality of non-randomised studies

Newcastle-Ottawa quality assessment scale - case-control studies

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

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) Representativeness 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 criterion 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) Representativeness 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 criterion could be modified to indicate specific control for a second important factor)

Outcome

1) Assessment of outcome

a) Independent blind assessment*
b) Record linkage*
c) Self report
d) No description

2) Was follow-up long enough for outcomes to occur

a) Yes (select an adequate follow-up period for outcome of interest)*
b) No

3) Adequacy of follow-up of cohorts

a) Complete follow-up - all participants accounted for*
b) Participants lost to follow-up unlikely to introduce bias - small number lost - > .... % (select an adequate %) follow-up, or description provided of those lost)*
c) Follow-up rate < ....% (select an adequate %) and no description of those lost
d) No statement

Appendix 8. Glossary

Efficacy

The impact of an intervention (drug, vaccines etc.) on a problem or disease in ideal conditions - in this case the capacity of vaccines to prevent or treat influenza and its complications.

Effectiveness

The impact of an intervention (drug, vaccines etc.) on a problem or disease in field conditions - in this case the capacity of vaccines to prevent or treat ILI and its complications.

Influenza

An acute respiratory infection caused by a virus of the *Orthomyxoviridae* family. Three serotypes are known (A, B and C). Influenza causes an acute febrile illness with myalgia, headache and cough. Although the median duration of the acute illness is three days, cough and malaise can persist for weeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease and bronchiolitis in children. These illnesses may require treatment in a hospital and can be life-threatening especially in 'high-risk' people, e.g. the elderly and people suffering from chronic heart disease. Additionally, influenza can cause a range of non-respiratory complications including febrile convulsions, Reye's syndrome and myocarditis. The influenza virus is composed of a protein envelope around an RNA core. On the envelope are two antigens: neuraminidase (N antigen) and haemagglutinin (H antigen). Haemagglutinin is an enzyme that facilitates the entry of the virus into cells of the respiratory epithelium, while neuraminidase facilitates the release of newly produced viral particles from infected cells. The influenza virus has a marked propensity to mutate its external antigenic composition to escape the hosts' immune defences. Given this extreme mutability, a classification of viral subtype A based on H and N typing has been introduced. Additionally, strains are classified on the basis of antigenic type of the nucleoprotein core (A, B), geographical location of first isolation, strain serial number and year of isolation. Every item is separated by a slash mark (e.g. A/Wuhan/359/95 (H3N2)). Unless otherwise specified such strains are of human origin. The production of antibodies against influenza beyond a conventional quantitative threshold is called seroconversion. Seroconversion in the absence of symptoms is called asymptomatic influenza.

Influenza-like illness (ILI)

An acute respiratory illness caused by scores of different viruses (including influenza A and B) presenting with symptoms and signs which are not distinguishable from those of influenza. ILI does not have documented laboratory isolation of the causative agent and is what commonly presents to physicians and patients (also known as 'the flu').

F E E D B A C K

Inconsistency between results and abstract, 6 April 2007

Summary

We feel there is some inconsistency between results and abstract of this review regarding off work time.
In the results it states that 0.4 days are saved, but that this result is not statistically significant. In the abstract, however, this difference is labelled significant. Can you help us in understanding this?
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

The difference is statistically significant as it says in the abstract. In the results the word "statistical" has been used instead of "clinical". Indeed the meaning of the comment was to underline that, although statistically significant, a difference of 0.4 day is clinically inconsistent.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms
Vittorio Demicheli

Contributors

JC van der Wouden

Comments regarding the conclusion, 5 April 2006

Summary

Your conclusion is confusing. You write: "Universal immunization of healthy adults is not supported by the results of this review." If so, why the first sentence? You wrote in the Discussion that "serologically confirmed cases of influenza are only part of the spectrum of clinical effectiveness." Furthermore, it would be helpful if you had explained the difference between influenza and influenza-like illness in the abstract. Also, the title of the synopsis is inaccurate. Why say "not enough evidence" when there are so many trials in your review? It should read: Clinical trials do not support the universal recommendation, etc. And "by a quarter" is not going to be understood by the general public. Please put in absolute terms.
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

This comment has been superseded and addressed by the 2006 latest update.

Contributors

Maryann Napoli

Vaccines for preventing influenza in healthy adults, 13 May 2013

Summary

There seems to be an inconsistency in the presentation of the Cochrane Summary: "Vaccines to prevent influenza in healthy adults". The Plain language summary states that "Vaccine use did not affect the number of people hospitalised or working days lost", but under Main Results we read that "Vaccination had a modest effect on time off work and had no effect on hospital admissions". These two claims seem to be at odds regarding working days/time lost.
I agree with the conflict of interest statement below:
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.

Robyn Kath

Reply

This review has now been updated and both paragraphs have been rewritten.

Contributors

Vittorio Demicheli

Vaccines for preventing influenza in healthy adults, 15 September 2014

Summary

In occupational health, there is a great interest in the effect of vaccination on the number of workdays lost. In this review, in the abstract it says vaccination had a modest effect on time off work. The results in the review that I can find for this outcome show a mean difference of 0.04 with a 95% confidence interval of -0.14 to 0.06. It depends on whose point of view you take, but I don't think that there is any stakeholder that will rate a 17 minutes decrease in worktime lost a modest effect. In addition, it is not significant. Did I overlook something or is this a mistake?
Best wishes,
Jos Verbeek
I agree with the conflict of interest statement below:
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.
Jos Verbeek
Email Address: jos.verbeek@ttl.fi
Affiliation: Finnish Institute of Occupational Health
Role: Senior Reseacher

WHAT'S NEW

Last assessed as up-to-date: 24 May 2013.

Date	Event	Description
15 September 2014	Feedback has been incorporated	Feedback comment submitted.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1999

Date	Event	Description
24 May 2013	Feedback has been incorporated	Feedback comment added to the review.
24 May 2013	New citation required and conclusions have changed	For this update we have added vaccine efficacy/effectiveness and safety evidence on pregnant women

(*Continued*)

24 May 2013	New search has been performed	We updated the searches and included 41 new trials (aa Barrett 2011; aa Frey 2010; aa Jackson 2010a; aa Jackson 2010b; aa Langley 2011; aa Monto 2009; aa Ohmit 2006; aa Ohmit 2008; bb Dieleman 2011a; bb Dieleman 2011b; bb Dieleman 2011c; bb Dieleman 2011d; bb Dieleman 2011e; bb Galeotti 2013; bb Garbe 2012; bb Grimaldi Bensouda 2011; bb Grimaldi-Bensouda 2012; bb Hernan 2004; bb Ray 2011; bb Zorzon 2003; cb Bardage 2011; cb Baxter 2012; cb Moro 2013; cb Ray 2011; pba Benowitz 2010; pba Poehling 2011; pbb Irving 2013; pca Black 2004; pca Eick 2011; pca France 2006; pca Hulka 1964; pca Munoz 2005; pca Yamada 2012; pcb Deinard 1981; pcb Fell 2012; pcb Håberg 2013; pcb Heikkinen 2012; pcb Källén 2012; pcb Launay 2012; pcb Lin 2012; pcb Nordin 2013; pcb Omer 2011; pcb Oppermann 2012; pcb Pasternak 2012; pcb Richards 2013; pcb Sheffield 2012; pcb Toback 2012), which corresponded to 47 data sets. We excluded 63 new trials
3 June 2010	New search has been performed	Searches conducted. For this update we screened 3729 titles and identified 44 studies for possible inclusion. We included two new trials (aa Beran 2009a; aa Beran 2009b) and excluded three new trials (Belongia 2009; Chou 2007; Khazeni 2009).
11 March 2010	New citation required but conclusions have not changed	For this update Eliana Ferroni (EF), Lubna Al Ansary and Ghada Bawazeer joined as new authors. Carlo Di Pietrantonj (CDP), Alessandro Rivetti (AR) and Tom Jefferson (TJ) remained
10 May 2009	Amended	Contact details updated.
26 April 2008	Amended	Converted to new review format.
15 April 2007	Feedback has been incorporated	Feedback comment added to review.
20 November 2006	New citation required and conclusions have changed	Substantive amendment. For the 2006 update we included 30 new studies but tightened up our inclusion criteria, excluding studies with influenza B vaccine as a control. These do not come within our comparator rules of placebo or do nothing. Twenty-two of the new included studies were clinical trials evaluating the efficacy or safety (or both) of different type of influenza vaccines. We also carried out a subanalysis of the five 1968 to 1969 pandemic trials (with numerous subtrials) in our

(*Continued*)

		dataset. Finally, we included more data (10 studies) on potential serious or rare harms, looking also at non-randomised evidence
4 April 2006	Feedback has been incorporated	Feedback commented added to review.
10 January 2006	New search has been performed	Searches conducted.
1 December 2003	New search has been performed	Searches conducted. In the 2004 update we included five more studies which were not identified by the original searches and we updated the text and references. We also assessed and excluded 25 more studies. We used the random-effects model for analysing all the comparisons and outcomes. The updated results and conclusions of our review did not change much
27 December 1997	New search has been performed	Searches conducted. Review first published Issue 4, 1999.

CONTRIBUTIONS OF AUTHORS

Carlo Di Pietrantonj (CDP) and Alessandro Rivetti (AR) designed the 2013 update.

AR carried out the searches and preliminary screening of references.

AR and CDP applied the inclusion criteria.

AR and CDP extracted data.

CDP checked the data extraction, performed the meta-analysis and carried out statistical testing.

CDP and AR wrote the final report.

All review authors contributed to the review update.

DECLARATIONS OF INTEREST

Dr Tom Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu [Roche] and in a labour case on influenza vaccines in health care workers in Canada. In 1997-99 Dr Jefferson acted as consultant for Roche, in 2001-2 for GSK and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral which did not get approval from FDA). Dr Jefferson is a consultant for IMS Health. Dr Jefferson is a co-recipient of a UK National Institute for Health Research grant (HTA - 10/80/01 Update and amalgamation of two Cochrane Reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - http: // www.hta.ac.uk/2352).

Vittorio Demicheli, Lubna A Al-Ansary, Eliana Ferroni, Alessandro Rivetti, Carlo Di Pietrantonj have no conflicts to declare.

SOURCES OF SUPPORT

Internal sources

- ASL 19 and 20, Piemonte, Italy.

External sources

- Ministry of Defence, UK.
- NHS Department of Health Cochrane Incentive Scheme, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Evidence about the safety and efficacy/effectiveness of influenza vaccine administration during pregnancy is now included.

INDEX TERMS

Medical Subject Headings (MeSH)

*Influenza A virus; *Influenza B virus; Drug Industry; Influenza, Human [prevention & control; virology]; Publication Bias; Research Support as Topic

MeSH check words

Adult; Humans