CR Review formatting

Vaccines for preventing influenza in healthy adults (Review)

rewritten to fit prototype format

September 26 2018

A review will have the following sections/pages:

Summary

Full text

Appendices

Related content

Messages for media

Article information

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# **Vaccines for preventing influenza in healthy adults (Review)**

Cochrane Systematic Review – Intervention

Published date: 1 February 2018| Date of last search: December 2016 (see what’s changed)

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View author’s declarations of interest

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

SUMMARY

# Background

Influenza is an acute respiratory infection caused by a virus and is spread between people by droplets or respiratory secretions. There are three different types of virus (A, B and C). Influenza causes an acute illness with fever, muscle aches, headache, and cough. In general, influenza lasts for three days, but symptoms can persist for weeks. The consequences of influenza in adults are mainly time off work. Vaccines can be used to prevent or minimise the impact of seasonal influenza. **This review aimed to assess the benefits and harms of vaccines against influenza in healthy adults, including pregnant women.** See more detail about vaccines for preventing influenza.

# More detail about influenza vaccines

## What are influenza vaccines?

Vaccines work by simulating an infection and stimulating the body to produce antibodies against the threat and to activate other defence mechanisms. Influenza vaccine can be made as an inactivated (killed) preparation that is injected and an attenuated (weakened) influenza vaccine normally delivered nasally.

## Who can use or administer influenza vaccines?

All people aged six months or older without contraindications can receive influenza vaccine. Pregnant women can receive the inactivated vaccine which has no live virus.

Vaccination is often directed at healthy individuals who are at higher risk of developing complications following influenza due to their age, medical conditions, or contact with high risk individuals.

Vaccination is administered by trained healthcare personnel.

## What other options are there?

People with influenza can pass on the virus to others before they are aware they are ill. It is therefore difficult to identify whether someone is infectious or not. Healthy adults can try to avoid influenza by washing hands regularly and avoiding being in contact with people who are obviously suffering from flu-like illnesses. See systematic reviews of other options.

## How do people experience the intervention?

Vaccines are given by injection (with a needle) and can also be given via a nasal spray. People who receive vaccination by injection may experience pain at the site.

## Is there anything else someone should know before using the intervention?

Every year the World Health Organization attempts to identify the most likely strain(s) of virus circulating globally and recommends which strain(s) are to be included in the vaccine for that year. The influenza vaccine therefore only protects against the most common circulating strain(s) for that year and vaccination is required every year for protection.

# What this review is based on

Cochrane Reviews are based on systematic and robust selection of relevant studies. We included 52 clinical trials of over 80,000 adults in this review. See what studies we searched for and what we found.

1st link to standard description of what a Cochrane Review is.

2nd link leads to the text below, which is a narrative summary of the table in the Full text called “What review authors searched for and found”:

## What studies we searched for

We searched for studies up until December 2016. We searched for randomised or non-randomised trials comparing vaccines of any type and given by any route in humans with placebo or no intervention, or comparing types, doses, or schedules of influenza vaccine. We only considered studies assessing protection from exposure to naturally-occurring influenza. Trials were included if they reported on the number and seriousness of symptomatic influenza and influenza-like illness.

Previous versions of this review included cohort and case-control studies if these reported on the association between influenza vaccines and serious adverse effects, or if effects on pregnant women were reported.

## What we found

We included 52 trials of data from over 80,000 people. Together with observational studies from previous reviews, the review includes data from a total of 160 studies.

# Main findings

## Seasonal vaccines

→ **Inactivated injected influenza vaccines:** Compared to placebo or non-placebo control groups, inactivated injected influenza vaccines probably reduce influenza and influenza-like illness in healthy adults (moderate-certainty evidence). They may slighltly reduce time off work (low-certainty evidence) and have little or no effect on hospitalisations (low-certainty evidence). They increase the proportion of people with a slight increase in fever (high-certainty evidence) and they may increase nausea and vomiting (low-certainty evidence).

→ **Live (attenuated) aerosol influenza vaccines:** Compared to placebo or non-placebo control groups, live aerosol vaccines probably reduce influenza and influenza-like illness in healthy adults. The certainty of evidence was not assessed.

→ **Inactivated aerosol influenza vaccines:** We are uncertain about whether inactivated aerosol vaccine reduces influenza.

Standard sentences: See current Plain language summary guidance: http://www.cochrane.no/sites/cochrane.no/files/public/uploads/how\_to\_write\_a\_cochrane\_pls\_27th\_march\_2017.pdf

## Summary of findings 1

## **Summary of Findings should be numbered when there is more than one. Number 1 should be the one that appears in the summary. This will have consequences for the order of the comparisons listed in the full text.**

iSoF generator: See isof.epistemonikos.org.

Create a log-in and let me add you to our organization.

Standard sentences: See current Plain language summary guidance: http://www.cochrane.no/sites/cochrane.no/files/public/uploads/how\_to\_write\_a\_cochrane\_pls\_27th\_march\_2017.pdf

# Authors’ conclusions

Inactivated vaccines probably reduce the proportion of healthy adults who have influenza and influenze-like illness. There is variation in the size of the effect, but overall the impact is modest. Vaccines increase the proportion of people with a small increase in fever, and they may increase the proportion with nausea and vomiting.

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

## Related content

* More information for patients and the public, health professionals and policy makers
* Cochrane Reviews of other options for uterotonic agents

(Links leads to texts in ‘Related content’ section – see end of document, after Appendices)

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

## Messages for media

(Link leads to ‘Messages for media’ section, created for the most part by people other than authors.)

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

FULL TEXT

References in the text will be linked to reference lists in the final published version, but I have not bothered to recreate these links in the prototype sketches.

# Background

## Description of the condition

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

Influenza is an acute respiratory infection caused by a virus of the *Orthomyxoviridae* family.Three serotypes are known (A, B, andC). 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 forweeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease, and bronchiolitis in children. Additionally, influenza can cause a range of non-respiratory complications, including febrile convulsions, Reye’s syndrome, and myocarditis (Treanor 2016;Wiselka 1994).

## Description of the intervention

Vaccines work by simulating an infection and stimulating the body to produce antibodies against the threat and activate other defence mechanisms. There are currently 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 vaccines, which are made of surface antigens (H and N) only; and
3. split-virion vaccines, in which the viral structure is broken up by a disrupting agent.

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

Efforts to prevent or minimise the impact of seasonal influenza in the second part of the 20th century were 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 an extensive scientific and logistic effort to ensure production and delivery of the vaccines.

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 sent swiftly 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 have followed their own recommendations for vaccine content. Surveillance and early

identification thus play a central part in the composition of the vaccine.

## Why it is important to do this review

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

An accurate assessment of the effects of influenza vaccines is essential to allow inform decision making.

This is an updated review and includes data from randomised trials. Previous versions of the review included evidence from both randomised and observational studies. Since the 2014 update of this review (Jefferson 2014), we have included evidence about influenza vaccination in pregnant women and newborns.

# Objectives

To assess the effects of vaccines against influenza in healthy adults, including pregnant women, on:

1. preventing influenza A or B and its complications;
2. preventing influenza-like illness and its consequences; and
3. any harmful events potentially associated with exposure to influenza vaccines.

# Methods

## Criteria for considering studies for this review

### Types of studies

Any randomised trial or non-randomised trial comparing influenza vaccines in humans with placebo or no intervention, or comparing types, doses, or schedules of influenza vaccine. We only considered studies assessing protection from exposure to naturally-occurring influenza.

### Types of participants

Healthy individuals aged 16 to 65 years, irrespective of influenza immune status. We excluded studies considering more than 25% of individuals outside this age range. We also included pregnant women together with their newborns.

### Types of interventions

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

### Types of outcome measures

The outcomes were selected according to clinical importance and those included in the Summary of Findings table were deemed to be critical to patients (isof.epistemonikos.org).

The primary outcomes of the review were:

**Benefits**

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 included 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 included abortion (spontaneous, internal, foetal death, and stillbirth), preterm birth (less than 37 weeks), and maternal death.
3. Neonatal outcomes: congenital malformations (minor and major), neonatal death.

Secondary outcomes were:

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

## Methods for identifying studies

See: Additional details: Methods for identifying studies

## Methods for collecting and analysing data

See: Additional details: Methods for collecting and analysing data

# Results

## Results of the search

Our searches resulted in 52 trials for inclusion in this review. Below, Table 1 presents more detail about what we searched for and found. Figure 1 illustrates our inclusion and exclusion process in a study flow diagram. Then, in a series of tables and figures, we present the characteristics of included, excluded, and ongoing studies, as well as our judgements about risk of bias. (See Additional Details for a list of all results tables and figures.)

‘Figure 1’ link is the flow chart of included and excluded studies in Additional Details section 3

**Table 1: What review authors searched for and found**

|  |  |  |
| --- | --- | --- |
|  | **What the review authors searched for** | **What the review authors found** |
| ***Study designs*** | Randomised or non-randomised trials of effectiveness or side-effects of vaccines for influenza. | 52 randomised trials  Some trials had more than 2 arms and these were divided into substudies (datasets). |
| ***Interventions*** | Influenza vaccines of any type and given by any route in humans. | *Types of vaccines, route of administration and number of datasets:*  *Seasonal vaccines*   * Inactivated parenteral (40) * Live aerosol vaccines (21) * Inactivated aerosol vaccines (1)   *Pandemic vaccines*   * Inactivated parenteral (7) * Live aerosol vaccines (4) * Inactivated aerosol vaccines (1) |
| ***Participants*** | Healthy adults including pregnant women | 86,490 healthy adults of which 2,342 were pregnant women |
| ***Settings*** | Any setting in any country. | The trials were conducted in community settings in various countries and often involved more than one country. |
| ***Outcomes*** | *Primary outcomes*  *Benefits*   * Influenza * Influenza-like illness * Time off work * Hospitalisation   *Harms*   * Fever * Nausea * Malaise * Fatigue * Rash * Headache * Arthralgia * Maternal outcomes related to pregnancy (abortion, preterm birth, maternal death) * Neonatal outcomes (congenital malformations, neonatal death)   *Secondary outcomes*   * Local adverse effects including induration, soreness, redness at site of inoculation | *Primary outcomes (N = number of trials)*  *Seasonal vaccines*  **Inactivated parenteral:** Influenza (25), influenza-like illness (16), physician visits (2), days ill (3), times any drug prescribed (2), times antibiotic prescribed (2), working days lost (4), hospitalisations (3), myalgia (11), fever (13), fatigue (12), headache (14), local harms (20)  **Live aerosol:** Influenza (9), influenza-like illness (6), myalgia (4), fever (4), fatigue (3), headache (2), local harms (13)  **Inactivated aerosol:** Influenza (1), myalgia (2), fever (1), fatigue (2), headache (2), local harms (3)  *Pandemic vaccines*  **Inactivated polyvalent parenteral:** Influenza (1), Influenza-like illness (3), hospitalisations (1), pneumonia (1)  **Inactivated monovalent parenteral:** Influenza (1), influenza-like illness (4), hospitalisations (1), pneumonia (1)  **Inactivated polyvalent aerosol**: Influenza-like illness (2)  **Inactivated monovalent aerosol:** Influenza-like illness (2)  **Live aerosol:** Influenza (1), complications (1) |

**Figure 1.** Study flow diagram of searches conducted for this update: How the authors selected the studies to be included in the review

**Table 2.** Characteristics of included studies: Details of the studies that the authors agreed to include in this review, according to the methods described for collecting and analysing data

**Table 3.** Characteristics of excluded studies: Details of the studies that the authors agreed to not include in this review

**Table 4.** Characteristics of ongoing studies

**Table 5.** Risk of bias of included studies: Details about the authors’ judgments about the risk of bias in the included studies

**Figure 2.** Risk of bias summary

## Effects of interventions

Effects according to conparison:

Summary of findings 1: *This table presents the effects of inactivated parenteral influenza vaccine compared to placebo or ’do nothing’ for preventing influenza in healthy adults*

Overview of analyses (with forestplots)

## Seasonal vaccines

## Comparison 1: *Inactivated parenteral influenza vaccine versus placebo or non-placebo control*

Key characteristics of included studies 1

Summary of findings 1

### Influenza:

Inactivated parenteral vaccines probably reduce the risk of confirmed influenza ((RR 0.41, 95% CI 0.36 to 0.47; moderate-certainty evidence) (Analysis 1.1). Based on the control group risk of 2.3%, 71 healthy adults need to be vaccinated in order to prevent one of them experiencing influenza. The effects were very similar when matching was absent or unknown. There was little heterogeneity (I2 = 17% for Analysis 1.2.1; I2 = 14% for Analysis 1.1.2). Restricting the analysis to studies at low risk of bias did not affect the direction or size of effect.

### Influenza-like illness:

Inactivated parenteral vaccines probably reduce the risk of influenza-like illness (RR 0.84, 95% CI 0.75 to 0.95; moderate-certainty evidence) (Analysis 1.2). Based on the median control group risk of 21.5%, 29 healthy adults need to be vaccinated to prevent one adult experiencing an influenza-like illness. However, there was wide variation in the control group risks. For low- and high-risk control groups the corresponding number needed to vaccinate (NNVs) were 167 and 7, respectively. Sensitivity analysis by risk of bias did not change the size or direction of effect. Results across the subgroups by matching criteria were very similar (I2 = 0%).

### Hospitalisations:

Inactivated parenteral vaccines may have little if any effect on hospitalisation (RR 0.96, 95% CI 0.85 to 1.08; low-certainty evidence) (Analysis 1.3). We found no evidence for cases of pneumonia.

### Time off work:

Inactivated parenteral vaccines may slightly reduce time off work. The result of the four trials that reported this outcome were heterogeneous (I2 = 82%). The overall estimate of 0.04 fewer lost working days per person during the influenza season was the same when a fixed-effect (95%CI -0.06 to -0.01) or random-effects (95%CI -0.14 to 0.06) model was used (Analysis 1.4). We rated the evidence as of low certainty.

### Other outcomes:

Two trials reported on effects on days of illness (Analysis 1.5) and two trials reported effects on physician visits (Analysis 1.6). There seemed to be no effect on the time an antibiotic or drug was prescribed (Analysis 1.7; Analysis 1.8). The certainty of evidence for these outcomes was not assessed.

### Adverse effects:

Inactivated parenteral influenza vaccines increase the proportion of people with a slight increase in fever (1.5% in unvaccinated versus 2.3% in vaccinated participants (RR 1.55, 95% CI 1.26 to 1.91; high-certainty evidence) (Analysis 1.9.1).

Inactivated parenteral influenza vaccines may increase nausea or vomiting (4% in unvaccinated population versus 7% with vaccines (RR 1.80, 95% CI 0.65 to 5.04; low certainty evidence) (Analysis 1.9.2).

Myalgia was associated with vaccination (RR 1.74, 95% CI 1.41 to 2.14) (Analysis 1.9.3), fatigue or indisposition (RR 1.19, 95% CI 1.05 to 1.36) (Analysis 1.9.4), and malaise (RR 1.51, 95%CI 1.18 to 1.92) (Analysis 1.9.5). The relative risk for the combined endpoint was 1.16 with a wide 95%CI (0.87 to 1.53) (Analysis 1.9.7). The certainty of evidence was not assessed for these adverse events.

Local tenderness and soreness were 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 were 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) (Analysis 1.10.3) but not in arm stiffness (Analysis 1.10.4). The combined local effects endpoint was higher for those receiving the vaccine (RR 2.44, 95% CI 1.82 to 3.28) (Analysis 1.10.5).

## Comparison 2: *Live attenuated aerosol influenza vaccine versus placebo or non-placebo control*

### Influenza:

Live attenuated aerosol vaccines reduce the risk of influenza (RR 0.47, 95% CI 0.35 to 0.62) (Analysis 2.1) with 39 healthy adults needing to be vaccinated in order to prevent one of them experiencing influenza. Neither content nor matching appeared to affect the result. There was moderate heterogeneity (I2 = 40%). The certainty of evidence was not assessed for this outcome.

### Influenza-like illness:

Live attenuated aerosol vaccines slightly reduce influenza-like illness (RR = 0.90, 95% CI 0.84, 0.96). Content and matching appeared not to affect the performance (Analysis

2.2) and there was minimal heterogeneity (I2 = 0%). The certainty of evidence was not assessed for this outcome.

### Other beneficial outcomes:

There were no trials which reported hospitalisations, time off work or other clinical outcomes.

### Adverse effects:

Live attenuated aerosol vaccines increased the proportion of people with 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) and sore throat (RR 1.66, 95% CI 1.49 to 1.86) (Analysis 2.3). Overall a combined endpoint (any or highest symptom) was higher in those vaccinated compared to those receving a placebo or control (RR 1.56,

95% CI 1.31 to 1.87). The certainty of evidence was not assessed for these outcomes.

There was no 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) were higher in the vaccine group than in the placebo group (Analysis 2.4). The certainty of evidence was not assessed for these outcomes.

## Comparison 3: *Inactivated aerosol influenza vaccine versus placebo or non-placebo control*

### Influenza:

A single RCT assessed inactivated aerosol influenza vaccines compared to a placebo group and showed that vaccine reduced the risk of influenza (RR 0.38, 95% CI 0.14 to 1.02) (Analysis 3.1). The certainty of evidence was not assessed for this outcome.

### Influenza-like illness:

The trial did not measure this outcome.

*Adverse effects:*

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

## Pandemic vaccines

Vaccine performance was poor when the content did not match the pandemic

Strain. One- or two-dose monovalent whole-virion (i.e. containing dead complete viruses) vaccines achieved a vaccine effect of 65% (95% CI 52% to 75%) protection against influenza-like illness (number needed to vaccinate = 16, 95% CI 14 to 20), a vaccine effect of 93% (95% CI 69% to 98%) with number needed to vaccinate of 35 (95% CI 33 to 47) protection against influenza, and a vaccine effect of 65% (95% CI 6% to 87%) with number needed to vaccinate of 94 (95% CI 70 to 1022) against hospitalisation. Approximately half a working day and half a day of illness were saved but no effect was observed on pneumonia. All comparisons except for influenza-like illness were based on a single study. The large effect on influenza-like illness 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. The uncertainty of these effects was not evaluated.

# Discussion

## Key findings and certainty of the evidence

Healthy adults who receive inactivated injected influenza vaccine rather than no vaccine probably have a 1% lower risk of experiencing influenza over a single influenza season and probably have a lower risk of experiencing influenza-like illness. We found that hospitalisation rates and time off work may be similar between vaccinated and unvaccinated adults, although this was less certain. These vaccines increase the risk of a number of minor adverse events, including a small increase in fever, but the effect on nausea or vomiting is less clear.

Live aerosol vaccines probably reduce influenza and influenza-like illness in healthy adults, although the certainty of evidence was not assessed. No firm conclusions could be made regarding inactivated aerosol vaccines as only a single trial assessed this vaccine.

## Applicability of evidence

**Table 2:** *Applicability of evidence*

|  |  |
| --- | --- |
| Findings | *Interpretation* |
| Inactivated vaccines probably have a small effect in preventing the symptoms of influenza and getting people back to work more quickly. | *This is likely to be generalizable to the general population of healthy adults globally.* |
| Methods of vaccine standardisation have changed significantly over time. Recent vaccines present significant differences in purity when compared with older ones and different doses and schedules were pooled in the analysis. | *These changes over time may limit the use of data obtained from prior vaccine studies in informing the current evidence base.* |
| Most trials exclude high-risk groups such as the older person and only one trial included pregnant women. | *The evidence base for high risk groups remains sparse, with issues of harms (especially in pregnancy) not well-studied.* |
| The quality of the evidence for influenza was downgraded due to indirectness reflecting the uncertainty in the methods to ascertain the outcome in older studies. | *These changes over time may limit the use of data obtained from prior vaccine studies in informing the current evidence base* |

## Agreements and disagreements with other studies or reviews

The conclusions of the cited reviews outlined in Table 3 are broadly comparable with ours, but the results are reported using relative effects-based estimates. In addition, none of the reviews identified effects of vaccines on important outcomes such as complications, hospitalisations, and deaths. These findings are also similar to ours.

**Table 3:** *Agreements and disagreements with other studies or reviews*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Author / Year | Influenza reported? | Safety  reported? | Study types included | No. of  included studies | Summary of main findings |
| DiazGranados 2012 | Yes.  PCR or serological confirmation | Unclear | RCTs of seasonal inactivated or live attenuated vaccines | 30 trials in adults and children | 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%). |
| Osterholm 2012 | Yes.  Laboratory-confirmed by PCR or culture | Unclear | RCTs and observational studies of live attentuated and inactivated vaccines | 6 RCTs of 8 datasets were meta-analysed | 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 because  none of the single estimates was statistically significant. |
| Skowronski 2009 | Yes. | Yes. | Studies of protection and harms specific to pregnant women |  | Immunisation against influenza at any stage of  pregnancy may be warranted during pandemics or for women  with comorbidity. Seasonal immunisation with trivalent inactivated  vaccine may be warranted in pregnancy, without potential  complications during the second half of the pregnancy. The  available evidence is insufficient to recommend standard routine vaccination in the early stages of pregnancy. |
| Farez 2011 |  | Yes. Multiple sclerosis or relapsing multiple sclerosis. | Case-control studies of incidence of MS following immunisation including influenza | 4 | Meta-analysis performed  by pooling the results of four case-control studies would exclude an increased risk of developing multiple sclerosis following  influenza vaccine administration (OR 0.97, 95% CI 0.77 to 1.23) |
| Tobrack 2012 | Yes.  Immunogenecoty | Yes | RCTs of new quadrivalent live attenuated influenza vaccine (Q-LAIV, already  licensed in the USA, where it will was available for the 2013  to 2014 season) containing two different B strains of different  lineage (B/Yamagata/16/88 and B/Victoria/2/87). | 1 RCT in adults; 1 in children | Findings were that 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 administration of other vaccines already in use. |

# Authors’ conclusions

## Implications for practice

Healthy adults who received inactivated parenteral influenza vaccine rather than no vaccine had, on average, a 1% lower risk of experiencing influenza over a single influenza season (2.3% versus 1%, moderate-certainty evidence) and a 3.4% lower risk of experiencing influenza-like illness (21.5% versus 18.1%, moderate-certainty evidence). The corresponding numbers needed to vaccinate for influenza and influenze-like illness were 71 and 29, respectively, reflecting high rates in the control groups for many of the trials. The number needed to vaccinate of 29 conceals variation in the absolute reduction for low- and high-risk groups, and the degree of benefit may vary at least in part due to inconsistent symptom classification. Extrapolating these effects to settings other than those of the studies is challenging due to uncertain methods for confirming influenza and variation in the absolute reductions in influenza-like illness following vaccination.

We found low-certainty evidence that hospitalisation rates and time off work may be similar between vaccinated and unvaccinated adults. However, the confidence interval around the effect for hospital admission is wide and there was substantial variation in the direction of effect on time off work. Vaccines increased the risk of a number of minor adverse events, including a small increase in fever, but the effect on nausea or vomiting is less clear.

## Implications for research

**Table 6:** *Implications for research*

|  |  |
| --- | --- |
| **Trialists** | When a new vaccination or preventive technology becomes available, an adequately powered, publicly funded, high-quality, placebo-controlled trial run over several seasons should be undertaken. |
| **Systematic  reviewers** | Future review authors should plan to update the randomised evidence in this review if any or all of these conditions are fulfilled in the future:   * a trial assessing the clinical effects of the evolution of current technologies becomes available; * a new type of vaccine is developed; or * a new credible causal paradigm for influenza is formulated.   Review authors should pay close attention to risk of bias issues and ensure publication bias is addressed. |
| **Other researchers** | New insights on the role of viruses and other agents in the genesis of influenza and ILI are also needed. |

# References

Jump to: Included studies | Excluded studies | Ongoing studies | Other references | Other published versions of this review

## Included studies

aa Barrett 2011

[CRSSTD: 2665662]

\* Barrett PN, Berezuk G, Fritsch S, Aichinger G, Hart MK, El-Amin W, et al. Efficacy, safety, and immunogenicity of a Vero-cell-culture-derived trivalent influenza vaccine: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2011;377(9767):751-9. [CRSREF: 2665663]

Ehrlich HJ, Berezuk G, Fritsch S, Aichinger G, Singer J, Portsmouth D, et al. Clinical development of a Vero cell culture-derived seasonal influenza vaccine. Vaccine 2011;30(29):4377-86. [CRSREF: 2665664]

Ehrlich HJ, Singer J, Berezuk G, Fritsch S, Aichinger G, Hart MK, et al. A cell culture-derived influenza vaccine provides consistent protection against infection and reduces the duration and severity of disease in infected individuals. Clinical Infectious Diseases 2012;54(7):946-54. [CRSREF: 2665665]

aa Beran 2009a

[CRSSTD: 2665666]

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Zorzon M, Zivadinov R, Nasuelli D, Dolfini P, Bosco A, Bratina A, et al. Risk factors of multiple sclerosis: a case-control study. Neurological Sciences 2003;24(4):242-7. [CRSREF: 2665843]

cb Bardage 2011

[CRSSTD: 2665844]

Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ 2011;343:d5956. [CRSREF: 2665845]

cb Baxter 2012

[CRSSTD: 2665846]

Baxter R, Toback SL, Sifakis F, Hansen J, Bartlett J, Aukes L, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in adults 18-49 years of age. Vaccine 2012;30(20):3053-60. [CRSREF: 2665847]

cb Kaplan 1982

[CRSSTD: 2665848]

Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. JAMA 1982;248(6):698-700. [CRSREF: 2665849]

cb Lasky 1998

[CRSSTD: 2665850]

Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. New England Journal of Medicine 1998;339(25):1797-802. [CRSREF: 2665851]

cb Moro 2013

[CRSSTD: 2665852]

Moro ML, Nobilio L, Voci C, Di Mario S, Candela S, Magrini N. A population based cohort study to assess the safety of pandemic influenza vaccine Focetria in Emilia-Romagna region, Italy - part two. Vaccine 2013;31(10):1438-46. [CRSREF: 2665853]

cb O'Flanagan 2014

[CRSSTD: 7515052]

O'Flanagan D, Barret AS, Foley M, Cotter S, Bonner C, Crowe C, et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010. Eurosurveillance 2014;19(17):15-25. [CRSREF: 7515053]

cb Persson 2014

[CRSSTD: 2665856]

Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. Journal of Internal Medicine 2014;275(2):172-90. [CRSREF: 2665857]

cb Ray 2011

[CRSSTD: 2665858]

Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15-59 years of age. Vaccine 2011;29(38):6592-7. [CRSREF: 2665859]

cb Shonberger 1979

[CRSSTD: 2665860]

Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976 - 1977. American Journal of Epidemiology 1979;110(2):105-23. [CRSREF: 2665861]

paa Ma 2014

[CRSSTD: 2665862]

Ma F, Zhang L, Jiang R, Zhang J, Wang H, Gao X, et al. Prospective cohort study of the safety of an influenza A (H1N1) vaccine in pregnant Chinese women. Clinical and Vaccine Immunology 2014;21(9):1282-7. [CRSREF: 2665863]

paa Madhi 2014

[CRSSTD: 2665864]

Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. New England Journal of Medicine 2014;371(10):918-31. [CRSREF: 2665865]

pba Benowitz 2010

[CRSSTD: 2665866]

Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clinical Infectious Diseases 2010;51(12):1355-61. [CRSREF: 2665867]

pba Poehling 2011

[CRSSTD: 2665868]

Poehling KA, Szilagyi PG, Staat MA, Snively BM, Payne DC, Bridges CB, et al. Impact of maternal immunization on influenza hospitalizations in infants. American Journal of Obstetrics and Gynecology 2001;204(Suppl 6):141-8. [CRSREF: 2665869]

pbb Irving 2013

[CRSSTD: 2665870]

Irving SA, Kieke BA, Donahue JG, Mascola MA, Baggs J, Destefano F, et al. Trivalent inactivated influenza vaccine and spontaneous abortion. Obstetrics and Gynecology 2013;121(1):159-65. [CRSREF: 2665871]

pca Ahrens 2014

[CRSSTD: 2665872]

Ahrens KA, Louik C, Kerr S, Mitchell AA, Werler MM. Seasonal influenza vaccination during pregnancy and the risks of preterm delivery and small for gestational age birth. Paediatric and Perinatal Epidemiology 2014;28(6):498-509. [CRSREF: 2665873]

pca Black 2004

[CRSSTD: 2665874]

Black SB, Shinefield HR, France EK, Fireman BH, Blatt ST, Shay D. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. American Journal of Perinatology 2004;21(6):333-9. [CRSREF: 2665875]

pca Eick 2011

[CRSSTD: 2665876]

Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Archives of Pediatrics and Adolescent Medicine 2011;165(2):104-11. [CRSREF: 2665877]

pca France 2006

[CRSSTD: 2665878]

France EK, Smith-Ray R, McClure D, Hambidge S, Xu S, Yamasaki K, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. Archives of Pediatrics and Adolescent Medicine 2006;160(12):1277-83. [CRSREF: 2665879]

pca Hulka 1964

[CRSSTD: 2665880]

Hulka JF. Effectiveness of polyvalent influenza vaccine in pregnancy. Report of a controlled study during an outbreak of Asian influenza. Obstetrics and Gynecology 1964;23:830-7. [CRSREF: 2665881]

pca Munoz 2005

[CRSSTD: 2665882]

Munoz FM, Greisinger AJ, Wehmanen OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. American Journal of Obstetrics and Gynecology 2005;192(4):1098-106. [CRSREF: 2665883]

pca Yamada 2012

[CRSSTD: 2665884]

Yamada T, Yamada T, Morikawa M, Cho K, Endo T, Sato SS, et al. Pandemic (H1N1) 2009 in pregnant Japanese women in Hokkaido. Journal of Obstetrics and Gynaecology Research 2012;38(1):130-6. [CRSREF: 2665885]

pcb Beau 2014

[CRSSTD: 2665886]

Beau AB, Hurault-Delarue C, Vidal S, Guitard C, Vayssiere C, Petiot D. Pandemic A/H1N1 influenza vaccination during pregnancy: a comparative study using the EFEMERIS database. Vaccine 2014;32(11):1254-8. [CRSREF: 2665887]

pcb Cantu 2013

[CRSSTD: 2665888]

Cantu J, Biggio J, Jauk V, Wetta L, Andrews W, Tita A. Selective uptake of influenza vaccine and pregnancy outcomes. Journal of Maternal-Fetal and Neonatal Medicine 2013;26(12):1207-11. [CRSREF: 2665889]

pcb Chambers 2013

[CRSSTD: 2665890]

Chambers CD, Johnson D, Xu R, Luo Y, Louik C, Mitchell AA, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. Vaccine 2013;31(44):5026-32. [CRSREF: 2665891]

pcb Cleary 2014

[CRSSTD: 2665892]

Cleary BJ, Rice U, Eogan M, Metwally N, McAuliffe F. 2009 A/H1N1 influenza vaccination in pregnancy: uptake and pregnancy outcomes - a historical cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology 2014;178:163-8. [CRSREF: 2665893]

pcb Deinard 1981

[CRSSTD: 2665894]

Deinard AS, Ogburn P Jr. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. American Journal of Obstetrics and Gynecology 1981;140(3):240-5. [CRSREF: 2665895]

pcb Dodds 2012

[CRSSTD: 2665896]

Dodds L, Macdonald N, Scott J, Spencer A, Allen VM, McNeil S. The association between influenza vaccine in pregnancy and adverse neonatal outcomes. Journal of Obstetrics and Gynaecology Canada 2012;34(8):714-20. [CRSREF: 2665897]

pcb Fell 2012

[CRSSTD: 2665898]

Fell DB, Sprague AE, Liu N, Yasseen AS 3rd, Wen SW, Smith G, et al. Better Outcomes Registry & Network (BORN) Ontario. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. American Journal of Public Health 2012;102(6):e33-40. [CRSREF: 2665899]

pcb Håberg 2013

[CRSSTD: 2665900]

Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. New England Journal of Medicine 2013;368(4):333-40. [CRSREF: 2665901]

\* Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. Obstetrical and Gynecological Survey 2013;68(5):348-9. [CRSREF: 2665902]

pcb Heikkinen 2012

[CRSSTD: 2665903]

Heikkinen T, Young J, van Beek E, Franke H, Verstraeten T, Weil JG, et al. Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study. American Journal of Obstetrics & Gynecology 2012;207(3):177.e1-8. [CRSREF: 2665904]

pcb Källén 2012

[CRSSTD: 2665905]

Källén B, Olausson PO. Vaccination against H1N1 influenza with Pandemrix during pregnancy and delivery outcome: a Swedish register study. British Journal of Obstetrics and Gynaecology 2012;119(13):1583-90. [CRSREF: 2665906]

pcb Launay 2012

[CRSSTD: 2665907]

Launay O, Krivine A, Charlier C, Truster V, Tsatsaris V, Lepercq J, et al. Low rate of pandemic A/H1N1 2009 influenza infection and lack of severe complication of vaccination in pregnant women: a prospective cohort study. PLoS ONE 2012;7(12):e52303. [CRSREF: 2665908]

pcb Lin 2012

[CRSSTD: 2665909]

Lin TH, Lin SY, Lin CH, Lin RI, Lin HC, Chiu TH, et al. AdimFlu-S influenza A (H1N1) vaccine during pregnancy: the Taiwanese Pharmacovigilance Survey. Vaccine 2012;30(16):2671-5. [CRSREF: 2665910]

pcb Louik 2013

[CRSSTD: 2665911]

Louik C, Ahrens K, Kerr S, Pyo J, Chambers C, Jones KL, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. Vaccine 2013;31(44):5033-40. [CRSREF: 2665912]

pcb Ludvigsson 2013

[CRSSTD: 2665913]

Ludvigsson JF, Zugna D, Cnattingius S, Richiardi L, Ekbom A, Ortqvist A, et al. Influenza H1N1 vaccination and adverse pregnancy outcome. European Journal of Epidemiology 2013;28(7):579-88. [CRSREF: 2665914]

pcb Nordin 2013

[CRSSTD: 2665915]

Nordin JD, Kharbanda EO, Benitez GV, Nichol K, Lipkind H, Naleway A, et al. Maternal safety of trivalent inactivated influenza vaccine in pregnant women. Obstetrics and Gynecology 2013;121(3):519-25. [CRSREF: 2665916]

pcb Nordin 2014

[CRSSTD: 2665917]

Nordin JD, Kharbanda EO, Vazquez Benitez G, Lipkind H, Vellozzi C, Destefano F. Maternal influenza vaccine and risks for preterm or small for gestational age birth. Journal of Pediatrics 2014;164(5):1051-7.e2. [CRSREF: 2665918]

pcb Omer 2011

[CRSSTD: 2665919]

Omer SB, Goodman D, Steinhoff MC, Rochat R, Klugman KP, Stoll BJ, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. PLoS Medicine 2011;8(5):e1000441. [CRSREF: 2665920]

pcb Oppermann 2012

[CRSSTD: 2665921]

Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine 2012;30(30):4445-52. [CRSREF: 2665922]

pcb Pasternak 2012

[CRSSTD: 2665923]

Pasternak B, Svanström H, Mølgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A (H1N1) vaccine during pregnancy. JAMA 2012;308(2):165-74. [CRSREF: 2665924]

pcb Richards 2013

[CRSSTD: 2665925]

Richards JL, Hansen C, Bredfeldt C, Bednarczyk RA, Steinhoff MC, Adjaye-Gbewonyo D, et al. Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age birth. Clinical Infectious Diseases 2013;56(9):1216-22. [CRSREF: 2665926]

pcb Rubinstein 2013

[CRSSTD: 2665927]

Rubinstein F, Micone P, Bonotti A, Wainer V, Schwarcz A, Augustovski F. Influenza A/H1N1 MF59 adjuvanted vaccine in pregnant women and adverse perinatal outcomes: multicentre study. BMJ Online 2013;346(7896):f393. [CRSREF: 2665928]

pcb Sheffield 2012

[CRSSTD: 2665929]

Sheffield JS, Greer LG, Rogers VL, Roberts SW, Lytle H, McIntire DD, et al. Effect of influenza vaccination in the first trimester of pregnancy. Obstetrics and Gynecology 2012;120(3):532-7. [CRSREF: 2665930]

pcb Toback 2012

[CRSSTD: 2665931]

Toback SL, Beigi R, Tennis P, Sifakis F, Calingaert B, Ambrose CS. Maternal outcomes among pregnant women receiving live attenuated influenza vaccine. Influenza and Other Respiratory Viruses 2012;6(1):44-51. [CRSREF: 2665932]

pcb Trotta 2014

[CRSSTD: 2665933]

Trotta F, Da Cas R, Spila Alegiani S, Gramegna M, Venegoni M, Zocchetti C, et al. Evaluation of safety of A/H1N1 pandemic vaccination during pregnancy: cohort study. BMJ 2014;348:g3361. [CRSREF: 2665934]

## Excluded studies

Top of Form

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ab López-Macías 2011a

[CRSSTD: 2665935]

López-Macías C, Ferat-Osorio E, Tenorio-Calvo A, Isibasi A, Talavera J, Arteaga-Ruiz O, et al. Safety and immunogenicity of a virus-like particle pandemic influenza A (H1N1) 2009 vaccine in a blinded, randomised, placebo-controlled trial of adults in Mexico. Vaccine 2011;29(44):7826-34. [CRSREF: 2665936]

ab López-Macías 2011b

[CRSSTD: 2665937]

López-Macías C, Ferat-Osorio E, Tenorio-Calvo A, Isibasi A, Talavera J, Arteaga-Ruiz O, et al. Safety and immunogenicity of a virus-like particle pandemic influenza A (H1N1) 2009 vaccine in a blinded, randomised, placebo-controlled trial of adults in Mexico. Vaccine 2011;29(44):7826-34. [CRSREF: 2665938]

ab Mallory 2010

[CRSSTD: 2665939]

Mallory RM, Malkin E, Ambrose CS, Bellamy T, Shi L, Yi T, et al. Safety and immunogenicity following administration of a live, attenuated monovalent 2009 H1N1 influenza vaccine to children and adults in two randomised controlled trials. PLoS ONE 2010;5(10):e13755. [CRSREF: 2665940]

ab Plennevaux 2010

[CRSSTD: 2665941]

Plennevaux E, Sheldon E, Blatter M, Reeves-Hoché MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. Lancet 2010;375(9708):41-8. [CRSREF: 2665942]

ab Precioso 2011

[CRSSTD: 2665943]

Precioso AR, Miraglia JL, Campos LM, Goulart AC, Timenetsky Mdo C, Cardoso MR, et al. A phase I randomised, double-blind, controlled trial of 2009 influenza A (H1N1) inactivated monovalent vaccines with different adjuvant systems. Vaccine 2011;29(48):8974-81. [CRSREF: 2665944]

ab Treanor 2010

[CRSSTD: 2665945]

Treanor JJ, Taylor DN, Tussey L, Hay C, Nolan C, Fitzgerald T, et al. Safety and immunogenicity of a recombinant hemagglutinin influenza-flagellin fusion vaccine (VAX125) in healthy young adults. Vaccine 2010;28(52):8268-74. [CRSREF: 2665946]

ab Turley 2011

[CRSSTD: 2665947]

Turley CB, Rupp RE, Johnson C, Taylor DN, Wolfson J, Tussey L, et al. Safety and immunogenicity of a recombinant M2e-flagellin influenza vaccine (STF2.4xM2e) in healthy adults. Vaccine 2011;29(32):5145-52. [CRSREF: 2665948]

ab Wacheck 2010

[CRSSTD: 2665949]

Wacheck V, Egorov A, Groiss F, Pfeiffer A, Fuereder T, Hoeflmayer D, et al. A novel type of influenza vaccine: safety and immunogenicity of replication-deficient influenza virus created by deletion of the interferon antagonist NS1. Journal of Infectious Diseases 2010;201(3):354-62. [CRSREF: 2665950]

Al-Dabbagh 2013

[CRSSTD: 2665951]

Al-Dabbagh M, Lapphra K, Scheifele DW, Halperin SA, Langley JM, Cho P, et al. Elevated inflammatory mediators in adults with oculo-respiratory syndrome following influenza immunization: a public health agency of Canada/Canadian Institutes of Health Research Influenza Research Network (PCIRN) Study. Clinical and Vaccine Immunology 2013;20(8):1108-14. [CRSREF: 2665952]

Ambrosch 1976

[CRSSTD: 2665953]

Ambrosch F, Balluch H. Studies of the non-specific clinical effectiveness of influenza vaccination. Laryngologie, Rhinologie, Otologie 1976;55:57-61. [CRSREF: 2665954]

Ambrose 2012

[CRSSTD: 2665955]

Ambrose CS, Wu X. The safety and effectiveness of self-administration of intranasal live attenuated influenza vaccine in adults. Vaccine 2013;31(6):857-60. [CRSREF: 2665956]

Andersson 2015

[CRSSTD: 2665957]

Andersson L. Response on the author's reply to the letter to the editor: Contradictory data on type 1 diabetes in a recently published article "Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix". Journal of Internal Medicine 2015;277(2):272-3. [CRSREF: 2665958]

Aoki 1986

[CRSSTD: 2665959]

Aoki FY, Sitar DS, Milley EV, Hammond GW, Milley EV, Vermeersch C, et al. Potential of influenza vaccine and amantadine to prevent influenza A illness in Canadian forces personnel 1980-83. Military Medicine 1986;151(9):459-65. [CRSREF: 2665960]

Arnou 2010

[CRSSTD: 2665961]

Arnou R, Eavis P, Pardo JR, Ambrozaitis A, Kazek MP, Weber F. Immunogenicity, large scale safety and lot consistency of an intradermal influenza vaccine in adults aged 18-60 years: randomized, controlled, phase III trial. Human Vaccines 2010;6(4):346-54. [CRSREF: 2665962]

Atmar 1995

[CRSSTD: 2665963]

Atmar RL, Keitel WA, Cate TR, Quarles JM, Couch RB. Comparison of trivalent cold-adapted recombinant (CR) influenza virus vaccine with monovalent CR vaccines in healthy unselected adults. Journal of Infectious Diseases 1995;172(1):253-7. [CRSREF: 2665964]

Atmar 2011

[CRSSTD: 2665965]

Atmar RL, Keitel WA, Quarles JM, Cate TR, Patel SM, Nino D, et al. Evaluation of age-related differences in the immunogenicity of a G9 H9N2 influenza vaccine. Vaccine 2011;29(45):8066-72. [CRSREF: 2665966]

Atsmon 2012

[CRSSTD: 2665967]

Atsmon J, Kate-Ilovitz E, Shaikevich D, Singer Y, Volokhov I, Haim KY, et al. Safety and immunogenicity of multimeric-001 - a novel universal influenza vaccine. Journal of Clinical Immunology 2012;32(3):595-603. [CRSREF: 2665968]

Ausseil 1999

[CRSSTD: 2665969]

Ausseil F. Immunization against influenza among working adults: the Philippines experience. Vaccine 1999;17(Suppl 1):59-62. [CRSREF: 2665970]

Banzhoff 2001

[CRSSTD: 2665971]

Banzhoff A, Kaniok W, Muszer A. Effectiveness of an influenza vaccine used in Poland in the 1998-1999 influenza season. Immunological Investigations 2001;30(2):103-13. [CRSREF: 2665972]

Baxter 2010

[CRSSTD: 2665973]

Baxter R, Ray GT, Fireman BH. Effect of influenza vaccination on hospitalizations in persons aged 50 years and older. Vaccine 2010;28(45):7267-72. [CRSREF: 2665974]

Baxter 2011

[CRSSTD: 2665975]

Baxter R, Patriarca PA, Ensor K, Izikson R, Goldenthal KL, Cox MM. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. Vaccine 2011;29(12):2272-8. [CRSREF: 2665976]

Baxter 2012

[CRSSTD: 2665977]

Baxter R, Lewis N, Bakshi N, Vellozzi C, Klein NP. Recurrent Guillain-Barre syndrome following vaccination. Clinical Infectious Diseases 2012;54(6):800-4. [CRSREF: 2665978]

Baxter 2013

[CRSSTD: 2665979]

Baxter R, Bakshi N, Fireman B, Lewis E, Ray P, Vellozzi C, et al. Lack of association of Guillain-Barre syndrome with vaccinations. Clinical Infectious Diseases 2013;57(2):197-204. [CRSREF: 2665980]

Belongia 2009

[CRSSTD: 2665981]

Belongia EA, Kieke BA, Donahue JG, Greenlee RT, Balish A, Foust A, et al. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season. Journal of Infectious Diseases 2009;199(2):159-67. [CRSREF: 2665982]

Belshe 2001

[CRSSTD: 2665983]

Belshe RB, Gruber WC. Safety, efficacy and effectiveness of cold-adapted, live, attenuated, trivalent, intranasal influenza vaccine in adults and children. Philosophical Transactions of the Royal Society of London 2001;356(1416):1947-51. [CRSREF: 2665984]

Benke 2004

[CRSSTD: 2665985]

Benke G, Abramson M, Raven J, Thien FCK, Walters EH. Asthma and vaccination history in a young adult cohort. Australian and New Zealand Journal of Public Health 2004;28(4):336-8. [CRSREF: 2665986]

Beran 2013

[CRSSTD: 2665987]

Beran JI, Peeters M, Dewe W, Raupachova J, Hobzova L, Devaster JM. Immunogenicity and safety of quadrivalent versus trivalent inactivated influenza vaccine: a randomised, controlled trial in adults. BMC Infectious Diseases 2013;13(1):224. [CRSREF: 2665988]

Betts 1977b

[CRSSTD: 2665989]

Betts RF, Douglas RG Jr. Comparative study of reactogenicity and immunogenicity of influenza A/New Jersey/8/76 (Hsw1N1) virus vaccines in normal volunteers. Journal of Infectious Diseases 1977;136(Suppl):443-9. [CRSREF: 2665990]

Beyer 1996

[CRSSTD: 2665991]

Beyer WEP, Palache AM, Kerstens R, Masurel N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. European Journal of Clinical Microbiology & Infectious Diseases 1996;15(1):65-70. [CRSREF: 2665992]

Carlson 1979

[CRSSTD: 2665993]

Carlson AJ, Davidson WL, McLean AA, Vella PP, Weibel RE, Woodhour AF, et al. Pneumococcal vaccine: dose, revaccination, and coadministration with influenza vaccine. Proceedings of the Society for Experimental Biology and Medicine 1979;161(4):558-63. [CRSREF: 2665994]

Cate 1977

[CRSSTD: 2665995]

Cate TR, Couch RB, Kasel JA, Six HR. Clinical trials of monovalent influenza A/New Jersey/76 virus vaccines in adults: reactogenicity, antibody response, and antibody persistence. Journal of Infectious Diseases 1977;136(Suppl):450-5. [CRSREF: 2665996]

Chavant 2013

[CRSSTD: 2665997]

Chavant F, Ingrand I, Jonville-Bera AP, Plazanet C, Gras-Champel V, Lagarce L, et al. The PREGVAXGRIP study: a cohort study to assess foetal and neonatal consequences of in utero exposure to vaccination against A (H1N1) v2009 influenza. Drug Safety 2013;36(6):455-65. [CRSREF: 2665998]

Chichester 2012

[CRSSTD: 2665999]

Chichester JA, Jones RM, Green BJ, Stow M, Miao F, Moonsammy G, et al. Safety and immunogenicity of a plant-produced recombinant hemagglutinin-based influenza vaccine (HAI-05) derived from A/Indonesia/05/2005 (H5N1) influenza virus: a phase 1 randomised, double-blind, placebo-controlled, dose-escalation study in healthy adults. Viruses 2012;4(11):3227-44. [CRSREF: 2666000]

Chlibek 2002

[CRSSTD: 2666001]

Chlibek R, Beran J, Splino M. Effectiveness of influenza vaccination in healthy adults - a fourfold decrease in influenza morbidity during one influenza season. Epidemiologie, Mikrobiologie, Imunologie 2002;51(2):47-51. [CRSREF: 2666002]

Choe 2011a

[CRSSTD: 2666003]

Choe YJ, Cho H, Song KM, Kim JH, Han OP, Kwon YH, et al. Active surveillance of adverse events following immunization against pandemic influenza A (H1N1) in Korea. Japanese Journal of Infectious Diseases 2011;64(4):297-303. [CRSREF: 2666004]

Choe 2011b

[CRSSTD: 2666005]

Choe YJ, Cho H, Bae GR, Lee JK. Guillain-Barre syndrome following receipt of influenza A (H1N1) 2009 monovalent vaccine in Korea with an emphasis on Brighton Collaboration case definition. Vaccine 2011;29(11):2066-70. [CRSREF: 2666006]

Choe 2011c

[CRSSTD: 2666007]

Choe YJ, Cho H, Kim SN, Bae GR, Lee JK. Serious adverse events following receipt of trivalent inactivated influenza vaccine in Korea, 2003-2010. Vaccine 2011;29(44):7727-32. [CRSREF: 2666008]

Chou 2007

[CRSSTD: 2666009]

Chou CH, Liou WP, Hu KI, Loh CH, Chou CC, Chen YH. Bell’s palsy associated with influenza vaccination: two case reports. Vaccine 2007;25:2839–41. [CRSREF: 2666010]

Clover 1991

[CRSSTD: 2666011]

Clover RD, Crawford S, Glezen WP, Taber LH, Matson CC, Couch RB. Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses. Journal of Infectious Diseases 1991;163(2):300-4. [CRSREF: 2666012]

Confavreux 2001

[CRSSTD: 2666013]

Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. New England Journal of Medicine 2001;344(5):319-26. [CRSREF: 2666014]

Conlin 2013

[CRSSTD: 2666015]

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Top of Form



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      2. Searching other resources

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# Methods details

## a. Methods for identifying studies

*Electronic searches*

We searched the following databases:

* + - 1. Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12) searched 31 December 2016 via the Cochrane Library, which contains the Cochrane Acute Respiratory Infections Group’s Specialised Register
      2. MEDLINE (PubMed) (January 1966 to 31 December 2016)
      3. Embase (Elsevier) (1990 to 31 December 2016)
      4. WHO International Clinical Trials Registry Platform ([www.who.int/ictrp/en](http://www.who.int/ictrp/en)) on 1 July 2017
      5. ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) on 1 July 2017).

See Appendix 1 for the search strategies used to identify trials.

See Appendix 2 for search strategies used prior to this 2018 update to identify observational studies.

See Appendix 3 for strategies used in the 2010 update, and Appendix 4 for the MEDLINE search strategy used in 2004.

* + 1. *Searching other resources*

In order 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 manufacturers and first or corresponding trial authors of studies in the review.

# Methods for collecting and analysing data

## 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. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and ’Characteristics of excluded

studies’ table (Moher 2009).

## 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 5 software (RevMan 2014).

We extracted data on the following:

* + 1. methodological quality of studies;
    2. study design (Appendix 6);
    3. description of setting;
    4. characteristics of participants;
    5. description of vaccines (content and antigenic match);
    6. description of outcomes;
    7. publication status;
    8. date of study;
    9. location of study.

One review author (CDP) carried out statistical analyses.

*Outcome data*

We assumed an ILI case (specific definition) to be the same as a ’flu-like illness’ according to a predefined list of symptoms (such as 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 postvaccination- or postepidemic-phase sera.

## Assessment of risk of bias in included studies

* + 1. *Experimental studies*

Two review authors (CDP, AR) independently assessed the methodological quality of the included studies using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In case of disagreement, one review author (VD) acted as arbitrator 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: e.g. a table of random numbers or computer-generated random numbers.
* High risk of bias: e.g. alternation, date of birth, day of the week, or case record number.
* Unclear risk of bias: if insufficient information was provided.

*Allocation concealment*

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

*Blinding*

* Low risk of bias: if adequate double-blinding (e.g. placebo vaccine) or single-blinding (i.e. blinded outcome assessment) was 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.

*Reporting bias*

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

* + 1. *Observational 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 for an additional beneficial outcome (NNTB), or in this case, the number needed to vaccinate (NNV). The NNV expresses the number of children needed to be vaccinated to prevent one case of influenza.The NNVcan be computed as 1/RD. Since meta-analysis estimates from RD are affected by statistical heterogeneity, we preferred to compute the NNV from the RD between assumed and corresponding risks. We used aggregate or median of the control group risks, giving a formula of: 1/(control event rate (CER) - CER\*RR).

We conducted quantitative synthesis of the evidence from observational studies using adjusted estimates, when these were available; in some cases we also used original data (unadjusted data) in order to compare meta-analysis results from adjusted and unadjusted estimates.

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, of which four trials measured the work absence in terms of the difference in the average number of days lost in two arms of the trial. These studies presented a standard error value measured accordingly. The remainder

expressed work absence in terms of rate ratio, which does not allow the recalculation of the correct estimate of the standard error (aa Nichol 1999a). We therefore 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 dropouts. We decided on this approach (complete-case scenario) because the majority of the included studies did not 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.

## Unit of analysis issues

*Multi-arm trials*

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.

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

* + 1. Interval between the first and the last virus isolation in the community.
    2. Interval during which the influenza virus was recovered from more than a stated percentage of ill participants.
    3. Period during which an increase of respiratory illness of more than a stated percentage was recorded.
    4. 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 that occurred during the former.

## 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 population.

## Assessment of heterogeneity

We calculated the I2 statistic for each pooled estimate to assess the impact on statistical heterogeneity. The I2 statistic can be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than sampling error, and it is

intrinsically independent from the number of studies. When the I2 statistic is less than 30%, there is little concern about statistical heterogeneity (Higgins 2011).We used random-effects models throughout to take into account 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.

## Data synthesis

We calculated all meta-analyses using a random-effects model due to expected variation in the efficacy and effectiveness of viral strain matching, and seasonal variation in virulence of the circulating influenza virus. We summarised evidence from non-randomised studies (cohort and case-control) according to Higgins 2011.

## Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses according to the degree of matching with that year’s World Health Organization (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. 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 whenever possible. In case of uncertainty due to ambiguity in the wording used (in the oldest trials), we took into account the opinion given by the trial authors.

We classified the compliance of a live attenuated vaccine with the recommendations according to the antigenic comparability of the wild strains. Since the degree of matching between vaccine and circulating strains could affect the effectiveness/efficacy of the vaccine, we analysed the data in separate subgroups according to this parameter.

For serious adverse events, whenever possible we analysed data frompregnant women and the general population in separate subgroups. When case-control studies reported safety outcomes, whenever 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 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 studies judged to

be at high risk of bias for one domain or unclear risk of bias for two or more domains. We restricted sensitivity analyses to the main comparison outcomes included in the Summary of Findings table (link to SOF table epistemonikis).

Historical versions of this review compared the results from the crude data with those from the adjusted data from observational studies.

## Summary of findings table

We restricted our focus in the ‘Summary of findings’ tables to the comparison of inactivated parenteral influenza vaccine with placebo or do nothing, which we regarded as the most commonly adopted strategy. We created a Summary of findings for the main

comparison using the following outcomes: ILI, influenza, hospitalisations, time off work, fever, and nausea/vomiting.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004).We used methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We used the results from randomised studies and justified all decisions to down- or upgrade the quality of studies using footnotes, making comments to aid the reader’s understanding of the review where necessary.

# Study Characteristics

**Table 1:** *What review authors searched for and found*

Same as above in Full text

**Figure 1.** *Study flow diagram of searches conducted for this update*



**Table 2.** *Characteristics of included studies*

**Key features of the included studies**

We included 52 clinical trials of over 80,000 people assessing the safety and effectiveness of influenza vaccines. We have presented

findings from 25 studies comparing inactivated parenteral influenza vaccine against placebo or do-nothing control groups as the

most relevant to decision-making. The studies were conducted over single influenza seasons in North America, South America, and

Europe between 1969 and 2009.

Sort tables by: comparison | study design

***Randomized controlled trials***

| **Study /setting**  **(RCT)** | **Participants** | | | **Interventions and comparisons** | **Outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Inclusion  criteria** | **Exclusion  criteria** | **Enrolled** |
| **aa Barrett 2011**  Community  2008 influenza season  USA | Healthy adults aged 18 to 48 years recruited at 36 centres throughout the USA. | Individuals were excluded if they belonged 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. | Total N: 7.236 participants from 36 centres In the USA data  Randomized to: 3,619 participants allocated to one 0.5 mL dose of vaccine and 3,617 allocated to receive 0.5mL placebo into the deltoid muscle.  Vaccinations were performed between 1 and 15 December 2008. | Intervention: 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.  Comparison: Placebo consisted of phosphate-buffered saline. | *Serological*:  The first serum samples were presumably collected before vaccine administration (this is not well described in any of the 3 reports), and the second 18 to 24 days later. Haemagglutination-inhibiting titres and GMT against vaccine strains were assessed by Focus Diagnostics (Cypress, CA, USA). Haemagglutination-inhibiting 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 days 18 to 24 after immunisation, participants were instructed to return to the clinic within 48 hours after the onset of symptoms of an influenza-like illness, should they have fever with cough, sore throat, muscle ache, headache, fatigue, nausea, or bloodshot eyes, or 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 using 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 using ferret antiserum to assess the antigenic relatedness of the isolate to the vaccine strains  *Safety:* Participants were provided with a diary card, on which they had to record their temperature daily 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 for a physical examination and final assessment of adverse events. |
| **aa Beran 2009a**  Community  2005 to 2006 influenza season  Czech Republic | Self referred healthy adults 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 seemed to be allowed but was not quantified. |  | Total N: 6203  Predominately Caucasian (understood to be white) (99.8%), aged between 18 and 64 years (mean 35 and SD: 13 years) of both genders (TIV group: female 55.3%, placebo group: female 54.2%) | Intervention: TIV vaccine: 0.5 mL single dose by IM injection. Use of more than 1 lot was not reported.  TIV contained 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.  Comparison: 0.5mL placebo (normal saline) by IM injection. | *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. A 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 MDCK cells. Confirmation of influenza A or B was determined using the following:   * + haemagglutination assay with turkey and guinea pig erythrocytes;   + haemagglutination inhibition 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). Influenza-like illness 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 1 event (240 in TIV and 113 in placebo) was used to calculate the attack rate. Reasons to exclude from the ATP cohort included:   * + 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: unclear what this means (did the participant 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 participants, not all efficacy cohort.  *Safety:* Data on 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". |
| **aa Beran 2009b**  Community  2006 to 2007 influenza season  Czech Republic and Finland | 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. |  | Total N: 7,652  No details given re study participant characteristics | **Intervention:** 1 dose of trivalent influenza vaccine (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).  (N = 5,103)  **Comparison:** Placebo (normal saline solution), IM injection, at the first day of the study (day 0). (N = 2,549) | *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 objectiveswere 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; * culture-confirmed influenza A and/or B attributable to any influenza A or B strain; * ILI, which was less stringently defined as at least 1 systemic symptom (fever or myalgia, or both) and 1 respiratory symptom (cough or sore throat, or both).   *Safety, vaccine reactogenicity and immunogenicity:*  Assessed in a random subset of participants by obtaining blood samples prior to vaccination and 21 to 28 days later. However, no harms data were reported. |
| **Aa Bridges 2000a**  Community  1997 to 1998 influenza season  USA | 1184 healthy factory employees aged 18 to 64. |  | Total N: 1,184. | Intervention: 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. (n = 595)  Comparison: Placebo was sterile saline for injection. Vaccine was recommended but did not match the circulating strain. (n = 589) | *Effectiveness:* Influenza-like illness, Influenza, Days ill, physician visits, times any drug was prescribed, times antibiotic was presrcibed, working days lost, admissions  *Safety:* Local effects were arm soreness and redness. Systemic adverse effects were: fever, sore throat, coryza, myalgia, headache, and fatigue. No harms data were reported. |
| **aa Bridges 2000b**  Community  1998 to 1999 influenza season  USA | Healthy factory workers aged 19 to 64. |  | Total N: 1,191  No Information from Table regarding additional characteristics | Intervention: 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. (N = 587)  Comparison: Placebo was sterile saline for injection. Vaccine was recommended and matched circulating strain. (N = 604) | *Effectiveness:* Influenza-like illness, Influenza, Days ill, physician visits, times any drug was prescribed, times antibiotic was presrcibed, working days lost, admissions  *Safety:* Local effects were arm soreness and redness. Systemic adverse effects were: fever, sore throat, coryza, myalgia, headache, and fatigue. No harms data were reported. |

***Observational studies***

**Table 3.** *Characteristics of excluded studies (ordered by study ID)*

|  |  |
| --- | --- |
| **Study** | **Reason for exclusion** |
| ab Wacheck 2010 | Experimental vaccine; dose escalation study |
| ab López-Macías 2011a | Experimental vaccine; no outcomes of interest |
| ab López-Macías 2011b | Experimental vaccine; no outcomes of interest |
| ab Mallory 2010 | No outcomes of interest |
| ab Plennevaux 2010 | No outcomes of interest |
| ab Precioso 2011 | No outcomes of interest |
| ab Treanor 2010 | Experimental vaccine |
| **ETC** | **ETC** |

**Table 4.** *Characteristics of ongoing studies*

| **Study /setting**  **(RCT)** | **Participants** | | | **Interventions and comparisons** | **Outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Inclusion  criteria** | **Exclusion  criteria** | **Enrolled** |

# Risk of Bias

**Figure 2.** *Risk of bias summary*

**

**Table 5.** *Risk of bias table*

**Aa Barrett 2011**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| 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 of participants  and personnel  (performance bias) | 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" |
| Blinding of outcome assessment  (detection bias) | 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 (those who completed the study without major protocol deviations) were 3316 and 3318 in the vaccine and placebo arms, respectively. Reasons for non-inclusion in the per-protocol population were not specified for 150 vaccine and 135 placebo recipients. |
| Summary assessment | Low risk |  |

**Aa Beran 2009a**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| 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 of participants  and personnel  (performance bias) | Unclear risk | Authors reported that the blinding assignment was maintained until study analysis.  Authors mentioned that the treatments were indistinguishable in appearance. |
| Blinding of outcome assessment  (detection bias) | 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 |  |

**Aa Beran 2009b**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Unclear risk | No details provided. |
| location concealment  (selection bias) | Unclear risk | No details provided. |
| Blinding of participants and personnel (performance bias) | Unclear risk | There is no mention of appearance of the injection content. |
| Blinding of outcome assessment  (detection bias) | Unclear risk | Attrition reasons for the whole cohort are provided by the participant flow. |
| Summary assessment | Unclear risk |  |

**Aa Bridges 2000a**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Unclear risk | Insufficient description |
| Allocation concealment  (selection bias) | Low risk | Adequate |
| Blinding of participants  and personnel  (performance bias) | Low risk | Adequate |
| Blinding of outcome assessment  (detection bias) | Low risk | Attrition reasons for the whole cohort are provided by the participant flow. |
| Summary assessment | Low risk |  |

**Aa Bridges 2000b**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Unclear risk | Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers. |
| Allocation concealment  (selection bias) | Low risk | Adequate |
| Blinding of participants and personnel (performance bias) | Unclear risk | Placebo was sterile saline for injection. Probably adequate |
| Blinding of outcome assessment  (detection bias) | Unclear risk | Attrition reasons for the whole cohort are provided by the participant flow. |
| Summary assessment | Low risk |  |

# Evidence tables

* 1. **Summary of findings 1**

Interactive table: isof.epistemonikos.org

Or see:

Isof.epistemonikos.org

For examples

**Table 6.** GRADE evidence profile

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient or population:** Healthy adults  **Intervention:** Inactivated parenteral influenza vaccine  **Comparison:** Placebo or non-placebo control | | | | | | | | | | | | | | |
| **Quality assessment** | | | | | | | | Illustrative comparative risks\* (95% CI) | | | | |  | |
| Number of participants (studies) | | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other  considerations | Assumed  risk1 | Corresponding risk | | Relative effect | Absolute effect | Certainty of the evidence  (GRADE) | Importance |
| Control | Vaccine | |
| **Influenza** | | | | | | | | | | | | | | |
| 71,221 (25 RCTs) | | RCT | Not serious2 | Not serious | Serious3 | Not serious | None | 721/31510 | 414/39711 | | RR 0.41 (0.36 to 0.47 |  | ⊕⊕⊕⊝  Moderate | CRITICAL |
| **Influenza-like illness** | | | | | | | | | | | | | | |
| 25,795 (16 RCTs) | | RCT | Not serious2 | Serious4 | Not serious | Not Serious | None | 1442/9223 | 1646/16572 | | RR 0.84 (0.75 to 0.95) |  | ⊕⊕⊕⊝  Moderate | CRITICAL |
| **Hospitalisation** | | | | | | | | | | | | | | |
| 11,924 (3 RCTs) | | RCT | Serious5 | Not serious | Not serious | Serious6 | None | 1331/9084 | 272/2840 | | RR 0.96 (0.85 to 1.08) |  | ⊕⊕⊝⊝  Low | CRITICAL |
| **Time off work** | | | | | | | | | | | | | | |
| 3726  (4 RCTs) | | RCT | Serious7 | Serious8 | Not serious | Not serious | None | 1865 | 1861 | | MD -0.04 (-0.14 to 0.06) |  | ⊕⊕⊝⊝  Low | CRITICAL |
| **Fever** | | | | | | | | | | | | | | |
| 23,850  (13 RCTs) | | RCT | Not serious | Not serious | Not serious | Not serious | None | 166/11295 | 357/12555 | RR 1.55 (1.26 to 1.91) | |  | ⊕⊕⊕⊕  High | CRITICAL |
| **Nausea or Vomiting** | | | | | | | | | | | | | | |
| 6,315  (4 RCTs) | | RCT | Serious7 | Not serious | Not serious | Serious6 | None | 166/11295 | 357/12555 | RR 1.80 (0.65 to 5.04) | |  | ⊕⊕⊝⊝  Low | CRITICAL |
|  | **CI:** Confidence interval; **RR:** Risk ratio; **RCT:** randomized controlled trial. | | | | | | | | | | | | | |
|  | \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). | | | | | | | | | | | | | |
|  | GRADE Working Group grades of evidence:  **High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different\* is low.  **Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different\* is moderate.  **Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different\* is high.  **Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially   different\*\* is very high.  \*\* Substantially different = a large enough difference that it might affect a decision | | | | | | | | | | | | | |
|  | 1 Control group risk calculated as the sum of events over total sample size from the control groups. For the outcome of influenza-like illness, control group risk was stratified as low, moderate (or median), and high due to variation in risk groups across the studies. For the remaining outcomes, the control group risk was taken as aggregate.  2Sensitivity analysis by excluding studies with two or more domains at unclear risk of bias did not meaningfully alter the direction, size, or precision of effect. We are confident that bias is unlikely to exaggerate the intervention effect because the absolute reduction in influenza and relative reduction in the risk of influenza-like illness are small with vaccination.  3Downgraded one level due to serious indirectness. Uncertainty over definition, surveillance and testing of influenza in older trials.  4Downgraded one level for serious inconsistency. There is discordance between the direction and size of effects across the studies. Different definitions of influenza-like illness across the studies could explain why there is variation in the event rates across the control arms.  5Downgraded one level due to serious risk of bias. Meta-analysis heavily influenced by a large study with high risk of bias across several domains.  6Downgraded one level due to serious imprecision. Confidence interval includes meaningful reduction and increase in effect.  7Downgraded one level due to serious risk of bias. Effect is influenced by studies judged to be at unclear risk of bias.  8Downgraded one level due to serious inconsistency. Direction and magnitude of effect differed across the studies (I2 = 82%). Wide confidence interval reflects the range of study effect sizes. | | | | | | | | | | | | | |

# Analyses with forest plots

* 1. *Overview of analyses*

**Comparison 1:** Inactivated parenteral vaccine versus placebo or non-placebo control

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analysis** | **Outcome or subgroup** | **Studies** | **Participants** | **Statistical method** | **Effect estimate** |
| Analysis 1.1 | 1.1 Influenza | 25 | 71221 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.36, 0.47] |
|  | 1.1.1 WHO recommended - matching vaccine | 15 | 46444 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.34, 0.49] |
|  | 1.1.2 WHO recommended - vaccine matching absent or unknown | 7 | 15068 | Risk Ratio (M-H, Random, 95% CI) | 0.45 [0.34, 0.59] |
|  | 1.1.3 Monovalent not WHO recommended - vaccine matching | 2 | 9675 | Risk Ratio (M-H, Random, 95% CI) | 0.22 [0.10, 0.52] |
|  | 1.1.4 Monovalent not WHO recommended - vaccine matching - high dose | 1 | 34 | Risk Ratio (M-H, Random, 95% CI) | 0.11 [0.00, 2.49] |
| Analysis 1.2 | 1.2. Influenza-like illness | 16 | 25795 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.75, 0.95] |
|  | 1.2.1 WHO recommended - matching vaccine | 7 | 4760 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.77, 0.91] |
|  | 1.2.2 WHO recommended - vaccine matching absent or unknown | 7 | 20942 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.69, 1.18] |
|  | 1.2.3 Monovalent not WHO recommended - vaccine matching | 1 | 59 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.28, 3.70] |
|  | 1.2.4 Monovalent not WHO recommended - vaccine matching - high dose | 1 | 34 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.09, 2.30] |
| Analysis 1.3 | 1.3 Hospitalisations | 3 | 11924 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.85, 1.08] |
|  | 1.3.1 WHO recommended - matching vaccine | 1 | 1178 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
|  | 1.3.2 WHO recommended - vaccine matching absent or unknown | 1 | 1130 | Risk Ratio (M-H, Random, 95% CI) | 2.89 [0.12, 70.68] |
|  | 1.3.3 Monovalent not WHO recommended - vaccine matching | 1 | 9616 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.85, 1.08] |
| Analysis 1.4 | 1.4 Working days lost | 4 | 3726 | Mean Difference (IV, Random, 95% CI) | -0.04 [-0.14, 0.06] |
|  | 1.4.1 WHO recommended - matching vaccine | 3 | 2596 | Mean Difference (IV, Random, 95% CI) | -0.09 [-0.19, 0.02] |
|  | 1.4.2 WHO recommended - matching absent or unknown | 1 | 1130 | Mean Difference (IV, Random, 95% CI) | 0.09 [0.00, 0.18] |
| Analysis 1.5 | 1.5 Days ill | 3 | 3133 | Mean Difference (IV, Random, 95% CI) | -0.21 [-0.98, 0.56] |
|  | 1.5.1 WHO recommended - matching vaccine | 2 | 2003 | Mean Difference (IV, Random, 95% CI) | -0.58 [-0.85, -0.32] |
|  | 1.5.2 WHO recommended - matching absent or unknown | 1 | 1130 | Mean Difference (IV, Random, 95% CI) | 0.66 [0.16, 1.16] |
| Analysis 1.6 | 1.6 Physician visits | 2 | 2308 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.40, 1.89] |
|  | 1.6.1 WHO recommended - matching vaccine | 1 | 1178 | Risk Ratio (M-H, Random, 95% CI) | 0.58 [0.37, 0.91] |
|  | 1.6.2 WHO recommended - vaccine matching absent or unknown | 1 | 1130 | Risk Ratio (M-H, Random, 95% CI) | 1.28 [0.90, 1.83] |
| Analysis 1.7 | 1.7 Times antibiotic was prescribed | 2 | 2308 | Mean Difference (IV, Random, 95% CI) | -0.02 [-0.03, -0.01] |
|  | 1.7.1 WHO recommended - matching vaccine | 1 | 1178 | Mean Difference (IV, Random, 95% CI) | -0.02 [-0.03, -0.01] |
|  | 1.7.2 WHO recommended - matching absent or unknown | 1 | 1130 | Mean Difference (IV, Random, 95% CI) | -0.01 [-0.03, 0.01] |
| Analysis 1.8 | 1.8 Times any drugs were prescribed | 2 | 2308 | Mean Difference (IV, Random, 95% CI) | -0.01 [-0.03, 0.01] |
|  | 1.8.1 WHO recommended - matching vaccine | 1 | 1178 | Mean Difference (IV, Random, 95% CI) | -0.02 [-0.04, -0.00] |
|  | 1.8.2 WHO recommended - matching absent or unknown | 1 | 1130 | Mean Difference (IV, Random, 95% CI) | 0.00 [-0.00, 0.00] |
| Analysis 1.9 | 1.9 Clinical cases (clinically defined without clear definition) | 3 | 4259 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.72, 1.05] |
|  | 1.9.1 WHO recommended - matching vaccine | 2 | 2056 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.64, 1.25] |
|  | 1.9.2 WHO recommended - vaccine matching absent or unknown | 1 | 2203 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.69, 0.99] |

**Comparison 2:** Live aerosol influenza vaccine versus placebo or non-placebo control

WILL FOLLOW SAME FORMAT AS COMPARISON 1

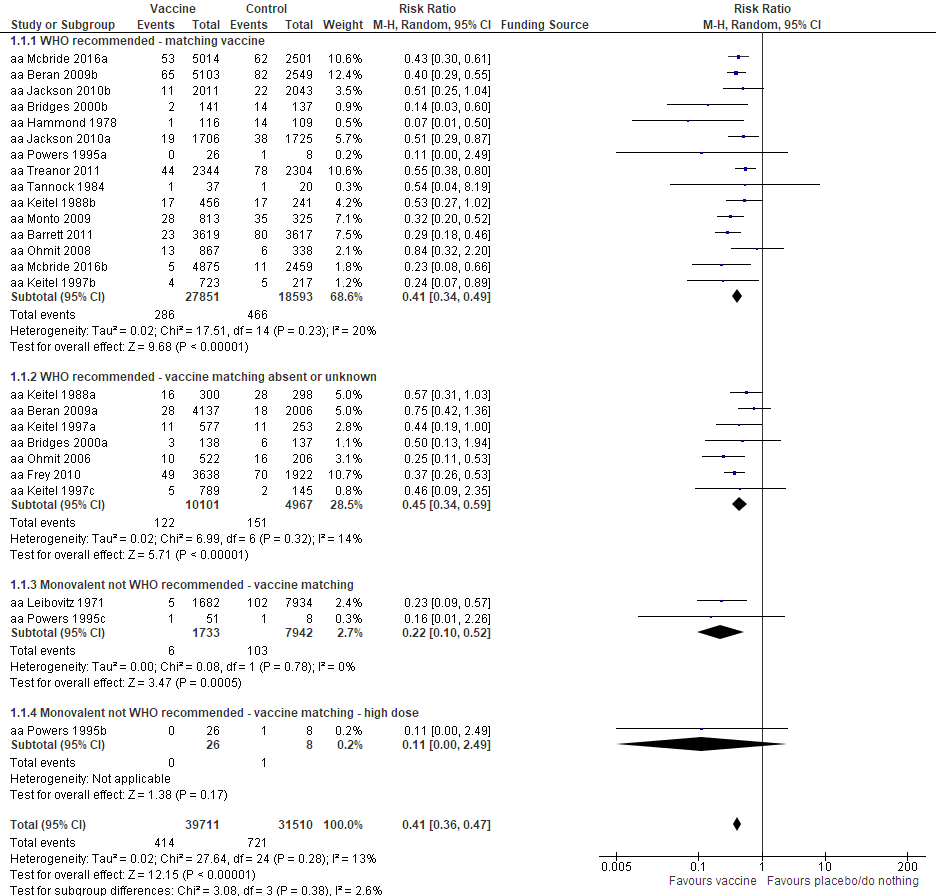
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analysis** | **Outcomes** | **Studies** | **Participants** | **Statistical method** | **Effect estimate** |
| Analysis 2.1 |  |  |  |  |  |
| Analysis 2.2 |  |  |  |  |  |
| Analysis 2.3 |  |  |  |  |  |

**Comparison 3:** Inactivated aerosol influenza vaccine versus placebo or non-placebo control

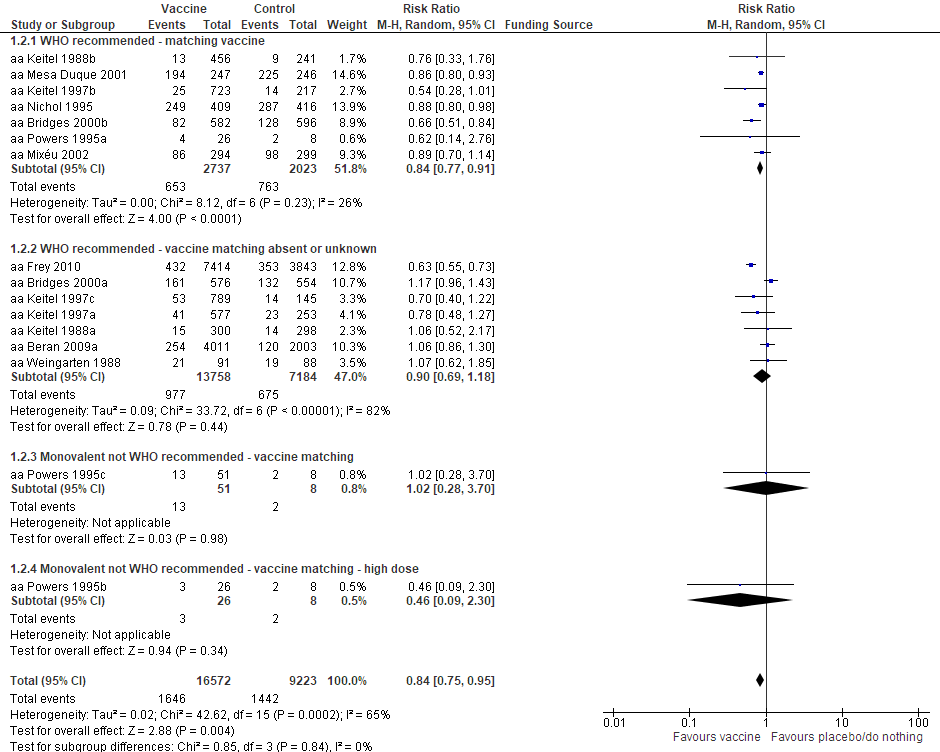
WILL FOLLOW SAME FORMAT AS COMPARISON 1

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analysis** | **Outcomes** | **Studies** | **Participants** | **Statistical method** | **Effect estimate** |
| Analysis 3.1 |  |  |  |  |  |
| Analysis 3.1 |  |  |  |  |  |
| Analysis 3.2 |  |  |  |  |  |

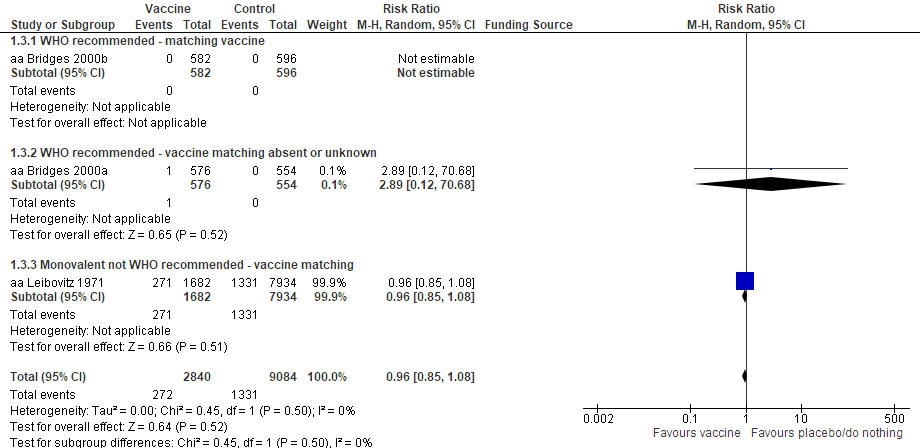
**b. Analysis 1.1. Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Influenza**



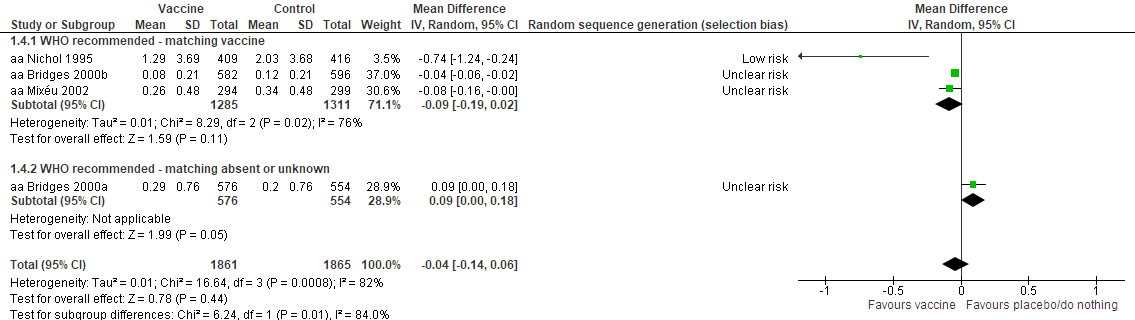
**Analysis 1.2. Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Influenza-like influenza**

****

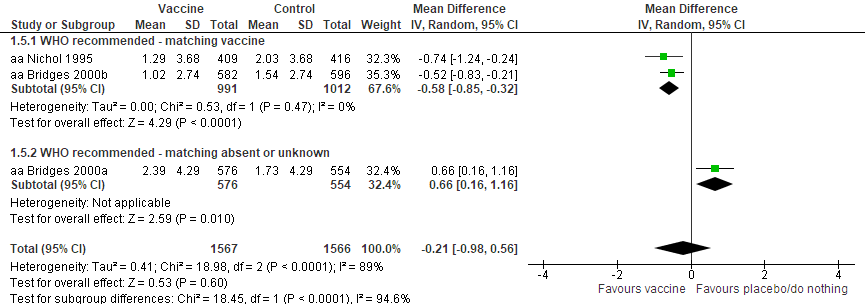
**Analysis 1.3. Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Hospitalisations**



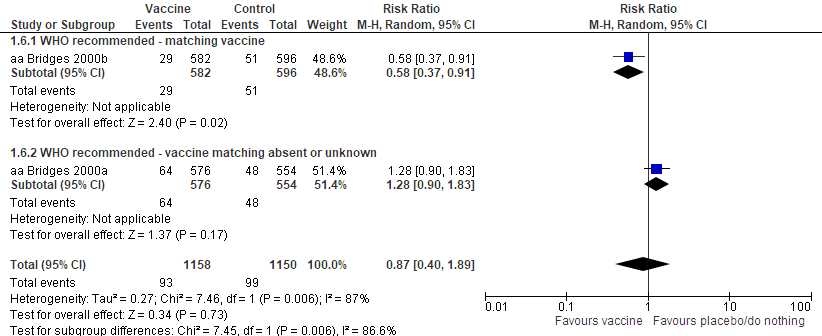
**Analysis 1.4 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Time off work**

****

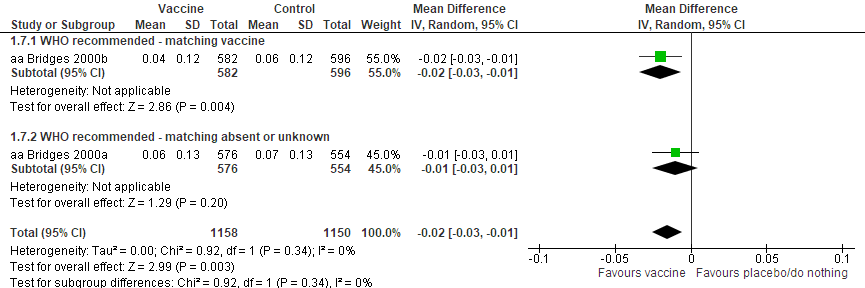
**Analysis 1.5 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Days of illness**

****

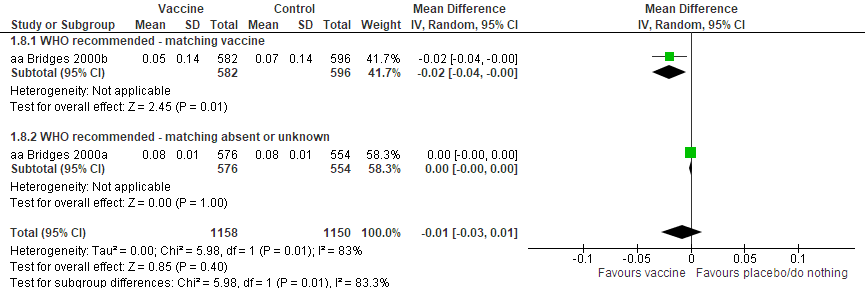
**Analysis 1.6 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Physician visits**

****

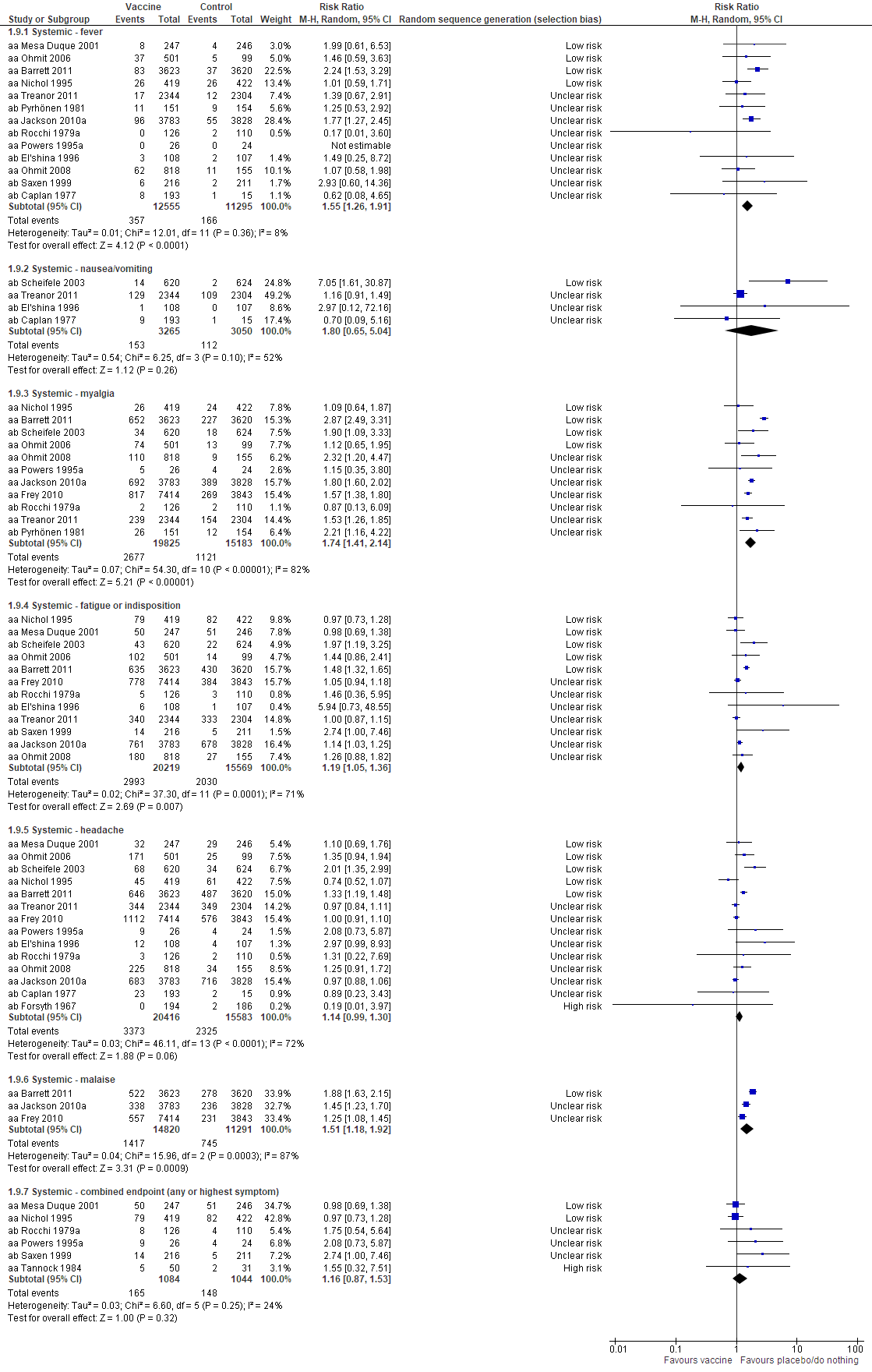
**Analysis 1.7 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Number of times an antibiotic was prescribed**

****

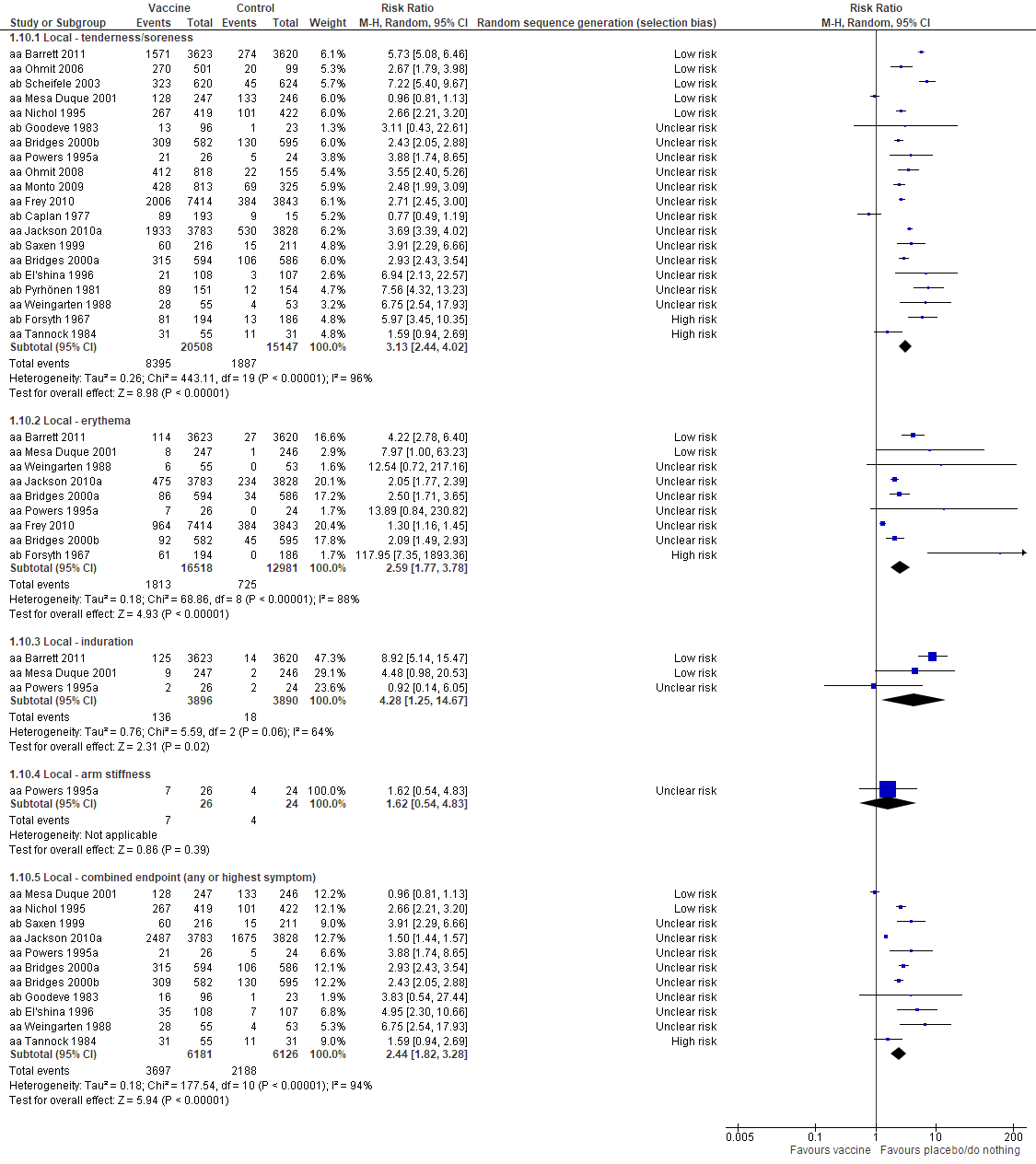
**Analysis 1.8 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Number of times any drug was prescribed**

****

**Analysis 1.9 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Systematic harms**

****

**Analysis 1.10 Inactivated parenteral influenza vaccine versus placebo or non-placebo control group: Local harms**

****

**Analysis 2.1.**

Will follow same format as above for comparisons and links to text

# Appendices

**Appendix 1: Search strategies to identify trials**

Search strategies to go here – reviewers sometimes present as tables or as text, so this should be clear in the guidance or allow for flexibility

**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 (Elsevier)**

#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

**WHO ICTRP**

vaccine\* AND influenza

immuni\* AND influenza

inocul\* AND influenza

vaccine\* AND flu

immuni\* AND flu

inocul\* AND flu

**ClinicalTrials.gov**

(vaccine OR vaccines OR vaccinate OR vaccination OR vaccinated OR vaccinating OR immunise OR immunised OR immunising

OR immunisation OR immunize OR immunized OR immunizing OR immunization) AND (influenza OR influenza OR flu)

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

**Appendix 2: Search strategies used to identify observational study searches (prior to the 2017 update)**

**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[TextWord])))

#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 “beforeafter”[

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:

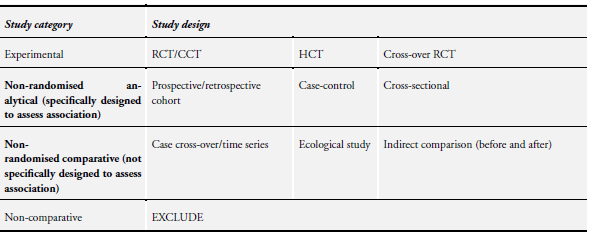
Number of studies included in this paper:

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):



Many more text and tables from the DE form appear here including the detailed Cochrane ROB form and definitions which is straight from the Handbook so probably doesn’t need to be replicated in appendices

**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 who are then followed to assess outcomes. Association between exposure and outcome are then estimated. Cohort studies are best performed prospectively, but can also be undertaken retrospectively if suitable data records are available.

A randomised controlled 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 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 amaximumof one star (i.e.asterisk) 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?

i) Yes, with independent validation\*

ii) Yes, e.g. record linkage or based on self reports

iii) No description

2. Representativeness of the cases

i) Consecutive or obviously representative series of cases\*

ii) Potential for selection biases or not stated

3. Selection of controls

i) Community controls\*

ii) Hospital controls

iii) No description

4. Definition of controls

i) No history of disease (endpoint)\*

ii) No description of source

**Comparability**

1. Comparability of cases and controls on the basis of the design or analysis

i) Study controls for ˙˙˙˙˙˙˙˙˙˙˙˙˙˙˙ (Select the most important factor)\* ii) Study controls for any additional factor\* (This criterion could be modified to indicate specific control for a second

important factor)

**Exposure**

1. Ascertainment of exposure

i) Secure record (e.g. surgical records)\*

ii) Structured interview where blind to case/control status\*

iii) Interview not blinded to case/control status

iv) Written self report or medical record only

v) No description

2. Same method of ascertainment for cases and controls

i) Yes\*

ii) No

3. Non-response rate

i) Same rate for both groups\*

ii) Non-respondents described

iii) Rate different and no designation

**Newcastle-Ottawa quality assessment scale - cohort studies**

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

**Selection**

1. Representativeness of the exposed cohort

i) Truly representative of the average ˙˙˙˙˙˙˙˙˙˙˙˙˙˙˙ (describe) in the community\*

ii) Somewhat representative of the average ˙˙˙˙˙˙˙˙˙˙˙˙˙˙ in the community\*

iii) Selected group of users, e.g. nurses, volunteers

iv) No description of the derivation of the cohort

2. Selection of the non-exposed cohort

i) Drawn from the same community as the exposed cohort\*

ii) Drawn from a different source

iii) No description of the derivation of the non-exposed cohort

3. Ascertainment of exposure

i) Secure record (e.g. surgical records)\*

ii) Structured interview \*

iii) Written self report

iv) No description

4. Demonstration that outcome of interest was not present at start of study

i) Yes\*

ii) No

**Comparability**

1. Comparability of cohorts on the basis of the design or analysis

i) Study controls for ˙˙˙˙˙˙˙˙˙˙˙˙˙ (select the most important factor)\*

ii) Study controls for any additional factor\* (This criterion could be modified to indicate specific control for a second

important factor)

**Outcome**

1. Assessment of outcome

i) Independent blind assessment\*

ii) Record linkage\*

iii) Self report

iv) No description

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

i) Yes (select an adequate follow-up period for outcome of interest)\*

ii) No

3. Adequacy of follow-up of cohorts

i) Complete follow-up - all participants accounted for\*

ii) Participants lost to follow-up unlikely to introduce bias - small number lost - > ˙˙˙˙ % (select an adequate %) follow-up, or

description provided of those lost)\*

iii) Follow-up rate < ˙˙˙˙% (select an adequate %) and no description of those lost

iv) No statement

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

Additional sections

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# Authorship

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## **Authors’ contributions**

Carlo Di Pietrantonj (CDP) and Alessandro Rivetti (AR) designed both the 2014 and the 2016 updates.  
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.  
For this 2016 update Tom Jefferson, Alex Rivetti and Vittorio Demicheli updated searches and content. The other authors approved the text.

# Declarations

## **Authors’ declarations of interest**

## Vittorio Demicheli: none known

## Tom Jefferson (TJ) was 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 ([www.nets.nihr.ac.uk/projects/hta/108001](http://www.nets.nihr.ac.uk/projects/hta/108001))). TJ receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. TJ is occasionally interviewed by market research companies for anonymous interviews about phase I or II pharmaceutical products. In 2011 to 2013, TJ acted as an expert witness in a litigation case related to oseltamivir phosphate (Tamiflu; Roche) and in a labour case on influenza vaccines in healthcare workers in Canada. TJ acted as a consultant for Roche (1997‐99), GSK (2001‐2), and Sanofi‐Synthelabo (2003) for the antirhinoviral pleconaril, which was not approved by the US Food and Drug Administration. TJ was a consultant for IMS Health in 2013, and in 2014 he was retained as a scientific adviser to a legal team acting on the drug oseltamivir (Tamiflu; Roche). In 2014 to 2015, TJ was a member of two advisory boards for Boerhinger and is in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane Reviews. TJ has a potential financial conflict of interest in the investigation of the drug oseltamivir. TJ acted as an expert witness in a legal case involving the drug oseltamivir (Roche) and the vaccine Pandemrix (GSK). TJ was a member of an Independent Data Monitoring Committee for a Sanofi Pasteur clinical trial.

## Eliana Ferroni: none known

## Alessandro Rivetti: none known

## Carlo Di Pietrantonj: none known

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### External support

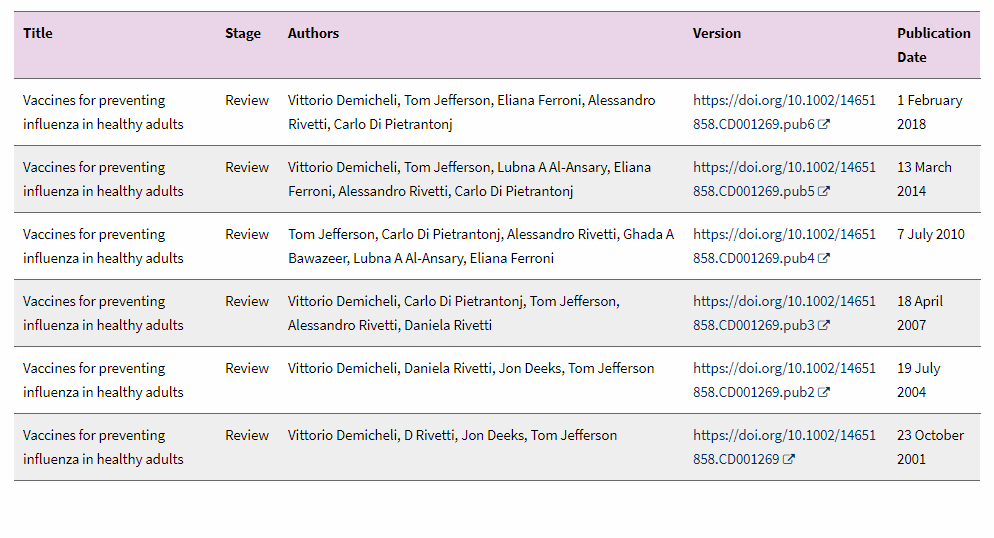
* NHS Department of Health Cochrane Incentive Scheme, UK.

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* Ministry of Defence, UK.

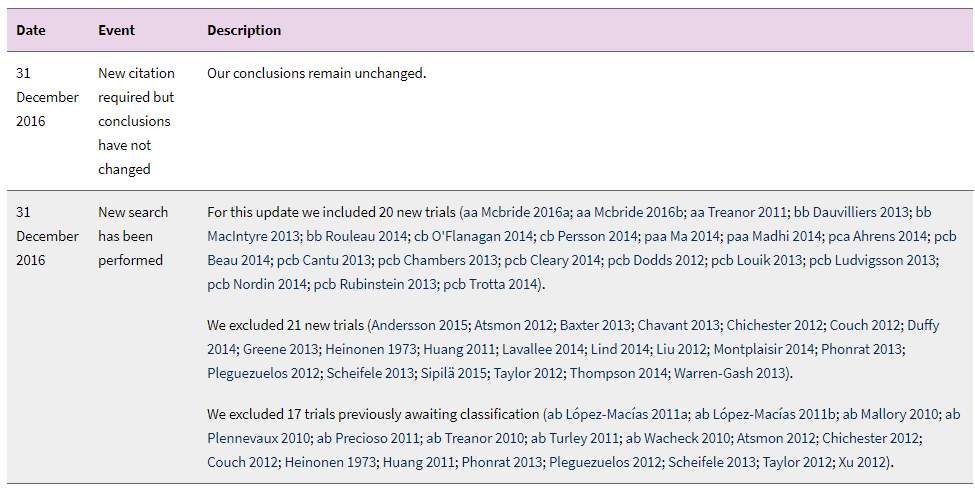
# History

## **Version history**



## **Search history**

## **What’s changed**



## **Difference between protocol and review**

Evidence about the safety and efficacy/effectiveness of influenza vaccine administration during pregnancy is included in this 2016 update. Previous versions of this review included observational comparative studies assessing serious and rare harms cohort and case‐control studies. Because of the uncertain quality of observational (i.e. non‐randomised) studies and their lack of influence on the review conclusions, we have decided to update only randomised evidence. We have no longer updated the searches for observational comparative studies.

# Messages for Media

Influenza is caused by a virus spread between people by coughing and sneezing. Populations are at risk of influenza every year when the so-called ‘flu season’ begins, usually in early autumn and through winter. Some groups, such as pregnant women, babies under six months old, older people, people living with chronic conditions, and healthcare provdiers are most at risk.

Each year, a new influenza vaccine is manufactured to match the predicted flu strain based on expert guidance and ratified by the World Health Organization. Many countries deliver country-wide programmes whereby vaccines are delivered to high-risk groups to reduce the incidence of illness.

In this review, we combined the findings of clinical trials conducted around the world. We found that the flu vaccine can halve the risk of a healthy adult contracting influenza, but the overall risk of acquiring influenza is low and the effect of the vaccine is therefore modest.

# Information for decision-makers

# For patients and the public - additional information

## What are influenza vaccines?

Vaccines work by simulating an infection and stimulating the body to produce antibodies against the threat and to activate other defence mechanisms. Influenza vaccine can be made as an inactivated (killed) preparation that is injected and an attenuated (weakened) influenza vaccine normally delivered nasally.

## Who can use or administer influenza vaccines?

All people aged six months or older without contraindications can receive influenza vaccine. Pregnant women can receive the inactivated vaccine which has no live virus.

Vaccination is often directed at healthy individuals who are at higher risk of developing complications following influenza due to their age, medical conditions, or contact with high risk individuals.

Vaccination is administered by trained healthcare personnel.

## What other options are there?

People with influenza can pass on the virus to others before they are aware they are ill. It is therefore difficult to identify whether someone is infectious or not. Healthy adults can try to avoid influenza by washing hands regularly and avoiding being in contact with people who are obviously suffering from flu-like illnesses. See systematic reviews of other options.

## How do people experience the intervention?

Vaccines are given by injection (with a needle) and can also be given via a nasal spray. People who receive vaccination by injection may experience pain at the site.

## Is there anything else someone should know before using the intervention?

Every year the World Health Organization attempts to identify the most likely strain(s) of virus circulating globally and recommends which strain(s) are to be included in the vaccine for that year. The influenza vaccine therefore only protects against the most common circulating strain(s) for that year and vaccination is required every year for protection.

# For clinical decisions

## **Indications and contraindications**

The WHO currently recommends that the following risk groups to be considered for influenza vaccination:

* Pregnant women (should have the highest priority)
* Children aged 6–59 months
* The elderly
* Individuals with specific chronic medical conditions
* Healthcare workers

Influenza vaccine is contraindicated in

* Infants younger than 6 months of age
* People who have experienced a severe (life-threatening) allergy to a prior dose of a seasonal influenza vaccine
* People who have a severe allergy to a component of the vaccine. Healthcare providers should consult the [package inserts](http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM110288) for vaccine components.

## **Delivery**

The delivery of the vaccine will depend on the type of vaccine and will be either via an intramuscular injection or via a nasal spray. Injection should be into the muscle of the non-dominant arm.

## **Cautions**

For optimal delivery of the vaccine via injection and to reduce side effects such as swelling and induration, healthcare providers require training to ensure use of suitable sterile technique.

## **Counselling patients**

Patients need to be informed that neither the injected vaccine nor the nasal spray can give healthy adults influenza. Some patients may experience a mild fever or myalgia a few days after injection as a response to the vaccine. Patients should be informed that the vaccine is only effective for a single season and that annual vaccination is required to ensure coverage. It is valuable to inform patients that if they are vaccinated they are also protecting other more vulnerable risk groups (babies, pregnant women, the elderly) from being exposed to the virus.

# For policy decisions

## **Policy options**

Policy options include decisions about which groups to target and strategies for communicating with targeted populations about influenza vaccination Targeting vulnerable groups more at risk of influenza may have greater benefit. There is limited evidence of the effects of alternative communication strategies. Consideration should be given to evaluating these.

## **Equity considerations**

Influenza is a potentially life-threatening disease especially in those groups who are more vulnerable such as pregnant women and babies less than six months old. Consideration should be given to prioritising those most at risk.

## **Economic considerations**

The cost of vaccines varies. Costs include the fact that vaccines require novel manufacture on an annual basis. Approprate storage, supply systems, and training of healthcare providers must be considered in the total cost of administering an influenza vaccination programme.

## **Monitoring and evaluation**

Influenza surveillance platforms are critical for monitoring and communicating the impact of seasonal influenza vaccination.

# Other options

## **Cochrane Reviews of other options to prevent influenza**

[Neuraminidase inhibitors for preventing and treating influenza in adults and children](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008965.pub4/full)

Tom Jefferson, Mark A Jones, Peter Doshi, Chris B Del Mar, Rokuro Hama, Matthew J Thompson, Elizabeth A Spencer, Igho J Onakpoya, Kamal R Mahtani, David Nunan, Jeremy Howick, Carl J Heneghan | **10 April 2014**

[Neuraminidase inhibitors for preventing and treating influenza in healthy adults](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001265.pub3/full)

Tom Jefferson, Mark A Jones, Peter Doshi, Chris B Del Mar, Liz Dooley, Ruth Foxlee **| 16 March 2011**

[Vaccines for preventing influenza in healthy children](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004879.pub5/full)

Tom Jefferson, Alessandro Rivetti, Carlo Di Pietrantonj, Vittorio Demicheli | **1 February 2018**

[Vaccines for preventing influenza in the elderly](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004876.pub4/full)

Vittorio Demicheli, Tom Jefferson, Carlo Di Pietrantonj, Eliana Ferroni, Sarah Thorning, Roger E Thomas, Alessandro Rivetti | **1 February 2018**

[Exercise prior to influenza vaccination for limiting influenza incidence and its related complications in adults](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011857.pub2/full)

Antonio Jose Grande, Hamish Reid, Emma E Thomas, David Nunan, Charles Foster | **22 August 2016**

[Neuraminidase inhibitors for preventing and treating influenza in children (published trials only)](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002744.pub4/full)

Kay Wang, Matthew Shun‐Shin, Peter Gill, Rafael Perera, Anthony Harnden | **18 April 2012**

[Homeopathic Oscillococcinum® for preventing and treating influenza and influenza‐like illness](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001957.pub6/full)

Robert T Mathie, Joyce Frye, Peter Fisher **| 28 January 2015**

## **Related systematic reviews**

[Amantadine and rimantadine for influenza A in adults](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001169.pub3/full)

Tom Jefferson, Vittorio Demicheli, Carlo Di Pietrantonj, Daniela Rivetti | **19 April 2006**

[Influenza vaccines for preventing acute otitis media in infants and children](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010089.pub3/full)

Mohd N Norhayati, Jacqueline J Ho, Mohd Y Azman | **17 October 2017**

[Vaccines for preventing herpes zoster in older adults](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008858.pub3/full)

Anna MZ Gagliardi, Brenda NG Andriolo, Maria Regina Torloni, Bernardo GO Soares | **3 March 2016**

# Related topics