Vaccines for preventing influenza in healthy adults (Review)

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[Intervention Review]

Vaccines for preventing influenza in healthy adults

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ABSTRACT

Background

Different types of influenza vaccines are currently produced worldwide. Healthy adults are presently targeted mainly in North America.

Objectives

Identify, retrieve and assess all studies evaluating the effects of vaccines against influenza in healthy adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2010, issue 2), MEDLINE (January 1966 to June 2010) and EMBASE (1990 to June 2010).

Selection criteria

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

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

We included 50 reports. Forty (59 sub-studies) were clinical trials of over 70,000 people. Eight were comparative non-RCTs and assessed serious harms. Two were reports of harms which could not be introduced in the data analysis. In the relatively uncommon circumstance of vaccine matching the viral circulating strain and high circulation, 4% of unvaccinated people versus 1% of vaccinated people developed influenza symptoms (risk difference (RD) 3%, 95% confidence interval (CI) 2% to 5%). The corresponding figures for poor vaccine matching were 2% and 1% (RD 1, 95% CI 0% to 3%). These differences were not likely to be due to chance. Vaccination had a modest effect on time off work and had no effect on hospital admissions or complication rates. Inactivated vaccines caused local harms and an estimated 1.6 additional cases of Guillain-Barré Syndrome per million vaccinations. The harms evidence base is limited.

Authors' conclusions

Influenza vaccines have a modest effect in reducing influenza symptoms and working days lost. There is no evidence that they affect complications, such as pneumonia, or transmission.

WARNING:

This review includes 15 out of 36 trials funded by industry (four had no funding declaration). An earlier systematic review of 274 influenza vaccine studies published up to 2007 found industry funded studies were published in more prestigious journals and cited more than other studies independently from methodological quality and size. Studies funded from public sources were significantly less likely to report conclusions favorable to the vaccines. The review showed that reliable evidence on influenza vaccines is thin but there is evidence of widespread manipulation of conclusions and spurious notoriety of the studies. The content and conclusions of this review should be interpreted in light of this finding.

PLAIN LANGUAGE SUMMARY

Vaccines to prevent influenza in healthy adults

Over 200 viruses cause influenza and influenza-like illness which produce the same symptoms (fever, headache, aches and pains, cough and runny noses). Without laboratory tests, doctors cannot tell the two illnesses apart. Both last for days and rarely lead to death or serious illness. At best, vaccines might be effective against only influenza A and B, which represent about 10% of all circulating viruses. Each year, the World Health Organization recommends which viral strains should be included in vaccinations for the forthcoming season.

Authors of this review assessed all trials that compared vaccinated people with unvaccinated people. The combined results of these trials showed that under ideal conditions (vaccine completely matching circulating viral configuration) 33 healthy adults need to be vaccinated to avoid one set of influenza symptoms. In average conditions (partially matching vaccine) 100 people need to be vaccinated to avoid one set of influenza symptoms. Vaccine use did not affect the number of people hospitalised or working days lost but caused one case of Guillian-Barré syndrome (a major neurological condition leading to paralysis) for every one million vaccinations. Fifteen of the 36 trials were funded by vaccine companies and four had no funding declaration. Our results may be an optimistic estimate because company-sponsored influenza vaccines trials tend to produce results favorable to their products and some of the evidence comes from trials carried out in ideal viral circulation and matching conditions and because the harms evidence base is limited..

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 which are not clinically distinguishable from one another. A variable proportion of ILI (7% to 15% on average) is caused by influenza viruses and is known as influenza (Jefferson 2009b).

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

Description of the intervention

Currently there are three types of influenza vaccines: (1) whole virion vaccines which consist of complete viruses which have been 'killed' or inactivated, so that they are not infectious but retain their strain-specific antigenic properties; (2) subunit virion vaccines which are made of surface antigens (H and N) only; (3) split virion vaccines in which the viral structure is broken up by a disrupting agent. These vaccines contain both surface and internal antigens. In addition a variety of non-European manufacturers produce live attenuated vaccines. Traditionally whole virion vaccines are thought to be the less well-tolerated because of the presence of a lipid stratum on the surface of the viral particles (a remnant of the host cell membrane coating the virion, when budding from the host cell). Influenza vaccines are produced worldwide. Periodic antigenic drifts and shifts pose problems for vaccine production and procurement, as a new vaccine closely matching 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 identification and isolation of viral strains circulating the different parts of the globe. Sentinel practices recover viral particles from the naso-pharynx of patients with influenza-like symptoms and the samples are swiftly sent to the laboratories of the national influenza centres (110 laboratories in 79 countries). When new strains are detected the samples are sent to one of the four WHO reference centres (London, Atlanta, Tokyo and Melbourne) for antigenic analysis. Information on the circulating strain is then sent to the WHO, who in February of each year recommends, through a committee, the strains to be included in the vaccine for the forthcoming 'season'. Individual governments may or may not follow the WHO recommendations. Australia, New Zealand and more recently South Africa, follow their own recommendations for vaccine content. Surveillance and early identification thus play a central part in the composition of the vaccine.

How the intervention might work

Every vaccination campaign has stated aims against which the effects of the campaign must be measured. Perhaps the most detailed document presenting the rationale for a comprehensive preventive programme was that by the US Advisory Committee on Immunization Practices (ACIP) published in 2006 (ACIP 2006). The document identified 11 categories at high risk of complications from influenza, among which are healthy adults 50 to 65 years of age and healthcare workers. The rationale for policy choices rests on the heavy burden which influenza imposes on the populations and on the benefits accruing from vaccinating them. Reductions in cases and complications (such as excess hospitalisations, absence from work, mortality and healthcare contacts) and the interruption of transmission, are the principal arguments for extending vaccination to healthy adults aged 50 to 65 years (ACIP 2006). The 2009 ACIP document update recommends vaccination for three categories of healthy adults: "Annual vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others. Vaccination is recommended for all adults without contraindications in the following groups, because these persons either are at higher risk for influenza complications, or are close contacts of persons at higher risk:
persons aged $\geq$ 50 years;
women who will be pregnant during the influenza season;
health-care personnel;
household contacts and caregivers of children aged below five years and adults aged $\geq$ 50 years, with particular emphasis on vaccinating contacts of children aged under six months; and household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza" (ACIP 2009).

Why it is important to do this review

Given the very high cost of yearly vaccination for large parts of the population and the extreme variability of influenza incidence during each 'season', we carried out a systematic review of the evidence. To enhance relevance for decision-makers in the 2007 update of the review (Jefferson 2007) we included comparative non-randomised studies reporting evidence of serious and/or rare harms.

OBJECTIVES

To identify, retrieve and assess all studies evaluating the effects (efficacy, effectiveness and harm) of vaccines against influenza in healthy adults we defined:

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

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

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

METHODS

Criteria for considering studies for this review

Types of studies

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

Comparative non-randomised studies were included if they reported evidence on the association between influenza vaccines and serious adverse effects (such as Guillain-Barré or oculo-respiratory syndromes).

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

Types of participants

Healthy individuals aged 16 to 65 years, irrespective of influenza immune status. Studies considering more than 25% of individuals outside this age range were excluded from the review.

Types of interventions

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

Types of outcome measures

Primary outcomes

Clinical

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

Harms

Number and seriousness of adverse effects (systemic and severe). Systemic adverse effects include cases of malaise, nausea, fever, arthralgia, rash, headache and more generalised and serious signs such as neurological harms.

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2010, issue 2) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (PubMed) (January 1966 to June 2010) and EMBASE.com (1990 to June 2010).

See Appendix 1 for the MEDLINE search strategy used in 2004, Appendix 2 and Appendix 3 for the 2009 strategies. There were no language or publication restrictions.

Searching other resources

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

Data collection and analysis

Review authors TJ and DR for the 2007 update and TJ, GB and LAA for the 2010 update independently applied inclusion criteria to all identified and retrieved articles. Four review authors (TJ, GB, LAA, EF) then extracted data from included studies on standard Cochrane Vaccines Field forms. The procedure was supervised and arbitrated by another review authors (CDP).

Selection of studies

One review author (AR) carried out an initial screening of retrieved citations. Subsequently two review authors (TJ, LAA) independently applied inclusion criteria to all identified and retrieved articles.

Data extraction and management

Four review authors (TJ, GB, LAA, EF) extracted data from included studies on standard Cochrane Vaccines Field forms. The procedure was supervised and arbitrated by another review author (CDP).

Assessment of risk of bias in included studies

Assessment of methodological quality for RCTs was carried out using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We assessed studies according to randomisation, generation of the allocation sequence, allocation concealment, blinding and follow up. We assessed quality of non-randomised studies in relation to the presence of potential confounders using the appropriate Newcastle-Ottawa Scales (NOS) (Wells 2004). We used quality at the analysis stage as a means of interpreting the results. We assigned risk of bias categories on the basis of the number of NOS items judged inadequate in each study: low risk of bias - up to one inadequate item; medium risk of bias - up to three inadequate items; high risk of bias - more than three inadequate items; very high risk of bias - when there was no description of methods.

Measures of treatment effect

Efficacy (against influenza) and effectiveness (against ILI) (effects) estimates were summarised as risk ratios (RR) and for the main findings risk difference (RD) within 95% confidence intervals (CIs) (in brackets after the summary estimate). Absolute vaccine efficacy (VE) was expressed as a percentage using the formula: VE = 1-RR whenever statistically significant.

Similar analyses were undertaken for other events, such as complications, hospital admissions and harms.

As the data on average time off work were reported as a continuous measurement, these results were expressed as differences in means and combined using the mean difference method. Caution should be exercised in interpreting these results as the data are very skewed.

Unit of analysis issues

Four different definitions of 'epidemic period' were found.

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

The data were included 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, those which occurred during the former were considered.

An ILI case (specific definition) was assumed to be the same as a 'flu-like illness' according to a predefined list of symptoms (including the Centers for Disease Control and Prevention (CDC) case definition for surveillance), or 'upper respiratory illness' according to a predefined list of symptoms. When more than one definition was given for the same trial, data related to the more specific definition were included.

The laboratory confirmation of influenza cases found were:

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

When more than one definition was given for the same trial, data related to the more sensitive definition (for example, influenza) were included.

Dealing with missing data

For the initial version of the review we wrote to first authors and manufacturers to identify possible unpublished studies and missing data. The response was disappointing and we desisted from any further attempts.

Assessment of heterogeneity

The I^2 statistic was calculated for each pooled estimate, in order to assess the impact on statistical heterogeneity. The I^2 statistic may be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than sampling error, and it is intrinsically independent of the number of studies. When I^2 statistic < 30% there is little concern about statistical heterogeneity (Higgins 2002; Higgins 2003). We used random-effects models throughout to take account of the between-study variance in our findings (DerSimonian 1986). 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 population in different settings. Not all studies reported sufficient details to enable a full analysis of the sources of heterogeneity, but we were able to take into account vaccine matching and circulating strain.

Assessment of reporting biases

The main problem with influenza vaccines studies is their poor quality and discrepancies between data presented, conclusions and authors' recommendations. For example, an earlier review of 274 influenza vaccines studies in all age groups (including the studies in this review) showed an inverse relationship between risk of bias and direction of study conclusions. Conclusions favorable to the use of influenza vaccines were associated with higher risk of bias. In these studies the authors made claims and drew conclusions unsupported by the data they presented. In addition, industry funded studies are more likely to have favorable conclusions and be published in significantly higher impact factor journals and have higher citation rates than non-industry funded studies. This difference is not explained by either their size or methodological quality (Jefferson 2009a). The review found no evidence of publication bias.

Any interpretation of the body of evidence in this review should be made with these findings in mind.

Data synthesis

We carried out a random-effects meta-analysis of efficacy and effectiveness data (Higgins 2009) but we did not perform a quantitative analysis of non-randomised studies.

The data and analyses tables were constructed according to the following criteria.

1. Inactivated parenteral (intramuscular or subcutaneous) influenza vaccines versus placebo or no intervention (Analysis 01).
2. Live aerosol vaccines (Analysis 02).
3. Inactivated aerosol vaccines (Analysis 03).

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

The following outcomes were included in the comparisons.

1. Cases of influenza (defined on the basis of a specific list of symptoms and/or signs backed up by laboratory confirmation of infection with influenza A or B viruses).
2. Cases of ILI (clinically defined on the basis of a specific list of symptoms and/or signs).
3. Hospital admissions.
4. Complications.
5. Working days lost.
6. Local harms.
7. Systemic harms.
8. Severe/rare harms.

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

Local symptoms are presented separately from systemic symptoms. Individual harms have been considered in the analysis, as well as a combined endpoint (any or highest symptom). All the data included in the analysis were used as presented by the authors in the primary study regardless of the number of drop-outs. This approach (complete case scenario) was decided because the majority of the studies did not present any attempt at using an intention to treat analysis nor mentioned the reasons for the loss to follow up and did not contain detailed information to allow estimations of the real number of participants.

Subgroup analysis and investigation of heterogeneity

Several trials included more than one active vaccine arm. Where several active arms from the same trial were included in the same analysis, the placebo group was split equally between the different arms, so that the total number of subjects in any one analysis did not exceed the actual number in the trials. As it was not possible to identify all sources of heterogeneity, we decided to carry out a sensitivity analysis on the results applying fixed-effect and a random-effects model to assess the impact of heterogeneity on our results. Finally, we carried out a separate analysis of trials carried out during the 1968 to 1969 (H3N2) pandemic.

Sensitivity analysis

Future updates of this review may include sensitivity analysis by funding source.

RESULTS

Description of studies

Results of the search

The first version of the review contained 20 studies (Demicheli 1999). The 2004 version added five more studies (Demicheli 2004). In 2007 we included 48 studies in all (Jefferson 2007). Some of them had more than two arms, comparing different vaccines, routes of administration, schedules or dosages and reported data from different settings and epidemic seasons. We split these studies into sub-studies (data sets). For the remainder of this review, the term 'study report' refers to the original study report, while the word 'dataset' refers to the sub-study. Details of the division of the reports of studies into data sets are given in the table

of included studies. In this 2010 update we included two new trials (Beran 2009a; Beran 2009b). We excluded three new studies (Belongia 2009; Chou 2007; Khazeni 2009).
Overall, 25 data sets contributed data on efficacy/effectiveness (16 on inactivated parenteral vaccines, seven on live aerosol vaccines and two on inactivated aerosol vaccines), 12 on all effects (seven on inactivated parenteral vaccines, three on live aerosol vaccines and two on inactivated aerosol vaccines) and 20 on harms only (nine on inactivated parenteral vaccines, nine on live aerosol vaccines and two on inactivated aerosol vaccines) (Table 1).

Included studies

Included trials assessed three types of vaccine: inactivated parenteral, live attenuated aerosol and inactivated aerosol.
Thirty-four data sets of inactivated parenteral vaccine were included. Eigtheen data sets (12 study reports) provided data about efficacy or effectiveness (Beran 2009a; Beran 2009b; Eddy 1970; Hammond 1978; Keitel 1988a; Keitel 1988b; Keitel 1997a; Keitel 1997b; Keitel 1997c; Leibovitz 1971; Mixéu 2002; Mogabgab 1970a; Mogabgab 1970b; Powers 1995b; Powers 1995c; Waldman 1969a; Waldman 1969b; Weingarten 1988). They involved 34,573 participants: 18,557 in the vaccines arm and 16,016 in the placebo arms.

Seven data sets (five study reports) reported both effectiveness and harms data (Bridges 2000a; Bridges 2000b; Mesa Duque 2001; Nichol 1995; Powers 1995a; Waldman 1972b; Waldman 1972d). The population sample of these consisted of 4227 participants: 2251 received the vaccine and 1976 received the placebo.

The remaining nine data sets (nine studies) with inactivated parenteral vaccines assessed harms outcomes only and were carried out on 2931 participants (Caplan 1977; El'shina 1996; Forsyth 1967; Goodeve 1983; Phyroenen 1981; Rocchi 1979a; Saxen 1999; Scheifele 2003; Tannock 1984). In this last group, 1560 participants were immunised and 1371 received the placebo.
Live aerosol vaccines were tested in 19 data sets.
Seven data sets (three studies) reported efficacy/effectiveness outcomes (Edwards 1994a; Edwards 1994b; Edwards 1994c; Edwards 1994d; Sumarokow 1971; Zhilova 1986a; Zhilova 1986b). Altogether 29,955 participants were involved: 15,651 in vaccines and 14,304 in the placebo arms. Three data sets (three studies) provided effectiveness and harms data (Monto 1982; Nichol 1999a; Rytel 1977), 5010 individuals in all; 3290 in vaccines arms and 1720 in placebo. Nine data sets (eight studies) reported harms data only (Atmar 1990; Betts 1977a; Evans 1976; Hrabar 1977; Keitel 1993a; Keitel 1993b; Lauteria 1974; Miller 1977; Rocchi 1979b): 630 in the vaccinated and 344 in the placebo arms; 974 observations in total.
Six data sets with inactivated aerosol vaccine were included.
Two data sets provided data on efficacy or effectiveness only (Waldman 1969c; Waldman 1969d). The total number of subjects was 1187: with 950 who were vaccinated and 237 who received placebo.
Two data sets (one study) evaluated efficacy/effectiveness and harms (Waldman 1972a; Waldman 1972c) with a total population of 487: 389 in the vaccine arms 389 and 98 in the placebo arms.
Two trials (two studies) reported data on harms outcomes only (Boyce 2000; Langley 2005), with a total population of 151,120 in the vaccine arms and 31 in the placebo arms).

Two studies with live aerosol vaccine (Reeve 1982; Spencer 1977) each one data set) could not be introduced in the harms analysis (secondary effects) because data did not allow quantitative analysis (systemic and local harms were reported as given cumulative in Spencer 1977 and data were not clearly reported in Reeve 1982).
Ten studies (eight of which were comparative non-randomised studies) investigated possible associations between influenza vaccines and serious harms.
Atmar 1990 (respiratory function), DeStefano 2003 (multiple sclerosis and optic neuritis), Kaplan 1982 (Guillan Barrè Syndrome (GBS)), Lasky 1998 (GBS) Mastrangelo 2000 (cutaneous melanoma), Mutsch 2004 (Bell's palsy), Payne 2006 (optic neuritis), Scheifele 2003 (oculo respiratory syndrome), Shoenberger 1979 (GBS), Siscovick 2000 (cardiac arrest).
Included studies are described in the relevant table.

Excluded studies

We excluded 92 studies (see Characteristics of excluded studies table).

Risk of bias in included studies

Thirty-three studies were properly randomised, seven stated that the allocation method was quasi-random and two studies were field trials. Three non-randomised studies were at high risk of bias (Kaplan 1982; Mastrangelo 2000; Siscovick 2000), one was at medium risk of bias (Mutsch 2004) and two were at low risk of bias (Atmar 1990; Lasky 1998).

Allocation

In the included trials, allocation concealment was adequate in 10, inadequate in four, unclear in 26 and not relevant in two.

Blinding

Assessment was double-blinded in 23 studies. Five studies were single blind and twelve did not mention blinding. Thirty-three studies were properly randomised, seven stated that the allocation method was quasi-random and two studies were field trials.

Incomplete outcome data

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

Selective reporting

The harms dataset from randomised studies is small. The trial authors appear to regard harms as less important than effectiveness assessment. For example, in the trials by Beran et al (Beran 2009a; Beran 2009b) data collection on harms began at the receipt of the vaccine or placebo and continued until the end of the study. However, harms data were solicited from a subset of subjects and no mention of method used to select them and no justification for not collecting harms data from all participants were reported.

Other potential sources of bias

It is now known that industry funding of influenza vaccines studies determines publication in high prestige journals and higher citation rates than other types of funding. In addition industry funding is associated with optimistic conclusions, but the quality of the majority of influenza vaccines studies is low, irrespective of funding. A previously cited review showed a complex web of interrelationships between these variables (Jefferson 2009a), but how this impacts on policy making is unknown.

Effects of interventions

Inactivated parenteral vaccines (Analysis 01)

Inactivated parenteral vaccines were 30% effective (95% CI 17% to 41%) against the symptoms of ILI if content matched WHO recommendations and circulating strain, but were not effective (RR 0.93, 95% CI 0.79 to 1.09) when these were unknown (Analysis 1.1.2)

Against influenza symptoms vaccines were 73% efficacious (54% to 84%) when content matched WHO recommendations and circulating strain but decreased to 44% (95% CI 23% to 59%) when it did not (Analysis 1.2).

An alternative to the use of risk ratio based formula 1-RR expressed as percentage is the use of risk difference (RD). In this case 30% of unvaccinated people versus 24% of people vaccinated with inactivated parenteral vaccines developed symptoms of ILI. This is the equivalent to saying that 70% of the unvaccinated study participants did not get ILI symptoms compared to 76% of the vaccinated study participants who did not get ILI symptoms (effectiveness). When the vaccine matched the viral circulating strain and circulation was high, 4% (2% to 5%) of unvaccinated people versus 1% of vaccinated people developed influenza symptoms (efficacy). These differences were not likely to be due to chance. When the vaccine content did not match the circulating influenza viruses 1% of vaccinated people developed symptoms compared to 2% of unvaccinated people.

Efficacy was lower (74%, 95% CI 45% to 87%) when the studies carried out during the 1968 to 1969 pandemic were excluded. Based on one study, 42% less (95% CI 9% to 63%) physician visits are carried out in those vaccinated with WHO recommended vaccines matching circulating viruses, but not in those not matching (RR 1.28, 95% CI 0.90 to 1.83) (Analysis 1.3.2). A similar result is seen in the effect on days of illness (Analysis 1.4), but there seems to be no effect on times an antibiotic or a drug were prescribed (Analysis 1.5 and 1.6). Five trials evaluated time off work, estimating that vaccination saved on average around 0.13 working days. This result was not statistically significant. Hospital admissions (evaluated in four trials) were also lower in vaccinated arms, but the difference was not statistically significant. There was little difference in complication rates between vaccinated and unvaccinated groups (Analyses 1.7 to 1.10). The conclusions of this comparison were unaffected by analysis using either random- or fixed-effect models

Harms

Local tenderness and soreness was more than three times as common among parenteral vaccine recipients than those in the placebo group (RR 3.11, 95% CI 2.08 to 4.66) (Analysis 1.11.1). There were also increases in erythema (RR 4.01, 95% CI 1.91 to 8.41) (Analysis 1.11.2), but not induration or arm stiffness. The combined local effects endpoint was significantly higher for those receiving the vaccine (RR 2.87, 95% CI 2.02 to 4.06) (Analysis 1.11.5). Myalgia was significantly associated with vaccination (RR 1.54, 95% CI 1.12 to 2.11) (Analysis 1.12.1). None other of the systemic effects were individually more common in parenteral vaccine recipients than in placebo recipients. However, the combined endpoint was increased (RR 1.29, 95% CI 1.01 to 1.64) (Analysis 1.12.6).

Live aerosol vaccines (Analysis 02)

Live aerosol vaccines have an effectiveness of 10% (95% CI 4% to 16%) and content and matching appear not to affect their performance significantly. However, overall their efficacy is 62% (95% CI 45% to 73%). Again, neither content nor matching appear to affect their performance significantly. The effectiveness of the aerosol vaccines against ILI (with no clear definition) was significant only for WHO recommended vaccine matching absent or unknown (11%, 95% CI 3% to 18%). The conclusions of this comparison were unaffected by analysis using either random- or fixed-effect models.

Harms

Significantly more recipients experienced symptoms of upper respiratory infection, sore throats and coryza after vaccine administration than placebo administration (upper respiratory infection RR 1.66, 95% CI 1.22 to 2.27; coryza RR 1.56, 95% CI 1.26 to 1.94; sore throat 1.73, 95% CI 1.44 to 2.08)). There was no significant increase in systemic harms, although rates of fever fatigue and myalgia were higher in vaccine than placebo groups.

Inactivated aerosol vaccines (Analysis 03)

Inactivated aerosol vaccines had effectiveness of 42% (95% CI 17% to 60%) although this observations is based on four data sets from two studies. The conclusions of this comparison were substantially unaffected by analysis using either random- or fixed-effect models although effectiveness against ILI - WHO recommended content and matching vaccine went from a fixed-effect RR 0.59 (95% CI 0.43 to 0.81) to a random-effects RR of 0.47 (95% CI 0.19 to 1.13) (Analysis 3.1.1) and the subcomparison ILI - WHO recommended but with content and matching unknown went from a fixed-effect RR 0.69 (95% CI 0.51 to 0.93) to a random-effects RR 0.63 (95% CI 0.37 to 1.07) (Analysis 3.1.2). We conclude that the presence of heterogeneity does not materially alter our conclusions. Sensitivity analysis by methodological study quality did not affect our findings.

Harms

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

Serious and rare harms

Oculo-respiratory syndrome (ORS)

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

Guillain-Barré Syndrome (GBS)

Three studies assessed the association between influenza vaccination and Guillain-Barré Syndrome (GBS) (rapidly progressing symmetric paralysis with usually spontaneous resolution). The first study compared GBS cases by vaccination status and the national incidence in vaccinated and unvaccinated national cohorts. The attributable risk from vaccination was just below 1 case of GBS every 100,000 vaccinations (Shoenberger 1979). The rise in GBS following rapid immunisation of millions of Americans in 1976 to 1977 led to the halting of the campaign. The second study (Kaplan 1982) was a retrospective cohort model comparing incidence of GBS in vaccinated and unvaccinated adults in the USA (minus the state of Maryland) within eight weeks from vaccination. The study reported a lack of evidence of association (RR of 0.6 and 1.4 for the two seasons included in the study; described as non-significant but with no confidence intervals reported). The study is a poor quality model with poor case ascertainment, no case definition and assumptions of the size of the exposed and non-exposed denominators. A similar design but with more sophistication was used in the Lasky et al study for the 1992 to 1993 and 1993 to 1994 seasons (Lasky 1998). Lasky et al. assessed the risk of GBS within six weeks from vaccination. Assessment of exposure was based on a random digit phone sample validated through state data on vaccine coverage and provider-sources data on vaccination timings. Two hundred and seventy three cases of GBS were identified through the CDC VAERS surveillance database and histories validated using hospital documentation. Only 180 cases were available for interview. Nineteen cases were assessed by the authors as being vaccine-associated (received vaccine in the previous six weeks (RR 1.8, 95% CI 1.0 to 3.5) adjusted for age, sex and season). The cases had a mean age of 66 years. The authors estimated the incidence of vaccine-induced GBS as 0.145 cases per million persons per week or 1.6 extra cases per million vaccinations. Despite its many limitations (mainly due to case attrition and variable reliability of exposure data) the study is well conducted and its conclusions credible, if conservative. We conclude that there may be a small additional risk of GBS. The studies demonstrate the danger of commencing a large vaccination campaign without adequate harms assessment.

Demyelinating diseases

Based on two case-control studies there is no evidence of an association between influenza vaccine and demyelinating disease (DeStefano 2003; Payne 2006).

Bell's palsy

One case-control study and case-series based in the German-speaking regions of Switzerland assessed association between an intranasal inactivated virosomal influenza vaccine and Bell's palsy (Mutsch 2004). Two hundred and fifty cases that could be evaluated (from an original 773 cases identified) were matched to 722 controls. All were aged around 50. The study reports a massive increase in risk (adjusted OR 84, 95% CI 20.1 to 351.9) within 1

to 91 days since vaccination. Despite its many limitations (case attrition - 187 cases could not be identified - and ascertainment bias - physicians picked controls for their own cases - confounding by indication - different vaccine exposure rate between controls and the reference population) it is unlikely that such a large OR could have been affected significantly by systematic error. The authors called for larger pre-licence harms trials, given the rarity of Bell's palsy. On the basis of this study the vaccine was withdrawn from commerce.

Cutaneous melanoma

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

Primary cardiac arrest

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

Pulmonary function

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

Vaccines for the 1968 to 1969 (H3N2) influenza pandemic (Comparisons 04 to 08)

Five studies yielded 12 data sets (Eddy 1970; Mogabgab 1970a; Mogabgab 1970b; Sumarokow 1971; Waldman 1969a; Waldman 1969b; Waldman 1969c; Waldman 1969d; Waldman 1972a; Waldman 1972b; Waldman 1972c; Waldman 1972d). As one would expect, vaccine performance was poor when content did not match the pandemic strain (Analysis 4). However, one-dose or two-dose monovalent whole-virion (i.e. containing dead complete viruses) vaccines achieved 65% (95% CI 52% to 75%) protection against ILI and 93% (95% CI 69% to 98%) protection against influenza, and 65% (95% CI 6% to 87%) against hospitalisations (Analysis 5). Approximately half a working day lost and half a day of illness were saved but no effect was observed against pneumonia. All comparisons except for influenza-like illness are based on a single study (Analysis 5). The large effect on ILI is coherent with the high proportion of these illnesses caused by influenza viruses in a pandemic (i.e. the gap between efficacy and effectiveness of the vaccines is narrow). Aerosol polyvalent or monovalent vaccines had modest performance (Analyses 6 to 8).

DISCUSSION

Although this review presents a large number of comparisons and outcomes based on a number of different groupings of studies and trials, most of the discussion was based on the results of the analysis of a WHO recommended vaccine against placebo. Parenterally administered influenza vaccines appear significantly better than their comparators and can reduce the risk of developing influenza symptoms by around 4%, if the WHO recommendations are adhered to and the match is right. However, whilst the vaccines do prevent influenza symptoms, this is only one part of the spectrum of "clinical effectiveness" as they reduce the risk of total "clinical" seasonal influenza (i.e. influenza-like illness) symptoms by around 1%. When the results of our analysis are expressed as RD the effect appears minimal. This is remarkable as healthy adults are the population in which inactivated vaccines perform best. We found no evidence that vaccines prevent viral transmission or complications.

It is not possible to give a definite indication on the practical use of live aerosol vaccines, because the assessment of their effectiveness is based on a limited number of studies presenting conflicting results. The effectiveness, according to WHO criteria, appears relatively low. Results regarding inactivated aerosol vaccine are based on the analysis of a few trials reporting only clinical outcomes not directly comparable, owing to non-homogeneous definitions. It

does not seem wise to draw conclusions from these data. Rates of complications caused by influenza in these trials were very low and analysis of the few trials which contained this outcome, did not reveal a significant reduction with the influenza vaccine. This result appears to contrast with assertions of policy makers (ACIP 2006) and may be due to the general rarity of complications caused by respiratory infection in healthy adults. Hospitalisation was assessed in four trials and did not show a significant benefit from vaccination. Working days lost in placebo recipient and vaccine recipients were significantly reduced in the vaccinated group, but by less than half a day on average.

Inactivated vaccines cause local (redness, induration) and systemic harms (myalgia, possibly fatigue). In rare cases there may be an increased risk of GBS, of ORS and Bell's palsy but this may be product-specific. Given the low effectiveness of the aerosol vaccines, the effects classified as harms (sore throat and cough) may be caused by influenza. Although the possibility of causing serious harm may be rare, it must be born in mind when proposing the inception of a mass campaign of immunisation to a whole population, i.e. when exposure to the vaccines is increased.

While the parenteral vaccine efficacy against seasonal (i.e. non-pandemic) influenza is around 75% for the WHO recommended and matched strain, its impact on the global incidence of clinical cases of influenza (i.e. ILI) is limited (around 16% in best case scenario). The universal immunisation of healthy adults should achieve a number of specific goals: reducing the spread of the disease, reducing the economic loss due to working days lost and reducing morbidity and hospitalization. None of the studies included in the review presented results evaluating the ability of this vaccination to interrupt the spread of the disease. Some studies presented data on reduction of working days lost and showed a very limited effect. Similarly a very limited effect was found on morbidity and no effect was found on hospitalization. Given the limited availability of resources for mass immunisation, the use of influenza vaccines should be primarily directed where there is clear evidence of benefit.

Whole-virion monovalent inactivated vaccines may help control a pandemic, if the antigenic match between virus and vaccine is right. Although this observation is based on a limited number of old trials, the high effectiveness of the vaccine (i.e. against ILI) would seem to confirm its potential for use. Efforts to update and enhance these vaccines should have priority.

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

1. None of the live aerosol vaccines included in the review were registered.

2. Methods of vaccine standardisation have changed significantly.

3. Recent vaccines present significant differences in purity when compared with older ones.

4. Different doses and schedules were pooled in the analysis

The content and results of previous versions of this review have been extensively misquoted especially in public policy documents (Jefferson 2009c). Two types of common misquotes are the generalisation of evidence from this review to all age and risk groups and the generalisation of estimates of effect to all outcomes (especially complications and deaths). The misquotes then assume that the performance of influenza vaccines is uniform across all age groups and from symptom prevention to all outcomes. Both generalisations are not supported by any evidence and seem to originate from the desire to use our review to support decisions already taken. The misquotes appear to be based on both the abstract and Plain language summary (which is what you would expect from a superficial reading of the review by people with a specific agenda). It is for these reasons that in this 2010 update we have tried to minimise the risk of being misquoted by presenting effects on major outcomes both in RR and RD format and have inserted a general warning on the quality of evidence in the field of influenza vaccines. Recent examples of misquotes of this review come from page 11 of the 2009 ACIP document (ACIP 2009). The 2007 version of the review is indicated as reference 121: "When the vaccine and circulating viruses are antigenically similar, TIV prevents laboratory-confirmed influenza illness among approximately 70% to 90% of healthy adults aged < 65 years in randomised controlled trials (*121, 124*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched (*121, 123*). Efficacy or effectiveness against laboratory-confirmed influenza illness was 47% - 77% in studies conducted during different influenza seasons when the vaccine strains were antigenically dissimilar to the majority of circulating strains (*117,119,121,124*). However, effectiveness among healthy adults against influenza-related hospitalization, measured in the most recent of these studies, was 90% (*125*)". There are three subtle manipulations in the text. First, the review is cited with single study references. Second, the impression reading the text is that vaccines have effect against all outcomes when the evidence quoted refers to cases (or symptoms as we call them in this latest update of the review). Third, our review (which only includes RCT evidence of effectiveness) shows no effect on hospitalisations, CDC quote reference 125 which is a 2007 observational study. The CDC authors clearly do not weight interpretation by quality of the evidence, but quote anything that supports their theory.

Summary of main results

Inactivated influenza vaccines decrease the risk of symptoms of influenza and time off work, but their effects are minimal, especially

if the vaccines and the circulating viruses are mismatched. There is no evidence that they affect complications or transmission.

Overall completeness and applicability of evidence

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

Quality of the evidence

We found evidence from more than 80,000 people in 50 randomised studies. Regardless of quality, all studies fail to report any evidence of effect on complications. The safety evidence base from randomised trials of inactivated vaccines is very small, probably indicating less concern with harms. Inactivated vaccines cause rare major harms which appear to be mostly linked to specific products or lots.

Potential biases in the review process

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

Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review seem to discourage the utilisation of vaccination against influenza in healthy adults as a routine public health measure. As healthy adults have a low risk of complications due to respiratory disease, the use of the vaccine may be only advised as an individual protection measure against symptoms in specific cases.

Implications for research

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

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REFERENCES

References to studies included in this review

Atmar 1990 ***{published data only}***
Atmar RL, Bloom K, Keitel W, Couch RB, Greenberg SB. Effect of live attenuated, cold recombinant (CR) influenza virus vaccines on pulmonary function in healthy and asthmatic adults. *Vaccine* 1990;**8**(3):217–24.

Beran 2009a ***{published data only}***
Beran J, Wertzova V, Honegr K, Kaliskova E, Havlickova M, Havlik J, et al.Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. *BMC Infectious Diseases* 2009;**9**: 2. [DOI: doi:10.1186/1471-2334-9-2]

Beran 2009b ***{published data only}***
Beran J, Vesikari T, Wertzova V, Karvonen A, Honegr K, Lindblad N, et al.Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: a prospective, randomized, placebo-controlled trial. *Journal of Infectious Diseases* 2009;**200**:1861–9.

Betts 1977a ***{published data only}***
Betts RF, Douglas RG Jr, Roth FK, Little JW 3rd. Efficacy of live attenuated influenza A/Scotland/74 (H3N2) virus vaccine against challenge with influenza A/Victoria/3/75

(H3N2) virus. *Journal of Infectious Diseases* 1977;**136**(6): 746–53.

Boyce 2000 ***{published data only}***
Boyce TG, Hsu HH, Sannella EC, Coleman-Dockery SD, Baylis E, Zhu Y, et al.Safety and immunogenicity of adjuvanted and unadjuvanted subunit influenza vaccines administered intranasally to healthy adults. *Vaccine* 2000; **19**(2-3):217–26.

Bridges 2000a ***{published data only}***
Buxton Bridges C, Thompson VV, Meltzer MI, Reeve GR, Talamonti VJ, Cox NJ, et al.Effectiveness and cost benefit of influenza vaccination of healthy working adults, a randomized controlled trial. *JAMA* 2000;**284**(13): 1655–63.

Bridges 2000b ***{published data only}***
Buxton Bridges C, Thompson VV, Meltzer MI, Reeve GR, Talamonti VJ, Cox NJ. Effectiveness and cost benefit of influenza vaccination of healthy working adults, a randomized controlled trial. *JAMA* 2000;**284**(13): 1655–63.

Caplan 1977 ***{published data only}***
Caplan ES, Hughes TP, O'Donnel S, Levine MM, Hornick RB. Reactogenicity and immunogenicity of parenteral monovalent influenza A/Victoria/3/75 (H3N2) virus vaccine in healthy adults. *Journal of Infectious Diseases* 1977; **136**(Suppl):484–90.

DeStefano 2003 ***{published data only}***
DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, et al.Vaccinations and risk of central nervous system demyelinating diseases in adults. *Archives of Neurology* 2003;**60**(4):504–9.

Eddy 1970 ***{published data only}***
Eddy TS, Davies NA. The effect of vaccine on a closed epidemic of Hong Kong influenza. *South African Medical Journal* 1970;**February 21**:214–6.

Edwards 1994a ***{published data only}***
Edwards KM, Dupont WD, Westrich MK, et al.A randomized controlled trial of cold adapted and inactivated vaccines for the prevention of influenza A disease. *Journal of Infectious Diseases* 1994;**169**:68–76.

Edwards 1994b ***{published data only}***
Edwards KM, Dupont WD, Westrich MK, et al.A randomized controlled trial of cold adapted and inactivated vaccines for the prevention of influenza A disease. *Journal of Infectious Diseases* 1994;**169**:68–76.

Edwards 1994c ***{published data only}***
Edwards KM, Dupont WD, Westrich MK, et al.A randomized controlled trial of cold adapted and inactivated vaccines for the prevention of influenza A disease. *Journal of Infectious Diseases* 1994;**169**:68–76.

Edwards 1994d ***{published data only}***
Edwards KM, Dupont WD, Westrich MK, et al.A randomized controlled trial of cold adapted and inactivated vaccines for the prevention of influenza A disease. *Journal of Infectious Diseases* 1994;**169**:68–76.

El'shina 1996 ***{published data only}***
El'shina GA, Masalin IuM, Shervali VI, Gorbunov MA, Lonskaia NI, Agafonova LV, et al.The trivalent polymer-subunit influenza vaccine Grippol studied in a controlled epidemiological trial. *Voenno-Meditsinskii Zhurnal* 1996; **317**(8):57–60.

Evans 1976 ***{published data only}***
Evans AE, Letley E, Ferris RD, Freestone DS. WRL 105 strain live attenuated influenza vaccine; comparison of one and two dose schedules. *Journal of Hygiene* 1976;**77**(3): 327–32.

Forsyth 1967 ***{published data only}***
Forsyth JR. An assessment of oil adjuvant and aqueous influenza vaccines. I. Reactions to the vaccines. *Journal of Hygiene* 1967 Dec;**65**(4):485–95.

Goodeve 1983 ***{published data only}***
Goodeve A, Potter CW, Clark A, Jennings R, Schild GC, Yetts R. A graded-dose study of inactivated, surface antigen influenza B vaccine in volunteers: reactogenicity, antibody response and protection to challenge virus infection. *Journal of Hygiene* 1983;**90**(1):107–15.

Hammond 1978 ***{published data only}***
Hammomd ML, Ferris AA, Faine S, et al.Effective protection against influenza after vaccination with subunit vaccine. *Medical Journal of Australia* 1978;**1**:301–3.

Hrabar 1977 ***{published data only}***
Hrabar A, Vodopija I, Andre FE, Mitchell JR, Maassab HF, Hennessy AV, et al.A placebo-controlled dose-response study of the reactogenicity and immunogenicity of a cold-adapted recombinant A/Victoria/3/75 (H3N2) live influenza virus candidate vaccine in healthy volunteers. *Developments in Biological Standardization* 1977;**39**:53–60.

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

Keitel 1988a ***{published data only}***
Keitel WA, Cate TR, Couch RB. Efficacy of sequential annual vaccination with inactivated influenza virus vaccine. *American Journal of Epidemiology* 1988;**127**(2):353–64.

Keitel 1988b ***{published data only}***
Keitel WA, Cate TR, Couch RB. Efficacy of sequential annual vaccination with inactivated influenza virus vaccine. *American Journal of Epidemiology* 1988;**127**(2):353–64.

Keitel 1993a ***{published data only}***
Keitel WA, Couch RB, Quarles JM, Cate TR, Baxter B, Maassab HF. Trivalent attenuated cold-adapted influenza virus vaccine: reduced viral shedding and serum antibody responses in susceptible adults. *Journal of Infectious Diseases* 1993;**167**(2):305–11.

Keitel 1993b ***{published data only}***
Keitel WA, Couch RB, Quarles JM, Cate TR, Baxter B, Maassab HF. Trivalent attenuated cold-adapted influenza virus vaccine: reduced viral shedding and serum antibody

responses in susceptible adults. *Journal of Infectious Diseases* 1993;**167**(2):305–11.

Keitel 1997a *{published data only}*
Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine* 1997;**15**(10):1114–22.

Keitel 1997b *{published data only}*
Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine* 1997;**15**(10):1114–22.

Keitel 1997c *{published data only}*
Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine* 1997;**15**(10):1114–22.

Langley 2005 *{published data only}*
Langley JM, Halperin SA, McNeil S, Smith B, Jones T, Burt D, et al.Safety and immunogenicity of a Proteosometrade mark-trivalent inactivated influenza vaccine, given nasally to healthy adults. *Vaccine* 2005;**24**(10):1601–8.

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

Lauteria 1974 *{published data only}*
Lauteria SF, Kantzler GB, High PC, Lee JD, Waldman RH. An attenuated influenza virus vaccine: Reactogenicity, transmissibility, immunogenicity, and protective efficacy. *Journal of Infectious Diseases* 1974;**130**(4):380–3.

Leibovitz 1971 *{published data only}*
Leibovitz A, Coultrip RL, Kilbourne ED, Legters LJ, Smith CD, Chin J, et al.Correlated studies of a recombinant influenza-virus vaccine. IV. Protection against naturally occurring influenza in military trainees. *Journal of Infectious Diseases* 1971;**124**(5):481–7.

Mastrangelo 2000 *{published data only}*
Mastrangelo G, Rossi CR, Pfahlberg A, Marzia V, Barba A, Baldo M, et al.Is there a relationship between influenza vaccinations and risk of melanoma? A population-based case-control study. *European Journal of Epidemiology* 2000; **16**(9):777–82.

Mesa Duque 2001 *{published data only}*
Mesa-Duque SS, Moreno AP, Hurtado G, Arbelàaz Montoya MP. Effectiveness of an Influenza Vaccine in a working population in Colombia [Effectividad de una vacuna anti gripal en una poblaciòn laboral colombiana]. *Pan American Journal of Public Health* 2001;**10**(4):232–9.

Miller 1977 *{published data only}*
Miller LW, Togo Y, Hornick RB. Clinical and serologic effects of live attenuated serum inhibitor-resistant influenza B vaccine in seronegative adults. *Journal of Medical Virology* 1977;**1**(3):193–9.

Mixéu 2002 *{published data only}*
Mixèu MA, Vespa GN, Forleo-Neto E, Toniolo-Neto J, Alves PM. Impact of influenza vaccination on civilian aircrew illness and absenteeism. *Aviation, Space, and Environmental Medicine* 2002;**73**(9):876–80.

Mogabgab 1970a *{published data only}*
Mogabgab WJ, Leiderman E. Immunogenicity of 1967 polyvalent and 1968 Hong Kong influenza vaccines. *JAMA* 1970;**211**(10):1672–6.

Mogabgab 1970b *{published data only}*
Mogabgab WJ, Leiderman E. Immunogenicity of 1967 polyvalent and 1968 Hong Kong influenza vaccines. *JAMA* 1970;**211**(10):1672–6.

Monto 1982 *{published data only}*
Monto AS, DeWolfe Miller F, Maassab HF. Evaluation of an attenuated, cold recombinant influenza B virus vaccine. *Journal of Infectious Diseases* 1982;**145**(1):57–64.

Mutsch 2004 *{published data only}*
Mutsch M, Zhou W, Rhodes P, Bopp M, Chen RT, Linder T, et al.Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *New England Jouranl of Medicine* 2004;**350**(9):896–903.

Nichol 1995 *{published data only}*
Nichol KL, Lind A, Margolis KL, et al.The effectiveness of vaccination against influenza in healthy, working adults. *New England Journal of Medicine* 1995;**333**(14):889–93.

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

Payne 2006 *{published data only}*
Payne DC, Rose CE Jr, Kerrison J, Aranas A, Duderstadt S, McNeil MM. Anthrax vaccination and risk of optic neuritis in the United States military, 1998-2003. *Archives of Neurology* 2006;**63**(6):871–5.

Phyroenen 1981 *{published data only}*
Pyrhonen S, Suni J, Romo M. Clinical trial of a subunit influenza vaccine. *Scandinavian Journal of Infectious Diseases* 1981;**13**:95–9.

Powers 1995a *{published data only}*
Powers DC, Smith GE, Anderson EL, et al.Influenza A virus vaccine containing purified recombinant H3 hemagglutinin are well tolerated and induce protective immune responses in healthy adults. *Journal of Infectious Diseases* 1995;**171**: 1595–9.

Powers 1995b *{published data only}*
Powers DC, Smith GE, Anderson EL, et al.Influenza A virus vaccine containing purified recombinant H3 hemagglutinin are well tolerated and induce protective immune responses in healthy adults. *Journal of Infectious Diseases* 1995;**171**: 1595–9.

Powers 1995c *{published data only}*
Powers DC, Smith GE, Anderson EL, et al.Influenza A virus vaccine containing purified recombinant H3 hemagglutinin

are well tolerated and induce protective immune responses in healthy adults. *Journal of Infectious Diseases* 1995;**171**: 1595–9.

Reeve 1982 ***{published data only}***
Reeve P, Pibermann M, Bachmayer H, Liehl E, Moritz A, Ganzinger U, et al.Studies in man with a cold-recombinant live influenza B virus vaccine. *Journal of Medical Virology* 1982;**9**(1):1–9.

Rocchi 1979a ***{published data only}***
Rocchi G, Ragona G, Piga C, Pelosio A, Volpi A, Vella S, et al.Influenza vaccination with live-attenuated and inactivated virus-vaccines during an outbreak of disease. *Journal of Hygiene* 1979;**83**(3):383–90.

Rocchi 1979b ***{published data only}***
Rocchi G, Ragona G, Piga C, Pelosio A, Volpi A, Vella S, et al.Influenza vaccination with live-attenuated and inactivated virus-vaccines during an outbreak of disease. *Journal of Hygiene* 1979;**83**(3):383–90.

Rytel 1977 ***{published data only}***
Rytel MW, Jakson LJ, Niebojewski RA, et al.Field trial of live attenuated influenza A/B ("Alice"/R-75) vaccine. *American Journal of Epidemiology* 1977;**105**(1):49–55.

Saxen 1999 ***{published data only}***
Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. *Pediatric Infectious Disease Journal* 1999;**18**(9):779–83.

Scheifele 2003 ***{published data only}***
Scheifele DW, Duval B, Russell ML, Warrington R, DeSerres G, Skowronski DM, et al.Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. *Clinical Infectious Diseases* 2003;**36**(7):850–7.

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

Siscovick 2000 ***{published data only}***
Siscovick DS, Raghunathan TE, Lin D, Weinmann S, Arbogast P, Lemaitre RN, et al.Influenza vaccination and the risk of primary cardiac arrest. *American Journal of Epidemiology* 2000;**152**(7):674–7.

Spencer 1977 ***{published data only}***
Spencer MJ, Cherry JD, Powell KR. Clinical trial with "R-75" strain live, attenuated, serum inhibitor-resistant intranasal influenza B vaccine. *Journal of Clinical Microbiology* 1977;**5**(6):584–7.

Sumarokow 1971 ***{published data only}***
Sumarokow AA, Popov VF, Nefedova LA, et al.A study of live influenza vaccines in a controlled trial. *Zhumal Mikrobiologii Epidemiologii Immunobiologii* 1971;**48**(2): 46–52.

Tannock 1984 ***{published data only}***
Tannock GA, Bryce DA, Hensley MJ, et al.Responses to one or two doses of a deoxycholate subunit influenza vaccine in a primed population. *Vaccine* 1984;**2**:100–5.

Waldman 1969a ***{published data only}***
Waldman RH, Bond JO, Levitt LP, et al.An evaluation of influenza Immunization. *Bulletin of the World Health Organization* 1969;**41**:543–8.

Waldman 1969b ***{published data only}***
Waldman RH, Bond JO, Levitt LP, et al.An evaluation of influenza Immunization. *Bulletin of the World Health Organization* 1969;**41**:543–8.

Waldman 1969c ***{published data only}***
Waldman RH, Bond JO, Levitt LP, et al.An evaluation of influenza Immunization. *Bulletin of the World Health Organization* 1969;**41**:543–8.

Waldman 1969d ***{published data only}***
Waldman RH, Bond JO, Levitt LP, et al.An evaluation of influenza Immunization. *Bulletin of the World Health Organization* 1969;**41**:543–8.

Waldman 1972a ***{published data only}***
Waldman RH, Coggins WJ. Influenza immunization: field trial on a university campus. *Journal of Infectious Diseases* 1972;**126**(3):242–8.

Waldman 1972b ***{published data only}***
Waldman RH, Coggins WJ. Influenza immunization: field trial on a university campus. *Journal of Infectious Diseases* 1972;**126**(3):242–8.

Waldman 1972c ***{published data only}***
Waldman RH, Coggins WJ. Influenza immunization: field trial on a university campus. *Journal of Infectious Diseases* 1972;**126**(3):242–8.

Waldman 1972d ***{published data only}***
Waldman RH, Coggins WJ. Influenza immunization: field trial on a university campus. *Journal of Infectious Diseases* 1972;**126**(3):242–8.

Weingarten 1988 ***{published data only}***
Weingarten S, Staniloff H, Ault M, et al.Do hospital employees benefit from the influenza vaccine?. *Journal of General Internal Medicine* 1988;**3**:32–7.

Zhilova 1986a ***{published data only}***
Zhilova GP, Ignat'eva GS, Orlov VA, Malikova EV, Maksakova VL. Results of a study of the effectiveness of simultaneous immunization against influenza with live and inactivated vaccines (1980 - 1983). *Voprosy Virusologii* 1986;**31**(1):40–4.

Zhilova 1986b ***{published data only}***
Zhilova GP, Ignat'eva GS, Orlov VA, Malikova EV, Maksakova VL. Results of a study of the effectiveness of simultaneous immunization against influenza with live and inactivated vaccines (1980 - 1983). *Voprosy Virusologii* 1986;**31**(1):40–4.

References to studies excluded from this review

Ambrosch 1976 *{published data only}*
Ambrosch F, Balluch H. Studies of the non-specific clinical effectiveness of influenza vaccination. *Laryngologie, Rhinologie, Otologie Laryngologie, Rhinologie, Otologie* 1976; **55**:57–61.

Aoki 1986 *{published data only}*
Aoki FY, Sitar DS, Milley EV, 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.

Atmar 1995 *{published data only}*
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.

Ausseil 1999 *{published data only}*
Ausseil F. Immunization against influenza among working adults: The Philippines experience. *Vaccine* 1999;**17**(Suppl 1):59–62.

Banzhoff 2001 *{published data only}*
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.

Belongia 2009 *{published data only}*
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.

Belshe 2001 *{published data only}*
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.

Benke 2004 *{published data only}*
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.

Betts 1977b *{published data only}*
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.

Beyer 1996 *{published data only}*
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.

Carlson 1979 *{published data only}*
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.

Cate 1977 *{published data only}*
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.

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

Chou 2007 *{published data only}*
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.

Clover 1991 *{published data only}*
Clover RD, Crawford S, Glezen WP, et al.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**: 300–4.

Confavreux 2001 *{published data only}*
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.

Das Gupta 2002 *{published data only}*
Das Gupta R, Guest JF. A model to estimate the cost benefit of an occupational vaccination programme for influenza with Influvac in the UK. *Pharmacoeconomics* 2002;**20**(7): 475–84.

Davies 1972 *{published data only}*
Davies JE, Howell RW, Meichen FW. A clinical trial of inhaled inactivated influenza vaccine. *British Journal of Clinical Practice* 1972;**26**(10):469–71.

Davies 1973 *{published data only}*
Davies JE, Howell RH, Meichen FW. A clinical trial of inhaled inactivated influenza vaccine. *British Journal of General Practice* 1970;**27**(6):219–21.

De Serres 2003a *{published data only}*
De Serres GI, Boulianne N, Duval B, Rochette L, Grenier JL, Roussel R, et al.Oculo-respiratory syndrome following influenza vaccination: evidence for occurrence with more than one influenza vaccine. *Vaccine* 2003;**21**(19-20): 2346–53.

De Serres 2003b *{published data only}*
De Serres GI, Grenier JL, Toth E, Menard S, Roussel R, Tremblay M, et al.The clinical spectrum of the oculo-respiratory syndrome after influenza vaccination. *Vaccine* 2003;**21**(19-20):2354–61.

De Serres 2004 *{published data only}*
De Serres G, Skowronski DM, Guay M, Rochette L, Jacobsen K, Fuller T, et al.Recurrence risk of

oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons. *Archives of Internal Medicine* 2004;**164**(20):2266–72.

Dolin 1977 ***{published data only}***
Dolin R, Wise TG, Mazur MH, Tuazon CU, Ennis FA. Immunogenicity and reactogenicity of influenza A/New Jersey/76 virus vaccines in normal adults. *Journal of Infectious Diseases* 1977;**136**(Suppl):435–42.

Edmonson 1970 ***{published data only}***
Edmonson KW, Graham SM, Warburton MF. A clinical trial of influenza vaccine in Canberra. *Medical Journal of Australia* 1970;**4**:6–13.

El'shina 1998 ***{published data only}***
El'shina GA, Gorbunov MA, Shervarli VI, Lonskaia NI, Pavlova LI, Khaitov RM, et al.Evaluation of the effectiveness of influenza trivalent polymer subunit vaccine "Grippol". *Zhumal Mikrobiologii Epidemiologii Immunobiologii* 1998;**3**: 40–3.

Finklea 1969 ***{published data only}***
Finklea JF, Sandifer SH, Peck FB, et al.A clinical and serologic comparison of standard and purified bivalent inactivated influenza vaccines. *Journal of Infectious Diseases* 1969;**120**(6):708–12.

Foy 1981 ***{published data only}***
Foy HM, Cooney MK, Allan ID, Frost F, Blumhagen JM, Fox JP. Influenza B virus vaccines in children and adults: adverse reactions, immune response, and observations in the field. *Journal of Infectious Diseases* 1981;**143**(5):700–6.

Frank 1981 ***{published data only}***
Frank AL, Webster RG, Glezen WP, Cate TR. Immunogenicity of influenza A/USSR (H1N1) subunit vaccine in unprimed young adults. *Journal of Medical Virology* 1981;**7**(2):135–42.

Freestone 1976 ***{published data only}***
Freestone DS. Clinical trials with intranasally administered WRL 105 strain live influenza vaccine in volunteers. *Developments in Biological Standardization* 1976;**33**:207–12.

Gerstoft 2001 ***{published data only}***
Gerstoft J. Influenza vaccination of healthy adults. *Ugeskrift for Laeger* 2001;**163**(19):2615–7.

Greenbaum 2002 ***{published data only}***
Greenbaum E, Furst A, Kiderman A, Stewart B, Levy R, Schlesinger M, et al.Mucosal [SIgA] and serum [IgG] immunologic responses in the community after a single intra-nasal immunization with a new inactivated trivalent influenza vaccine. *Vaccine* 2002;**20**(7-8):1232–9.

Gross 1999 ***{published data only}***
Gross PA, Sperber SJ, Donabedian A, Dran S, Morchel G, Cataruozolo P, et al.Paradoxical response to a novel influenza virus vaccine strain: the effect of prior immunization. *Vaccine* 1999;**17**(18):2284–9.

Grotto 1998 ***{published data only}***
Grotto I, Mandel Y, Green MS, Varsano N, Gdalevich M, Ashkenazi I, et al.Influenza vaccine efficacy in young, healthy adults. *Clinical Infectious Diseases* 1998;**26**(4): 913–7.

Gruber 1994 ***{published data only}***
Gruber WC, Campbell PW, Thompson MJ, et al.Comparison of live attenuated and inactivated influenza vaccines in Cystic Fibrosis Patients and their families: results of a 3-years study. *Journal of Infectious Diseases* 1994;**169**: 241–7.

Haber 2004 ***{published data only}***
Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E, et al.Guillain-Barre syndrome following influenza vaccination. *JAMA* 2004;**292**(20):2478–81.

Haigh 1973 ***{published data only}***
Haigh W, Howell RW, Meichen FW. A comparative trial of influenza immunization by inhalation and hypojet method. *The Practitioner* 1973;**211**:365–70.

Halperin 2002 ***{published data only}***
Halperin SA, Smith B, Mabrouk T, Germain M, Trepanier P, Hassell T, et al.Safety and immunogenicity of a trivalent, inactivated, mammalian cell culture-derived influenza vaccine in healthy adults, seniors, and children. *Vaccine* 2002;**20**(7-8):1240–7.

Hobson 1970 ***{published data only}***
Hobson D, Baker FA, Chivers CP, et al.A comparison of monovalent Hong Kong influenza virus vaccine with vaccines containing only pre-1968 Asian strains in adult volunteers. *Journal of Hygiene* 1970;**68**:369–78.

Hobson 1973 ***{published data only}***
Hobson D, Baker FA, Curry RL, et al.The efficacy of live and inactivated vaccines of Hong Kong influenza virus in an industrial community. *Journal of Hygiene* 1973;**71**:641–7.

Hoskins 1973 ***{published data only}***
Hoskins TW, Davies JR, Allchin A, et al.Controlled trial of inactivated influenza vaccine containing the A/Hong Kong strain during an outbreak of influenza due to the A/ England/42/72 strain. *Lancet* 1973;**July 21**:116–20.

Hoskins 1976a ***{published data only}***
Hoskins TW, Davies JR, Smith AJ, et al.Influenza at Christ's Hospital: March, 1974. *Lancet* 1976;**January 17**:105–8.

Hoskins 1976b ***{published data only}***
Hoskins TW, Davies JR, Smith AJ, et al.Influenza at Christ's Hospital: March, 1974. *Lancet* 1976;**January 17**:105–8.

Hoskins 1979 ***{published data only}***
Hoskins TW, Davies JR, Smith AJ, et al.Assessment of inactivated influenza A vaccine after three outbreaks of influenza A at Christ's Hospital. *Lancet* 1979;**January 6**: 33–5.

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

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

Jianping 1999 *{published data only}*
Jianping H, Xin F, Changshun L, Bo Z, Linxiu G, Wei X, et al.Assessment of effectiveness of Vaxigrip. *Vaccine* 1999;**17** (Suppl 1):57–8.

Keitel 2001 *{published data only}*
Keitel WA, Cate TR, Nino D, Huggins LL, Six HR, Quarles JM, et al.Immunization against influenza: comparison of various topical and parenteral regimens containing inactivated and/or live attenuated vaccines in healthy adults. *Journal of Infectious Diseases* 2001;**183**(2):329–32.

Khazeni 2009 *{published data only}*
Khazeni N, Hutton D, Garber A, Hupert N, Owens D. Effectiveness and cost-effectiveness of vaccination against pandemic influenza (H1N1) 2009. *Annals of Internnal Medicine* 2009;**151**:829–39.

Kiderman 2001 *{published data only}*
Kiderman A, Furst A, Stewart B, Greenbaum E, Morag A, Zakay-Rones Z. A double-blind trial of a new inactivated, trivalent, intra-nasal anti-influenza vaccine in general practice: relationship between immunogenicity and respiratory morbidity over the winter of 1997-98. *Journal of Clinical Virology* 2001;**20**(3):155–61.

Kunz 1977 *{published data only}*
Kunz C, Hofmann H, Bachmayer H, Liehl E, Moritz AJ. Clinical trials with a new influenza subunit vaccine in adults and children. *Developments in Biological Standardization* 1977;**39**:297–302.

Langley 2004 *{published data only}*
Langley JM, Faughnan ME. Prevention of influenza in the general population. *CMAJ* 2004;**171**(10):1213–22.

Liem 1973 *{published data only}*
Liem KS, Marcus EA, Jacobs J, et al.The protective effect of intranasal immunization with inactivated influenza virus vaccine. *Postgraduate Medical Journal* 1973;**49**:175–9.

Mackenzie 1975 *{published data only}*
Mackenzie JS, Mackenzie I, Lloyd J, Dent V. Comparative trials of live attenuated and detergent split influenza virus vaccines. *Journal of Hygiene* 1975;**75**(3):425–43.

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

Maynard 1968 *{published data only}*
Maynard JE, Dull HB, Hanson ML, et al.Evaluation of monovalent and polyvalent influenza vaccines during an epidemic of type A2 and B influenza. *American Journal of Epidemiology* 1968;**87**(1):148–57.

McCarthy 2004 *{published data only}*
McCarthy MW, Kockler DR. Trivalent intranasal influenza vaccine, live. *Annals of Pharmacotherapy* 2004 Dec;**38**(12): 2086–93.

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

Merelli 2000 *{published data only}*
Merelli E, Casoni F. Prognostic factors in multiple sclerosis: role of intercurrent infections and vaccinations against influenza and hepatitis B. *Neurological Sciences* 2000;**21**(4 Suppl 2):853–6.

Meyers 2003a *{published data only}*
Meyers DG. Could influenza vaccination prevent myocardial infarction, stroke and sudden cardiac death?. *American Journal of Cardiovascular Drugs* 2003;**3**(4):241–4.

Meyers 2003b *{published data only}*
Meyers DG. Myocardial infarction, stroke, and sudden cardiac death may be prevented by influenza vaccination. *Current Atherosclerosis Reports* 2003;**5**(2):146–9.

Monto 2000 *{published data only}*
Monto AS. Preventing influenza in healthy adults: the evolving story. *JAMA* 2000;**284**(13):1699–701.

Morris 1975 *{published data only}*
Morris CA, Freestone DS, Stealey VM, Oliver PR. Recombinant WRL 105 strain live attenuated influenza vaccine. Immunogenicity, reactivity, and transmissibility. *Lancet* 1975;**2**(7927):196–9.

Mostow 1977 *{published data only}*
Mostow SR, Eichkoff TC, Chelgren GA, et al.Studies of inactivated influenza virus vaccines in hospital employees: reactogenicity and absenteeism. *Journal of Infectious Diseases* 1977;**136**:533–8.

Muennig 2001 *{published data only}*
Muennig PA, Khan K. Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults. *Clinical Infectious Diseases* 2001;**33**(11):1879–85.

Nichol 1996 *{published data only}*
Nichol KL, Margolis KL, Lind A, et al.Side effects associated with influenza vaccination in healthy working adults. *Archives of Internal Medicine* 1996;**156**:1546–50.

Nichol 1999b *{published data only}*
Nichol KL. Clinical effectiveness and cost effectiveness of influenza vaccination among healthy working adults. *Vaccine* 1999;**17**(Suppl 1):67–73.

Nichol 2001 *{published data only}*
Nichol KL. Live attenuated influenza virus vaccines: new options for the prevention of influenza. *Vaccine* 2001;**19** (31):4373–7.

Nichol 2003 *{published data only}*
Nichol KL, Mallon KP, Mendelman PM. Cost benefit of influenza vaccination in healthy, working adults: an economic analysis based on the results of a clinical trial of trivalent live attenuated influenza virus vaccine. *Vaccine* 2003;**21**(17-18):2207–17.

Nichol 2004 *{published data only}*
Nichol KL, Mendelman P. Influence of clinical case definitions with differing levels of sensitivity and specificity on estimates of the relative and absolute health benefits of

influenza vaccination among healthy working adults and implications for economic analyses. *Virus Research* 2004; **103**(1-2):3–8.

Pyhala 2001 *{published data only}*
Pyhala R, Haanpaa M, Kleemola M, Tervahauta R, Visakorpi R, Kinnunen L. Acceptable protective efficacy of influenza vaccination in young military conscripts under circumstances of incomplete antigenic and genetic match. *Vaccine* 2001;**19**(23-24):3253–60.

Rimmelzwaan 2000 *{published data only}*
Rimmelzwaan GF, Nieuwkoop N, Brandenburg A, Sutter G, Beyer WE, Maher D, et al.A randomized, double blind study in young healthy adults comparing cell mediated and humoral immune responses induced by influenza ISCOM vaccines and conventional vaccines. *Vaccine* 2000;**19**(9-10): 1180–7.

Rocchi 1979c *{published data only}*
Rocchi G, Carlizza L, Andreoni M, Ragona G, Piga C, Pelosio A, et al.Protection from natural infection after live influenza virus immunization in an open population. *Journal of Hygiene* 1979;**82**(2):231–6.

Ruben 1972 *{published data only}*
Ruben FL, Jackson GG. A new subunit influenza vaccine: acceptability compared with standard vaccines and effect of dose on antigenicity. *Journal of Infectious Diseases* 1972;**125** (6):656–64.

Ruben 1973 *{published data only}*
Ruben FL, Akers LW, Stanley ED, et al.Protection with split and whole virus vaccines against influenza. *Archives of Internal Medicine* 1973;**132**:568–71.

Safranek 1991 *{published data only}*
Safranek TJ, Lawrence DN, Kurland LT, Culver DH, Wiederholt WC, Hayner NS, et al.Reassessment of the association between Guillain-Barre syndrome and receipt of swine influenza vaccine in 1976-1977: results of a two-state study. Expert Neurology Group. *American Journal of Epidemiology* 1991;**133**(9):940–51.

Sarateanu 1980 *{published data only}*
Sarateanu DE, Ehrengut W, Pressler K, Peukert M, Schenk KD. Serological response to whole, split and subunit influenza vaccines of persons with and without immunological experience towards influenza A/U.S.S.R. 90/77 virus. *Comparative Immunology, Microbiology and Infectious Diseases* 1980;**3**(1-2):225–36.

Schonberger 1981 *{published data only}*
Schonberger LB, Hurwitz ES, Katona P, Holman RC, Bregman DJ. Guillain-Barre syndrome: its epidemiology and associations with influenza vaccination. *Annals of Neurology* 1981;**9 Suppl**:31–8.

Schwartz 1996 *{published data only}*
Schwartz K. Influenza vaccine for healthy adults. *Journal of Family Practice* 1996;**42**(4):351–2.

Skowronski 2002 *{published data only}*
Skowronski DM, Strauss B, Kendall P, Duval B, De Serres G. Low risk of recurrence of oculorespiratory syndrome following influenza revaccination. *CMAJ* 2002;**167**(8): 853–8.

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

Smith 1977a *{published data only}*
Smith AJ, Davies JR. The response to inactivated influenza A (H3N2) vaccines: the development and effect of antibodies to the surface antigens. *Journal of Hygiene* 1977; **78**:363–75.

Smith 1977b *{published data only}*
Smith CD, Leighton HA, Shiromoto RS. Antigenicity and reactivity of influenza A/New Jersey/8/76 virus vaccines in military volunteers at Fort Ord, California. *Journal of Infectious Diseases* 1977;**136**(Suppl):460–5.

Spencer 1975 *{published data only}*
Spencer MJ, Cherry JD, Powell KR, et al.Clinical trials with Alice strain, live attenuated, serum inhibitor-resistant intranasal influenza A vaccine. *Journal of Infectious Diseases* 1975;**132**(4):415–20.

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

Taylor 1969 *{published data only}*
Taylor PJ, Miller CL, Pollock TM, et al.Antibody response and reactions to aqueous influenza vaccine, simple emulsion vaccine and multiple emulsion vaccine. A report to the Medical Research Council Committee on influenza and other respiratory virus vaccines. *Journal of Hygiene* 1969;**67**: 485–90.

Treanor 2001 *{published data only}*
Treanor JJ, Wilkinson BE, Masseoud F, Hu-Primmer J, Battaglia R, O'Brien D, et al.Safety and immunogenicity of a recombinant hemagglutinin vaccine for H5 influenza in humans. *Vaccine* 2001;**19**(13-14):1732–7.

Treanor 2002 *{published data only}*
Treanor J, Keitel W, Belshe R, Campbell J, Schiff G, Zangwill K, et al.Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. *Vaccine* 2002;**20**(7-8):1099–105.

Tyrrell 1970 *{published data only}*
Tyrrell DA, Buckland R, Rubenstein D, Sharpe DM. Vaccination against Hong Kong influenza in Britain, 1968-9. A report to the Medical Research Council Committee on Influenza and other Respiratory Virus Vaccines. *Journal of Hygiene* 1970 Sep;**68**(3):359–68.

Warshauer 1976 *{published data only}*
Warshauer DM, Minor TE, Inhorn SL, et al.Use of an inhibitor-resistant live attenuated influenza vaccine in

normal and asthmatic adults. 14th Congress of the International Association of Biological Standardization, Douglas, Isle of Man 1975. *Developments in Biological Standardization* 1975;**33**:184–90.

Wilde 1999 ***{published data only}***
Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals. *JAMA* 1999;**281**(10):908–13.

Williams 1973 ***{published data only}***
Williams MC, Davignon L, McDonald JC, et al.Trial of aqueous killed influenza vaccine in Canada, 1968-69. *WHO Bull* 1973;**49**:333–40.

Wood 1999 ***{published data only}***
Wood SC, Alexseiv A, Nguyen VH. Effectiveness and economical impact of vaccination against influenza among a working population in Moscow. *Vaccine* 1999;**17**(Suppl 3):81–7.

Wood 2000 ***{published data only}***
Wood SC, Nguyen VH, Schmidt C. Economic evaluations of influenza vaccination in healthy working-age adults. Employer and society perspective. *Pharmacoeconomics* 2000;**18**(2):173–83.

Additional references

ACIP 2006
Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Recommendations and Reports: Morbidity and Mortality Weekly Report* 2006;**55**:1–41.

ACIP 2009
Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Recommendations and Reports: Morbidity and Mortality Weekly Report* 2009;**58** (RR-8):2.

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

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

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

Higgins 2009
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. Available from www.cochrane-handbook.org 2009.

Jefferson 2009a
Jefferson T, Di Pietrantonj C, Debalini MG, Rivetti A, Demicheli V. Relation of study quality, concordance, take home message, funding, and impact in studies of influenza vaccines: systematic review. *BMJ* 2009;**338**:b354. [DOI: 10.1136/bmj.b354]

Jefferson 2009b
Jefferson TO. Mistaken identity: seasonal influenza versus influenza-like illness. *Clinical Evidence* 2009;**329**:1–4.

Jefferson 2009c
Jefferson T, Di Pietrantonj C, Debalini MG, Rivetti A, Demicheli V. Inactivated influenza vaccines: methods, policies, and politics. *Journal of Clinical Epidemiology* 2009; **62**(7):677–86.

Wells 2004
Wells GA, Shea B, O'Connell D, et al.The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxfordweb.ppt 2004.

Wiselka 1994
Wiselka M. Influenza: diagnosis, management and prophylaxis. *BMJ* 1994;**308**:1341–5.

References to other published versions of this review

Demicheli 1999
Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD001269.pub3]

Demicheli 2001
Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD001269.pub3]

Demicheli 2004
Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD001269.pub3]

Jefferson 2007
Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD001269.pub3]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Atmar 1990

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

Risk of bias

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

Beran 2009a

Methods	Randomised double blind, placebo controlled study conducted in Czech Republic during the 2005 to 2006 influenza season. This was defined retrospectively as starting the first week with two culture-confirmed cases in the study area and ending the last week with one culture-confirmed case in the study area. Randomisation was generated by GSK (sponsor) using SAS program, in 2:1 blocking scheme using a minimisation procedure (no explanation of why to use such method or ratio). Allocation concealment method was not explicitly mentioned. However, authors mentioned that placebo and vaccine treatments were indistinguishable in appearance and that blinding to treatment assignment was maintained until study analysis
Participants	Self-referred healthy adults (n = 6203), predominately Caucasian (99.8%), aged between 18 and 64 years (mean 35 + 13 years) of both genders (TIV group: F 55.3%, placebo group: F 54.2%) and with no history of influenza vaccination within the last 3 influenza seasons.

	A subset of participants who were randomly selected for vaccine safety and reactogenicity were given a calibrated thermometer and a diary card to record symptoms. The method of selection of this subset was not explained. Use of antimicrobial/influenza antiviral therapy seem to be allowed but was not quantified
Interventions	TIV vaccine: 0.5 ml single dose by IM injection or placebo (normal saline) administered intramuscularly. Use of more than one lot was not reported TIV contain hemagglutinin 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. Two modes of surveillance were used. Passive: started on the day of vaccination, participants self report through a toll free number of ILI symptoms Active: started 2 weeks after vaccination day: a biweekly telephone contact of the subjects by someone (not clear who) for ILI symptoms It is not clear if the surveillance included the entire cohort or just a subset, or why the authors did carry out harms surveillance using the 2 surveillance methods already in-place
Outcomes	Serological Blood samples were collected for the specified subset and were tested/analyzed 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 Hemagglutination-inhibition test was done using chicken red blood cells with the three 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 hemagglutination Serology was not a primary outcome in this study Effectiveness **Incidence of culture-confirmed ILI (primary outcome, reported as the attack rate in the efficacy cohort)** **Nasal and throat swab collected by a nurse on the same day** swab samples were stored at 28°C and transferred within 5 days of the onset of ILI symptoms Sample sent to the National Reference Laboratory for Influenza (NRL, Prague, Czech Republic) for conventional influenza virus culture using Madin Darby Canine Kidney (MDCK) cells Confirmation of influenza A or B was determined using the following: • hemagglutination assay with turkey and guinea pig erythrocytes • hemagglutination inhibition was used to identify virus type, subtype and drift variant • direct immunoperoxidase assay using anti-influenza A and anti-influenza B nucleoprotein antibodies There were 814 reported ILI episodes, only 46 gave positive culture **Clinical** **Incidence of ILI symptoms (secondary outcome, reported as attack rate in the ATP cohort)** IL was defined as fever (oral temperature greater or equal to 37.8°C) plus cough and/or sore throat. An ILI episode was defined as the period from the first day of ILI symptoms until the last day of ILI symptoms. A new episode was taken into account only after the

	complete resolution of the previous one. To count as a separate episode at least 7 days free of any symptoms should pass Number of events was 370 reported events (254 in TIV and 120 in placebo) Number of subjects reporting at least one event (240 in TIV and 113 in placebo) was used to calculate the attack rate Reasons to exclude from the ATP cohort include: • protocol violation (inclusion/exclusion criteria): seems that the selected subset have certain criteria but not mentioned by the authors • underlying medical condition: not specified what? Or why not excluded from the efficacy cohort as well since participants are reported to be healthy • forbidden by the protocol: protocol not clear • subjects not exposed during the influenza season: not understood what it meant (did the patient travel after getting the study treatment?) **Immunogenicity**: blood sample obtained prior to vaccination and at 21 days following vaccination. Performed only for a subset of patient not all efficacy cohort **Safety** Data on serious adverse events (SAEs) began at the receipt of vaccine/placebo and continued until the end of the study. However safety was solicited from a subset of subjects (no mention of method used to randomly select them, no justification for not collecting SAEs from all participants, especially with the presence of two surveillance methods) **Reactogenicity**: defined as the presence and intensity of the following symptoms within 4 days of vaccination: pain, redness and swelling (found to occur more in the TIV group) other general symptoms of fatigue, fever, headache, muscle aches, shivering and joint pain (found to occur more in the TIV group) The intensities of adverse events were recorded according to a standard 0 to 3 grade scale: "absent", "easily tolerated", "interferes with normal activity" and "prevents normal activity"
Notes	The authors report that due to the atypical nature of the influenza season during this study we were unable to assess TIV efficacy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	**Generation of allocation schedule** b) computer random-number generator **Concealment of treatment allocation** No explicit description of the method of concealment, authors only mentioned that treatments were numbered and that they were indistinguishable in appearance) **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)

Beran 2009a (*Continued*)

		for exclusion? yes, details were reported in the study flow chart. Of the 6213 enrolees, 10 were excluded because the identification number assigned to the same 4 subjects who were **Measures to implement double blinding** a) Did the report mention explicitly measures to implement and protect double blinding? No, authors reported that the blinding assignment was maintained until study analysis b) Did the author(s) report on the physical aspect of compound administration - (i.e. appearances, colour, route administration). Authors mentioned the treatments were indistinguishable in appearance Medium risk of bias. Basis for selection of follow up and allocation concealment not described

Beran 2009b

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

Beran 2009b (*Continued*)

	Who provided written informed consent
Interventions	**Intervention** 1 dose of TIV (lot 1 or lot 2 of Fluarix), IM injection, at the first day of the study (Day 0). Each 0.5 mL dose of TIV contained 15 mg of each of the hemagglutinin antigens of strains A/New/Caledonia/20/99(H1N1) IVR-116, A/Wisconsin/67/2005(H3N2), and B/Malaysia/2506/2004 (from the Victoria lineage) **Comparator** placebo (normal saline solution), IM injection, at the first day of the study (Day 0)
Outcomes	Serological (only carried out for the TIV group) Effectiveness Evaluate efficacy of TIV versus placebo in the prevention of culture-confirmed influenza A and/or B due to strains antigenically matched to the vaccine **(their primary objective)**. **Secondary objectives** • Evaluation of TIV in the prevention of culture-confirmed influenza due to strains antigenically matched to the vaccine for each of the 2 vaccine lots • Evaluation of TIV in the prevention of culture-confirmed Influenza A and/or B attributable to any influenza A or B strain • Evaluation of TIV in the prevention of ILI which was less-stringently- defined as at least 1 systemic symptom (fever and/or myalgia) and 1 respiratory symptom (cough and/or sore throat). Safety vaccine reactogenicity and immunogenicity in a random subset of subjects by obtaining blood samples prior to vaccination and 21-28 days later. However, no harms data are reported
Notes	The authors conclude that TIV is efficacious against culture-confirmed influenza in healthy adults

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No details provided of either randomisation or allocation concealment. There is no mention of appearance of the injection content Attrition reasons for the whole cohort are as follows • Administration of vaccines forbidden in the protocol • Administration of medication forbidden in the protocol • Underlying medical condition forbidden by the protocol • Subjects not exposed during the influenza season • Randomisation code broken at the investigation site • Protocol violation (inclusion/

		exclusion criteria) The additional stated reasons for the 'Safety' subset study: • Non compliance with blood sampling Essential serological data missing

Betts 1977a

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

Risk of bias

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

Boyce 2000

Methods	Open label/single blind randomised controlled trial to assess safety and immunogenicity of adjuvanted and unadjuvanted subunit influenza vaccine, prepared with the strains recommended for and isolated in the 1997 to 1998 season
Participants	74 healthy adults aged between 10 and 40 years, who did not receive influenza immunisation during the 6 months preceding the trial
Interventions	1) M-59 adjuvanted subunit trivalent flu vaccine (prepared with A/Bayern/795 H1N1, A/Wuhan/359/95 H3N2, B/Beijing/184/93 -like strains, each 15 mcg/ 0.5 ml-dose) 2) Unadjuvated vaccine (prepared with the same strains at the same concentrations as the adjuvanted preparation) 3) Placebo (consisting of 0.5 ml sterile saline)

Boyce 2000 (*Continued*)

	All preparation were intranasal administered in two doses 28 days apart. 24 individuals received their first dose of adjuvanted (n = 12) or unadjuvanted (n = 12) subunit vaccine in open label manner. After it was stated that they tolerated the first dose, the randomised phase of the trial (n = 50) was begun. In this phase 18 subjects received two doses of unadjuvanted vaccine, 19 adjuvanted and 13 placebo
Outcomes	After each immunisation, subjects were observed for 30 minutes, were examined after 2 days and then completed a diary card reporting symptoms occurred within 7 days after. Local reactions: nasal symptoms, unpleasant taste, bloody nasal discharge, sneezing. Systemic reactions: chills, pulmonary, nausea, malaise, myalgia or arthralgia, urticarial rash, headache, Oral temperature >= 38°C, stay at home, due to use of analgesic or antipyretic. Data were not given separately for randomised and open-label phase of the study
Notes	It is not possible to consider separately safety data for the two study phases. Safety data only were extracted

Risk of bias

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

Bridges 2000a

Methods	Randomised controlled trial, double blind conducted in USA during the 1997 to 1998 influenza season. Follow up lasted from November to March. Influenza period was defined as the period during which clinical specimens collected from ill subjects yielded influenza viruses: Dec 8 1997 through Mar 2, 1998 and lasted 12 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random number. Pharyngeal swab and paired sera were collected from ill people
Participants	1184 healthy factory employees: 595 treated and 589 placebo. Age of participants was 18 to 64
Interventions	Commercial trivalent, inactivated, intramuscular vaccine. Schedule and dose were not indicated. Vaccine composition was: A/Johannesburg/82/96, A/Nanchang/933/95 and B/Harbin/7/94. Placebo was sterile saline for injection. Vaccine was recommended but did not match circulating strain
Outcomes	Influenza-like illness, influenza, days ill, physician visits, times any drug was prescribed, times antibiotic was prescribed, working days lost, admissions, adverse effects. They were defined as follow: Influenza-like illness: fever = 37.7 °C with cough or sore throat); upper respiratory illness: cough with sore throat or fever = 37.7 °C. Local adverse effects were arm soreness and redness. Systemic adverse effect were: fever, sore throat, coryza, myalgia, headache and fatigue, but authors reported no data. Surveillance was passive
Notes	For analysis we chose the Influenza-like illness definition. ITT was performed. Systemic adverse effects were not reported. Circulating strain was A/Sidney/5/97-like

Bridges 2000a (*Continued*)

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

Bridges 2000b

Methods	Randomised controlled trial, double blind conducted in USA during 1998 to 1999 influenza season. Follow up lasted from November to March. The influenza period was defined as the period during which clinical specimens collected from ill subjects yielded influenza viruses: Jan 4, 1998 through Mar 14, 1999 and lasted 10 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random number. Pharyngeal swab and paired sera were collected from ill people
Participants	1191 healthy factory employees: 587 treated and 604 placebo. Age of participants was 19 to 64
Interventions	Commercial trivalent, inactivated, intramuscular vaccine. Schedule and dose were not indicated. Vaccine composition was: A/Beijing/262/95, A/Sydney/5/97 and B/Harbin/7/94. Placebo was sterile saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza, days ill, physician visits, times any drug was prescribed, times antibiotic was prescribed, working days lost, admissions, adverse effects. They were defined as follow: Influenza-like illness: fever = 37.7 °C with cough or sore throat); upper respiratory illness: cough with sore throat or fever = 37.7 °C. Local adverse effects were arm soreness and redness. Systemic adverse effect were: fever, sore throat, coryza, myalgia, headache and fatigue, but authors reported no data. Surveillance was passive
Notes	For analysis we chose the influenza-like illness definition. ITT was performed. Systemic adverse effects were not reported. Circulating strain was A/Sidney/5/97-like and B/Beijing/184/93-like

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

Caplan 1977

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

Risk of bias

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

DeStefano 2003

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

Risk of bias

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

Eddy 1970

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

Risk of bias

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

Edwards 1994a

Methods	Randomised controlled trial, double blind conducted in USA during 1986 to 1987 influenza season. Follow up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 8 weeks. Subjects were recruited from seven organisations and assigned to one of the study groups using a permuted block randomisation scheme that was stratified by treatment center and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1311 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 872 treated and 439 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live cold adapted, aerosol administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single dose; cold adapted 107-107,6 pfu/ml; inactivated 15 micrograms each strain. Vaccine composition was: cold adapted: Texas/1/85 H1N1 and Bethesda/1/85 H3N2; inactivated: Chile/1/83 H1N1 and Mississippi/1/85 H3N2 . Placebo was allantoic fluid. Vaccine was recommended but did not match circulating strain

Edwards 1994a (*Continued*)

Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least one of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (only patients who presented for culture were considered); throat culture. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold adapted and inactivated vaccines were antigenically comparable. Since cold adapted influenza B vaccines were not sufficiently characterised to include in the study, authors used monovalent inactivated influenza B vaccine in all subjects in cold adapted arm and as placebo in the control group of inactivated arm. Only cold adapted comparison was included in analysis. Circulating strain was Taiwan/1/86. Effectiveness data only were extracted

Risk of bias

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

Edwards 1994b

Methods	Randomised controlled trial, double blind conducted in USA during 1987 to 1988 influenza season. Follow up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 14 weeks. Subjects were recruited from seven organisations and assigned to one of the study groups using a permuted block randomisation scheme that was stratified by treatment center and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1561 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 1029 treated and 532 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live cold adapted, aerosol administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single dose; cold adapted 107-107.6 pfu/ml; inactivated 15 micrograms each strain. Vaccine composition was: cold adapted: Kawasaki/9/86 H1N1 and Bethesda/1/85 H3N2; inactivated: Taiwan/1/86 H1N1 and Leningrad/360/86 H3N2. Placebo was allantoic fluid. Vaccine was recommended but did not match circulating strain
Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least one of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (ILI retrospectively reported were considered); fourfold antibody rise between post-vaccination and spring sera. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold adapted and inactivated vaccines were antigenically

Edwards 1994b (*Continued*)

	comparable. Since cold adapted influenza B vaccines were not sufficiently characterised to include in the study, authors used monovalent inactivated influenza B vaccine in all subjects in cold adapted arm and as placebo in the control group of inactivated arm. Only cold adapted comparison was included in analysis. Circulating strain was Sichuan/2/87 (H3N2) (antigen drift from vaccine strain) and B/Victoria/2/87 Effectiveness data only were extracted

Risk of bias

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

Edwards 1994c

Methods	Randomised controlled trial, double blind conducted in USA during 1988 to 1989 influenza season. Follow up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 11 weeks. Subjects were recruited from seven organisations and assigned to one of the study groups using a permuted block randomisation scheme that was stratified by treatment center and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1676 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 1114 treated and 562 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live cold adapted, aerosol administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single dose; cold adapted 107-107,6 pfu/ml; inactivated 15 micrograms each strain. Vaccine composition was: cold adapted: Kawasaki/9/86 H1N1 and Los Angeles/2/87 H3N2; inactivated: Taiwan/1/86 H1N1 and Sichuan/2/87 H3N2. Placebo was allantoic fluid. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least one of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (ILI retrospectively reported were considered); fourfold antibody rise between postvaccination and spring sera. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold adapted and inactivated vaccines were antigenically comparable. Since cold adapted influenza B vaccines were not sufficiently characterised to include in the study, authors used monovalent inactivated influenza B vaccine in all subjects in cold adapted arm and as placebo in the control group of inactivated arm. Only cold adapted comparison was included in analysis. Circulating strain was Taiwan/1/86 (H1N1) and B/Yamata/16/88. Effectiveness data only were extracted

Risk of bias

Edwards 1994c (*Continued*)

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

Edwards 1994d

Methods	Randomised controlled trial, double blind conducted in USA during 1989 to 1990 influenza season. Follow up lasted the whole epidemic period. The epidemic period in any study year started on the day that the first influenza A virus isolate was obtained in Nashville and ended on the day that the last isolate was obtained and lasted 11 weeks. Subjects were recruited from seven organisations and assigned to one of the study groups using a permuted block randomisation scheme that was stratified by treatment center and age group. Sealed randomisation envelopes contained vaccine codes. Pharyngeal swab and paired sera were collected from ill people
Participants	1507 healthy children and adults of metropolitan Nashville. 85% of people were older than 16: 999 treated and 508 placebo. Age of participants was 1 to 65
Interventions	Bivalent, live cold adapted, aerosol administered influenza A vaccine and the commercial inactivated intramuscularly administered influenza vaccine. Schedule and dose were: single dose; cold adapted 107-107,6 pfu/ml; inactivated 15 micrograms each strain. Vaccine composition was: Kawasaki/9/86 H1N1 and Los Angeles/2/87 H3N2; inactivated: Taiwan/1/86 H1N1 and Shanghai/11/87 H3N2 . Placebo was allantoic fluid. Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, influenza. They were defined as follows: fever of abrupt onset with at least one of the following: chills, headache, malaise, myalgia, cough, pharyngitis or other respiratory complaints (ILI retrospectively reported were considered); fourfold antibody rise between postvaccination and spring sera. Surveillance was passive
Notes	Influenza B strain contained in the commercial and monovalent vaccines was not described. Strains used yearly to develop cold adapted and inactivated vaccines were antigenically comparable. Since cold adapted influenza B vaccines were not sufficiently characterised to include in the study, authors used monovalent inactivated influenza B vaccine in all subjects in cold adapted arm and as placebo in the control group of inactivated arm. Only cold adapted comparison was included in analysis. Circulating strain was Shanghai/11/87 (H3N2). Effectiveness data only were extracted

Risk of bias

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

El'shina 1996

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

Risk of bias

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

Evans 1976

Methods	Randomised controlled trial
Participants	162 healthy subjects aged 18 to 61 years
Interventions	Bivalent live attenuated vaccine WRL 105 (recombinant of A/Okuda/57 and A/Finland/4/74) containing 107.0 EID50 virus/ 0.5 ml dose vs. placebo. Both preparations were administered intranasally 3 to 4 weeks apart
Outcomes	Reactions to immunisation were observed for 7 days after each dose. Local symptoms (referable to the upper respiratory tract, mainly nasal obstruction, nasal discharge or sore throat) reported as mild moderate or severe. General symptoms (mainly headache fever or myalgia).These two are further reported in different intensity class (mild, moderate, severe, lasting for at least 4 days) reported as mild moderate or severe. Use of analgesics
Notes	Safety data only were extracted

Risk of bias

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

Forsyth 1967

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

Risk of bias

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

Goodeve 1983

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

Risk of bias

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

Goodeve 1983 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hammond 1978

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

Risk of bias

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

Hrabar 1977

Methods	Randomised controlled trial, double blind, carried out during the season 1976 to 1977
Participants	167 students at the technical school in Zagreb, former Republic of Yugoslavia, without sensitivity to egg proteins, pregnancy, acute or chronic diseases
Interventions	Cold-adapted recombinant A/Victoria/3/75 vaccine administered in 3 different antigen concentration (107.5, 106.5, 105.5 EID50 /0.5 ml) versus placebo. One 0.5 ml dose intranasal
Outcomes	Subjects were medically examined on each of the successive 5 days after immunisation (lasting for at least 1 day). Throat infection, granular palate, oedematous uvula, fever (no cases) as cases and subject-days. For the following outcomes, authors give the total number

Hrabar 1977 (*Continued*)

	of observed cases, without indication of the corresponding arm: malaise, swollen tonsils, fever (1), rhinorrhea (1), conjunctivitis (7), laryngitis or hoarseness (3), cough (1), swollen tonsils (1), malaise (1). Surveillance was active	
Notes	Safety data only were extracted	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kaplan 1982

Methods	Surveillance population-based study conducted in USA, during the 1979 to 1980 and 1980 to 1981 influenza season. The study tested the association between influenza vaccination and Guillan-Barrè Syndrome. Reports form for each case was obtained from neurologists. All case reports were included. Follow up period was 01/09/79 to 31/03/80 and 01/09/80 to 31/03/81	
Participants	USA (minus Maryland) adult population, 18 years or older	
Interventions	Seasonal parenteral vaccine	
Outcomes	Cases of Guillain-Barré syndrome. Vaccine associated cases were defined as those with onset within the eight-week period after influenza vaccination	
Notes	Vaccination rates in population were obtained from national immunisation survey Rare events (safety)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Keitel 1988a

Methods	Randomised controlled trial, double-blind conducted in USA during 1983 to 1984 influenza season. Follow up lasted the whole epidemic period. Influenza period was defined as the interval during which community surveillance recovered influenza viruses from 10% or more of persons with febrile respiratory illness per calendar week (from January 8 to March 17, 1984) and lasted 9 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time volunteers were asked to record any illness occurred during epidemic period and blood specimens were collected
Participants	598 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 300 treated and 298 placebo. Age of participants was 30 to 60
Interventions	Trivalent, killed whole, intramuscularly administered vaccine. Schedule and dose were: single dose; 15 micrograms of hemagglutinin of each influenza strains. Vaccine composition was: A/Philippines/2/82 (H3N2), A/Brazil/11/78 (H1N1) and B/Singapore/222/79. Placebo was sterile saline for injection. Vaccine was recommended but did not match circulating strain
Outcomes	Outcomes were: ILI, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 or higher). Laboratory confirmation was based on culture and/or four-fold or greater rise in antibody titre occurred between post-vaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera
Notes	Influenza-like illness and influenza were detected in three groups: first vaccinated, multi vaccinated and placebo. Febrile illnesses were included in analysis; first two groups cases were added up. Circulating strain was A/Victoria/7/83 (H1N1) and B/USSR/100/83. Efficacy data only were extracted

Risk of bias

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

Keitel 1988b

Methods	Randomised controlled trial, double-blind conducted in USA during 1984 to 1985 influenza season. Follow up lasted the whole epidemic period. Influenza period was defined as the interval during which community surveillance recovered influenza viruses from 10% or more of persons with febrile respiratory illness per calendar week (from January 6 to March 9, 1985) and lasted 9 weeks. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time volunteers were asked to record any illness occurred during epidemic period and blood specimens were collected
Participants	697 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 456 treated and 241 placebo. Age of participants was 30 to 60
Interventions	456 trivalent, killed whole, intramuscularly administered vaccine: 241 treated and 30 - 60 placebo. Age of participants was: healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies
Outcomes	Outcomes were: ILI, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 or higher). Laboratory confirmation was based on culture and/or four-fold or greater rise in antibody titre occurred between postvaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera. Surveillance was passive
Notes	Efficacy data only were extracted

Risk of bias

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

Keitel 1993a

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

Keitel 1993a (*Continued*)

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

Keitel 1993b

Methods	This paper reports about results of two randomised controlled trials carried out in the USA
Participants	Healthy volunteers recruited at Texas A&M University and Texas Medical Center , aged between 18 and 40 years
Interventions	A/Kawasaki/9/86 (H1N1, CR 125, but different lot from 1st) + A/Los Angeles/2/87 (H3N2, CR149) + B/Ann Arbor/1/86 (B, CRB117 but different lot from 1st)3) 1st : A/Kawasaki/9/86 (H1N1, CR125) + A/Bethesda/1/85 (H3N2, CR90)2nd : B/Ann Arbor/1/86 (B, CRB117)4) 1st : B/Ann Arbor/1/86 (B, CRB1172nd : A/Kawasaki/9/86 (H1N1, CR125) + A/Los Angeles/2/87 (H3N2, CR149)
Outcomes	Mild upper respiratory symptoms. Fever >= 37.8°C Within one week after each inoculation
Notes	See Keitel 1993 a. Safety data only were extracted

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

Keitel 1997a

Methods	Randomised controlled trial, double-blind conducted in USA during 1985 to 1986 influenza season. Follow up lasted the whole epidemic period. Influenza period was defined by viral surveillance. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers according to prior vaccination experience. Specimens for culture and acute-convalescent blood specimens were obtained from ill people. At spring time volunteers were asked to record any illness occurred during epidemic period and blood specimens were collected
Participants	830 healthy employees working in the Texas Medical Center in Houston, Texas, or in surrounding industrial companies: 577 treated and 253 placebo. Age of participants was 30 to 60
Interventions	Trivalent, killed whole, intramuscularly administered vaccine. Schedule and dose were: single dose; 15 micrograms of hemagglutinin of each influenza strains. Vaccine composition was: A/Philippines/2/82 (H3N2), A/Chile/1/83 (H1N1) and B/USSR/100/83. Placebo was sterile saline for injection. Vaccine was recommended but did not match circulating

Keitel 1997a (*Continued*)

	strain
Outcomes	Influenza-like illness, influenza. Illnesses were classified in "any", "flu-like" (lower respiratory and/or systemic illness) and "febrile" (oral temperature of 37.8 or higher). Laboratory confirmation was based on culture and/or four-fold or greater rise in antibody titre occurred between post-vaccination (pre-epidemic), acute, convalescent and/or spring (post-epidemic) sera. Surveillance was active
Notes	Influenza-like illness and influenza cases were detected in three groups: first vaccinated, multi vaccinated and placebo. Febrile illnesses were included in analysis; first two groups cases were added up. Circulating strains were B/Ann Arbor/1/86, A/Mississippi/1/85 Efficacy data only were extracted

Risk of bias

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

Keitel 1997b

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

Keitel 1997b (*Continued*)

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

Keitel 1997c

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

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

Langley 2005

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

Risk of bias

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

Lasky 1998

Methods	Surveillance population-based study conducted in USA (four states: Illinois, Maryland, North Carolina, Washington), during the 1992 to 1993 and 1993 to 1994 influenza season. Discharge diagnoses database were used to identify cases. Hospital charts were reviewed to confirm diagnosis. Follow up period was 01/09/92 to 28/02/93 and 01/09/93 to 28/02/94
Participants	Approximately 21 million people, 18 years or older
Interventions	Seasonal parenteral vaccine
Outcomes	Cases of Guillain-Barré syndrome. Vaccine associated cases were defined a priori as those with onset within the six-week period after influenza vaccination
Notes	Results were stratified by age and adjusted by season and sex. Vaccination rates in population were estimated from a random-digit dialling telephone survey. Rare events (safety)

Risk of bias

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

Lauteria 1974

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

Risk of bias

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

Leibovitz 1971

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

Leibovitz 1971 (*Continued*)

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

Mastrangelo 2000

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

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

Mesa Duque 2001

Methods	Randomised controlled trial, double-blind conducted in Columbia during 1997 influenza season. Follow up lasted from March, 15 to August, 31. Influenza period was not defined. Volunteers were randomly allocated to receive vaccine or placebo using a table of random numbers. Double-blind was ensured by pre-labelled, coded identical looking vials. Virologic surveillance was not performed
Participants	493 bank employees: 247 treated and 246 placebo. Age of participants was 18 to 60
Interventions	Sub-unit inactivated, intramuscularly administered vaccine. Schedule and dose were: single dose. Vaccine composition was: A/Wahan/359/95, A/Texas/36/91 and B/Beijing/184/93. Placebo was vitamin C. Vaccine was recommended and matched circulating strain

Mesa Duque 2001 (*Continued*)

Outcomes	Episodes of clinical illness, working days lost (wdl), and adverse effects. Clinical disease was defined as upper respiratory illness (fever, sore throat and cough lasting more than 24 hours) according to ICD IX codes 381, 382, 460, 466, 480 and from 487 to 490. Local adverse effects were oedema, erythema, pain, swelling. Systemic adverse effects were fever, headache and indisposition within 5 days by vaccination. Surveillance was passive
Notes	Circulating strains were not isolated from local cases but by WHO and Columbia surveillance system, and matched vaccine components. Wdl were detected all the year round, so they were not included in analysis. Efficacy and safety data were extracted

Risk of bias

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

Miller 1977

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

Risk of bias

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

Mixéu 2002

Methods	Randomised controlled trial, double-blind conducted in Brazil during 1997 influenza season. Follow up lasted 6 to 7 months. Influenza period was not defined. Authors did not describe the methods used to ensure randomisation and blinding. Virologic surveillance was not performed

Mixéu 2002 (*Continued*)

Participants	813 flight crews of an airline company: 405 vaccinated and 408 given placebo. Age of participants was 18 to 64
Interventions	Split trivalent, intramuscularly administered vaccine. Schedule and dose were: single dose. Vaccine composition was: A/Nanchang/933/95, A/Texas/36/91 and B/Harbin/7/94. Placebo was vaccine diluent . Vaccine was recommended and matched circulating strain
Outcomes	Influenza-like illness, working days lost. Clinical illness was defined as follow: fever > 37.6°C and cough, headache, myalgia, rhinorrhea, sore throat lasting at least 24 hours. Surveillance was passive
Notes	Local and systemic effects were reported together and therefore not included in the review. Only 294 treated subjects and 299 controls completed follow up. Efficacy data were extracted

Risk of bias

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

Mogabgab 1970a

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

Risk of bias

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

Mogabgab 1970a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mogabgab 1970b

Methods	Randomised study conducted in USA during 1968 to 1969 influenza season. Influenza outbreak lasted 9 weeks, from December 9 to February 3 and lasted. Randomisation methods were not described. Laboratory confirmation was obtained (by culture or 4-fold antibody titre increase in acute convalescent sera) on 20 men randomly selected each week among the ill
Participants	1551 airmen previously unvaccinated: 1030 vaccinated and 521 given placebo. Age of participants was 18 to 21
Interventions	Polyvalent inactivated influenza A and B vaccine (the 1967 military formula). Schedule and dose were: single dose. Vaccine composition was: A/Swine/33 100 CCA, A/PR8/34 100 CCA, A1/AA/1/57 100 CCA, A2/Taiwan 1/64 400 CCA, B/Lee/40 100 CCA, B/Mass 3/66 200 CCA . Placebo was saline for injection. Vaccine was recommended but did not match circulating strain
Outcomes	Influenza-like illness and influenza cases, complications and admissions. All respiratory illnesses were classified as febrile (38.3°C or greater), afebrile, pharyngitis, bronchitis or pneumonia (complications). Surveillance was passive
Notes	Cases occurring during the first 15 days after vaccination were not included in analysis. Circulating strain was A2/Hong Kong. Efficacy data were extracted

Risk of bias

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

Monto 1982

Methods	Randomised, single blind study conducted in USA during the 1979 to 1980 influenza season. Follow up lasted the whole epidemic period. The epidemic period was defined by first and last isolation (February 11 to march 18) and lasted 5 weeks. Each subject was given a serial number that had previously been assigned randomly by a code to either the vaccine or the placebo group. Specimens for culture were obtained from ill people. At spring time blood specimens were collected
Participants	306 students: 154 vaccinated and 152 given placebo. Age of participants was not reported
Interventions	Monovalent, live attenuated, intranasal influenza B . Schedule and dose were: single dose. Vaccine composition was: the vaccine virus, cold recombinant, was produced by recombining the attenuated B/Ann Arbor/1/66 with a wild strain B/Hong Kong/8/73. Placebo was vaccine diluent. Vaccine was not recommended and did not match circulating strain

Monto 1982 (*Continued*)

Outcomes	Clinical and laboratory confirmed cases and adverse effects. Patients suffered a respiratory illness if they had at least 2 respiratory symptoms. Cases were laboratory confirmed if they had an increase in antibody titre against 3 influenza B virus antigens, i.e. if there was a four-fold increase from an initial sample. Side effects were sore throat, coryza, hoarseness, cough, muscle aches, temperature >100 F occurring during the first three days after vaccination. Surveillance was active
Notes	Vaccine content was not recommended nor matching. Circulating strain was B/Singapore/79-like and B/Buenos Aires/79-like Efficacy and safety data were extracted

Risk of bias

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

Mutsch 2004

Methods	One case-control study and case-series based in the German-speaking regions of Switzerland which assessed the association between an intranasal inactivated virosomal influenza vaccine and Bell's palsy
Participants	250 cases that could be evaluated (from an original 773 cases identified) were matched to 722 controls for age, date of clinic visit. All were aged around 50
Interventions	Immunisation with influenza vaccine took place within 91 days before disease onset
Outcomes	
Notes	The study reports a massive increase in risk (adjusted OR 84, 95% CI 20.1 to 351.9) within 1 to 91 days since vaccination. Despite its many limitations (case attrition - 187 cases could not be identified - and ascertainment bias - physicians picked controls for their own cases - confounding by indication - different vaccine exposure rate between controls and the reference population) it is unlikely that such a large OR could have been affected significantly by systematic error. The authors called for larger pre-licence safety trials, given the rarity of Bell's palsy. On the basis of this study the vaccine was withdrawn from commerce Rare events (safety)

Risk of bias

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

Nichol 1995

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

Risk of bias

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

Nichol 1999a

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

	tiredness); severe febrile illness (3 days of symptoms and 1 day of fever); febrile upper respiratory tract illness (3 days of upper respiratory tract symptoms and 1 day of fever). We chose the febrile illness outcome for analysis. Systemic adverse effects were defined as headache, muscle aches, chills, tiredness and fever. Surveillance was passive
Notes	Complete follow up data were obtained for 2874 subjects in the treatment arm and for 1433 subject in the placebo arm. The outcome working days lost is presented as rate ratio, even if data are presented in a way that allows to compute difference in mean days lost but not to compute the standard error. Circulating strain was A/Sidney/5/97-like. Efficacy and safety data were extracted

Risk of bias

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

Payne 2006

Methods	Case control study assessing the association between influenza and other vaccines (data not extracted for this review) and optic neuritis
Participants	US military personnel aged at least 18 years
Interventions	Cases (n = 1131) were subjects with a diagnosis of optic neuritis between 1.1.1998 and 31. 12.2003. The following ICD-9 codes were considered : 377.30-32, 377.39. Controls (n = 4524): subjects were matched to the cases on the basis of sex, deployment during the 18 weeks before diagnosis, military component. The study was carried out by using data from the Defense Medical Surveillance System, a longitudinal surveillance database
Outcomes	Date of case diagnosis was ascertained and immunisation status (Anthrax, smallpox, Hepatitis b, influenza) verified by means of electronic record in respect of three time intervals: 6, 12, 18 weeks before onset. For controls vaccination status was determined for the three interval before index date. Results were focused on the 18-week time interval
Notes	Rare events (safety)

Risk of bias

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

Phyroenen 1981

Methods	Randomised controlled trial carried out in the 1976 to 1977 season in Finland
Participants	307 healthy adults
Interventions	One of the following 4 preparations were administered to one of the 4 groups of participants: Live attenuated A/Victoria/3/75 ; two 2 ml doses (2 104.5 Bivalent subunit vaccine containing 1200 IU of A/Victoria/3/75 (H3N2) and 800 IU of B/Hong Kong/8/73 per dose (0.5 ml) B versus placebo (phosphate buffered saline). Participant received one dose subcutaneously administered. Vaccination were performed between Dec 15-23, 1976, epidemics occurred Feb to Jun 1977
Outcomes	Harms assessed by questionnaires filled out by each subject within 3 days after immunisation. Fever: vacc 11/151; Pl 9/154 - muscle ache; vacc 26/ 151; Pl 12/154 - redness: vacc 53/151; Pl 3/154 - tenderness at vaccination site: vacc 89/151; Pl 12/154 - tenderness of axillary glands: vacc 6/151 ; Pl 2/154
Notes	Safety data only were extracted

Risk of bias

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

Powers 1995a

Methods	Randomised controlled trial conducted in USA during 1993 to 1994 influenza season. Follow up was not indicated. Influenza period was not defined. Subjects were randomly assigned to receive one of the following five vaccine preparations in a double-blinded manner: 15 mg of rHA0, 15 mg of rHA0 plus alum, 90 mg of rHA0, licensed and placebo. Spring sera were collected
Participants	34 healthy university students: 26 treated and 8 placebo. Age of participants was: 18 to 45
Interventions	Subvirion licensed trivalent parenteral AB vaccine. Schedule and dose were: single dose; 15 micrograms each strain. Vaccine composition was: A/Texas/36/91 (H1N1), A/Beijing/32/92 (H3N2) and B/Panama/45/90. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical and laboratory confirmed cases and adverse effects. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of myalgias or chills. Laboratory evidence of influenza A (H3N2) virus infection was defined as either or both of the isolation of virus from nasopharyngeal secretion and a >= four-fold increase in serum HAI antibody titre between the 3-week post-vaccination (preseason) specimen and the corresponding post-season specimen collected in the following spring. Local adverse effects were erythema, pain, tenderness, induration, arm stiffness; systemic adverse effects: were headache, generalized myalgia, diarrhea, nausea, feverishness, temperature > 37.8°C

Powers 1995a (*Continued*)

Notes	Efficacy and safety data were extracted	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Powers 1995b

Methods	Single blind randomised controlled trial conducted in USA during 1974 to 1975 influenza season. Follow up lasted from winter to spring. A "two month" epidemic period was described by the authors with no reference to a definition and lasted 6 weeks. Study subjects were randomly assigned into three subgroups to receive either two doses of the vaccine (n = 47), one dose of vaccine and one dose of placebo (n = 48) or two doses of placebo (n = 48) at 14 days apart. Six months sera were collected on all study subjects	
Participants	34 healthy university students: 26 treated and 8 placebo. Age of participants was 18 to 45	
Interventions	Subvirion monovalent parenteral vaccine. Schedule and dose were: single dose; 90 micrograms rHAO. Vaccine composition was: The recombinant HA vaccine contained full-length uncleaved haemagglutinin (HA0) glycoprotein from the influenza A/Beijing/32/92 (H3N2) virus. Placebo was saline for injection. Vaccine was not recommended but matched circulating strain	
Outcomes	Clinical and laboratory confirmed cases. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of myalgias or chills. Laboratory evidence of influenza A (H3N2) virus infection was defined as either or both of the isolation of virus from nasopharyngeal secretion and a >= four-fold increase in serum HAI antibody titre between the 3-week post-vaccination (pre-season) specimen and the corresponding post-season specimen collected in the following spring	
Notes	Safety data were not included; effectiveness data were extracted	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	D - Not used

Powers 1995c

Methods	Randomised controlled trial conducted in USA during 1993 to 1994 influenza season. Follow up was not indicated. Influenza period was not defined. Subjects were randomly assigned to receive one of the following five vaccine preparations in a double-blinded manner: 15 mg of rHA0, 15 mg of rHA0 plus alum, 90 mg of rHA0, licensed and placebo. Spring sera were collected
Participants	59 healthy university students: 51 treated and 8 placebo. Age of participants was 18 to 45
Interventions	Subvirion monovalent parenteral vaccine. Schedule and dose were: single dose; 15 micrograms rHAO. Vaccine composition was: The recombinant HA vaccine contained full-length uncleaved haemagglutinin (HA0) glycoprotein from the influenza A/Beijing/32/92 (H3N2) virus. Placebo was saline for injection. Vaccine was not recommended but matched circulating strain
Outcomes	Clinical and laboratory confirmed cases. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of myalgias or chills. Laboratory evidence of influenza A (H3N2) virus infection was defined as either or both of the isolation of virus from nasopharyngeal secretion and a >= four-fold increase in serum HAI antibody titre between the 3-week post-vaccination (pre-season) specimen and the corresponding post-season specimen collected in the following spring
Notes	Efficacy data only were extracted

Risk of bias

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

Reeve 1982

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

Reeve 1982 (*Continued*)

Notes	Safety data only were extracted	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rocchi 1979a

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

Rocchi 1979b

Methods	As above
Participants	
Interventions	
Outcomes	

Rocchi 1979b (*Continued*)

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

Rytel 1977

Methods	Single blind randomised controlled trial conducted in the USA during 1974 to 1975 influenza season. Follow up lasted from winter to spring. A "two month" epidemic period was described by the authors with no reference to a definition and lasted 6 weeks. Study subjects were randomly assigned into three subgroups to receive either two doses of the vaccine (n = 47), one dose of vaccine and one dose of placebo (n = 48) or two doses of placebo (n = 48) at 14 days apart. Six months sera were collected on all study subjects	
Participants	143 young adult female student nurse volunteers: 95 treated and 48 placebo. Age of participants was 18 to 35	
Interventions	Live attenuated, bivalent, intranasal influenza A (containing 107,2 EID50) and B (containing 107,8 EID50) vaccines. Schedule and dose were single or double doses. Vaccine composition was: A/England/42/72 (H3N2) and B/Hong Kong/5/72. Placebo was 5% sucrose. Vaccine was not recommended and did not match circulating strain	
Outcomes	Influenza and adverse effects. An influenza case was defined as the presence of an influenza-like illness (three or more symptoms of acute respiratory disease and temperature greater then 37.2) and virus isolation and/or four fold rise in antibody titre in sera obtained ad 30 days and 6 months following immunisation. Local adverse effects were upper respiratory symptoms and cough. These were subdivided into moderate and severe. A definition of general adverse effects (again distinguished among moderate and severe) was not given	
Notes	One dose and two doses were analyzed together. Circulating strain was A/PortChalmers/1/73 (H3N2). Efficacy and safety data extracted	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Saxen 1999

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

Risk of bias

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

Scheifele 2003

Methods	Randomised double-blind placebo controlled cross over trial assessing the association between exposure to the vaccine and onset of oculo-respiratory syndrome (ORS) in healthy adults with no previous history of ORS. The trial took place in five centres in Canada in September 2001 and was one of the conditions of registration of the vaccine, given the high incidence of ORS in the previous season. Centralised randomisation and allocation of centrally prepared coded opaque syringes took place. Cross over to either vaccine or placebo took place 5 to 7 days after the initial injection
Participants	Six hundred and fifty one adults with a mean age of 45 took part. Seventeen participants are unaccounted for
Interventions	Fluviral (Shire) split trivalent containing A/New Caledonia/20/99 (H1N1); A/Panama/2007/99 (H3N2) ; B/Victoria/504/2000 with additional splitting with Triton X-100 splitting agent or saline placebo 0.5 mls. Additional splitting was necessary to test the hypothesis that large clumps of virions were responsible for the ORS seen the previous season
Outcomes	ORS (bilateral conjunctivitis, facial swelling - lip, lid or mouth, difficulty in breathing and chest discomfort, including cough, wheeze, dysphagia or sore throat). Local signs/symptoms (redness, swelling, pain). Follow up was by phone interview at 24 hours and 6 days after vaccination
Notes	The authors conclude that (mild) ORS is significantly associated with split TIV immunisation (attributable risk 2.9%, 0.6 to 5.2). Other adverse effects associated with TIV are

Scheifele 2003 (*Continued*)

	hoarseness (1.3%, 0.3 to 1.3) and coughing 1.2%, 0.2 to 1.6). The study is good quality and the authors conclusions are robust. It is extraordinary that no one has looked for these symptoms before but it may be that the relatively young age of participants and the hypothesis contributed to this. Safety-only study

Risk of bias

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

Shoenberger 1979

Methods	Surveillance population-based study conducted in USA, during the 1976 to 1977 influenza season. The study tested the association between influenza vaccination and Guillan-Barrè Syndrome. Neurologists were directly contacted; physician and hospital records were reviewed . Suspected cases reported to CDC directly by patients or medical personnel were included only if accepted by a state health department. Follow up period was 01/10/76-31/01/77
Participants	USA population
Interventions	Monovalent A/New Jersey/76 or bivalent A/New Jersey/76 and A/Victoria/75 parenteral vaccine
Outcomes	Cases of Guillain-Barré syndrome
Notes	Results were stratified by age group and vaccine type. Vaccination rates in population were obtained from national immunisation survey Rare events (safety)

Risk of bias

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

Siscovick 2000

Methods	Study assessing the association between influenza vaccination the previous year and the risk of primary (i.e. occurring in people with no previous history of cardiac disease) cardiac arrest. Case-control study on 360 cases and 418 controls
Participants	Cases: subjects who experienced primary cardiac arrest, aged between 25 to 74 years Controls: healthy subjects selected randomly from the community, who were matched to the cases for age and sex

Siscovick 2000 (*Continued*)

Interventions	Immunisation with influenza vaccine, assessed by means of questionnaires
Outcomes	Cardiac arrest
Notes	The authors concluded that vaccination is protective against primary cardiac arrest (OR 0. 51, 95% CI 0.33 to 0.79). The difficulty of case ascertainment (77% of potential cases had no ME report and/or autopsy), recall bias (spouses provided exposure data for 304 cases, while 56 survivor cases provided data jointly with their spouses) make the conclusions of this study unreliable. It is impossible to judge the reliability of this study because of a lack of details on the circulation of influenza in the study areas in the 12 months preceding cardiac arrest (the causal hypothesis is based on the effects of influenza infection on the oxygen supply to the myocardium through lung infection and inflammation). Rare events (safety)

Risk of bias

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

Spencer 1977

Methods	Controlled trial, single blind
Participants	21 pairs of students and employers at the University of California, aged between 24 and 50 years who lived together or worked in close proximity
Interventions	Recombinant, live attenuated R 75 vaccine (B/Hong Kong/5/72 and B/Russia/69) containing 107.5 EID / dose versus placebo (allantoic fluid). Lyophilized vaccine was supplied by Smith, Kline and French Laboratories and diluted with 2.5 ml of a 5% sucrose solution just before administration. Both preparations were administered intranasally (5 drops/nostril). In each pair one individual received vaccine and the other one placebo. A second dose was administered 14 days apart
Outcomes	Any clinical symptoms within 7 days after each immunisation (rhinitis, cough, pharyngitis, headache, malaise and myalgia were the prominent observed symptoms, but given as aggregates)
Notes	Reported safety data don't allow quantitative analysis

Risk of bias

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

Sumarokow 1971

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

Risk of bias

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

Tannock 1984

Methods	Controlled clinical trial, double blind, conducted in Australia during the 1981 influenza season. Follow up lasted from winter to spring. Influenza period was not defined. Voluntary were alternatively allocated to groups in a double blind manner. Six months sera were collected
Participants	88 volunteer staff from Newcastle Hospital and the Commonwealth Steel Corporation: 56 treated and 32 placebo. Age of participants was 16 to 64
Interventions	Trivalent subunit parenteral vaccine. Schedule and dose were: 7 micrograms each, one or two doses. Vaccine composition was: A/Brazil/11/78, A/Bangkok/1/79, B/Singapore/222/79. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Influenza and adverse effects. A case of influenza was defined as a respiratory illness, retrospectively reported, associated with a 4-fold antibody titre increase between post-vaccination and post-epidemic sera. Local side effects were redness, swelling, warmth or irritation,

Tannock 1984 (*Continued*)

	pain on contact, pain with pressure, continuous pain, or restriction of arm movement; systemic reactions were fever, chills, sweating, drowsiness or insomnia
Notes	One dose and two doses were analyzed together; very high drop out . Circulating strain was A/Bangkok/1/79. Safety data only were extracted

Risk of bias

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

Waldman 1969a

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

Risk of bias

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

Waldman 1969b

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

Risk of bias

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

Waldman 1969c

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

Waldman 1969c (*Continued*)

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

Waldman 1969d

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

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

Waldman 1972a

Methods	Randomised controlled trial, double blind conducted in USA during 1968 to 1969 influenza season. Follow up lasted the whole epidemic period. Epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Identical looking coded vials were used to dispense material. Sampling virological and serological survey of ill people was performed. Two doses were administered but as outbreak occurred mostly between them only effectiveness of the first dose was assessed
Participants	244 volunteer students and staff members: 195 treated and 49 placebo. Age of participants was not indicated

Waldman 1972a (*Continued*)

Interventions	Monovalent A aerosol vaccine. Schedule and dose were: 200 CCA . Vaccine composition was: A2/Aichi/1/68. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first one or two weeks after vaccination was not excluded, but authors stated that this fact did not affect the results. Circulating strain was A2/Aichi/2/68. Efficacy and safety data were extracted

Risk of bias

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

Waldman 1972b

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

Risk of bias

Waldman 1972b (*Continued*)

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

Waldman 1972c

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

Risk of bias

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

Waldman 1972d

Methods	Randomised controlled trial, double blind, conducted in USA during 1968 to 1969 influenza season. Follow up lasted the whole epidemic period. Epidemic curve was traced by absenteeism in the local industries and schools and virus isolation and lasted 7 weeks. Identical looking coded vials were used to dispense material. Sampling virological and serological survey of ill people was performed. Two doses were administered but as outbreak occurred mostly between them only effectiveness of the first dose was assessed
Participants	236 volunteer students and staff members: 187 treated and 49 placebo. Age of participants was not indicated

Waldman 1972d (*Continued*)

Interventions	Bivalent AB subcutaneous vaccine. Vaccine composition was: A2/Japan/170/62 150 CCA, A2/Taiwan/1/64 150 CCA and B/Massachusset/3/66 200 CCA. Placebo was saline for injection. Vaccine was recommended but did not match circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first one or two weeks after vaccination was not excluded, but authors stated that this fact did not affect the results. Circulating strain was A2/Aichi/2/68. Efficacy and safety data were extracted

Risk of bias

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

Weingarten 1988

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

Risk of bias

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

Weingarten 1988 (*Continued*)

Allocation concealment (selection bias)	Low risk	A - Adequate

Zhilova 1986a

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

Risk of bias

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

Zhilova 1986b

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

Risk of bias

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

FEV1 = Forced respiratory volume in 1 second
FVC = Forced expiratory vital capacity
ITT = intention-to-treat
I.M. = intramuscular
ADR =
wdl = working days lost
vacc = vaccine

i.u. = international units
TIV = trivalent inactivated vaccine

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

Study	Reason for exclusion
Ambrosch 1976	Data tables and figure missing
Aoki 1986	Randomised controlled trial, single blind. Outcomes were clinical cases and adverse effects. Follow up data were not reported by arms
Atmar 1995	No outcomes of interest
Ausseil 1999	No design (average days of sick leave in vaccinated and not vaccinated subjects during 1996 and 1997 in staff personal of an international banking institution)
Banzhoff 2001	No design (cohort), no safety outcomes
Belongia 2009	Case control study, no harm assessment
Belshe 2001	No original data
Benke 2004	Questionnaire survey; non comparative analysis
Betts 1977b	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Beyer 1996	Review
Carlson 1979	No adequate control, no outcome of interest
Cate 1977	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Chlibek 2002	The study is not a randomised controlled trial
Chou 2007	Case report
Clover 1991	Randomised controlled trial. More than 75% of the study population is out of the range of age stated in the protocol
Confavreux 2001	Participants are MS cases
Das Gupta 2002	The study does not contain effectiveness data
Davies 1972	Cohort with efficacy outcomes. Experimental and control group were separately selected

(*Continued*)

Davies 1973	The study was not randomised. Subjects volunteered for immunisation and comparison was made with a randomly selected non immunised control group
De Serres 2003a	No comparison, absence of adequate control group
De Serres 2003b	No control
De Serres 2004	Population at risk of further Oculo-respiratory syndrome episodes
Dolin 1977	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Edmonson 1970	Influenza B vaccine was used as control
El'shina 1998	Major inconsistencies in the study text
Finklea 1969	Randomised controlled trial, double blind. Two bivalent inactivated influenza vaccines, with the same viral composition, differing in purification procedures, were compared. Outcomes were clinical cases and adverse effects. Raw data about clinical cases were not reported by arm. Circulating virus showed significant antigenic differences from the A2 vaccine strain
Foy 1981	Absence of adequate control
Frank 1981	No usable safety data (scores)
Freestone 1976	Conference proceedings
Gerstoft 2001	The study is not a randomised controlled trial
Greenbaum 2002	No outcome of interest
Gross 1999	Outcome measures outside inclusion criteria
Grotto 1998	The study is not a randomised controlled trial
Gruber 1994	Randomised controlled trial conducted in USA on 41 cystic fibrosis (CF) patients and 89 family members, recruited through a clinic. Subjects were randomly assigned in a double-blinded fashion by family to receive either intranasal live cold-adapted influenza A vaccine or the recommended intramuscular trivalent inactivated influenza vaccine. The study lasted 3 years (from 1989 to 1991). Subjects were immunised each fall staying in the same assigned vaccine group. The live vaccine arm counted 20 CF and 33 family members; the trivalent vaccine arm 21 and 56 respectively. 69 of them (17 CF patients and 52 family members) dropped out. The reasons were stated in the article. The live vaccine was the same all over the period: A/Kawasaki/9/86 (H1N1) 107,3 pfu, A/Los Angeles/2/87 107,3 pfu. The viral strains used in the inactivated vaccines were: - 1989-1990: A/Taiwan/1/86 (H1N1), A/Shaghai/11/87 (H3N2), B/Yagamata/16/88,15 mg/dose of each - 1990-1991: A/Taiwan/1/86 (H1N1), A/Shaghai/16/89 (H3N2), B/Yagamata/16/88,15 mg/dose of each

(*Continued*)

	- 1991-1992: A/Taiwan/1/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90, 15 mg/dose of each Live vaccine recipient also received monovalent inactivated influenza B vaccine (identical to that contained in the trivalent vaccine) as intramuscular placebo. Allantoic fluid was the placebo for aerosol administration. Data were extracted and loaded for family members only. Outcomes were clinical and laboratory confirmed cases, working days lost (WDL), admissions, deaths and adverse effects. Clinical cases were classified as "respiratory illness" or "febrile respiratory illness". Laboratory-confirmed cases were defined by an influenza virus isolation from a throat swab. Adverse effects were defined as temperature > 38°C, rhinorrhea, sore throat, cough, increasing sputum, redness, swelling, chills. Results are expressed as % of subject-days with symptoms. Subjects were followed throughout the period. Owing to the drop outs, vaccinated were counted as subject-years: 54 in the live vaccine arm; 56 in the trivalent vaccine arm. The influenza illness surveillance period for study subjects was defined as the interval from the date of the first influenza isolate from population under routine surveillance to 2 weeks after the last isolate for each year. Viral strains circulating during the outbreaks were: - 1989-1990: A/Shaghai/11/87 (H3N2) - 1990-1991: A/Beijing/353/89 (H3N2), B/Panama/45/90-like - 1991-1992: A/Beijing/353/89 (H3N2). This trial was excluded since it was not placebo controlled and authors didn't specify if the strains used to develop cold adapted and inactivated vaccines were antigenically comparable or not
Haber 2004	Analysis of temporal trends of Guillan Barrè Syndrome (GBS) 1990-2003, comparison with temporal trends of non-GBS Adverse Event reports from the Vaccine Adverse Event Reporting System (VAERS)
Haigh 1973	The study is not randomised: all the volunteers were immunised on a single day and the intention to allocate patients randomly was not strictly adhered to
Halperin 2002	Outcome measures outside inclusion criteria
Hobson 1970	Polivalent influenza vaccine was used as control
Hobson 1973	Randomised controlled trial. Clinical outcomes were side effects only
Hoskins 1973	Influenza B vaccine was used as control
Hoskins 1976a	The trial was excluded since it was not placebo/do-nothing controlled
Hoskins 1976b	The trial was excluded since it was not placebo/do-nothing controlled
Hoskins 1979	No control group
Howell 1967	The study is not prospective. It appears as an historical cohort
Hurwitz 1983	Report of GBS surveillance 1978-79, non-comparative study
Jianping 1999	The study is not a randomised controlled trial
Keitel 2001	Efficacy outcome measures outside inclusion criteria. The safety data are presented in a non-analysable way

(*Continued*)

Khazeni 2009	the study is review and a cost effectiveness analysis
Kiderman 2001	Tables and text show inconsistencies that do not allow data extraction
Kunz 1977	No adequate control
Langley 2004	Review
Liem 1973	Liem reported the results of 9 placebo controlled clinical trials and two field studies, involving a total of about 10000 subjects, carried out in several countries to assess the efficacy of killed influenza spray vaccines. Studies were conducted during the years 1969-71. Allocation of the subjects to the arms of the trials was done according to a pre-determined randomisation scheme. 8 of them were double-blind. The field studies were not randomised. The attack rate for influenza among the population study was very low, and in two of the trials vaccination procedure started too late, when the outbreak was ongoing. The attack rates, exclusively based on the serologically confirmed cases, are only reported by a graph and it is impossible to derive the crude data
Mackenzie 1975	No design (allocation is arbitrary and groups with different characteristics were formed)
Mair 1974	Influenza B vaccine was used as control
Maynard 1968	Influenza B vaccine was used as control
McCarthy 2004	Review
Mendelman 2001	The study does not repot original results
Merelli 2000	Review
Meyers 2003a	Review
Meyers 2003b	Review
Monto 2000	The study is not a randomised controlled trial
Morris 1975	Design is unclear (no standard random allocation. Only 25 out of 30 seem to have been immunized, but in the method description 30 were considered for exposure to natural influenza A/Scotland/840/74. One of these was prior excluded because had tonsillitis
Mostow 1977	Outcomes were safety only. Absence of adequate control
Muennig 2001	The study is not a randomised controlled trial
Nichol 1996	Same data as Nichol 1995
Nichol 1999b	The study is a review
Nichol 2001	The study is not a randomised controlled trial

(*Continued*)

Nichol 2003	The study contain data from previous studies
Nichol 2004	Re-analysis of Nichol 1999 (already included)
Pyhala 2001	The study is not a randomised controlled trial
Rimmelzwaan 2000	Outcome measures outside inclusion criteria
Rocchi 1979c	Very poor reporting, unclear definition, no description of methods
Ruben 1972	Absence of adequate control
Ruben 1973	The study was excluded since both arms contained the same vaccine strains
Safranek 1991	Re-assessment of Schoenberger 1979
Sarateanu 1980	Absence of adequate control
Schonberger 1981	Review of the evidence of the aetiology of GBS, no original data presented
Schwartz 1996	Report about Nichol 1995
Skowronski 2002	Non-comparative (survey)
Skowronski 2003	Population at risk of further ORS episodes
Smith 1977a	The article reports a little part of the Hoskins trial. It compared illness occurring among a group of vaccinated boys against non vaccinated controls that had no part in the trial
Smith 1977b	Trial with swine vaccine (Hsw1N1, A/New Jersey/76)
Spencer 1975	Authors didn't report crude data on the clinical outcomes
Spencer 1979	Reporting doesn't allow one to understand the methods used to allocate subjects and to conceal allocation. Clinical outcome data are not reported
Taylor 1969	No outcomes of interest, rhinovirus vaccine as control
Treanor 2001	Outcome measures outside inclusion criteria
Treanor 2002	Outcome measures outside inclusion criteria
Tyrrell 1970	None of the 3 studies reported in this paper are includible for the following reasons 1. No design, no comparison, no outcomes 2. Probable controlled clinical trial, but subjects age probably out of range (schools) 3. No design, even if an unvaccinated control group for school 3 and ICI is present

(*Continued*)

Warshauer 1976	The study was not randomised. Data reporting was not complete
Wilde 1999	Pneumococcal vaccine was used as control
Williams 1973	No placebo/do-nothing control
Wood 1999	The study is not a randomised controlled trial
Wood 2000	The study is not a randomised controlled trial

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	21	19139	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.71, 0.89]
1.1 WHO recommended - matching vaccine	10	6984	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.59, 0.83]
1.2 WHO recommended - vaccine matching absent or unknown	9	12062	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.09]
1.3 Monovalent not WHO recommended - vaccine matching	1	59	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.28, 3.70]
1.4 Monovalent not WHO recommended - vaccine matching - high dose	1	34	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.09, 2.30]
2 Influenza	17	31325	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.30, 0.52]
2.1 WHO recommended - matching vaccine	8	11285	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.16, 0.46]
2.2 WHO recommended - vaccine matching absent or unknown	6	10331	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.41, 0.77]
2.3 Monovalent not WHO recommended - vaccine matching	2	9675	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.10, 0.52]
2.4 Monovalent not WHO recommended - vaccine matching - high dose	1	34	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.00, 2.49]
3 Physician visits	2	2308	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.40, 1.89]
3.1 WHO recommended - matching vaccine	1	1178	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.37, 0.91]
3.2 WHO recommended - vaccine matching absent or unknown	1	1130	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.90, 1.83]
4 Days ill	4	4800	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.72, 0.15]
4.1 WHO recommended - matching vaccine	3	3670	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.62, -0.34]
4.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	0.66 [0.16, 1.16]
5 Times any drugs were prescribed	2	2308	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
5.1 WHO recommended - matching vaccine	1	1178	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.04, -0.00]
5.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	0.0 [-0.00, 0.00]
6 Times antibiotic was prescribed	2	2308	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.03, -0.01]

6.1 WHO recommended - matching vaccine	1	1178	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.03, -0.01]
6.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
7 Working days lost	5	5393	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.25, -0.00]
7.1 WHO recommended - matching vaccine	4	4263	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.36, -0.05]
7.2 WHO recommended - matching absent or unknown	1	1130	Mean Difference (IV, Random, 95% CI)	0.09 [0.00, 0.18]
8 Hospitalisations	5	14877	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.65, 1.20]
8.1 WHO recommended - matching vaccine	2	2580	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.12, 1.12]
8.2 WHO recommended - vaccine matching absent or unknown	2	2681	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.38, 1.91]
8.3 Monovalent not WHO recommended - vaccine matching	1	9616	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.08]
9 Pneumonia	2	2953	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.13, 4.93]
9.1 WHO recommended - matching vaccine	1	1402	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.04, 9.43]
9.2 WHO recommended - vaccine matching absent or unknown	1	1551	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.09, 11.13]
10 Clinical cases (clinically defined without clear definition)	4	5926	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.41, 0.99]
10.1 WHO recommended - matching vaccine	3	3723	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.27, 1.16]
10.2 WHO recommended - vaccine matching absent or unknown	1	2203	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 0.99]
11 Local harms	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Local - tenderness/soreness	14	6833	Risk Ratio (M-H, Random, 95% CI)	3.11 [2.08, 4.66]
11.2 Local - erythema	6	3388	Risk Ratio (M-H, Random, 95% CI)	4.01 [1.91, 8.41]
11.3 Local - induration	2	543	Risk Ratio (M-H, Random, 95% CI)	2.24 [0.48, 10.59]
11.4 Local - arm stiffness	1	50	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.54, 4.83]
11.5 Local - combined endpoint (any or highest symptom)	12	5171	Risk Ratio (M-H, Random, 95% CI)	2.87 [2.02, 4.06]
12 Systemic harms	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Systemic - myalgia	5	2676	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.12, 2.11]
12.2 Systemic - fever	8	2775	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.80, 1.72]
12.3 Systemic - headache	8	3667	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.84, 2.03]
12.4 Systemic - fatigue or indisposition	6	3456	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.94, 2.02]
12.5 Systemic - nausea/vomiting	3	1667	Risk Ratio (M-H, Random, 95% CI)	2.68 [0.55, 13.08]
12.6 Systemic - combined endpoint (any or highest symptom)	8	2603	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.01, 1.64]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	6	12688	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.84, 0.96]
1.1 WHO recommended - matching vaccine	2	4254	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.12]
1.2 WHO recommended - vaccine matching absent or unknown	3	8150	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.97]
1.3 Non WHO recommended - vaccine matching absent or unknown	1	284	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
2 Influenza	6	8524	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.27, 0.55]
2.1 WHO recommended - matching vaccine	2	4254	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.24, 0.81]
2.2 WHO recommended - vaccine matching absent or unknown	2	3843	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.16, 0.82]
2.3 Non WHO recommended - vaccine matching absent or unknown	2	427	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.08, 0.56]
3 Complications (bronchitis, otitis, pneumonia)	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.24]
3.1 Non WHO recommended - vaccine matching absent or unknown	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.24]
4 Influenza cases (clinically defined without clear definition)	3	23900	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.71, 1.11]
4.1 WHO recommended - matching vaccine	1	1931	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.80]
4.2 WHO recommended - vaccine matching absent or unknown	1	2082	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.25]
4.3 Non WHO recommended - vaccine matching absent or unknown	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
5 Local harms	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Local - upper respiratory infection symptoms	6	496	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.22, 2.27]
5.2 Local - cough	4	852	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.69, 2.22]
5.3 Local - coryza	2	4782	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.26, 1.94]
5.4 Local - sore throat	5	5391	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.44, 2.08]
5.5 Local - hoarseness	1	306	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.51, 2.83]
5.6 Local - combined endpoint (any or highest symptom)	3	4921	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.31, 1.87]
6 Systemic harms	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Systemic - myalgia	3	713	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.81, 6.45]
6.2 Systemic - fever	3	713	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.43, 3.79]

6.3 Systemic - fatigue or indisposition	2	413	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.66, 3.49]
6.4 Systemic - headache	1	370	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.52, 10.33]
6.5 Systemic - combined endpoint (any or highest symptom)	5	1018	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.82, 2.38]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	4	1674	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.40, 0.83]
1.1 WHO recommended - matching vaccine	2	841	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.19, 1.13]
1.2 WHO recommended - vaccine matching absent or unknown	2	833	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.37, 1.07]
2 Local harms	4	716	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.85, 1.40]
2.1 Local - sore throat	2	151	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.43, 1.56]
2.2 Local - combined endpoint (any or highest symptom)	3	565	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.88, 1.50]
3 Systemic harms	4	1018	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.77, 1.31]
3.1 Systemic - myalgia	2	151	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.36, 2.25]
3.2 Systemic - fatigue or indisposition	2	151	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.52, 3.75]
3.3 Systemic - headache	2	151	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.85, 2.72]
3.4 Systemic - combined endpoint (any or highest symptom)	3	565	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.54, 1.27]

Comparison 4. 1968 to 1969 pandemic: inactivated polyvalent parenteral vaccine versus placebo

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

3 Hospitalisations	1	2072	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.68]
3.1 Standard recommended parenteral - non matching	1	2072	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.68]
4 Pneumonia	1	2072	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.14, 7.17]
4.1 Standard recommended parenteral - non matching	1	2072	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.14, 7.17]

Comparison 5. 1968 to 1969 pandemic: inactivated monovalent parenteral vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	4	4580	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.48]
1.1 WHO recommended parenteral - matching vaccine - 1 dose	4	4226	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.23, 0.53]
1.2 WHO recommended parenteral - matching vaccine - 2 doses	1	354	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.22, 0.57]
2 Influenza	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.02, 0.31]
2.1 WHO recommended parenteral - matching vaccine	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.02, 0.31]
3 Hospitalisations	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.94]
3.1 WHO recommended parenteral - matching vaccine	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.94]
4 Pneumonia	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.05, 6.51]
4.1 WHO recommended parenteral - matching vaccine	1	1923	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.05, 6.51]
5 Working days lost	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]
5.1 WHO recommended parenteral - matching vaccine	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]
6 Days ill	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]
6.1 WHO recommended - matching vaccine	1	1667	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.30]

Comparison 6. 1968 to 1969 pandemic: inactivated polyvalent aerosol vaccine versus placebo

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