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 world-wide. Healthy adults are at present targeted only in North America. Despite the publication of a large number of clinical trials, there is still substantial uncertainty about the clinical effectiveness of influenza vaccines and this has a negative impact on their acceptance and uptake.

Objectives

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

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* Issue 4, 2005) which contains the Cochrane Acute Respiratory Infections Group trials register; MEDLINE (January 1966 to January 2006); and EMBASE (1990 to January 2006). We wrote to vaccine manufacturers and first or corresponding authors of studies in the review.

Selection criteria

Any randomised or quasi-randomised studies comparing influenza vaccines in humans with placebo, no intervention. Live, attenuated, or killed vaccines or fractions of them administered by any route, irrespective of antigenic configuration were assessed. Only studies assessing protection from exposure to naturally occurring influenza in healthy individuals aged 16 to 65 years were considered. Comparative non-randomised studies were included if they assessed evidence of the possible association between influenza vaccines and serious harms.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

Forty-eight reports were included: 38 (57 sub-studies) were clinical trials providing data about effectiveness, efficacy and harms of influenza vaccines and involved 66,248 people; 8 were comparative non-randomised studies and tested the association of the vaccines with serious harms; 2 were reports of harms which could not be introduced in the data analysis.

Inactivated parenteral vaccines were 30% effective (95% CI 17% to 41%) against influenza-like illness, and 80% (95% CI 56% to 91%) efficacious against influenza when the vaccine matched the circulating strain and circulation was high, but decreased to 50% (95% CI 27% to 65%) when it did not. Excluding the studies of the 1968 to 1969 pandemic, effectiveness was 15% (95% CI 9% to 22%) and efficacy was 73% (95% CI 53% to 84%). Vaccination had a modest effect on time off work, but there was insufficient evidence to draw conclusions on hospital admissions or complication rates. Inactivated vaccines caused local tenderness and soreness and erythema. Spray vaccines had more modest performance. Monovalent whole-virion vaccines matching circulating viruses had high efficacy (VE 93%, 95% CI 69% to 98%) and effectiveness (VE 66%, 95% CI 51% to 77%) against the 1968 to 1969 pandemic.

Authors' conclusions

Influenza vaccines are effective in reducing cases of influenza, especially when the content predicts accurately circulating types and circulation is high. However, they are less effective in reducing cases of influenza-like illness and have a modest impact on working days lost. There is insufficient evidence to assess their impact on complications. Whole-virion monovalent vaccines may perform best in a pandemic.

PLAIN LANGUAGE SUMMARY

There is not enough evidence to decide whether routine vaccination to prevent influenza in healthy adults is effective

Influenza is a virus which causes symptoms of fever, headache, aches and pains, cough and runny noses. It can last for weeks and lead to serious illness, even death. It spreads easily and new strains develop regularly. The World Health Organization recommends each year which strains should be included in vaccinations for the forthcoming season. The review of trials found vaccinations against influenza avoided 80% of cases at best (in those confirmed by laboratory tests, and using vaccines directed against circulating strains), but only 50% when the vaccine did not match, and 30% against influenza-like illness, in healthy adults. It did not change the number of people needing to go to hospital or take time off work.

BACKGROUND

Viral respiratory disease imposes a heavy burden on society. The majority of viral respiratory disease (influenza-like illness) is caused by a many different agents, which are not clinically distinguishable from one another. A proportion of influenza-like illness is caused by influenza viruses and is known as influenza (Jefferson 2004).

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 impact of seasonal influenza in the second part of the 20th century have 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.

Current influenza vaccines are of three types: (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.

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 is that by the US Advisory Committee on Immunization Practices (ACIP) which is regularly updated (ACIP 2006). The current version identifies 11 categories at high risk of complications from influenza, among which are healthy adults aged 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). 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 2006 update of the review 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;

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 or quasi-randomised studies* 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).

*A study is 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 health care 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 health care 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 percent 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

Clinical

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

Harms

Number and seriousness of adverse effects (classified as local, systemic and severe). Systemic adverse effects include cases of malaise, nausea, fever, arthralgia, rash, headache and more generalised and serious signs. Local adverse effects include induration, soreness and redness at the site of inoculation.

Search methods for identification of studies

For the previous (2004) update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1, 2004) which contains the Cochrane Acute Respiratory Infections Group's trials register; MEDLINE (January 1966 to December 2003); and EMBASE (1990 to December 2003). There were no language restrictions.

See Appendix 1 for the MEDLINE search strategy used. This search strategy was modified and repeated in CENTRAL and EMBASE databases. There were no language restrictions. In order to identify further trials, we read the bibliography of retrieved articles and handsearched the journal Vaccine from its first issue to the end of 2003. 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 authors of studies in the review.

For the present update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 4, 2005) which contains the Cochrane Acute Respiratory Infections Group's trials register; MEDLINE (January 1966 to January 2006); and EMBASE (1990 to January 2006) without language restrictions. The following search strategy was used for MEDLINE and the search terms were adapted for the other searched databases:

MEDLINE

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

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

#3 #1 OR #2

#4 (randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomized controlled trials[MeSH Terms] OR random allocation[MeSH Terms] OR double-blind method[MeSH Terms] OR single-blind method[MeSH Terms] OR clinical trial[Publication Type] OR clinical trials[MeSH Terms]) OR ("clinical trial"[Text Word]) OR ((singl*[Text Word] OR doubl*[Text Word] OR trebl*[Text Word] OR tripl*[Text Word]) AND (mask*[Text Word] OR blind*[Text Word])) OR (placebos[MeSH Terms] OR placebo*[Text Word] OR random*[Text Word] OR research design [mh:noexp]) NOT (animals[MeSH Terms] NOT human[MeSH Terms])

#5 "Case-Control Studies"[MeSH] OR (cases[Title/Abstract] AND controls[Title/Abstract]) OR case control stud*[Title/Abstract]

#6 "Cohort Studies"[MeSH] OR cohort stud*[Title/Abstract]

#7 confidence interval[Title/Abstract] OR relative risk[Title/Abstract] OR CI[Title/Abstract] OR RR[Title/Abstract] OR epidemic[Title/Abstract]

#8 #4 OR #5 OR #6 OR #7

#9 #3 AND #8

#10 #3 AND #8 Field: All Fields, Limits: Adult: 19-64 years

#11 adult OR adults OR adulthood

#12 #8 AND #11

#13 #10 AND #12

Data collection and analysis

Inclusion procedure

Two review authors (TJ and DR) independently applied inclusion criteria to all identified and retrieved articles. Three review authors (TJ, DR and AR) extracted data from included studies on standard Cochrane Vaccines Field forms. The procedure was supervised and arbitrated by CDP. Assessment of methodological quality for RCTs was carried out using criteria from the Cochrane Reviewers' Handbook (Higgins 2005). 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 (Wells 2004). We used quality at the analysis stage as a means of interpretation of 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 1 inadequate item; medium risk of bias - up to 3 inadequate items; high risk of bias - more than 3 inadequate items; very high risk of bias - when there was no description of methods.

Data synthesis

The tables of comparisons were constructed according to the following criteria.

1. Inactivated parenteral (intramuscular or subcutaneous) influenza vaccines versus placebo or no intervention (Comparison 01).
2. Live aerosol vaccines (Comparison 02).
3. Inactivated aerosol vaccines (Comparison 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 influenza-like illness (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.

The statistic I^2 was calculated for each pooled estimate, in order to assess the impact on statistical heterogeneity . I^2 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 < 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. Efficacy (against influenza) and effectiveness (against ILI) (effects) estimates were summarised as relative risk (RR) within 95% confidence intervals (CI) (in brackets after the summary estimate). Absolute vaccine efficacy (VE) was expressed as a percentage using the formula: VE = 1-RR whenever statistically significant. We did not perform a quantitative analysis of non-randomised studies.

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

As the data on average time off work was 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. 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 models to assess the impact of heterogeneity on our results. Finally, because of the widespread concern about the possible impact of a future influenza pandemic we carried out a separate analysis of trials carried out during the 1968 to 1969 (H3N2) pandemic.

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 influenza-like illness case (specific definition) was assumed to be the same as a "flu-like illness" according to a predefined lists of symptoms (including the Centres for Disease Control (CDC) case definition for surveillance), or "upper respiratory illness" according to a predefined lists 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.

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 (Comparison 01 07). 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.

RESULTS

Description of studies

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

The first version of the review contained 20 studies. The 2004 version added five more. In 2006 we included 48 studies in all. 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 (datasets). For the remaining of this review the word "study report" will identify the original study report while the wold "dataset" will identify the sub-study. Details of the division of the reports of studies into datasets are given in the table of included studies.

Overall, 25 datasets contributed data on efficacy/effectiveness (16 on inactivated parentereral 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 parentereral vaccines, nine on live aerosol vaccines and two on inactivated aerosol vaccines) (Table 1).

Table 1. Study datasets by type of vaccine and outcomes

Vaccine type	Efficacy only	Efficacy and safety	Safety only	Total
Inactivated parenteral	16	7	9	32
Live aerosol	7	3	9	19
Inactivated aerosol	2	2	2	6
Total	25	12	20	57

Included trials assessed three types of vaccine: inactivated parenteral, live attenuated aerosol and inactivated aerosol.

Thirty-two datasets of inactivated parenteral vaccine were included. Sixteen datasets (10 study reports) provided data about efficacy or effectiveness (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 20,718 subjects, 9317 in the vaccines arm and 11,401 in the placebo arms.

Seven datasets (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 people, 2251 received vaccine, and 1976 received placebo.

The remaining nine datasets (nine studies) with inactivated parentereral vaccines assessed harms outcomes only and were carried out on 2931 subjects (Caplan 1977; El'shina 1996; Forsyth 1967; Goodeve 1983; Phyroenen 1981; Rocchi 1979a; Saxen 1999; Scheifele 2003; Tannock 1984). In this last group, 1560 subjects

were immunised, and 1371 received placebo.

Live aerosol vaccines were tested in 19 datasets.

Seven datasets (three studies) reported efficacy / effectiveness outcomes (Edwards 1994a; Edwards 1994b; Edwards 1994c; Edwards 1994d; Sumarokow 1971; Zhilova 1986a; Zhilova 1986b). Altogether 29,955 subjects were involved, 15,651 in vaccines and 14,304 in the placebo arms. Three datasets (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 datasets (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 datasets with inactivated aerosol vaccine were included.

Two datasets 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 datasets (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.

Risk of bias in included studies

In the included trials, allocation concealment was adequate in 10, inadequate in four, unclear in 24 and not relevant in two. Assessment was double-blinded in 23 studies. Five studies were single blind and twelve did not mention blinding. Thirty-one 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).

Effects of interventions

Inactivated parenteral vaccines (Comparison 01)

Inactivated parenteral vaccines were 30% effective (95% CI 27% to 41%) against influenza-like illness if content matched WHO recommendations and circulating strain, but this decreased to 12% (95% CI 28% to 0%) when these were unknown (Comparison 01 01). However, effectiveness was considerably lower (16%, 95% CI 9% to 23%) when the studies carried out during the 1968 to 1969 pandemic were excluded.
Against influenza they were 80% (95% CI 56% to 91%) efficacious when content matched WHO recommendations and circulating strain but decreased to 50% (95% CI 27% to 65%) when it did not (Comparison 01 02). 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) (Comparison 01 03). A similar result is seen in the effect on days of illness (Comparison 01 04), but there seems to be no effect on times an antibiotic or a drug were prescribed (Comparisons 01 05 and 01 06). 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 (Comparisons 01 07 to 01 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 twice as common among parenteral vaccine recipients than those in the placebo group (RR 3.11, 95% CI 2.08 to 4.66). There were also increases in erythema (RR 4.01, 95% CI 1.91 to 8.41), 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). Myalgia was significantly associated with vaccination (RR 1.54, 95% CI 1.12 to 2.11). No 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).

Live aerosol vaccines (Comparison 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 influenza-like illness (with no clear definition) was significant only for WHO recommended and matched vaccine (47%, 95% CI 20% to 51%). Only one trial considered death as an outcome and did not register any event. 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 (Comparison 03)

Inactivated aerosol vaccines had effectiveness of 42% (95% CI 17% to 60%) although this observations is based on four datasets from two studies. The conclusions of this comparison were substantially unaffected by analysis using either random- or fixed-effect models although effectiveness against influenza-like illness - 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) and the subcomparison influenza-like illness - 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). 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 US (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 6 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 demylelinating disease (Payne 2006; DeStefano 2003).

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 datasets (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 (Comparison 04). However, 1-dose or two-dose monovalent whole-virion (i.e. containing dead complete viruses) vaccines achieved 65% (95% CI 52% to 75%) protection against influenza-like illness and 93% (95% CI 69% to 98%) protection against influenza, and 65% (95% CI 6% to 87%) against hospitalisations (Comparison 05). 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 (Comparison 05). The large effect on influenza-like illness is coherent with the high proportion of these illnesses caused by influenza viruses in a pandemic (i.e. the gap between efficacy and effectiveness of the vaccines is narrow). Aerosol polyvalent or monovalent vaccines had modest performance (Comparisons 06 to 08).

DISCUSSION

Although this review presents a large number of comparisons and outcomes based on a number of different groupings of studies and trials, the mainstream 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 incidence of influenza by around 80%, if the WHO recommendations are adhered to and the match is right. However, whilst the vaccines do prevent influenza, this is only one part of the spectrum of "clinical effectiveness" as they reduce total "clinical" seasonal influenza (i.e. influenza-like illness) rates by around 15%. 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 manyfold.

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. influenza-like illness) 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 hospitalisation. 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 hospitalisation. 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 influenza-like illness) 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.

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 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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* *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

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

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) vs. placebo, one 0.5 ml-dose intranasal. On day 37 after immunisation subjects were challenged with A/Victoria/3/75

Betts 1977a (*Continued*)

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

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

Boyce 2000

Methods	Open label / single blind randomised controlled trial to assess safety and immunogenicity of adjuvated and unadjuvated 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 adjuvated 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 adjuvated preparation) 3) Placebo (consisting of 0.5 ml sterile saline) All preparation were intranasal administered in two doses 28 days apart. 24 individuals received their first dose of adjuvated (n = 12) or unadjuvated (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 unadjuvated vaccine, 19 adjuvated 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Bridges 2000b (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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 enrollment, matched on age (within 1 year) and gender
Notes	Rare events (safety)

DeStefano 2003 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	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

Edwards 1994a (*Continued*)

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
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Edwards 1994b (*Continued*)

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 Sichuan/2/87 (H3N2) (antigen drift from vaccine strain) and B/Victoria/2/87 Effectiveness data only were extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	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*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

El'shina 1996 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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 adjuvated 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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 of observed cases, without indication of the corresponding arm: malaise, swollen tonsils, fever (1), rhinorrhoea (1), conjunctivitis (7), laryngitis or hoarseness (3), cough (1), swollen tonsils (1), malaise (1). Surveillance was active
Notes	Safety data only were extracted

Risk of bias

Item	Authors' judgement	Description

Hrabar 1977 (*Continued*)

Allocation concealment?	Unclear	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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	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)

Keitel 1988a (*Continued*)

	, 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Keitel 1997b (*Continued*)

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 extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	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 dialing telephone survey. Rare events (safety)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	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 neutralizing 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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: hospitalisation for upper respiratory infection (without definition), hospitalisation 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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-labeled, 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
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

Item	Authors' judgement	Description

Mesa Duque 2001 (*Continued*)

Allocation concealment?	Yes	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

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

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

Mixéu 2002 (*Continued*)

Allocation concealment?	Unclear	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

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

Mogabgab 1970b (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Mutsch 2004 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Payne 2006 (*Continued*)

	on the 18-week time interval
Notes	Rare events (safety)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Powers 1995a (*Continued*)

Outcomes	Clinical and laboratory confirmed cases and adverse effects. An "influenza-like illness" was defined as the presence of any respiratory symptom(s) for >= 2 days, accompanied by fever or systemic symptoms of 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, diarrhoea, nausea, feverishness, temperature > 37.8°C
Notes	Efficacy and safety data were extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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 (preseason) 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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 (preseason) specimen and the corresponding post-season specimen collected in the following spring
Notes	Efficacy data only were extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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
Notes	Safety data only were extracted

Risk of bias

Item	Authors' judgement	Description

Reeve 1982 (*Continued*)

Allocation concealment?	Unclear	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

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

Rocchi 1979b

Methods	As above
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	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 analysed together. Circulating strain was A/PortChalmers/1/73 (H3N2). Efficacy and safety data extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Saxen 1999 (*Continued*)

Notes	Efficacy data were not extracted because episodes of respiratory infections were unclearly defined. Safety data only were extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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 immunization (attributable risk 2.9%, 0.6 to 5.2). Other adverse effects associated with TIV are hoarseness (1.3%, 0.3 to 1.3) and coughing 1.2%, 0.2 to 1.6). The study is good quality and the authors conclusions are robust. It is extraordinary that no one has looked for these symptoms before but it may be that the relatively young age of participants and the hypothesis contributed to this. Safety-only study

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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
Interventions	Immunisation with influenza vaccine, assessed by means of questionnaires
Outcomes	
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

Item	Authors' judgement	Description

Siscovick 2000 (*Continued*)

Allocation concealment?	Unclear	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

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

Sumarokow 1971 (*Continued*)

	Effectiveness data only were extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	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, 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 analysed together; very high drop out . Circulating strain was A/Bangkok/1/79. Safety data only were extracted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	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

Waldman 1969a (*Continued*)

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

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

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	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

Item	Authors' judgement	Description

Waldman 1969d (*Continued*)

Allocation concealment?	Unclear	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
Interventions	Monovalent A aerosol vaccine. Schedule and dose were: 200 CCA . Vaccine composition was: A2/Aichi/1/68. Placebo was saline for injection. Vaccine was recommended and matched circulating strain
Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	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

Waldman 1972b (*Continued*)

Outcomes	Clinical cases and adverse effects. Clinical cases were defined as febrile respiratory illness with oral temperature higher then 99.5 F. Local adverse effects were defined as pain and/or tenderness and redness and/or swelling. Systemic adverse effects were defined as general (fever, muscle pain, nausea or vomiting, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out
Notes	Illness during the first 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out.
Notes	Illness during the first 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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
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, diarrhoea and malaise) or respiratory (runny and/or stuffy nose, sore throat, cough, shortness of breath). Passive surveillance was carried out.
Notes	Illness during the first 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Weingarten 1988 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Yes	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

Item	Authors' judgement	Description

Zhilova 1986a (*Continued*)

Allocation concealment?	Unclear	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

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

FEV1 = Forced respiratory volume in 1 second
FVC = Forced expiratory vital capacity
ITT - intention-to-treat
I.M. = intramuscular

wdl = working days lost
vacc = vaccine
i.u. = international units

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

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
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
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
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

(*Continued*)

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 - 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

(*Continued*)

	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-analyzable way
Kiderman 2001	Tables and text show inconsistencies that do not allow data extraction
Kunz 1977	No adequate control

(*Continued*)

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 predetermined 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
Nichol 2003	The study contain data from previous studies
Nichol 2004	Re-analysis of Nichol 1999 (already included)

(*Continued*)

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
Warshauer 1976	The study was not randomised. Data reporting was not complete
Wilde 1999	Pneumococcal vaccine was used as control

(*Continued*)

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	20	13125	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.68, 0.87]
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	8	6048	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.72, 1.08]
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	15	17530	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.49]
2.1 WHO recommended - matching vaccine	7	3633	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.09, 0.44]
2.2 WHO recommended - vaccine matching absent or unknown	5	4188	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.35, 0.73]
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)	Not estimable
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]

1.2 Inactivated polyvalent aerosol vaccine versus placebo - non matching - 2 doses	1	356	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.97]

Comparison 7. 1968 to 1969 pandemic: Inactivated monovalent aerosol vaccine versus placebo

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

Comparison 8. 1968 to 1969 pandemic: Live aerosol vaccine versus placebo

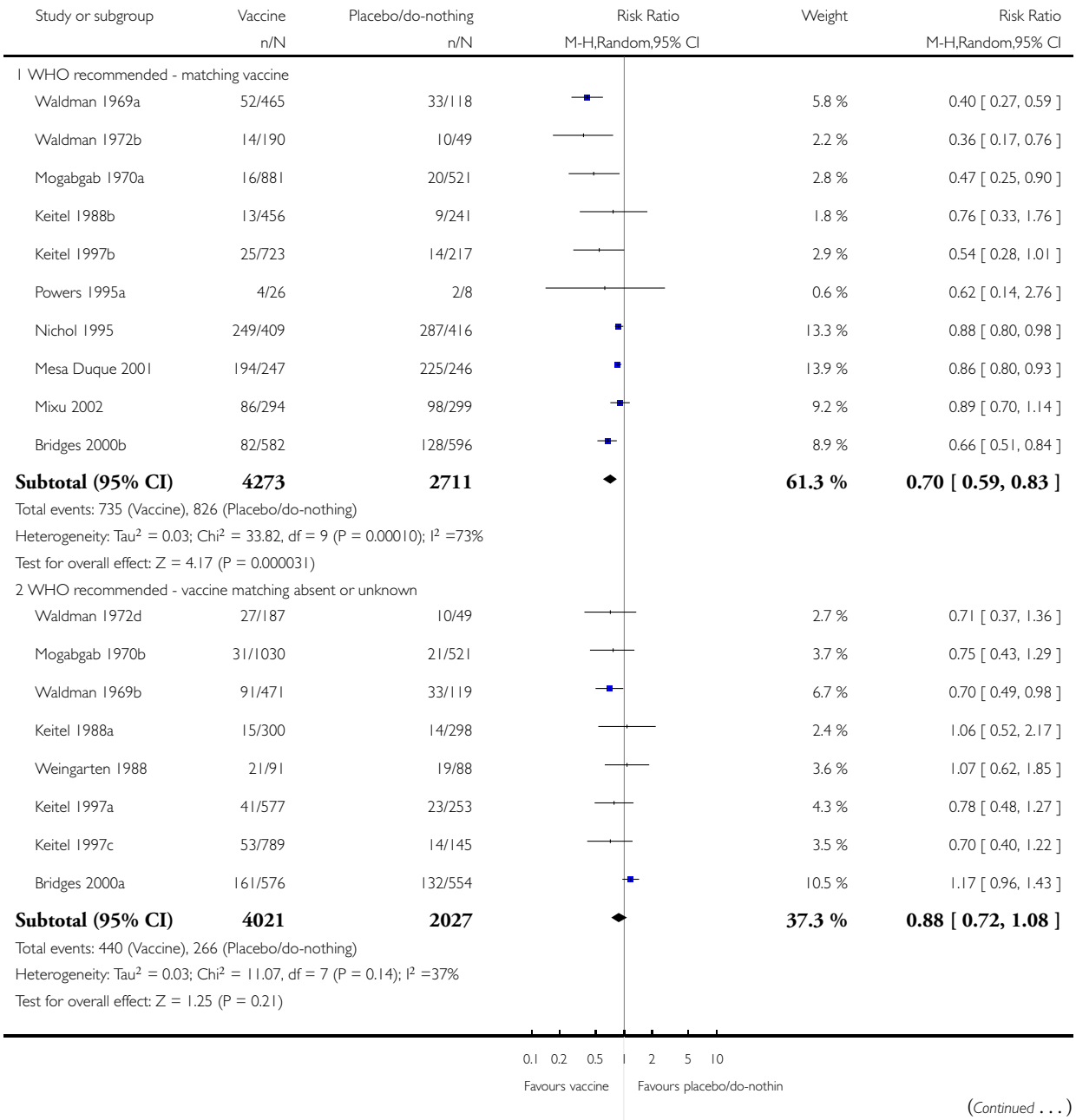
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza cases (clinically defined without clear definition)	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
1.1 Non matching	1	19887	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
2 Complications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

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 1 Influenza-like illness



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Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Monovalent not WHO recommended - vaccine matching					
Powers 1995c	13/51	2/8		0.8 %	1.02 [0.28, 3.70]
Subtotal (95% CI)	**51**	**8**		**0.8 %**	**1.02 [0.28, 3.70]**
Total events: 13 (Vaccine), 2 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
4 Monovalent not WHO recommended - vaccine matching - high dose					
Powers 1995b	3/26	2/8		0.5 %	0.46 [0.09, 2.30]
Subtotal (95% CI)	**26**	**8**		**0.5 %**	**0.46 [0.09, 2.30]**
Total events: 3 (Vaccine), 2 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.34)					
Total (95% CI)	**8371**	**4754**		**100.0 %**	**0.77 [0.68, 0.87]**
Total events: 1191 (Vaccine), 1096 (Placebo/do-nothing)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 44.87$, df = 19 (P = 0.00072); $I^2 = 58\%$					
Test for overall effect: Z = 4.22 (P = 0.000024)					

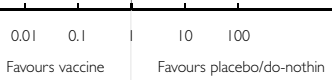
Analysis 1.2. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 2 Influenza

Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Mogabgab 1970a	2/881	16/521		4.5 %	0.07 [0.02, 0.32]
Hammond 1978	1/116	14/109		2.5 %	0.07 [0.01, 0.50]
Tannock 1984	1/37	1/20		1.4 %	0.54 [0.04, 8.19]
Keitel 1988b	17/456	17/241		15.6 %	0.53 [0.27, 1.02]
Keitel 1997b	4/723	5/217		5.5 %	0.24 [0.07, 0.89]
Powers 1995a	0/26	1/8		1.1 %	0.11 [0.00, 2.49]
Bridges 2000b	2/141	14/137		4.5 %	0.14 [0.03, 0.60]
Subtotal (95% CI)	**2380**	**1253**		**35.1 %**	**0.20 [0.09, 0.44]**
Total events: 27 (Vaccine), 68 (Placebo/do-nothing)					
Heterogeneity: Tau^2 = 0.45; Chi^2 = 10.99, df = 6 (P = 0.09); I^2 =45%					
Test for overall effect: Z = 4.01 (P = 0.000061)					
2 WHO recommended - vaccine matching absent or unknown					
Mogabgab 1970b	15/1030	16/521		14.4 %	0.47 [0.24, 0.95]
Keitel 1988a	16/300	28/298		17.5 %	0.57 [0.31, 1.03]
Keitel 1997a	11/577	11/253		11.5 %	0.44 [0.19, 1.00]
Keitel 1997c	5/789	2/145		3.7 %	0.46 [0.09, 2.35]
Bridges 2000a	3/138	6/137		5.1 %	0.50 [0.13, 1.94]
Subtotal (95% CI)	**2834**	**1354**		**52.2 %**	**0.50 [0.35, 0.73]**
Total events: 50 (Vaccine), 63 (Placebo/do-nothing)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.31, df = 4 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 3.65 (P = 0.00026)					
3 Monovalent not WHO recommended - vaccine matching					
Leibovitz 1971	5/1682	102/7934		10.1 %	0.23 [0.09, 0.57]
Powers 1995c	1/51	1/8		1.5 %	0.16 [0.01, 2.26]
Subtotal (95% CI)	**1733**	**7942**		**11.6 %**	**0.22 [0.10, 0.52]**
Total events: 6 (Vaccine), 103 (Placebo/do-nothing)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 3.47 (P = 0.00052)					



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Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
4 Monovalent not WHO recommended - vaccine matching - high dose					
Powers 1995b	0/26	1/8		1.1 %	0.11 [0.00, 2.49]
Subtotal (95% CI)	**26**	**8**		**1.1 %**	**0.11 [0.00, 2.49]**
Total events: 0 (Vaccine), 1 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
Total (95% CI)	**6973**	**10557**		**100.0 %**	**0.35 [0.25, 0.49]**
Total events: 83 (Vaccine), 235 (Placebo/do-nothing)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 17.09, df = 14 (P = 0.25); I^2 =18%					
Test for overall effect: Z = 6.24 (P < 0.00001)					

0.01 0.1 1 10 100

Favours vaccine Favours placebo/do-nothin

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 3 Physician visits

Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Bridges 2000b	29/582	51/596		48.6 %	0.58 [0.37, 0.91]
Subtotal (95% CI)	**582**	**596**		**48.6 %**	**0.58 [0.37, 0.91]**
Total events: 29 (Vaccine), 51 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.40 (P = 0.016)					
2 WHO recommended - vaccine matching absent or unknown					
Bridges 2000a	64/576	48/554		51.4 %	1.28 [0.90, 1.83]
Subtotal (95% CI)	**576**	**554**		**51.4 %**	**1.28 [0.90, 1.83]**
Total events: 64 (Vaccine), 48 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Total (95% CI)	**1158**	**1150**		**100.0 %**	**0.87 [0.40, 1.89]**
Total events: 93 (Vaccine), 99 (Placebo/do-nothing)					
Heterogeneity: Tau^2 = 0.27; Chi^2 = 7.46, df = 1 (P = 0.01); I^2 =87%					
Test for overall effect: Z = 0.34 (P = 0.73)					

0.01 0.1 1 10 100

Favours vaccine Favours placebo/do-nothin

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 4 Days ill

Study or subgroup	Vaccine N	Mean(SD)	Placebo/do-nothing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
Eddy 1970	1254	0.09 (0.69)	413	0.53 (1.7)		29.6 %	-0.44 [-0.61, -0.27]
Nichol 1995	409	1.29 (3.68)	416	2.03 (3.68)		21.9 %	-0.74 [-1.24, -0.24]
Bridges 2000b	582	1.02 (2.74)	596	1.54 (2.74)		26.7 %	-0.52 [-0.83, -0.21]
Subtotal (95% CI)	**2245**		**1425**			**78.1 %**	**-0.48 [-0.62, -0.34]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.31$, df = 2 (P = 0.52); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.62 (P < 0.00001)							
2 WHO recommended - matching absent or unknown							
Bridges 2000a	576	2.39 (4.29)	554	1.73 (4.29)		21.9 %	0.66 [0.16, 1.16]
Subtotal (95% CI)	**576**		**554**			**21.9 %**	**0.66 [0.16, 1.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.59 (P = 0.0097)							
Total (95% CI)	**2821**		**1979**			**100.0 %**	**-0.29 [-0.72, 0.15]**
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 19.78$, df = 3 (P = 0.00019); $I^2 = 85\%$							
Test for overall effect: Z = 1.29 (P = 0.20)							

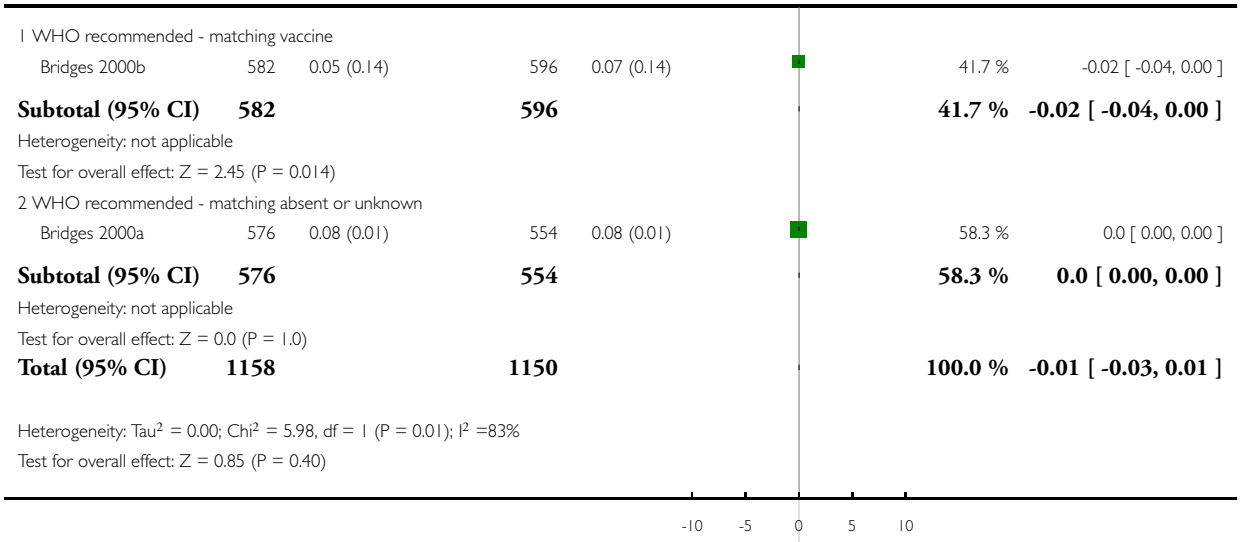
Analysis 1.5. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 5 Times any drugs were prescribed.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 5 Times any drugs were prescribed

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



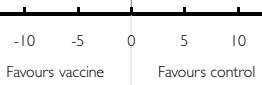
Analysis 1.6. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 6 Times antibiotic was prescribed.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 6 Times antibiotic was prescribed

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



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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 7 Working days lost

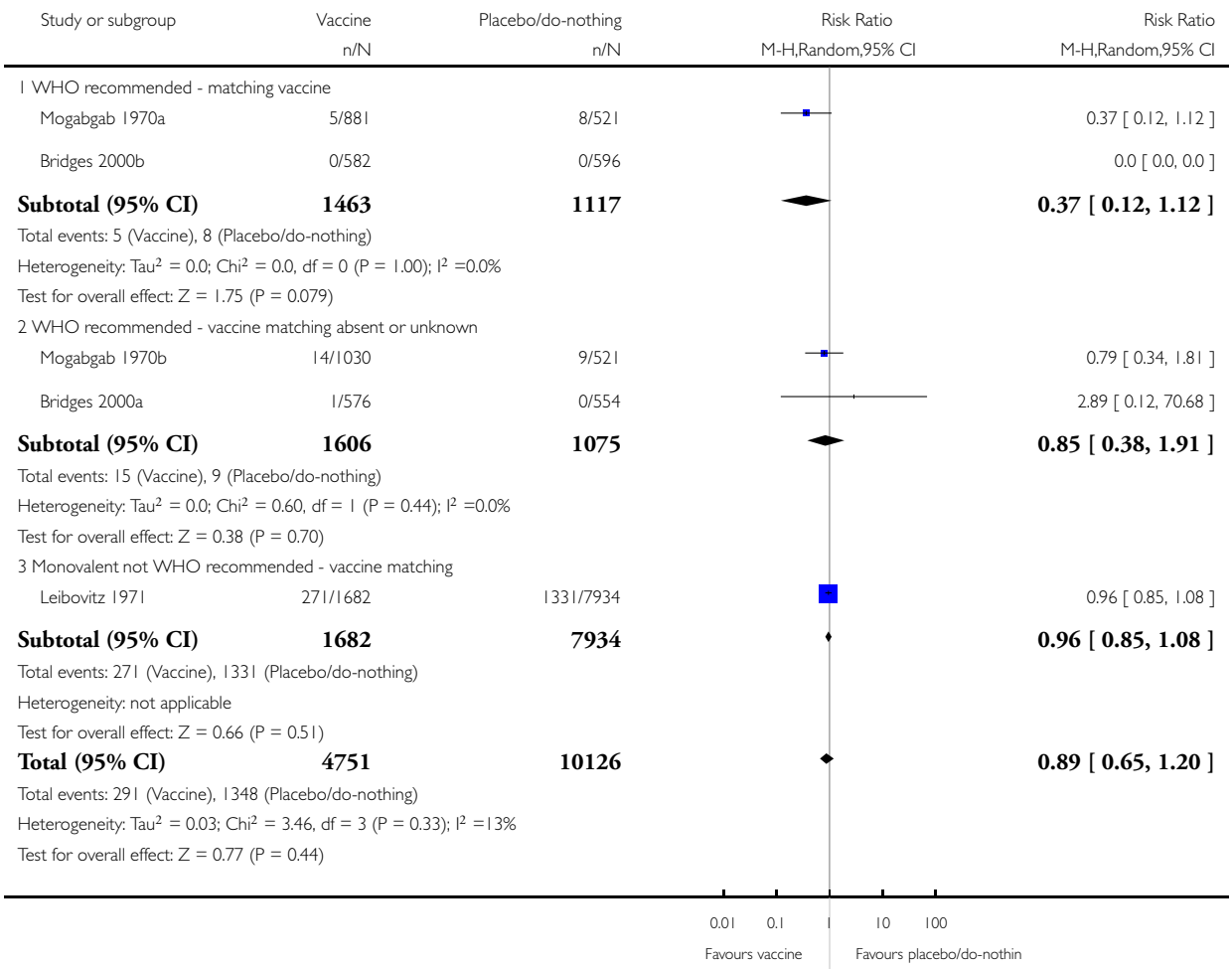
Study or subgroup	Vaccine N	Mean(SD)	Placebo/do-nothing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
Eddy 1970	1254	0.09 (0.69)	413	0.53 (1.7)		18.5 %	-0.44 [-0.61, -0.27]
Nichol 1995	409	1.29 (3.69)	416	2.03 (3.68)		5.1 %	-0.74 [-1.24, -0.24]
Mixu 2002	294	0.26 (0.48)	299	0.34 (0.48)		24.9 %	-0.08 [-0.16, 0.00]
Bridges 2000b	582	0.08 (0.21)	596	0.12 (0.21)		27.2 %	-0.04 [-0.06, -0.02]
Subtotal (95% CI)	**2539**		**1724**			**75.8 %**	**-0.21 [-0.36, -0.05]**
Heterogeneity: Tau² = 0.02; Chi² = 29.06, df = 3 (P<0.00001); I² =90%							
Test for overall effect: Z = 2.59 (P = 0.0097)							
2 WHO recommended - matching absent or unknown							
Bridges 2000a	576	0.29 (0.76)	554	0.2 (0.76)		24.2 %	0.09 [0.00, 0.18]
Subtotal (95% CI)	**576**		**554**			**24.2 %**	**0.09 [0.00, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.99 (P = 0.047)							
Total (95% CI)	**3115**		**2278**			**100.0 %**	**-0.13 [-0.25, 0.00]**
Heterogeneity: Tau² = 0.02; Chi² = 38.33, df = 4 (P<0.00001); I² =90%							
Test for overall effect: Z = 1.99 (P = 0.046)							

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 8 Hospitalisations

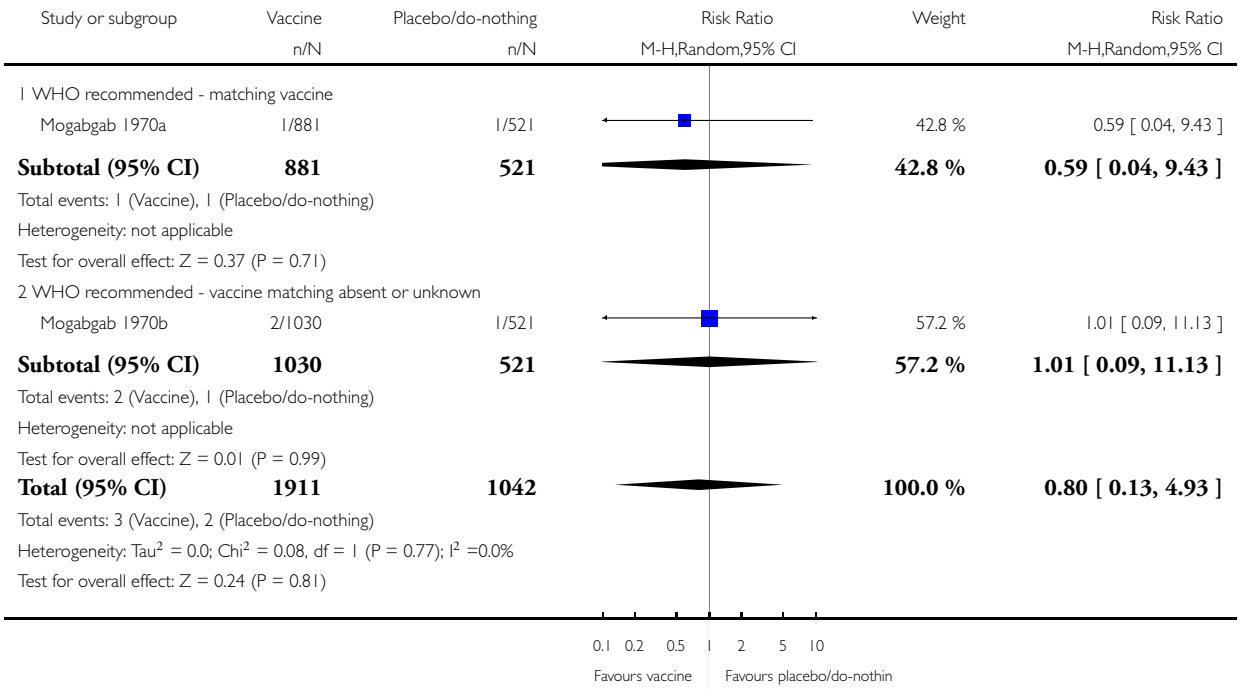


Analysis 1.9. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 9 Pneumonia.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 9 Pneumonia



Analysis 1.10. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 10 Clinical cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 10 Clinical cases (clinically defined without clear definition)

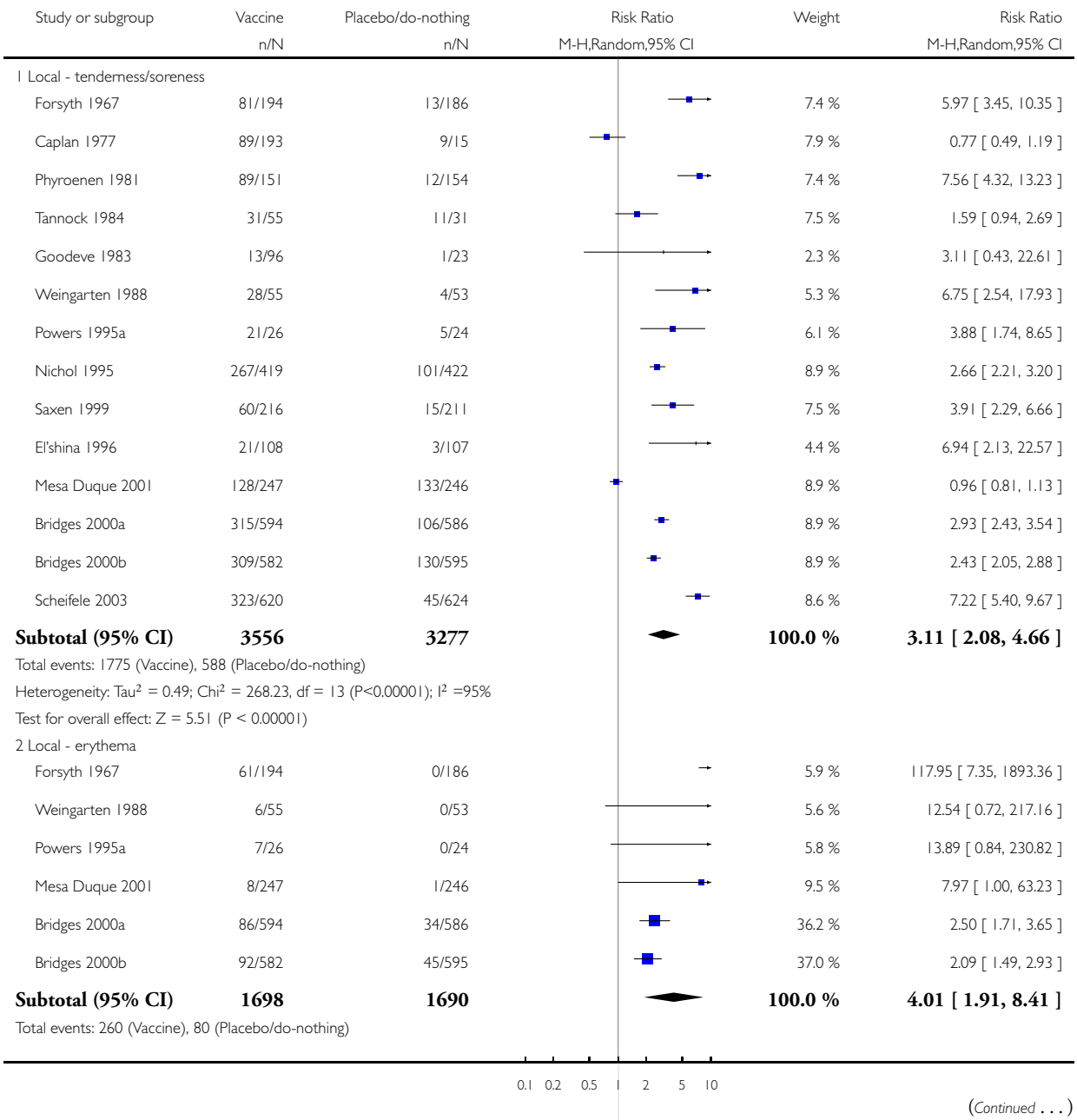
Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Eddy 1970	25/1254	42/413		21.1 %	0.20 [0.12, 0.32]
Hammond 1978	75/116	68/109		26.5 %	1.04 [0.85, 1.26]
Zhilova 1986b	100/895	138/936		25.8 %	0.76 [0.60, 0.96]
Subtotal (95% CI)	**2265**	**1458**		**73.3 %**	**0.56 [0.27, 1.16]**
Total events: 200 (Vaccine), 248 (Placebo/do-nothing)					
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 42.30$, df = 2 (P<0.00001); I^2 =95%					
Test for overall effect: Z = 1.56 (P = 0.12)					
2 WHO recommended - vaccine matching absent or unknown					
Zhilova 1986a	139/818	285/1385		26.7 %	0.83 [0.69, 0.99]
Subtotal (95% CI)	**818**	**1385**		**26.7 %**	**0.83 [0.69, 0.99]**
Total events: 139 (Vaccine), 285 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.041)					
Total (95% CI)	**3083**	**2843**		**100.0 %**	**0.63 [0.41, 0.99]**
Total events: 339 (Vaccine), 533 (Placebo/do-nothing)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 40.75$, df = 3 (P<0.00001); I^2 =93%					
Test for overall effect: Z = 2.00 (P = 0.045)					

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 11 Local harms



Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Local - tenderness/soreness					
Forsyth 1967	81/194	13/186		7.4 %	5.97 [3.45, 10.35]
Caplan 1977	89/193	9/15		7.9 %	0.77 [0.49, 1.19]
Phyroenen 1981	89/151	12/154		7.4 %	7.56 [4.32, 13.23]
Tannock 1984	31/55	11/31		7.5 %	1.59 [0.94, 2.69]
Goodeve 1983	13/96	1/23		2.3 %	3.11 [0.43, 22.61]
Weingarten 1988	28/55	4/53		5.3 %	6.75 [2.54, 17.93]
Powers 1995a	21/26	5/24		6.1 %	3.88 [1.74, 8.65]
Nichol 1995	267/419	101/422		8.9 %	2.66 [2.21, 3.20]
Saxen 1999	60/216	15/211		7.5 %	3.91 [2.29, 6.66]
El'shina 1996	21/108	3/107		4.4 %	6.94 [2.13, 22.57]
Mesa Duque 2001	128/247	133/246		8.9 %	0.96 [0.81, 1.13]
Bridges 2000a	315/594	106/586		8.9 %	2.93 [2.43, 3.54]
Bridges 2000b	309/582	130/595		8.9 %	2.43 [2.05, 2.88]
Scheifele 2003	323/620	45/624		8.6 %	7.22 [5.40, 9.67]
Subtotal (95% CI)	**3556**	**3277**		**100.0 %**	**3.11 [2.08, 4.66]**
Total events: 1775 (Vaccine), 588 (Placebo/do-nothing)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 268.23, df = 13 (P<0.00001); I^2 =95%					
Test for overall effect: Z = 5.51 (P < 0.00001)					
2 Local - erythema					
Forsyth 1967	61/194	0/186		5.9 %	117.95 [7.35, 1893.36]
Weingarten 1988	6/55	0/53		5.6 %	12.54 [0.72, 217.16]
Powers 1995a	7/26	0/24		5.8 %	13.89 [0.84, 230.82]
Mesa Duque 2001	8/247	1/246		9.5 %	7.97 [1.00, 63.23]
Bridges 2000a	86/594	34/586		36.2 %	2.50 [1.71, 3.65]
Bridges 2000b	92/582	45/595		37.0 %	2.09 [1.49, 2.93]
Subtotal (95% CI)	**1698**	**1690**		**100.0 %**	**4.01 [1.91, 8.41]**
Total events: 260 (Vaccine), 80 (Placebo/do-nothing)					

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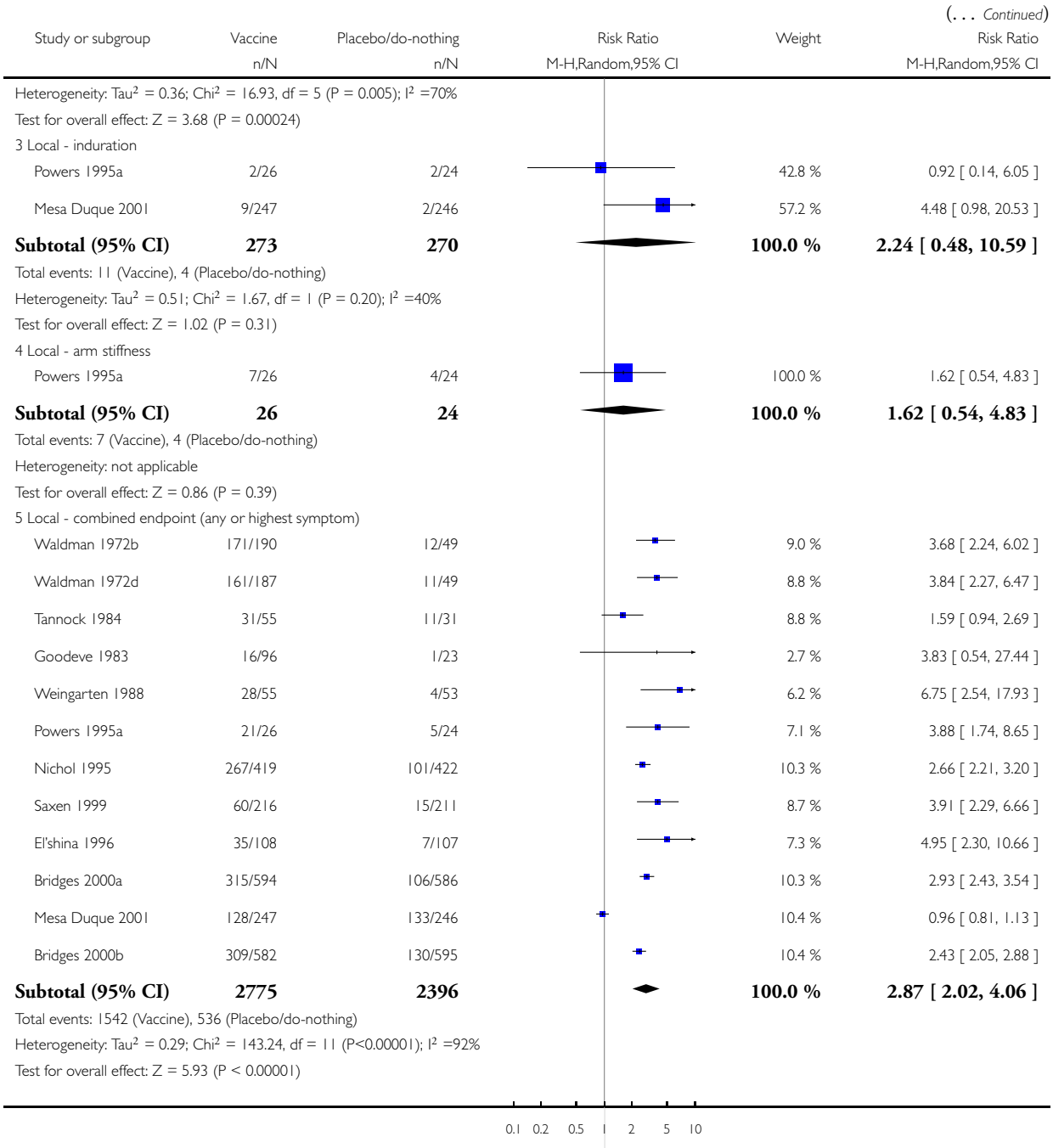

Analysis 1.12. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 12 Systemic harms.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 12 Systemic harms

Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Systemic - myalgia				
Powers 1995a	5/26	4/24		1.15 [0.35, 3.80]
Nichol 1995	26/419	24/422		1.09 [0.64, 1.87]
Scheifele 2003	34/620	18/624		1.90 [1.09, 3.33]
Phyroenen 1981	26/151	12/154		2.21 [1.16, 4.22]
Rocchi 1979a	2/126	2/110		0.87 [0.13, 6.09]
Subtotal (95% CI)	**1342**	**1334**		**1.54 [1.12, 2.11]**
Total events: 93 (Vaccine), 60 (Placebo/do-nothing)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.87, df = 4 (P = 0.42); I^2 =0.0%				
Test for overall effect: Z = 2.67 (P = 0.0076)				
2 Systemic - fever				
Caplan 1977	8/193	1/15		0.62 [0.08, 4.65]
Rocchi 1979a	0/126	2/110		0.17 [0.01, 3.60]
Phyroenen 1981	11/151	9/154		1.25 [0.53, 2.92]
Powers 1995a	0/26	0/24		0.0 [0.0, 0.0]
Nichol 1995	26/419	26/422		1.01 [0.59, 1.71]
El'shina 1996	3/108	2/107		1.49 [0.25, 8.72]
Saxen 1999	6/216	2/211		2.93 [0.60, 14.36]
Mesa Duque 2001	8/247	4/246		1.99 [0.61, 6.53]
Subtotal (95% CI)	**1486**	**1289**		**1.17 [0.80, 1.72]**
Total events: 62 (Vaccine), 46 (Placebo/do-nothing)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.35, df = 6 (P = 0.63); I^2 =0.0%				
Test for overall effect: Z = 0.80 (P = 0.42)				
3 Systemic - headache				
Forsyth 1967	0/194	2/186		0.19 [0.01, 3.97]
Caplan 1977	23/193	2/15		0.89 [0.23, 3.43]
Powers 1995a	9/26	4/24		2.08 [0.73, 5.87]
Nichol 1995	45/419	61/422		0.74 [0.52, 1.07]
El'shina 1996	12/108	4/107		2.97 [0.99, 8.93]

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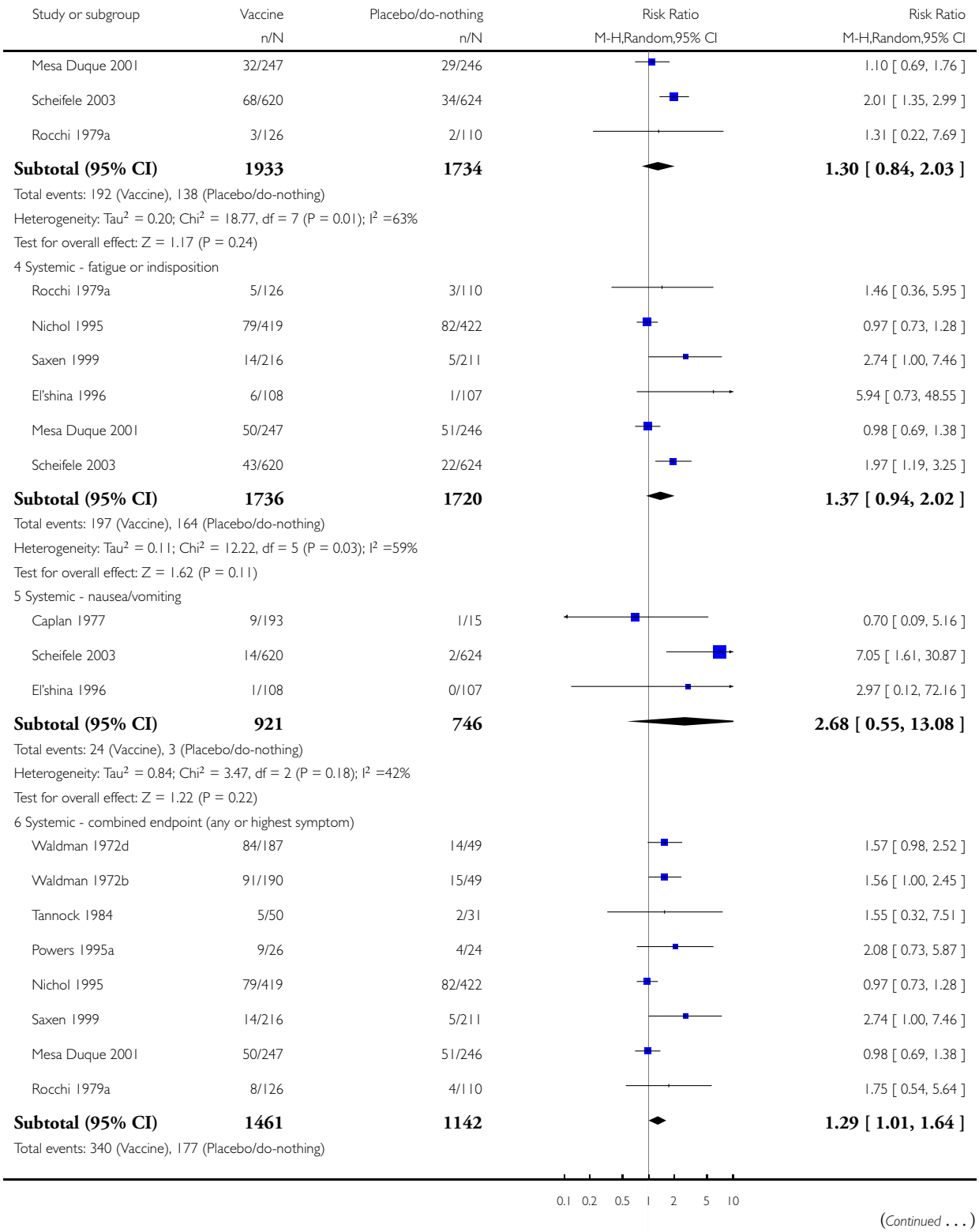

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Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.03; Chi² = 10.39, df = 7 (P = 0.17); I² =33%				
Test for overall effect: Z = 2.08 (P = 0.038)				

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 1 Influenza-like illness

Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Edwards 1994c	201/1114	240/1125		15.8 %	0.85 [0.71, 1.00]
Edwards 1994d	148/999	146/1016		10.0 %	1.03 [0.83, 1.27]
Subtotal (95% CI)	**2113**	**2141**		**25.7 %**	**0.92 [0.76, 1.12]**
Total events: 349 (Vaccine), 386 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.01; Chi² = 2.07, df = 1 (P = 0.15); I² =52%					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 WHO recommended - vaccine matching absent or unknown					
Edwards 1994a	89/872	92/878		5.8 %	0.97 [0.74, 1.28]
Edwards 1994b	208/1029	262/1064		17.3 %	0.82 [0.70, 0.96]
Nichol 1999a	751/2874	412/1433		42.7 %	0.91 [0.82, 1.01]
Subtotal (95% CI)	**4775**	**3375**		**65.8 %**	**0.89 [0.82, 0.97]**
Total events: 1048 (Vaccine), 766 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.0; Chi² = 1.55, df = 2 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 2.77 (P = 0.0057)					
3 Non WHO recommended - vaccine matching absent or unknown					
Monto 1982	70/144	74/140		8.5 %	0.92 [0.73, 1.16]
Subtotal (95% CI)	**144**	**140**		**8.5 %**	**0.92 [0.73, 1.16]**
Total events: 70 (Vaccine), 74 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	**7032**	**5656**		**100.0 %**	**0.90 [0.84, 0.96]**

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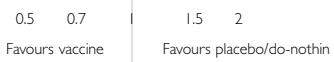
Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 1467 (Vaccine), 1226 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.0; Chi² = 3.76, df = 5 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 3.14 (P = 0.0017)					



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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 2 Influenza

Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Edwards 1994c	23/1114	70/1125		27.4 %	0.33 [0.21, 0.53]
Edwards 1994d	20/999	33/1016		23.0 %	0.62 [0.36, 1.07]
Subtotal (95% CI)	**2113**	**2141**		**50.5 %**	**0.44 [0.24, 0.81]**
Total events: 43 (Vaccine), 103 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.13; Chi² = 2.86, df = 1 (P = 0.09); I² =65%					
Test for overall effect: Z = 2.62 (P = 0.0087)					
2 WHO recommended - vaccine matching absent or unknown					
Edwards 1994a	6/872	28/878		12.3 %	0.22 [0.09, 0.52]
Edwards 1994b	23/1029	47/1064		25.9 %	0.51 [0.31, 0.83]
Subtotal (95% CI)	**1901**	**1942**		**38.2 %**	**0.36 [0.16, 0.82]**
Total events: 29 (Vaccine), 75 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.24; Chi² = 2.80, df = 1 (P = 0.09); I² =64%					
Test for overall effect: Z = 2.44 (P = 0.015)					
3 Non WHO recommended - vaccine matching absent or unknown					
Rytel 1977	3/95	8/48		6.6 %	0.19 [0.05, 0.68]
Monto 1982	2/144	8/140		4.8 %	0.24 [0.05, 1.12]
Subtotal (95% CI)	**239**	**188**		**11.3 %**	**0.21 [0.08, 0.56]**
Total events: 5 (Vaccine), 16 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.0; Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%					
Test for overall effect: Z = 3.11 (P = 0.0018)					

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Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**4253**	**4271**	◆	**100.0 %**	**0.38 [0.27, 0.55]**
Total events: 77 (Vaccine), 194 (Placebo/do-nothing)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.54$, df = 5 (P = 0.18); $I^2 = 34\%$					
Test for overall effect: Z = 5.34 (P < 0.00001)					

Analysis 2.3. Comparison 2 Live aerosol vaccine versus placebo or do-nothing, Outcome 3 Complications (bronchitis, otitis, pneumonia).

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 3 Complications (bronchitis, otitis, pneumonia)

Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Non WHO recommended - vaccine matching absent or unknown					
Sumarokow 1971	1/9945	4/9942	◆	100.0 %	0.25 [0.03, 2.24]
Total (95% CI)	**9945**	**9942**	◆	**100.0 %**	**0.25 [0.03, 2.24]**
Total events: 1 (Vaccine), 4 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					

Analysis 2.4. Comparison 2 Live aerosol vaccine versus placebo or do-nothing, Outcome 4 Influenza cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 4 Influenza cases (clinically defined without clear definition)

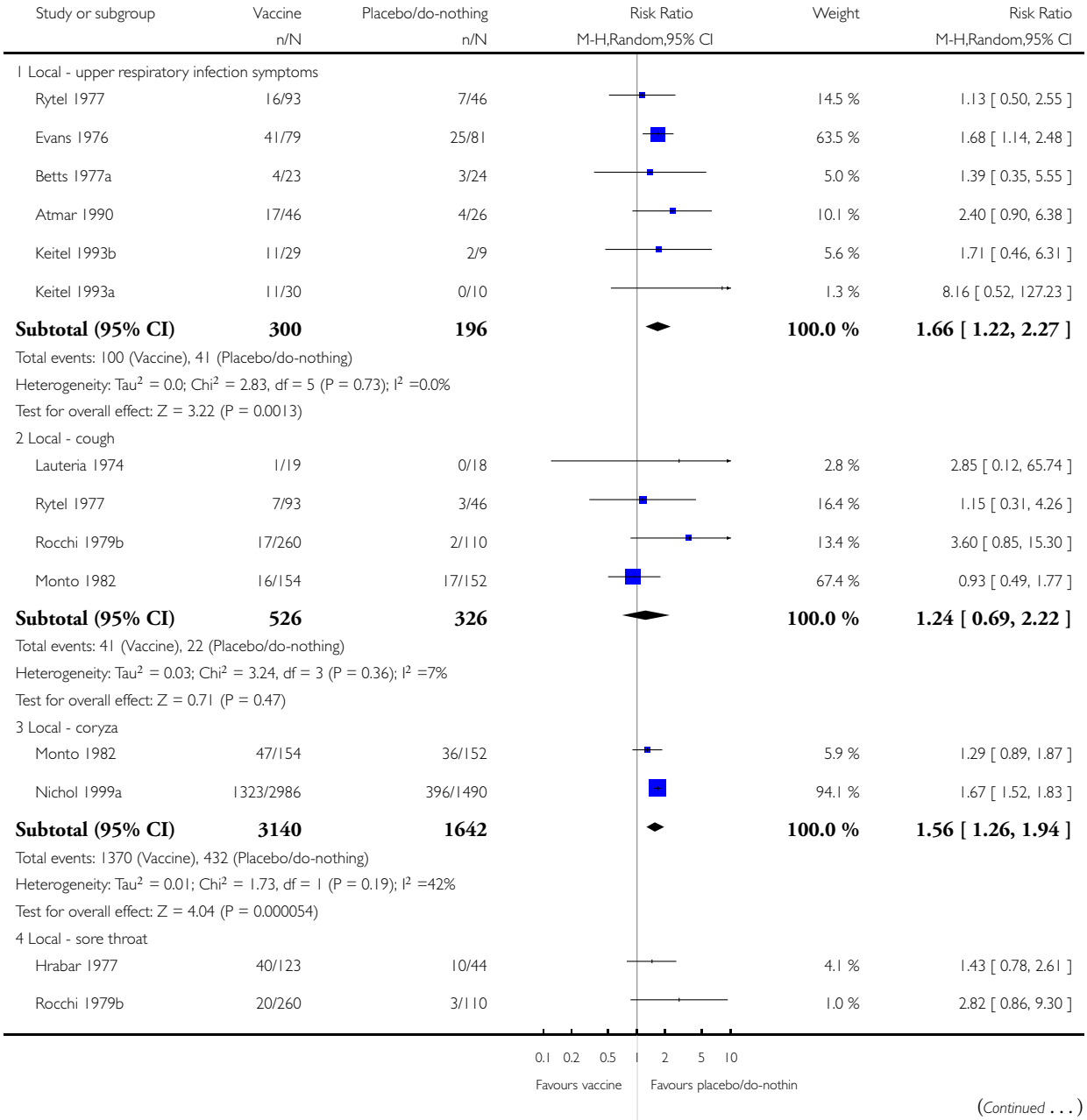
Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Zhilova 1986b	92/995	138/936		27.6 %	0.63 [0.49, 0.80]
Subtotal (95% CI)	**995**	**936**		**27.6 %**	**0.63 [0.49, 0.80]**
Total events: 92 (Vaccine), 138 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.68 (P = 0.00023)					
2 WHO recommended - vaccine matching absent or unknown					
Zhilova 1986a	150/697	285/1385		33.0 %	1.05 [0.88, 1.25]
Subtotal (95% CI)	**697**	**1385**		**33.0 %**	**1.05 [0.88, 1.25]**
Total events: 150 (Vaccine), 285 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					
3 Non WHO recommended - vaccine matching absent or unknown					
Sumarokow 1971	1407/9945	1429/9942		39.4 %	0.98 [0.92, 1.05]
Subtotal (95% CI)	**9945**	**9942**		**39.4 %**	**0.98 [0.92, 1.05]**
Total events: 1407 (Vaccine), 1429 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
Total (95% CI)	**11637**	**12263**		**100.0 %**	**0.89 [0.71, 1.11]**
Total events: 1649 (Vaccine), 1852 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.03; Chi² = 12.72, df = 2 (P = 0.002); I² =84%					
Test for overall effect: Z = 1.03 (P = 0.30)					

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 5 Local harms



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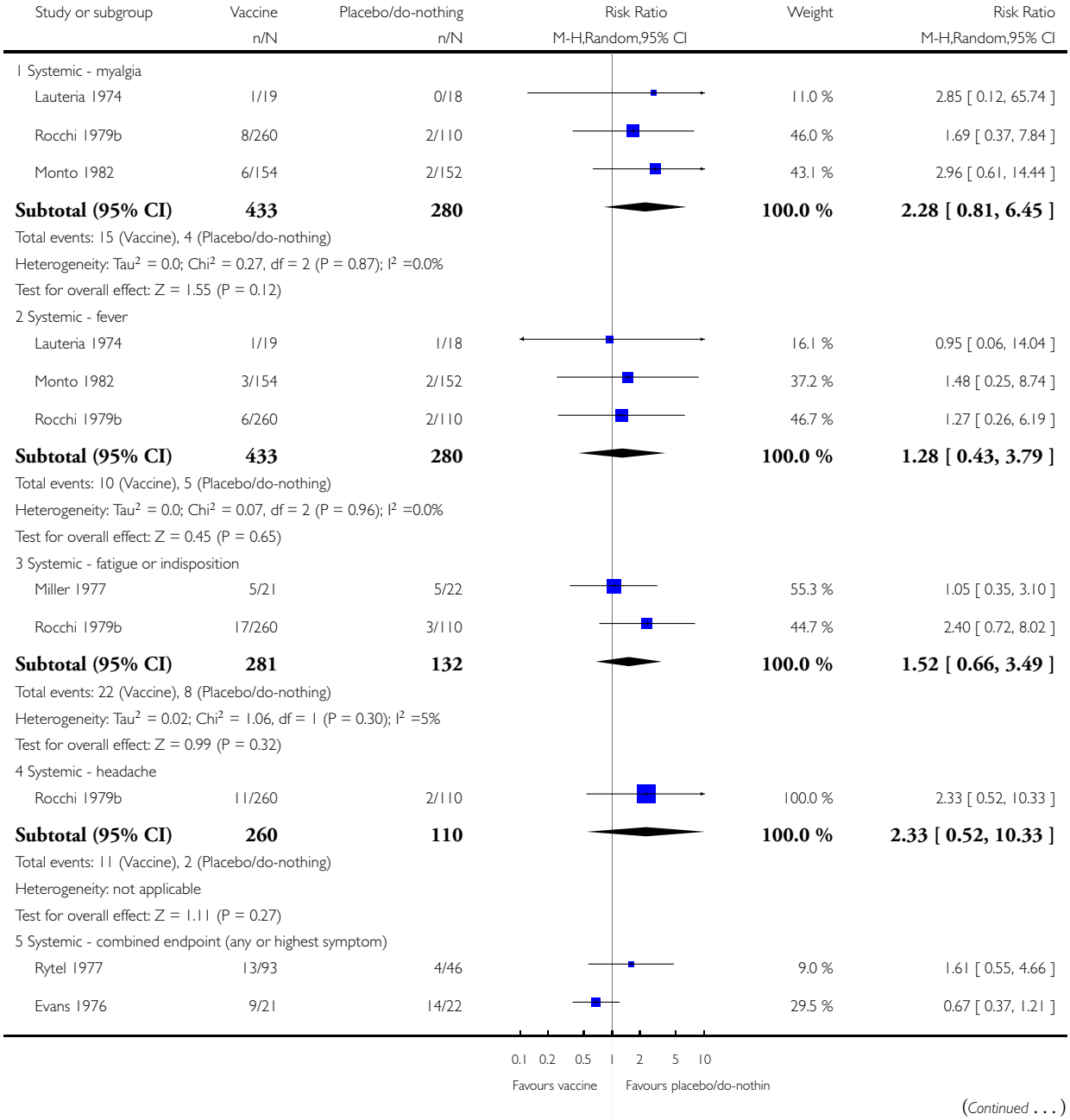
Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Monto 1982	40/154	16/152		5.2 %	2.47 [1.45, 4.21]
Atmar 1990	13/46	2/26		0.8 %	3.67 [0.90, 15.03]
Nichol 1999a	794/2986	243/1490		88.9 %	1.63 [1.43, 1.86]
Subtotal (95% CI)	**3569**	**1822**		**100.0 %**	**1.73 [1.44, 2.08]**
Total events: 907 (Vaccine), 274 (Placebo/do-nothing)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.38$, df = 4 (P = 0.36); $I^2 = 9\%$					
Test for overall effect: Z = 5.83 (P < 0.00001)					
5 Local - hoarseness					
Monto 1982	11/154	9/152		100.0 %	1.21 [0.51, 2.83]
Subtotal (95% CI)	**154**	**152**		**100.0 %**	**1.21 [0.51, 2.83]**
Total events: 11 (Vaccine), 9 (Placebo/do-nothing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
6 Local - combined endpoint (any or highest symptom)					
Rytel 1977	16/93	7/46		1.2 %	1.13 [0.50, 2.55]
Monto 1982	47/154	36/152		5.9 %	1.29 [0.89, 1.87]
Nichol 1999a	1323/2986	396/1490		92.9 %	1.67 [1.52, 1.83]
Subtotal (95% CI)	**3233**	**1688**		**100.0 %**	**1.56 [1.31, 1.87]**
Total events: 1386 (Vaccine), 439 (Placebo/do-nothing)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.53$, df = 2 (P = 0.28); $I^2 = 21\%$					
Test for overall effect: Z = 4.92 (P < 0.00001)					

Analysis 2.6. Comparison 2 Live aerosol vaccine versus placebo or do-nothing, Outcome 6 Systemic harms.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 6 Systemic harms



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Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Miller 1977	31/79	21/81		48.1 %	1.51 [0.96, 2.40]
Monto 1982	6/154	2/152		4.0 %	2.96 [0.61, 14.44]
Rocchi 1979b	23/260	4/110		9.4 %	2.43 [0.86, 6.87]
Subtotal (95% CI)	**607**	**411**		**100.0 %**	**1.40 [0.82, 2.38]**
Total events: 82 (Vaccine), 45 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.17; Chi² = 8.39, df = 4 (P = 0.08); I² =52%					
Test for overall effect: Z = 1.24 (P = 0.22)					

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 1 Influenza-like illness

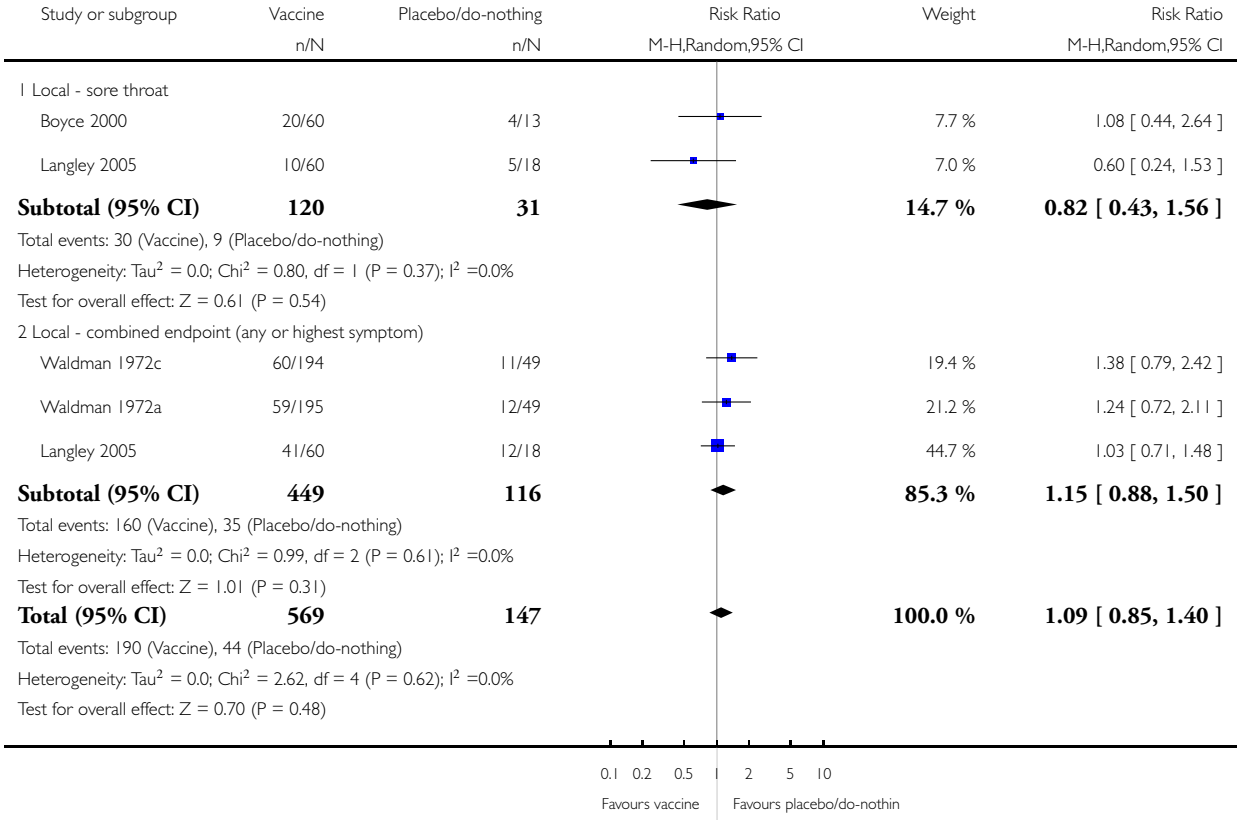
Study or subgroup	Vaccine n/N	Placebo/do-nothing n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended - matching vaccine					
Waldman 1972a	11/195	10/49		14.7 %	0.28 [0.12, 0.61]
Waldman 1969c	92/479	33/118		34.0 %	0.69 [0.49, 0.97]
Subtotal (95% CI)	**674**	**167**		**48.7 %**	**0.47 [0.19, 1.13]**
Total events: 103 (Vaccine), 43 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.32; Chi² = 4.23, df = 1 (P = 0.04); I² =76%					
Test for overall effect: Z = 1.69 (P = 0.092)					
2 WHO recommended - vaccine matching absent or unknown					
Waldman 1972c	17/194	10/49		17.0 %	0.43 [0.21, 0.88]
Waldman 1969d	100/471	33/119		34.3 %	0.77 [0.55, 1.07]
Subtotal (95% CI)	**665**	**168**		**51.3 %**	**0.63 [0.37, 1.07]**
Total events: 117 (Vaccine), 43 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.09; Chi² = 2.05, df = 1 (P = 0.15); I² =51%					
Test for overall effect: Z = 1.70 (P = 0.090)					
Total (95% CI)	**1339**	**335**		**100.0 %**	**0.58 [0.40, 0.83]**
Total events: 220 (Vaccine), 86 (Placebo/do-nothing)					
Heterogeneity: Tau² = 0.07; Chi² = 6.70, df = 3 (P = 0.08); I² =55%					
Test for overall effect: Z = 2.95 (P = 0.0031)					

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

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 2 Local harms

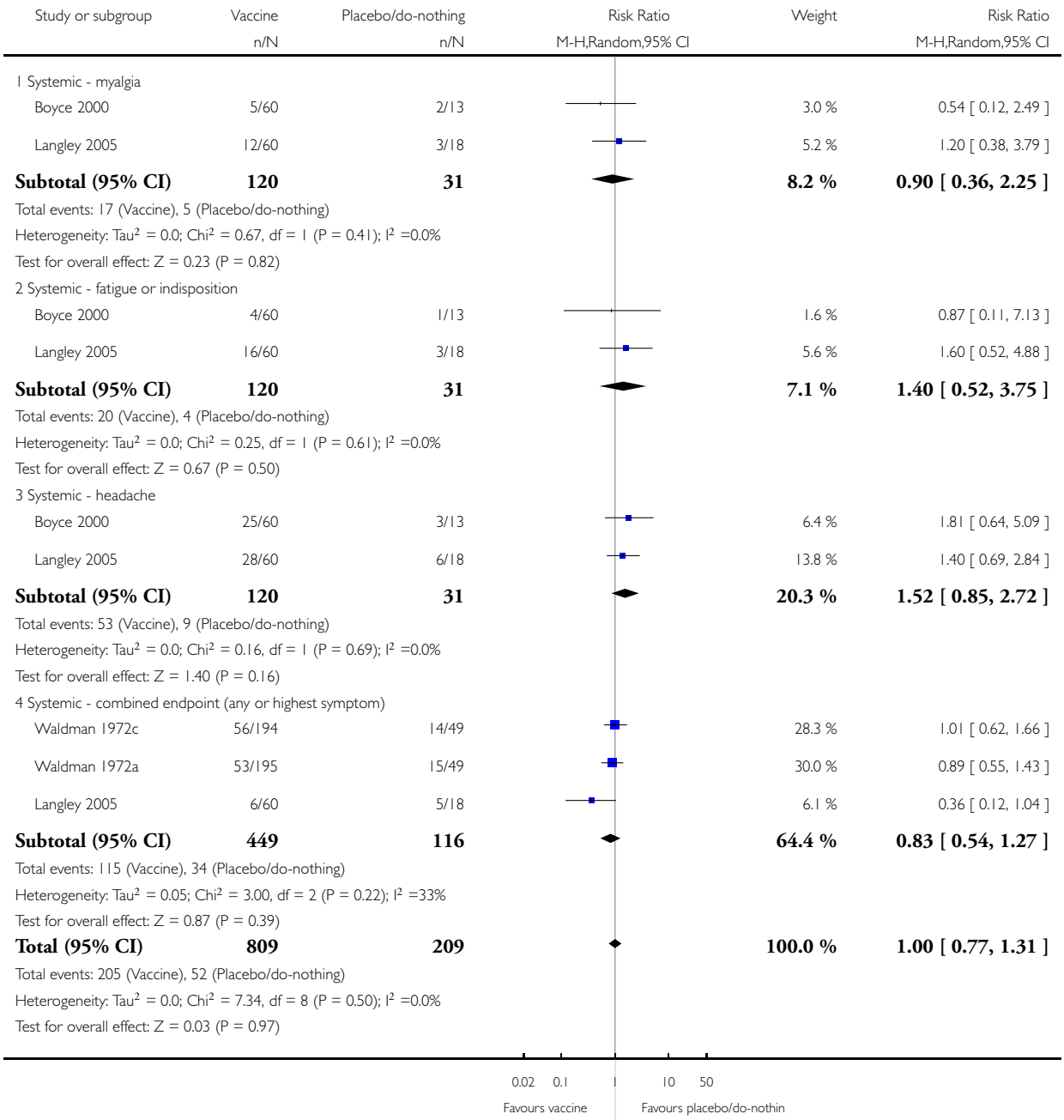


Analysis 3.3. Comparison 3 Inactivated aerosol vaccine versus placebo or do-nothing, Outcome 3 Systemic harms.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 3 Systemic harms



Analysis 4.1. Comparison 4 1968 to 1969 pandemic: Inactivated polyvalent parenteral vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 1 Influenza-like illness

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

Analysis 4.2. Comparison 4 1968 to 1969 pandemic: Inactivated polyvalent parenteral vaccine versus placebo, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 2 Influenza

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

Analysis 4.3. Comparison 4 1968 to 1969 pandemic: Inactivated polyvalent parenteral vaccine versus placebo, Outcome 3 Hospitalisations.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 3 Hospitalisations

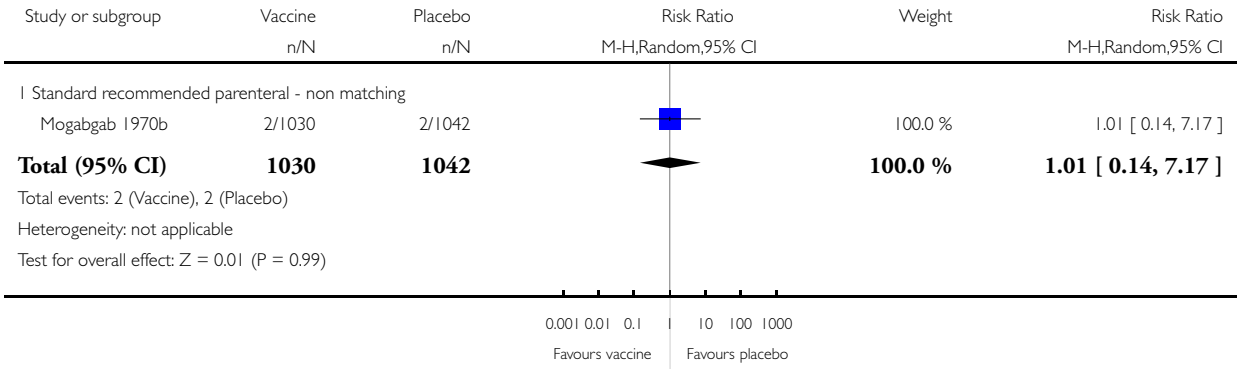
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Standard recommended parenteral - non matching					
Mogabgab 1970b	14/1030	17/1042		100.0 %	0.83 [0.41, 1.68]
Total (95% CI)	**1030**	**1042**		**100.0 %**	**0.83 [0.41, 1.68]**
Total events: 14 (Vaccine), 17 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					

Analysis 4.4. Comparison 4 1968 to 1969 pandemic: Inactivated polyvalent parenteral vaccine versus placebo, Outcome 4 Pneumonia.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 4 Pneumonia

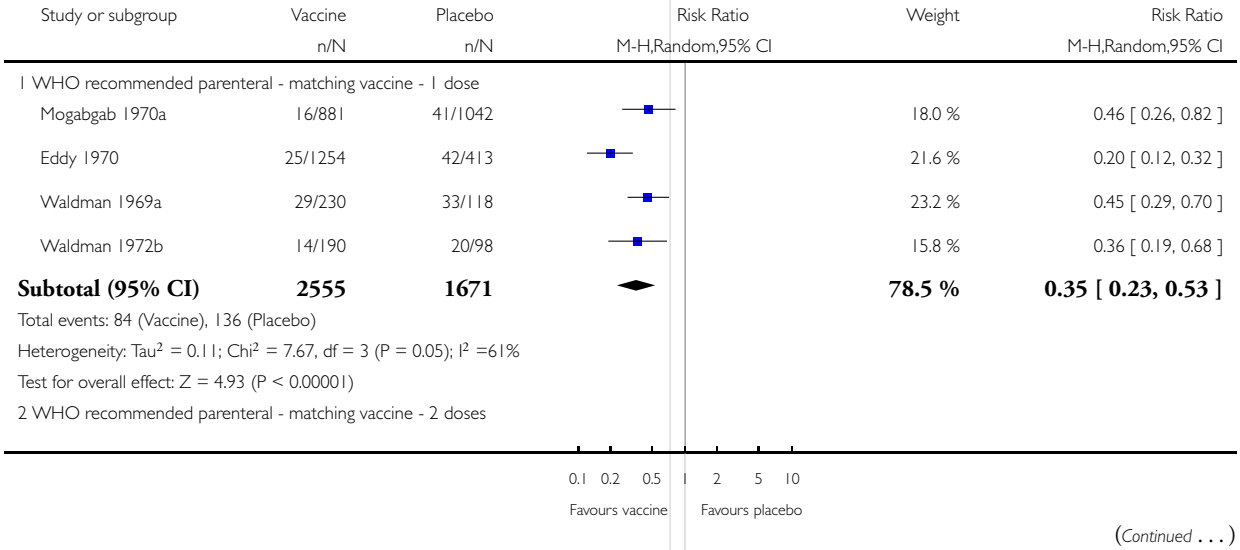


Analysis 5.1. Comparison 5 1968 to 1969 pandemic: Inactivated monovalent parenteral vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 1 Influenza-like illness



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Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Waldman 1969a	23/235	33/119		21.5 %	0.35 [0.22, 0.57]
Subtotal (95% CI)	**235**	**119**		**21.5 %**	**0.35 [0.22, 0.57]**
Total events: 23 (Vaccine), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.21 (P = 0.000025)					
Total (95% CI)	**2790**	**1790**		**100.0 %**	**0.35 [0.25, 0.48]**
Total events: 107 (Vaccine), 169 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 7.68, df = 4 (P = 0.10); I^2 =48%					
Test for overall effect: Z = 6.47 (P < 0.00001)					

Analysis 5.2. Comparison 5 1968 to 1969 pandemic: Inactivated monovalent parenteral vaccine versus placebo, Outcome 2 Influenza.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 2 Influenza

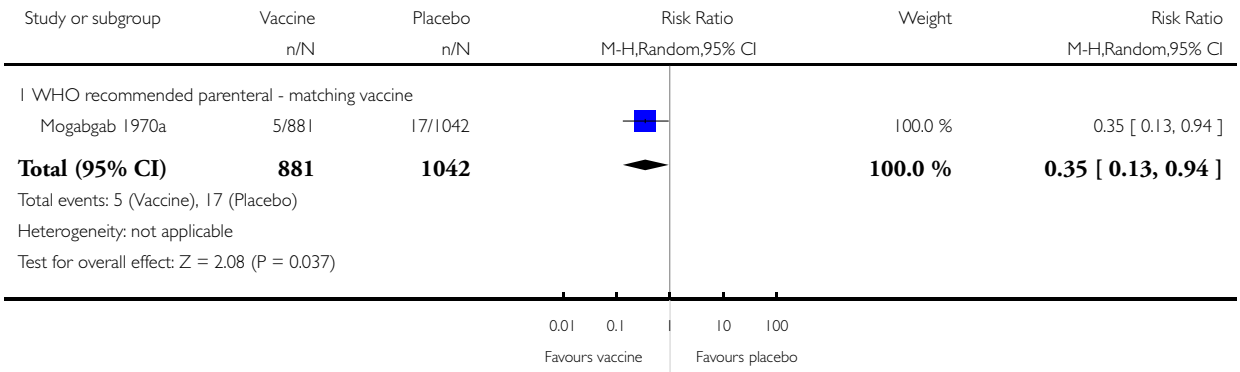
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 WHO recommended parenteral - matching vaccine					
Mogabgab 1970a	2/881	32/1042		100.0 %	0.07 [0.02, 0.31]
Total (95% CI)	**881**	**1042**		**100.0 %**	**0.07 [0.02, 0.31]**
Total events: 2 (Vaccine), 32 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.58 (P = 0.00034)					

Analysis 5.3. Comparison 5 1968 to 1969 pandemic: Inactivated monovalent parenteral vaccine versus placebo, Outcome 3 Hospitalisations.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 3 Hospitalisations

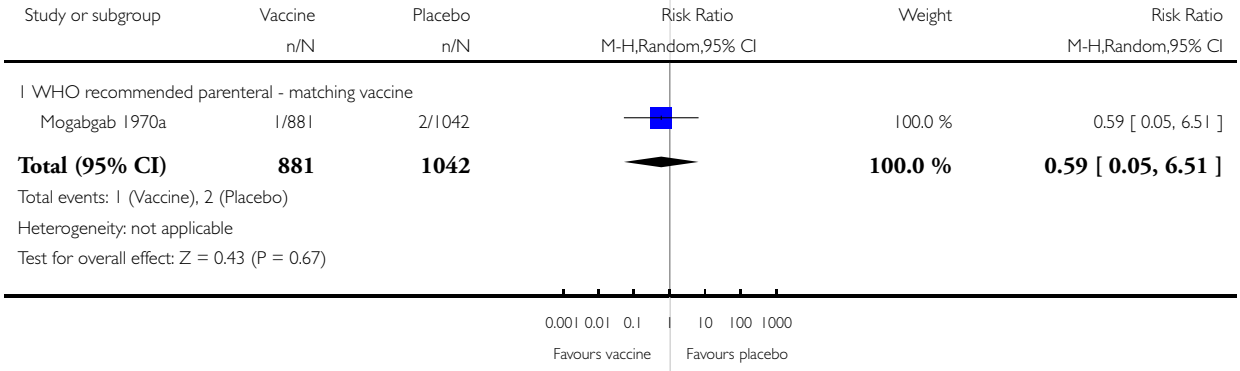


Analysis 5.4. Comparison 5 1968 to 1969 pandemic: Inactivated monovalent parenteral vaccine versus placebo, Outcome 4 Pneumonia.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 4 Pneumonia



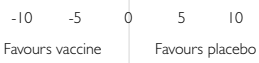
Analysis 5.5. Comparison 5 1968 to 1969 pandemic: Inactivated monovalent parenteral vaccine versus placebo, Outcome 5 Working days lost.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 5 Working days lost

Study or subgroup	Vaccine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended parenteral - matching vaccine							
Eddy 1970	1254	0.09 (0.69)	413	0.54 (1.52)		100.0 %	-0.45 [-0.60, -0.30]
Total (95% CI)	**1254**		**413**			**100.0 %**	**-0.45 [-0.60, -0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.82 (P < 0.00001)							



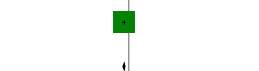
Analysis 5.6. Comparison 5 1968 to 1969 pandemic: Inactivated monovalent parenteral vaccine versus placebo, Outcome 6 Days ill.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 6 Days ill

Study or subgroup	Vaccine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 WHO recommended - matching vaccine							
Eddy 1970	1254	0.09 (0.69)	413	0.54 (1.52)		100.0 %	-0.45 [-0.60, -0.30]
Total (95% CI)	**1254**		**413**			**100.0 %**	**-0.45 [-0.60, -0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.82 (P < 0.00001)							

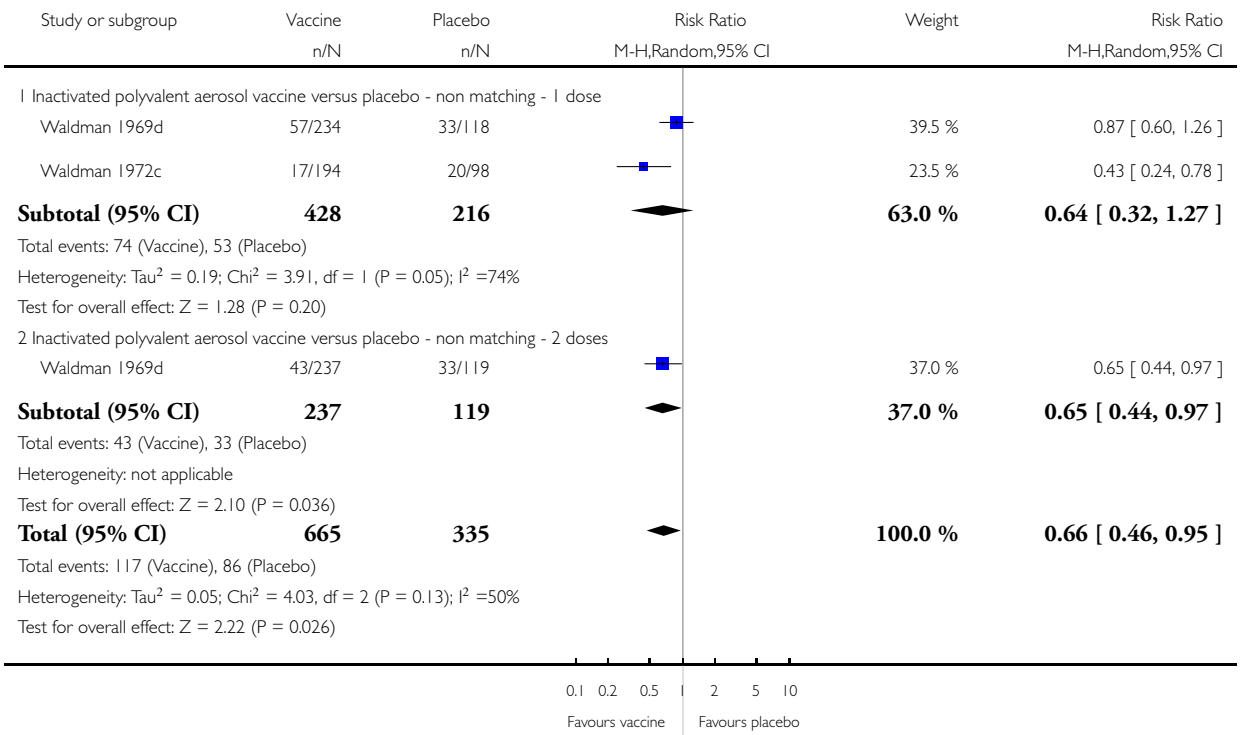


Analysis 6.1. Comparison 6 1968 to 1969 pandemic: Inactivated polyvalent aerosol vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

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

Outcome: 1 Influenza-like illness



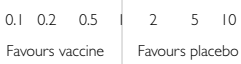
Analysis 7.1. Comparison 7 1968 to 1969 pandemic: Inactivated monovalent aerosol vaccine versus placebo, Outcome 1 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy adults

Comparison: 7 1968 to 1969 pandemic: Inactivated monovalent aerosol vaccine versus placebo

Outcome: 1 Influenza-like illness

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Inactivated monovalent aerosol vaccine versus placebo - matching - 1 dose					
Waldman 1969c	54/239	33/118		37.9 %	0.81 [0.56, 1.17]
Waldman 1972a	11/195	20/98		25.7 %	0.28 [0.14, 0.55]
Subtotal (95% CI)	**434**	**216**		**63.6 %**	**0.49 [0.17, 1.41]**
Total events: 65 (Vaccine), 53 (Placebo)					
Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 7.18$, df = 1 (P = 0.01); $I^2 = 86\%$					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Inactivated monovalent aerosol vaccine versus placebo - matching - 2 doses					
Waldman 1969c	38/240	33/119		36.4 %	0.57 [0.38, 0.86]
Subtotal (95% CI)	**240**	**119**		**36.4 %**	**0.57 [0.38, 0.86]**
Total events: 38 (Vaccine), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.67 (P = 0.0076)					
Total (95% CI)	**674**	**335**		**100.0 %**	**0.54 [0.32, 0.91]**
Total events: 103 (Vaccine), 86 (Placebo)					
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 7.31$, df = 2 (P = 0.03); $I^2 = 73\%$					
Test for overall effect: Z = 2.31 (P = 0.021)					



Analysis 8.1. Comparison 8 1968 to 1969 pandemic: Live aerosol vaccine versus placebo, Outcome 1 Influenza cases (clinically defined without clear definition).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 8 1968 to 1969 pandemic: Live aerosol vaccine versus placebo

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

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Non matching					
Sumarokow 1971	1407/9945	1429/9942		100.0 %	0.98 [0.92, 1.05]
Total (95% CI)	**9945**	**9942**		**100.0 %**	**0.98 [0.92, 1.05]**
Total events: 1407 (Vaccine), 1429 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					

Analysis 8.2. Comparison 8 1968 to 1969 pandemic: Live aerosol vaccine versus placebo, Outcome 2 Complications (bronchitis, otitis, pneumonia).

Review: Vaccines for preventing influenza in healthy adults

Comparison: 8 1968 to 1969 pandemic: Live aerosol vaccine versus placebo

Outcome: 2 Complications (bronchitis, otitis, pneumonia)

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Non matching					
Sumarokow 1971	1/9945	4/9942		100.0 %	0.25 [0.03, 2.24]
Total (95% CI)	**9945**	**9942**		**100.0 %**	**0.25 [0.03, 2.24]**
Total events: 1 (Vaccine), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					

APPENDICES

Appendix 1. MEDLINE search strategy for 2004 update

MEDLINE

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

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

#3 #1 OR #2

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

#5 controlled clinical trial*[Title/Abstract] OR randomised controlled trial*[Title/Abstract] OR clinical trial*[Title/Abstract] OR random allocation[Title/Abstract] OR random*[Title/Abstract] OR placebo[Title/Abstract] OR double - blind[Title/Abstract] OR single - blind[Title/Abstract] OR RCT[Title/Abstract] OR CCT[Title/Abstract] OR allocation[Title/Abstract] OR follow - up[Title/Abstract]

#6 #4 OR #5

#7 #3 AND #6

FEEDBACK

Inconsistency between results and abstract

Summary

We feel there is some inconsistency between results and abstract of this review regarding off work time.

In the results it states that 0.4 days are saved, but that this result is not statistically significant. In the abstract, however, this difference is labelled significant. Can you help us in understanding this?

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

The difference is statistically significat as it says in the abstract. In the results the word "statistical" has been used instead of "clinical". Indeed the meaning of the comment was to underline that, although statistically significant, a difference of 0.4 day is clinically inconsistent.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms

Vittorio Demicheli

Contributors

JC van der Wouden

Feedback added 16/04/07

Comments regarding the conclusion

Summary

Your conclusion is confusing. You write: "Universal immunization of healthy adults is not supported by the results of this review." If so, why the first sentence? You wrote in the Discussion that "serologically confirmed cases of influenza are only part of the spectum of clinical effectiveness." Furthermore, it would be helpful if you had explained the difference between influenza and influenza-like illness in the abstract. Also, the title of the synopsis is inaccurate. Why say "not enough evidence" when there are so many trials in your review? It should read: Clinical trials do not support the universal recommendation, etc. And "by a quarter" is not going to be understood by the general public. Please put in absolute terms.
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

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

Contributors

Maryann Napoli
Feedback added 05/04/06

WHAT'S NEW

Last assessed as up-to-date: 8 January 2006.

10 May 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1999

26 April 2008	Amended	Converted to new review format.
15 April 2007	Feedback has been incorporated	Feedback added to review
20 November 2006	New citation required and conclusions have changed	Substantive amendment
4 April 2006	Feedback has been incorporated	Feedback commented added to review.
9 January 2006	New search has been performed	Searches conducted.

(*Continued*)

30 November 2003	New search has been performed	Searches conducted.
27 December 1997	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

For the 2006 update Tom Jefferson (TJ), Daniela Rivetti (DR) and and Vittorio Demicheli (VD) designed the update.

TJ and DR wrote the protocol, Alessandro Rivetti (AR) carried out the searches.

TJ and DR applied inclusion criteria.

TJ, DR and AR extracted data.

Carlo Di Pietrantonj (CDP) arbitrated and checked the data extraction.

CDP and DR performed the meta-analysis and carried out statistical testing.

TJ and AR wrote the final report.

All authors contributed to both the protocol and final report.

Statistical support to previous review versions was provided by JJ Deeks.

DECLARATIONS OF INTEREST

TJ owned shares in Glaxo SmithKline and received consultancy fees from Sanofi Synthelabo and Roche. All other authors have no conflicts to declare.

Glossary

Efficacy:

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

Effectiveness:

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

Influenza:

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

Influenza-like illness (ILI):

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

SOURCES OF SUPPORT

Internal sources

- ASL 19 and 20, Piemonte, Italy.

External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

Influenza, Human [*prevention & control]; Influenza Vaccines [adverse effects; *therapeutic use]

MeSH check words

Adult; Humans