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Influenza vaccine for chronic obstructive pulmonary disease (COPD) (Review)

Kopsaftis Z, Wood-Baker R, Poole P

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[Intervention Review]

Influenza vaccine for chronic obstructive pulmonary disease (COPD)

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ABSTRACT

Background

Influenza vaccinations are currently recommended in the care of people with COPD, but these recommendations are based largely on evidence from observational studies, with very few randomised controlled trials (RCTs) reported. Influenza infection causes excess morbidity and mortality in people with COPD, but there is also the potential for influenza vaccination to cause adverse effects, or not to be cost effective.

Objectives

To determine whether influenza vaccination in people with COPD reduces respiratory illness, reduces mortality, is associated with excess adverse events, and is cost effective.

Search methods

We searched the Cochrane Airways Trials Register, two clinical trials registries, and reference lists of articles. A number of drug companies we contacted also provided references. The latest search was carried out in December 2017.

Selection criteria

RCTs that compared live or inactivated virus vaccines with placebo, either alone or with another vaccine, in people with COPD.

Data collection and analysis

Two review authors independently extracted data. All entries were double-checked. We contacted study authors and drug companies for missing information. We used standard methods expected by Cochrane.

Main results

We included 11 RCTs with 6750 participants, but only six of these included people with COPD (2469 participants). The others were conducted on elderly and high-risk individuals, some of whom had chronic lung disease. Interventions compared with placebo were inactivated virus injections and live attenuated intranasal virus vaccines. Some studies compared intra-muscular inactivated vaccine and intranasal live attenuated vaccine with intra-muscular inactivated vaccine and intranasal placebo. Studies were conducted in the UK, USA and Thailand.

Inactivated vaccine reduced the total number of exacerbations per vaccinated participant compared with those who received placebo (mean difference (MD) -0.37, 95% confidence interval (CI) -0.64 to -0.11; $P = 0.006$; two RCTs, 180 participants; low quality evidence). This was due to the reduction in 'late' exacerbations, occurring after three or four weeks (MD -0.39, 95% CI -0.61 to -0.18; $P = 0.0004$; two RCTs,

180 participants; low quality evidence). Both in people with COPD, and in older people (only a minority of whom had COPD), there were significantly more local adverse reactions in people who had received the vaccine, but the effects were generally mild and transient.

There was no evidence of an effect of intranasal live attenuated virus when this was added to inactivated intramuscular vaccination.

Two studies evaluating mortality for influenza vaccine versus placebo were too small to have detected any effect on mortality. However, a large study (N=2215) noted that there was no difference in mortality when adding live attenuated virus to inactivated virus vaccination,

Authors' conclusions

It appeared, from the limited number of RCTs we were able to include, all of which were more than a decade old, that inactivated vaccine reduced exacerbations in people with COPD. The size of effect was similar to that seen in large observational studies, and was due to a reduction in exacerbations occurring three or more weeks after vaccination, and due to influenza. There was a mild increase in transient local adverse effects with vaccination, but no evidence of an increase in early exacerbations. Addition of live attenuated virus to the inactivated vaccine was not shown to confer additional benefit.

PLAIN LANGUAGE SUMMARY

Influenza vaccine for people with chronic obstructive pulmonary disease (COPD)

Question

Do influenza vaccines reduce episodes of respiratory illness or death in people with chronic obstructive pulmonary disease (COPD)?

Background

COPD is an umbrella term used to describe progressive lung diseases, including emphysema, chronic bronchitis, and refractory (non-reversible) asthma. The disease is characterized by increasing breathlessness. Despite the almost universal recommendation that people with COPD should receive an annual influenza vaccination, very few randomised controlled trials (studies in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention) have evaluated the effect of this treatment. Influenza vaccines may be produced with an inactivated virus (small particles of the virus wall) or live attenuated virus (reduced power but still alive).

To try to answer our question, we conducted a detailed search for studies from around the world that investigated the use of influenza vaccines for people with COPD.

Study characteristics

We included six studies with 2469 participants with COPD, and a further five studies with 4281 older or high risk participants, a proportion of whom had chronic lung disease.

Key results

We found some moderate-quality evidence that inactivated influenza vaccine did decrease 'flare ups' of COPD, especially those that are related to the influenza virus itself. The inactivated influenza virus vaccine was given as an injection in the muscle, and was associated with an increase in local side effects (such as pain) at the site of injection, which were short-lived. The inactivated virus vaccine did not cause influenza, or any significant worsening of COPD. Adding a live attenuated virus to the inactivated virus did not add any further protection for the participants.

Quality of the evidence

The evidence was of moderate quality. There have been no new trials since 2004. We conducted the last literature search in December 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Influenza vaccine compared to placebo for chronic obstructive pulmonary disease (COPD)

Influenza vaccine compared to placebo for chronic obstructive pulmonary disease (COPD)

Patient or population: chronic obstructive pulmonary disease (COPD)

Setting: community

Intervention: inactivated influenza vaccine

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Influenza vaccine				
Total exacerbations per participant	The mean number of total exacerbations per participant ranged across placebo groups from 0.83 to 1.35	MD 0.37 lower (0.64 lower to 0.11 lower)	-	180 (2 RCTs)	⊕⊕⊕⊕ Low ^a	Despite the effect size, this is based on a very small number of trials and participants. However there was good agreement between these two studies (low I ²). One study was not conducted in an epidemic year. We extrapolated some data. Ideally more trials would be done to refine these effect sizes.
Early exacerbations per participant	The mean number of early exacerbations per participant ranged across placebo groups from 0.14 to 0.34	MD 0.01 higher (0.11 lower to 0.13 higher)	-	180 (2 RCTs)	⊕⊕⊕⊕ Low ^a	See above
Late exacerbations per participant	The mean number of late exacerbations per participant ranged across placebo groups from 0.48 to 1.21	MD 0.39 lower (0.61 lower to 0.18 lower)	-	180 (2 RCTs)	⊕⊕⊕⊕ Low ^a	See above
Days disability from respiratory illness	not reported					
Hospital admissions	76 per 1000	26 per 1000 (7 to 93)	OR 0.33 (0.09 to 1.24)	180 (2 RCTs)	⊕⊕⊕⊕ Low ^{a,b}	
Mortality	76 per 1000	67 per 1000	OR 0.87	180	⊕⊕⊕⊕	

		(23 to 182)	(0.28 to 2.70)	(2 RCTs)	Low a,b	
Local effects at injection site	63 per 1000	274 per 1000 (106 to 546)	OR 5.57 (1.75 to 17.71)	125 (1 RCT)	⊕⊕○○ Low ^a	Single study on participants who all had COPD (Wongsurakiat 2004a), but very similar findings in studies with a mixed population (Cate 1977 ; Gov-aert 1994)

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^aSmall number of studies which are over ten years old limit our confidence in the generalisability of these findings to currently available vaccines (downgraded once for indirectness).

^bStudies too small and events too infrequent to detect a consistent effect (downgraded once for imprecision)

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) occurs predominantly in older people who have smoked, and is characterised by progressive airflow obstruction that is largely irreversible. As the disease progresses, exacerbations may occur several times per year, and may require hospital admission. These exacerbations can take several weeks to resolve, during which time considerable morbidity may occur and result in significant health care costs. Infection with influenza is an important cause of excess mortality and morbidity in people with COPD (Rothbart 1995). It may affect the progression of the disease (Centanni 1997), and frequency of exacerbations (Sethi 2002). People with COPD are at an increased risk for respiratory illness-related hospitalisation during influenza outbreaks, irrespective of age and degree of morbidity (Monto 1987).

Description of the intervention

Annual influenza vaccination is almost universally recommended in COPD guidelines (ATS 1995; ATS 2004; BTS 1997; GOLD 2018; NICE 2010; Siafakas 1995; Yang 2017). The largest body of evidence to support this recommendation comes from observational studies in the older population. In a large, serial cohort study of nearly 150,000 older people, those who had been vaccinated had a reduction of about 32% in the rates of hospitalisation for all respiratory conditions, and a reduction of approximately 50% in all-cause mortality over their untreated counterparts (Nichol 1998). In people with chronic lung disease, those who were vaccinated had a 52% reduction in hospitalisations and a 70% reduction in death rate during influenza seasons (Nichol 1999). A meta-analysis of 20 cohort studies of influenza vaccination in older people showed a 56% reduction in respiratory illness, a 53% reduction in pneumonia, a 50% reduction in hospitalisation, and a 68% reduction in deaths from all causes during influenza outbreaks (Gross 1995). The benefit was seen especially in epidemic years, when the vaccine strain was identical or similar to the epidemic strain (Gross 1995). Most studies suggest that vaccination is very cost effective. For example, Nichol and colleagues estimated that vaccination was associated with a reduction in health care costs of about USD 171 per year per high risk person vaccinated (Nichol 1998).

How the intervention might work

The effectiveness of the vaccine depends on the immunocompetence of the vaccine recipient and the degree of similarity between virus strains in the vaccine and those in circulation (ACIP 1999). Most vaccine programmes use an inactivated virus vaccine, which contains three virus strains (usually 2 type A and 1 type B), representing the influenza viruses likely to circulate in the upcoming winter. The vaccine is made from highly purified, egg-grown viruses that have been inactivated. These vaccines may be whole virus, sub virion, or purified-surface-antigen preparations. The mechanism of protection by the vaccine is thought to occur via circulating antibodies to HA (Hemagglutinin) and NA (Neuramidase), acting against severe infection of the lower respiratory tract. Stimulation of cytotoxic T-cell responses may also be important (Patriarca 1994). In general, older people have lower phagocytic function, and mount less of an immune response to vaccination than younger people (Treanor 1992). To improve vaccine efficacy, live attenuated viruses have been trialled. Levels

of secretory anti-HAs, immunoglobulins (Igs) and anti-influenza A virus cytotoxic T-cell responses were better in people with COPD after immunisation with monovalent live attenuated vaccine than with inactivated influenza A virus vaccines (Gorse 1991; Gorse 1995; Gorse 1996). Some investigators have co-administered more than one type of vaccine, such as cold attenuated virus with inactivated virus vaccine, in an attempt to increase vaccine efficacy in people with COPD (Gorse 1997).

Why it is important to do this review

Despite guideline recommendations, vaccination of older people (the age group that includes most people with COPD) is not universal. In the USA in 1997, only 65.5% of older people were vaccinated in the previous year (BRFSS 1998). Yet, the only absolute contraindication to vaccination is chicken egg allergy. Other reasons for not vaccinating include uncertainty about the degree and longevity of protection in the older population and concern about adverse effects (Patriarca 1994). People with COPD, and their doctors, often express concern that vaccination precipitates exacerbations, despite the fact that it is not possible to contract influenza from inactivated virus. Adverse effects usually manifest within 24 hours of vaccination, and can be local or systemic. Several studies have shown that mild local side effects, at the site of injection, are more common in those who were vaccinated, than in those given placebo (Govaert 1994; Nichol 1995). Systemic reactions include myalgia, fatigue, headache, and low-grade fever. These are more common in females, and after the administration of whole-virus than sub virion vaccines. Higher doses and levels of pre-existing antibody also increase the likelihood of these reactions (Cate 1977). The most feared complication of influenza vaccination is Guillain-Barre Syndrome (GBS). However, this is extremely rare (approximately 1/1,000,000), and the benefits of the vaccine are thought to far out-weigh the risks of developing vaccine-associated GBS (ACIP 1999).

This systematic review evaluated the evidence from RCTs that had studied the effect of influenza vaccination in people with COPD. The review was originally published in 2000 (Poole 2000), and updated in 2006 (Poole 2006).

OBJECTIVES

To determine whether influenza vaccination in people with COPD:

1. Reduces respiratory illness;
2. Reduces mortality;
3. Is associated with excess adverse events; and
4. Is cost effective.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCT).

Types of participants

We included studies of adults with COPD, as defined by the American Thoracic Society (ATS 1995), or European Respiratory Society (Siafakas 1995). We also included studies with participants who were defined as having chronic bronchitis.

Types of interventions

We included studies randomising people to receive at least one annual influenza vaccination. Influenza vaccination may have been one of the following types: live attenuated whole virus, inactivated, or a split-virus type vaccine, and may have been administered by either intramuscular injection or intranasal spray.

Types of outcome measures

We classified outcomes as early or late. 'Early' referred to the early post vaccination period, when immunity may not yet have developed, but adverse effects may have occurred

Primary outcomes

1. Exacerbations of COPD, defined as an increase in breathlessness, volume or purulence of sputum, or a combination. This was assessed in terms of both total numbers of exacerbations and participants with one or more exacerbations in the study period.
2. Days of disability from respiratory illness, defined as days in bed, days off work, or days when the person was unable to undertake normal activities
3. Hospital admissions
4. Mortality in the year following vaccination (All cause and respiratory-related)

Secondary outcomes

1. Change in lung function from baseline, at the end of the study period
2. Adverse effects: acute
3. Acute respiratory illnesses subsequently proven to be influenza-related
4. Cost effectiveness

Studies would be excluded if they:

1. Did not report outcomes of interest for this review
2. Were not placebo controlled

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The most recent search was conducted in December 2017. The Cochrane Airways Trials Register contains studies identified from several sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
2. Weekly searches of MEDLINE Ovid SP;
3. Weekly searches of Embase Ovid SP;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in [Appendix 1](#). See [Appendix 2](#) for search terms used to identify studies for this review.

Searching other resources

We searched for additional articles of interest in the bibliographic lists from all full-text papers we retrieved. In 2006, we searched bibliographies of large reviews of influenza vaccination trials ([Galasso 1977](#); [Gross 1995](#)), and recommendations of Advisory Councils ([ACIP 1999](#); [BRFSS 1998](#)).

To locate other published or unpublished RCT data in 2006, we contacted pharmaceutical companies that had been involved in the conduct of vaccine trials, the manufacture of vaccines, or both. We contacted the following companies: Smith Kline Beecham, Glaxo-Wellcome, Merck Sharp and Dohme, Astra, Parke Davis, Wyeth, Pasteur Merieux, and Commonwealth Serum Laboratories. In 2006, we also wrote to authors who had published extensively in the field to ask if they were aware of any further RCTs, published or unpublished.

For the review update (December 2017), we searched clinical trials registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform) for current, recently completed, and ongoing studies.

Data collection and analysis

Selection of studies

For the original review, three review authors (PJP, RWB, EC) independently screened the titles and abstracts for potentially eligible studies and then retrieved the full texts to further screen for inclusion. For the updates this was done by two review authors (PJP and ZK). We resolved disagreement through discussion.

Data extraction and management

Review authors agreed the format of data extraction sheets. Two review authors independently extracted data. One review author entered the data onto the data extraction sheets, and then into Review Manager 4. A second review author double-checked each entry. For versions of this review published after the 2006 update, we used Review Manager 5 ([RevMan 2014](#)).

Assessment of risk of bias in included studies

Two review authors (PJP, ZK) independently assessed the risk of bias for all included studies, using the criteria outlined in the *Cochrane Handbook of Systematic Reviews of interventions* ([Higgins 2011](#)). We resolved disagreements through discussion. We assessed the risk of bias according to the following items:

- Random sequence generation;
- Allocation concealment;
- Blinding;
- Incomplete outcome data
- Selective outcome reporting;
- Other potential bias.

We judged each potential source of bias as high, low or unclear risk of bias. We summarised our judgements of the risk of bias across different studies for each of the items listed.

Measures of treatment effect

We analysed continuous data as mean differences (MD) with 95% confidence intervals (CI) and dichotomous data as odds ratios (OR) with 95% CI or Peto odds ratios (Peto) with 95% CIs where pooling of odds ratios, or approximation to the odds ratio (i.e. for rare events) was required and appropriate i.e. intervention and control groups have similar numbers and number of events were rare ([Higgins 2011](#)).

Unit of analysis issues

The participant was the unit of analysis.

Dealing with missing data

Where there were insufficient data in the paper, we requested further data by writing to the author or pharmaceutical company sponsoring the study.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots and calculation of the I^2 value; which was interpreted broadly as follows:

- 0 to 40%: may represent negligible/low heterogeneity
- 30 to 60%: moderate heterogeneity
- 50 to 90%: substantial heterogeneity
- 75 to 100%: considerable heterogeneity ([Higgins 2011](#)).

Assessment of reporting biases

We had planned to assess publication bias using a funnel plot, if there were a sufficient number of studies in a forest plot (more than 10).

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis with a random-effects model.

We anticipated that the follow-up period would be 12 months. Because of the small number of studies involved in this review, we did not annualise the event rate. If further data become available, it may be necessary to annualise the event rate, particularly if follow-up periods vary.

Subgroup analysis and investigation of heterogeneity

In the case of significant heterogeneity, we had planned to run a sensitivity analysis based on risk of bias. If any heterogeneity could not be explained in terms of risk of bias, we planned the following sub-group analyses:

1. Type of control group
2. Vaccine type
3. Severity of COPD (by baseline lung function)
4. Setting of study
5. Match between strain of vaccine and infecting strains
6. Age of participants

'Summary of findings' tables

We created a 'Summary of findings' table using the GRADEPro software ([GRADEpro GDT 2015](#)). We included all primary outcomes and adverse events. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We justified all decisions to downgrade the quality of studies using footnotes.

RESULTS

Description of studies

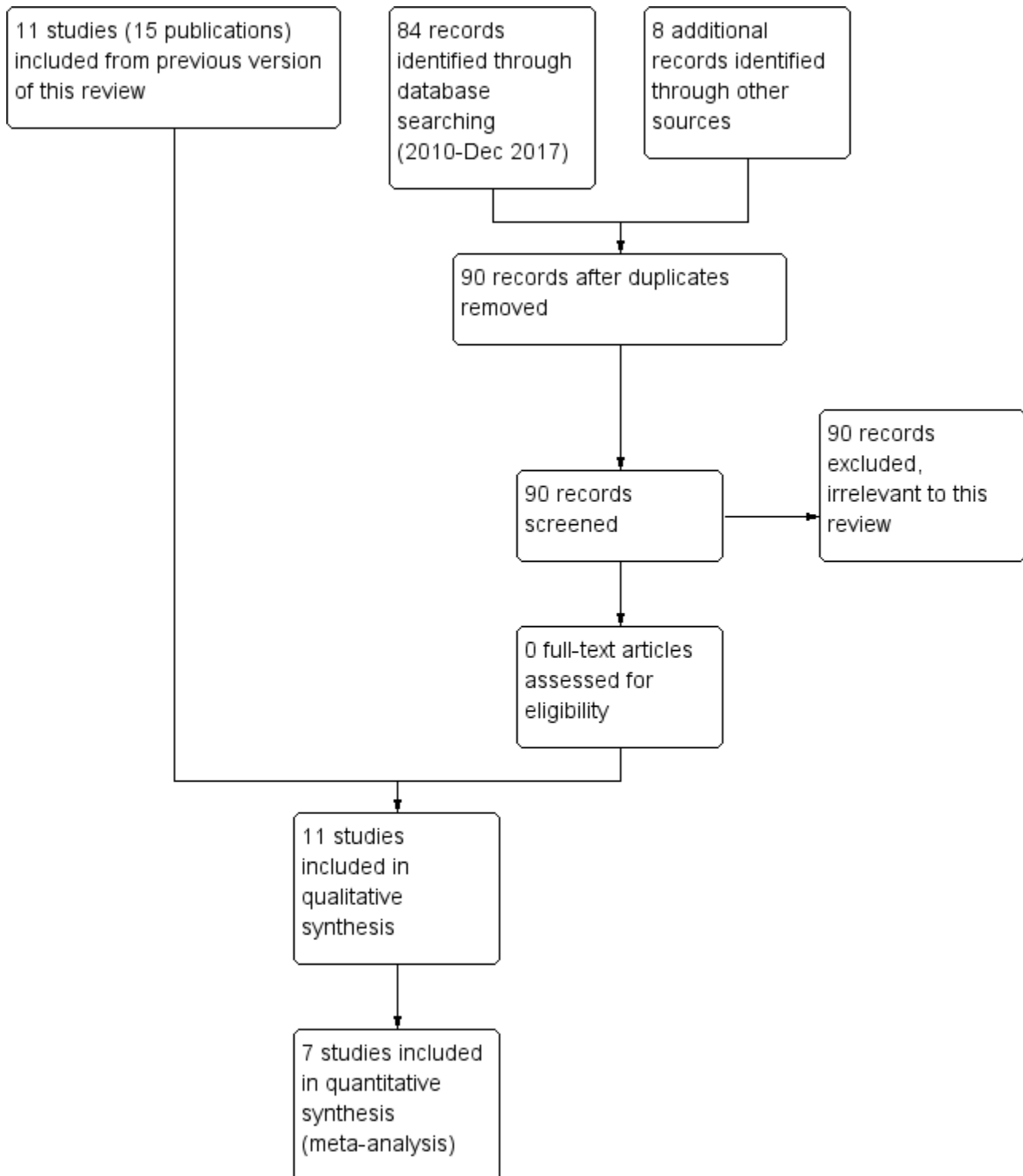
Results of the search

For the original review, we screened 105 abstracts of papers from the initial searches. After excluding those that were clearly ineligible, we obtained full texts for 25. An additional 40 articles were identified from bibliographies and references provided by pharmaceutical companies. Commonwealth Serum Laboratories provided another 70 references from an independent search. We obtained full-text articles when the title and abstract indicated the study was possibly eligible. We reviewed a total of 70 full texts for possible inclusion.

The 2003 search yielded four new abstracts, including two reports of the same eligible study ([Gorse 2003](#); [Neuzil 2003](#)). The 2004 search yielded a further five abstracts, including two reports of the same eligible study ([Wongsurakiat 2003](#); [Wongsurakiat 2004a](#)). Dr Wongsurakiat identified a further study, published after the 2006 search ([Wongsurakiat 2004b](#)).

We did not identify any new eligible studies from searches conducted in December 2017 (see [Figure 1](#) and 'Characteristics of excluded studies' table for further detail).

Figure 1. Study flow diagram for 2018 update



We included 11 studies (reported in 16 publications) in this review, with 6750 participants. We wrote, requesting more information, on six of them (Cate 1977; Gorse 1995; Govaert 1994/Govaert 1994a; Treanor 1992; Treanor 1994; Wongsurakiat 2004a). Dr Treanor and Dr Cate kindly supplied individual participant data. We received a reply from Dr Gorse but he was unable to supply us with further data. Dr Wongsurakiat kindly provided useful further information.

Included studies

Eleven studies met the entry criteria (see 'Characteristics of included studies' table); all were RCTs, using a parallel group design. All studies were double-blind and placebo-controlled, except for Gorse 1995 and Gorse 1997. These two studies were single-blind and compared intra-muscular inactivated vaccine and intranasal live attenuated vaccine with intra-muscular inactivated

vaccine and intranasal placebo. Because these studies assessed the additional benefit of a second vaccine, we assessed them as a separate comparison in this review.

Population

Six of the 11 trials in this review studied participants with COPD or chronic bronchitis alone (Fell 1977; Gorse 1997; Gorse 2003; Howells 1961; MRC 1980; Wongsurakiat 2004a). These studies ranged in size from 29 participants in Gorse 1997, to 2215 in Gorse 2003, and included a total of 2469 participants. The other five trials were conducted in older or chronically ill people, or both, a proportion of whom had chronic lung disease. In these studies, the percentage of people with chronic lung diseases varied from 32% in Gorse 1995, to 5% in Cate 1977. From these authors, we sought individual participant data for the subgroup with chronic lung disease, in particular COPD. Where possible, data from the lung disease subgroup are included, although in none of these studies was it possible to ascertain whether this lung disease subgroup had COPD. The studies that included a minority of people with chronic lung disease are described in the discussion section for comparison with the six studies carried out exclusively in people with COPD.

The following descriptions refer only to the six studies specifically investigating influenza vaccination in COPD or chronic bronchitis alone:

Timing: three studies were conducted during winter months (Fell 1977; Gorse 2003; Howells 1961).

Setting: Fell 1977 was in a group practice, and four were in hospital outpatient clinics (Gorse 1997; Gorse 2003; Howells 1961; Wongsurakiat 2004a).

Duration: length of trials varied from as little as three weeks with MRC 1980, to one year (Wongsurakiat 2004a).

Inclusion and exclusion criteria: Howells 1961, MRC 1980, and Fell 1977 studied people with chronic bronchitis. Gorse 1997, Gorse 2003, and Wongsurakiat 2004a specifically studied people with pre-existing COPD, categorised by FEV₁/FVC ratio less than 70% (forced expiratory volume in the first second/Forced vital capacity). Exclusion criteria were varied. They were explicit in Gorse 1997, Gorse 2003, Wongsurakiat 2004a, and MRC 1980, limited in Howells 1961 to Grade 4 bronchitis, and were not reported at all in Fell 1977.

Participant characteristics: the mean age was 67.3 years in the five studies that reported it (Fell 1977; Gorse 1997; Gorse 2003; Howells 1961; Wongsurakiat 2004a). The percentage of males ranged from 64% in Fell 1977 to 100% (Gorse 1997). The latter was a study in US veterans.

Comorbidities: 31% of the treatment group in Gorse 1997 had underlying liver disease. Both treatment and control groups in this study had similar proportions of other underlying diseases. 30% of the treatment group of Fell 1977 was on digoxin, and 8% had coexistent asthma and chronic bronchitis. In Gorse 2003, 95% had comorbidities, and in Wongsurakiat 2004a, this level was 33%.

Smoking history: 97% of the participants of Gorse 1997 had a smoking history, 93% in Fell 1977, 95% in Gorse 2003, and 96% in Wongsurakiat 2004a.

Lung function: the mean peak flow was 280 L/min from the two studies that reported these measurements. Wongsurakiat 2004a stratified the participants in the study by baseline FEV₁. Thirty-six per cent of people had an FEV₁ ≥ 70% predicted, 26% an FEV₁ of 50% to 69%, and 38% an FEV₁ < 50%. The mean baseline FEV₁ in Gorse 2003 was 1.38 L (43.5% predicted).

The treatment and control samples were generally well matched, except in Fell 1977, where baseline adverse symptoms were higher in the vaccinated group. This particular study was unusual in that it used the early post vaccination symptoms as the baseline for assessing late post vaccination symptoms. In this study, despite randomisation, there was a significant difference between treatment and control in baseline symptom scores, serum antibody levels, and comorbidities. No details of baseline characteristics were provided by one study (MRC 1980).

Intervention

Vaccination type: two studies used inactivated virus (Howells 1961; Wongsurakiat 2004a). Four studies assessed the effects of live attenuated intranasal virus vaccines (Fell 1977; Gorse 1997; Gorse 2003; MRC 1980), with Gorse 1997 and Gorse 2003 assessing the add-on benefit of live intranasal virus, while both treatment and control groups received inactivated virus vaccine intramuscularly. We examined these studies separately in the analysis.

Match between vaccine and influenza strains: Fell 1977 reported that their study was carried out in a non-epidemic year. Wongsurakiat 2004a reported their study was carried out in a non-epidemic year; however, there was a good match between the influenza that did occur and the serotypes in the vaccine. Gorse 2003 reported a regional outbreak in the study area, with a virus antigenically similar to a vaccine strain. The other studies did not report the match.

Outcome measures

Clinical outcomes that could be evaluated included: exacerbations (Fell 1977; Gorse 1997; Gorse 2003; Howells 1961; Wongsurakiat 2004a), hospitalisations, lung function, adverse effects, and mortality. An assessment of serological outcomes alone was not the purpose of this review. Outcomes were defined as 'early' and 'late' to try and address whether vaccination led to an increase in exacerbations before immunity had developed. We had planned to define 'early' as one to two weeks after vaccination, but Howells 1961 used a period of three weeks, and Wongsurakiat 2004a, four weeks. Wongsurakiat 2004a recorded all acute respiratory infections (ARIs; total of 269 events), which were then subdivided by presentation into common cold (85 events), influenza-like illnesses (20 events), acute exacerbations (161 events), and pneumonia (three events). Thus, the commonest presentation was 'acute exacerbation' (60% of events). He also conducted an economic evaluation (Wongsurakiat 2003). Gorse 2003a assessed health status by the chronic lung disease index (CLDI), reported by vaccination status.

Dropouts: there was a range of 0% to 19% of participant withdrawals. There were none reported in Gorse 1997. In the MRC 1980 multi-centre study, 16 participants from one centre had no baseline data and 15 had incomplete records. In Gorse 2003 (the largest study with 2215 participants), 9% dropped out. In Wongsurakiat 2004a, three out of 125 participants dropped out.

Excluded studies

The main reasons for study exclusion were a lack of randomisation, and absence of primary outcome data (Gorse 1988; Gorse 1996; Lama 1998). We excluded another two studies because they lacked a placebo control (Ambrosch 1979; MRC 1959). See 'Characteristics of excluded studies' table for full details.

Risk of bias in included studies

See Figure 2 for a summary of the 'Risk of bias' assessments. We judged many domains as unclear risk of bias, due to lack of detail present in the publications. This is unsurprising, considering all included trials were published in 2004 or earlier, when standards and guidelines for reporting were less stringent.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cate 1977	?	?	?	?	?	?	?
Fell 1977	?	?	+	+	+	?	?
Gorse 1995	?	?	?	-	?	?	?
Gorse 1997	?	?	?	?	+	?	?
Gorse 2003	+	?	?	?	?	?	?
Govaert 1994	+	+	+	+	+	?	?
Howells 1961	?	+	+	+	+	?	?
MRC 1980	?	?	?	?	-	?	?
Treanor 1992	?	?	?	?	+	?	?
Treanor 1994	?	?	?	?	+	?	?
Wongsurakiat 2004a	+	+	+	?	+	?	?

Allocation

We judged three trials ([Gorse 2003](#); [Govaert 1994](#); [Wongsurakiat 2004a](#)) at low risk of bias for random sequence generation, but the remaining eight studies reported insufficient information to permit a judgement. We judged three trials ([Govaert 1994](#); [Howells 1961](#); [Wongsurakiat 2004a](#)) to be at low risk of bias for concealment of the allocation sequence, while the remaining eight were unclear.

Blinding

We judged four trials to be at low risk for performance bias ([Fell 1977](#); [Govaert 1994](#); [Howells 1961](#); [Wongsurakiat 2004a](#)) and three at low risk of detection bias ([Fell 1977](#); [Govaert 1994](#); [Howells 1961](#)) as they described suitably identical placebos, however, the remaining studies were unclear; this was due either to not describing the nature of the placebo, the nurse delivering the intervention not being blinded, or a lack of detail about blinding procedures.

One trial did not blind the outcome assessor and consequently, we marked it as high risk of bias ([Gorse 1995](#)). We judged three as low risk because they used blinded outcome assessors, but seven studies didn't describe this in sufficient detail to permit a judgement other than unclear.

Incomplete outcome data

We judged one study to be at high risk of attrition bias owing to the fact that 11 of the vaccinated participants were excluded from the study from a single centre ([MRC 1980](#)). Seven studies were judged to be at low risk ([Fell 1977](#); [Gorse 1997](#); [Govaert 1994](#); [Howells 1961](#); [Treanor 1992](#); [Treanor 1994](#); [Wongsurakiat 2004a](#)), and three were at unclear risk ([Cate 1977](#); [Gorse 1995](#); [Gorse 2003](#)).

Selective reporting

All studies were reported in insufficient detail to permit a decision.

Other potential sources of bias

None noted.

Effects of interventions

See: [Summary of findings for the main comparison Influenza vaccine compared to placebo for chronic obstructive pulmonary disease \(COPD\)](#)

Influenza vaccination versus placebo

Results that follow relate to the six trials in people with COPD, chronic bronchitis, or both.

Primary outcome

Exacerbations of COPD

Two studies in 180 participants with COPD, chronic bronchitis, or both (both used inactivated virus vaccination) reported continuous data for exacerbation rates ([Howells 1961](#); [Wongsurakiat 2004a](#)). Vaccination significantly reduced the number of exacerbations per participant during the follow-up period (MD -0.37 exacerbations, 95% CI -0.64 to -0.11; $P = 0.006$; two RCTs, 180 participants; [Analysis 1.1](#)).

We determined the number of early or late exacerbations per participant by further interpretation of the data. For the

placebo group of [Howells 1961](#), 20 participants experienced 24 exacerbations. Since there were eight participants experiencing early exacerbations, there would have been at least eight early exacerbations. Similarly, since there were 12 participants experiencing late exacerbations, there would have been at least 12 late exacerbations. Thus the assumption was made that in order to make up the total of 24 exacerbations, there were two more early and two more late exacerbations. In support of this conclusion is the statement in the paper that similar numbers of early exacerbations were recorded in both placebo and vaccinated groups. Sensitivity analysis using 12 early and 12 late exacerbations showed no difference in the significance of our results. [Wongsurakiat 2004a](#) provided the number of early and late exacerbations without a spread. As the number of early exacerbations was small, it was assumed that these occurred in separate participants, and we calculated the SD accordingly. We allocated the SD of the 'total exacerbations' per participant provided by the author to the 'late exacerbations'.

While there was no statistically significant effect of vaccination on early exacerbation rates (MD 0.01, 95% CI -0.11 to 0.13; $P = 0.87$; two RCTs, 180 participants; [Analysis 1.2](#)), inactivated influenza vaccination significantly reduced late exacerbation rates (MD -0.39, 95% CI -0.61 to -0.18; $P < 0.001$; two RCTs, 180 participants; [Analysis 1.3](#)).

[Wongsurakiat 2004a](#) reported no clear difference in the overall incidence or severity of acute respiratory infections (ARIs) between the vaccination and placebo groups.

Participants with at least one exacerbation or acute respiratory illness in the study period

Three studies, with 444 participants, contributed to this outcome ([Fell 1977](#); [Howells 1961](#); [Wongsurakiat 2004a](#)). There was no significant difference between vaccination and placebo-treated participants with respect to the number of participants having at least one exacerbation or acute respiratory illness (Peto 0.81, 95% CI 0.44 to 1.48; $P = 0.49$; three RCTs, 444 participants; [Analysis 1.4](#)). However, there was significant heterogeneity in this result ($P = 0.001$), so it must be treated with caution. A sensitivity analysis by vaccine type showed that if only the two studies that used inactivated virus vaccine were included, this heterogeneity was removed, with a reduction in the number of participants with at least one exacerbation or acute respiratory illness in the study period with vaccination (OR 0.42, 95% CI 0.21 to 0.85; $P = 0.02$; two RCTs, 180 participants). Results from [Howells 1961](#) and [Wongsurakiat 2004a](#) showed no significant difference in the number of individual participants with early exacerbations (Peto 1.08, 95% CI 0.52 to 2.26; $P = 0.84$; two RCTs, 180 participants; [Analysis 1.5](#)), but [Howells 1961](#) did show a significant reduction in the number of participants with late exacerbations (Peto 0.13, 95% CI 0.04 to 0.45; $P = 0.002$; one RCT, 55 participants; [Analysis 1.6](#)). In [Wongsurakiat 2004a](#), nine of 76 exacerbations in the vaccination group were early; while 10 of 85 exacerbations in the placebo group were early. We assumed that they each occurred in a different participant. Clearly, over the course of the study, there were some participants who had more than one exacerbation; the number of individual participants in each group who had late exacerbations was not reported.

Days of disability from respiratory illness

Not reported.

Hospital admissions

Two studies, with 180 participants, reported data on this outcome (Howells 1961; Wongsurakiat 2004a). There was no significant effect of vaccination over placebo on hospitalisation (Peto 0.33, 95% CI 0.09 to 1.24; $P = 0.52$; two RCTs, 180 participants; Analysis 1.7). In Howells 1961 there were no hospitalised participants in the treatment group, and only two in the control group. Wongsurakiat 2004a reported the number of hospitalisations for influenza-related respiratory infections only. There were two in the vaccine group and five in the placebo group. They reported no clear difference in the severity of acute respiratory infections between groups, including no clear difference in the chance of being hospitalised ($P = 0.2$ by log rank test). None of the vaccinated participants required mechanical ventilation for acute respiratory infection, whereas five in the placebo group did.

Mortality

Two studies, with 180 participants, reported all-cause mortality; there was a total of 13 deaths (Howells 1961; Wongsurakiat 2004a). There was no significant difference between vaccine and placebo-treated groups (Peto 0.87, 95% CI 0.28 to 2.70; $P = 0.81$; two RCTs, 180 participants; Analysis 1.8). One control participant died during an acute exacerbation (Howells 1961). In Wongsurakiat 2004a, 12 of 125 participants died (eight of which were unrelated to acute respiratory infection); of those that were ARI related there was no demonstrable difference between vaccination and control (OR 0.33, 95% CI 0.03 to 3.24; Analysis 1.9).

Secondary outcomes

Lung function

One small study (55 participants) reported FEV₁ changes from baseline (MRC 1980). There was no significant difference between the groups' overall change in FEV₁ (MD -0.02, 95% CI -0.12 to 0.08; Analysis 1.10), nor in their change in early FEV₁ (MD -0.01, 95% CI -0.09 to 0.07; Analysis 1.11) but there was insufficient evidence to prove no difference in treatments. Wongsurakiat 2004b reported no clear difference in lung function between groups at one and four weeks after vaccination.

Adverse effects and acute respiratory illness subsequently proven to be influenza-related

Wongsurakiat 2004b evaluated local and systemic symptoms in the weeks following vaccination. There was no significant difference in the incidence of systemic adverse effects between the treated and placebo groups (OR 0.74, 95% CI 0.31 to 1.74; Analysis 1.12). The only significant difference observed was in the local reaction at the injection site; seen in 27% of vaccinees and 6% of the placebo group (OR 5.57, 95% CI 1.75 to 17.71; Analysis 1.13).

Fell 1977 (44 participants) reported early (within two weeks of vaccination) upper respiratory tract symptoms. One vaccinated participant also developed pleuritic pain. There was no statistically significant difference between vaccinated and control participants in terms of breathlessness or tightness (Peto 1.28, 95% CI 0.38 to 4.31; $P = 0.696$; Analysis 1.14; Analysis 1.15). The occurrence of a wheeze within the first two weeks was greater in vaccinated participants (Peto 3.57, 95% CI 1.10 to 11.56; $P = 0.034$; Analysis 1.16). No statistically significant difference between groups was noted for cough (Peto 4.09, 95% CI 0.74 to 22.49; $P = 0.106$; Analysis 1.17).

Two studies assessed the clinical presentations to see if they were related to influenza virus infection (Howells 1961; Wongsurakiat 2004a). Howells 1961 used the hemagglutination inhibition (HAI) test, and Wongsurakiat 2004a used both serology and virology swabs. Overall, inactivated influenza vaccination resulted in a marked decrease in influenza-related respiratory infections (OR 0.19, 95% CI 0.07 to 0.48; $P < 0.001$; two RCTs, 180 participants; Analysis 1.18). The effect was similar whether participants had mild, moderate, or severe COPD, or chronic bronchitis (test for heterogeneity $P = 0.73$). Influenza accounted for 8% (13/161) of the acute exacerbations in the Wongsurakiat 2004a study. Further, the study demonstrated that there was no significant difference in early ARI (OR 0.72, 95% CI 0.34 to 1.50; Analysis 1.19).

In terms of sputum production no significant difference was noted between the vaccination group and control (Peto 2.03, 95% CI 0.48 to 8.66; $P = 0.338$; Analysis 1.20). Breathlessness was recorded significantly less often ($P < 0.05$) in the 5 of 21 participants who had a serological response to vaccination than in the placebo group.

The Treanor 1994 paper reports that 12% of the older people vaccinated with live attenuated virus reported systemic symptoms of malaise and myalgias, as did 10% of inactivated virus vaccinees. The placebo group reported none. Twenty-six per cent of those who received the live virus reported lower respiratory tract symptoms of hoarseness and non-productive cough, as did 13% of those who received the inactivated virus, and 9% of those who received placebo. Twenty-nine per cent of those who received live virus reported upper respiratory tract symptoms of sneezy, runny, or stuffy nose or sore throat, as did 37% of those who received the inactivated virus, and 18% of those who received placebo. Six per cent of those who received the live virus experienced fever, as did 2.5% of those who received the inactivated virus. None of the placebo group reported any febrile illness. In the subgroup of participants with chronic lung disease in this study, of the 20 participants who received some form of influenza vaccination, 11 reported a total of 20 adverse effects, while of the two participants who received the placebo, one participant reported two adverse effects.

The Govaert 1994 paper reports 25% of high risk vaccinees experienced one or more adverse reactions, compared to 16% of those who received placebo, however, effects, if any, appeared to have been mild and transitory. Eleven per cent of all vaccinees experienced systemic effects, as did 9.4% of the placebo recipients. When a multiple regression analysis that looked at the effect of lung disease on systemic adverse reactions was performed, the difference between vaccinees and the placebo group was statistically significant (OR 1.95, 95% CI 1.24 to 3.07). Local effects were experienced by 17.5% of all vaccinees in this study, but in only 7.3% of the placebo group ($P < 0.001$). This study also showed that differences between the treatment groups for adverse effects reduced with age.

The Cate 1977 paper reports 7.8% of those who received inactivated virus reported mild systemic reactions, and 4.9% reported moderate to severe ones. The control group who received saline placebo reported similar numbers of mild systemic reactions, but no moderate to severe ones. Most systemic reactions resolved within two days of vaccination. In the vaccinated group, 18.5% of participants experienced erythema (local redness) with or without induration (hardening) at the injection site, compared to none in the control group.

Cost effectiveness

Wongsurakiat calculated the incremental cost effectiveness ratios of inactivated virus vaccination by applying the direct medical costs from a Thai health provider perspective to the results obtained in the RCT (Wongsurakiat 2004a). There were two types of cost: cost of treatment as an outpatient, and cost of hospitalisation. More than 90% of the costs of influenza-related acute respiratory illness (ARI) were costs of hospitalisation. In people with moderate or severe COPD, more than 90% of the hospital costs were due to costs of treating those who required mechanical ventilation. The costs were based on 1997 prices using Thai Bhat (THB), with vaccination costing 248.40 THB. In the paper the author concluded that cost savings would be 629,538 THB for every 100 people with mild COPD vaccinated, 184 THB for every 100 with moderate COPD, and 680,647 THB for those with severe COPD, i.e. vaccination was very cost effective, but more so in those with more severe COPD.

Live attenuated intranasal vaccine plus inactivated intramuscular vaccine versus placebo intranasal or inactivated intramuscular vaccine

Four studies (2817 participants) evaluated the effect of adding live attenuated virus to inactivated virus vaccination (Gorse 2003; Gorse 1995; Gorse 1997; Treanor 1992). The Gorse 1997 and Gorse 2003 studies were specifically conducted on people with COPD, but the others were carried out in older people, only a minority of whom had lung disease. For simplicity, 'treatment' refers to the live intranasal plus inactivated group, and 'control' to the placebo intranasal plus inactivated vaccine group. Only the Gorse 1997 and Gorse 2003 studies provided data in a form that could be used in analyses.

Primary outcomes

Exacerbations of COPD

There were no significant differences in the total number of exacerbations per participant between the two groups (MD 0.01, 95% CI -0.35 to 0.37; $P = 0.96$; two RCTs; 1137 participants; Analysis 2.1). In the former, exacerbations were defined as the occurrence of increased cough, shortness of breath, sputum production, or a combination. There was no clear difference in either the early exacerbation rate per participant (MD -0.21, 95% CI -0.55 to 0.13; $P = 0.23$; one RCT, 29 participants; Analysis 2.2), or late exacerbations (MD -0.23, 95% CI -0.08 to 0.54, $P = 0.14$; one RCT, 29 participants; Analysis 2.3) between groups. In the latter, participants were asked to report any febrile influenza-like illness (ILI). This was then investigated by serology, swabs, or both to determine if it was influenza-related.

There was no clear difference in the number of participants who reported improvements in their exacerbations (Peto 1.48, CI 0.30 to 7.42; $P = 0.63$; one RCT, 29 participants; Analysis 2.4); this finding was consistent when broken down into early improvements (Peto 1.65, 95% CI 0.16 to 17.49; one RCT, 29 participants; Analysis 2.5), and late improvements (Peto 1.26, 95% CI 0.19 to 8.43; one RCT, 29 participants; Analysis 2.6).

In the Gorse 2003a paper, a univariate and stepwise multivariate logistic regression analysis of associations was performed, with at least a 15% improvement or worsening in health status, as measured by the chronic lung disease symptom index. This was a secondary study outcome. Analysis showed that 217 (21%) in the group that received inactive vaccine plus intranasal vaccine had at

least a 15% improvement at the end of the study over pre-vaccine status, compared with 163 (16%) in the control group that had received inactivated virus vaccine alone (OR 1.39, CI 1.10 to 1.74).

Days of disability from respiratory illness

Not reported

Hospital admissions

Not reported

Mortality

In the Gorse 2003 paper, the largest study with 2215 participants, there were 64 deaths (3%); there was no difference between intervention and control groups for this outcome (OR 1.14, 95% CI 0.69 to 1.87; one RCT, 215 participants; Analysis 2.7). Of the 64 participants who died, five participants in the treatment group and two in the placebo group had influenza-like illnesses, four of which were laboratory-documented.

Secondary outcomes

Lung function

There was no consistent effect on early changes in lung function in Gorse 1997 either in terms of percent predicted FEV₁ (MD 2.90; 95% CI -14.14 to 19.94; one RCT, 20 participants; Analysis 2.8) or FEV₁/FVC ratio (MD -0.90; 95% CI -12.02 to 10.22; one RCT, 29 participants; Analysis 2.9). The results from Gorse 2003 suggested significant effect on lung function in favour of the active virus group (MD -0.05; 95% CI -0.10 to 0.00, one RCT, 2215 participants; Analysis 2.10), however, there was a significant difference between the two study groups at baseline reported in the paper, with the active group being lower, and improving more. The investigators reported that they did not believe this to be clinically important. The lung functions of the two groups at the end of the study were similar. Gorse 1997 reported that more participants in the active virus group experienced a one category improvement in lung function compared to control, however, this was found to be non-significant (Peto 4.00; 95% CI 0.68 to 23.60; one RCT, 29 participants; Analysis 2.11). The investigators also reported that a small number of participants in the active virus group experienced a one-category decrease in lung function, however, once again this was found to be non-significant (Peto 7.04; 95% CI 0.66 to 74.68; one RCT, 29 participants; Analysis 2.12). Gorse 2003 measured FEV₁ at the end of the study period and found that there was no evidence of an effect on lung function for those receiving the active virus compared to control (MD -0.05; 95% CI -0.16 to 0.06; one RCT, 382 participants; Analysis 2.13).

The Treanor 1994 paper reported no significant differences in lung function between groups. From data supplied by the author, for the subgroup with underlying chronic lung disease, those who were vaccinated had a mean decrease in FEV₁ from 1.8 litres to 1.6 litres, whereas for the one placebo recipient for whom lung function was recorded, there was a small increase in FEV₁.

Adverse effects

There were no significant differences in the reports of new upper respiratory tract symptoms between the groups in the Gorse 1997 study (Peto 1.89, 95% CI 0.45 to 8.04; $P = 0.39$; one RCT, 29 participants; Analysis 2.14).

There were no statistically significant differences between treatment and control for any adverse effects in the early period (Peto 0.86, 95% CI 0.63 to 1.17; $P = 0.34$; two RCTs, 2244 participants; [Analysis 2.15](#)). When evaluating the results of [Gorse 2003](#) alone, the number of days participants displayed early signs and symptoms favoured control (MD 0.40; 95% CI 0.19 to 0.61; one RCT, 2215 participants; [Analysis 2.16](#)). Furthermore, analysis of the number of participants with early adverse events, divided into sub-groups by type, showed no evidence of an effect between intervention or control for any single adverse effect; however, the pooled effect was significantly in favour of the active virus group (OR 0.49; 95% CI 0.26 to 0.92; $P = 0.027$; one RCT, 2215 participants; [Analysis 2.17](#)).

There was some evidence of an effect for adverse effects in the late period following vaccination, favouring the control group (Peto 2.33, 95% CI 1.22 to 4.46; $P = 0.011$; two RCTs, 2244 participants; [Analysis 2.18](#)). [Gorse 2003](#) stated in their paper that the proportion of participants with adverse effects at least possibly related to immunisation, did not differ between groups. There were, however, significantly fewer participants with early signs and symptoms in the group receiving inactivated virus vaccine only, as well as a smaller number of participants with late adverse effects. In this group, there was a total number of 99 events in 88 individuals (7.9% of total).

From one RCT ([Gorse 2003](#)) there was no evidence of an effect between active virus and control for the outcome of influenza-related ARI (OR 0.84; 95% CI 0.57 to 1.24; one RCT, 2215 participants; [Analysis 2.19](#)). Further, data from the same study demonstrated no statistical difference in the number of participants with at least one influenza-like illness between groups (OR 1.07; 95% CI 0.86 to 1.33; one RCT, 2215 participants; [Analysis 2.20](#)).

In [Treanor 1992](#) (523 participants), which was a study with a lung disease subgroup, 24% of the treatment group experienced respiratory illnesses compared to 28% of the control group. In the treatment group, 12% of participants experienced an influenza-like illness, compared to 16% of the control group. In the control group, there were two cases of laboratory-documented influenza A infection, which resulted in hospitalisation. One death due to influenza virus A infection occurred in the control group, compared to none in the treatment group. This study also showed that 10.1% of the treatment group experienced early adverse reactions, compared to 8.3% of the control group. In the treatment group, 3.9% of participants reported early systemic effects consisting of headache, myalgias, malaise, or fatigue, compared to 5.0% of the control group. Of the control group, 1.1% reported fever, and 2.7% of them reported respiratory symptoms consisting of rhinitis or pharyngitis. However, 2.2% of the treatment group reported fever, and 6.7% reported respiratory symptoms. Five per cent of the live virus vaccinees experienced sore arms, compared to 18% of the inactivated virus vaccinees. None of the placebo group reported sore arms. The tendency for inactivated virus to cause local side effects to a greater extent than live virus was statistically significant in this study ($P = 0.02$).

In the [Gorse 1995](#) paper it was reported that 12% of all participants experienced transient, mild pain at the site of local intramuscular injection.

Acute respiratory illness subsequently proven to be influenza-related

Not reported

Cost effectiveness

Not reported

DISCUSSION

Summary of main results

This systematic review evaluated the few RCTs that have reported on the effects of influenza vaccination in people with COPD. Despite iterative and exhaustive searches, we only identified 11 studies that met our inclusion criteria, with only six of these having been performed solely on 2562 people with COPD or chronic bronchitis. The entry criteria for these studies were variously reported, but where reported, they showed that the majority of participants had a smoking history and airway obstruction. The earlier studies enrolled younger participants than the more recent studies. The other studies in the review included older participants, those with chronic illnesses, or both, of whom a subset had chronic lung disease.

Influenza vaccination versus placebo

There was no evidence of any significant effect on hospitalisation, mortality rates, lung function decline, or exercise tolerance between the vaccine and placebo groups. For the infrequent outcomes of hospitalisation and mortality, the studies were probably too small to detect any difference. One participant in the control group in [Gorse 2003](#) developed Guillain-Barré syndrome, although further details of severity and outcome were not provided. Thus, this review showed no evidence of an increase in Guillain-Barré syndrome with vaccination.

We did not intend to evaluate serological outcomes, such as a significant rise in antibody titre in this review. However, some authors looked at outcomes in the subgroup with a serological response to vaccination. The limited data from these comparisons was consistent with that of the clinical outcomes alone. It also suggested that if people seroconverted, they had fewer adverse effects.

[Neuzil 2003](#) and [Wongsurakiat 2004a](#) studied the clinical presentation of symptomatic laboratory-documented influenza (LDI). Using stepwise logistic regression, [Neuzil 2003](#) found that during an influenza outbreak period, only fever and myalgia were associated with LDI. Together, they had a positive predictive value of 41%. In [Wongsurakiat 2004a](#), the most specific presentation of LDI was 'influenza-like illness' (namely generalised aches, fever and headache, with or without respiratory tract symptoms). However, LDI occurred in only 10% of participants, indicating a low positive predictive value of this symptom complex for LDI. The conclusion was that it was difficult to diagnose influenza infection clinically, with certainty, in people with COPD.

The one cost-effectiveness analysis that was conducted, based on an RCT, suggested that inactivated virus vaccination was highly cost-effective in people with COPD, particularly those with severe airways obstruction. This analysis took into account direct health care costs only, and not indirect costs, or any future health care costs that might be incurred by people with COPD living longer. It was conducted in a non-epidemic year, and therefore, underestimated the benefits that would be gained in an epidemic year.

Influenza vaccinations were generally well tolerated. There was a significant increase in local effects ranging from pain at the site of injection, to erythema, with or without induration, but all effects appeared to be mild and transitory. These findings were consistent with results from [Nichol 1994](#), a large, well conducted randomised placebo-controlled trial of influenza vaccination in healthy adults, in which they observed no significant side effects of vaccination, except for arm soreness (63.8% of vaccinees compared to 24.1% placebo; $P = 0.001$).

One of the main barriers to increasing vaccination rates in people with COPD is the concern of patients and their health professionals that vaccination may increase early exacerbations, before immunity has developed. The evidence in this review showed that inactivated virus vaccination did not have a significant impact, on either the total number of early exacerbations, or on the number of people with COPD who had early exacerbations or early acute respiratory illnesses.

Live attenuated intranasal plus inactivated intramuscular versus placebo intranasal plus inactivated intramuscular vaccination

Because of the risk of influenza and the lesser immunogenicity of vaccines in the elderly (including people with COPD), there is interest in the extra protection afforded by the addition of live attenuated virus to inactivated virus vaccination. This approach to clinical trial design has the advantage that high-risk groups are not denied vaccination, but larger numbers of participants are needed if the study is to have sufficient power to detect an effect. The studies in this review showed that there was no greater protective effect of live plus inactivated vaccine over inactivated vaccine alone in any of the clinical outcomes of interest. On the other hand, there may be a slight increase in adverse effects with the combination, although this was seen only in [Gorse 2003](#), and the investigators did not regard it as significant.

Overall completeness and applicability of evidence

Recent literature searches indicated that new RCTs for influenza vaccine in COPD have stagnated, with no studies meeting our inclusion criteria since 2006. This is perhaps a reflection of consistent recommendations in major clinical guidelines for COPD management over the last decade, based on existing observational studies and limited placebo controlled RCTs. The most recent updated search for this review returned a number of studies investigating immunostimulants for COPD management, and while outside the scope of this review, may present an adjunct to disease management, by preventing respiratory tract infection and subsequent COPD exacerbations ([Collet 1997](#)).

Quality of the evidence

The main issue was that there were few RCTs of influenza vaccinations in COPD, and data were generally not reported in the same way. Where data were combined, confidence intervals were wide, making it difficult to determine whether 'no evidence of effect' actually meant 'evidence of no effect', or an effect was missed. However, the studies that were found were of satisfactory methodological quality, with almost all low or unclear risk of bias assessments in all domains. The effects observed in RCTs were internally consistent, biologically plausible, and supported by observational studies. Furthermore, result from the two main studies had little heterogeneity between them.

Potential biases in the review process

We performed the review in accordance with a pre-published protocol to reduce biases. However, we did make some post hoc changes, See [Differences between protocol and review](#).

Agreements and disagreements with other studies or reviews

In the original Cochrane Review in 2000, we wrote "the strong recommendations in current guidelines make it ethically difficult now to conduct large, randomised, placebo-controlled trials of influenza vaccination, even though it would appear desirable to do so". Interestingly, and without our knowledge, such a trial had been conducted but not reported at the time ([Wongsurakiat 2004a](#)). The authors believed the study to be justified on the grounds that prior to 1997, influenza vaccine had been unavailable in Thailand. This study of inactivated influenza vaccination tracked 125 participants over one year following vaccination, with only three dropouts. An analysis with the results from [Howells 1961](#), another carefully conducted RCT, showed that inactivated influenza vaccine significantly reduced COPD exacerbations with an effectiveness ($(1-RR) \times 100\%$) of over 60%. Moreover, inactivated influenza vaccination had an effectiveness of over 80% in reducing influenza-related acute respiratory illness (ARI).

The effectiveness of vaccination was confined to late exacerbations, i.e. those occurring more than three to four weeks after inactivated virus vaccination. The investigators chose to study this time period specifically, in order to allow time for immunity to develop. The authors of [Wongsurakiat 2004a](#) and others made the point that the effectiveness of the vaccine in reducing exacerbations depended on how much influenza-related ARI was present during the study period, i.e. whether there was an epidemic or not. [Fell 1977](#) and [Wongsurakiat 2004a](#) were conducted in non-epidemic years, whereas [Howells 1961](#) was undertaken in an epidemic year. Influenza virus caused 8% of the 'acute exacerbation' and 10% of the 'influenza-like illness' presentations in [Wongsurakiat 2004a](#), but was responsible for 37% of the acute exacerbations in [Howells 1961](#).

To further emphasise this point, the findings of [Howells 1961](#) and [Wongsurakiat 2004a](#) were both consistent with [Govaert 1994a](#), a large ($N = 1906$), high quality RCT conducted in older people, 9% of whom had chronic lung disease. It assessed the effect of inactivated influenza virus vaccination on the development of influenza or influenza-like illnesses. When such illnesses were diagnosed by clinical assessment, the relative risk for influenza-related illness was 0.53 (95% CI 0.39 to 0.73). When the diagnosis was made using the International Classification of Health Problems in Primary Care (ICHPPC-2-Defined), the relative risk was 0.83 (95% CI 0.65 to 1.05). However, post hoc analysis showed that during an epidemic, the relative risk for influenza-related illness diagnosed by clinical assessment was 0.41 (95% CI 0.28 to 0.61), and by ICHPPC-2-Defined criteria was 0.74 (95% CI 0.24 to 1.00). This study also demonstrated an overall halving of influenza risk by vaccination. Results for subgroups of those participants at high risk (including those with lung conditions) and those over the age of 70 years were not statistically significant, but the numbers in each group were small. In [Treanor 1994](#), a study of older people who were in institutions where laboratory-documented outbreaks of influenza A occurred, only 8% of the treatment group, compared to 20% of the control group, had respiratory illnesses. Similarly, only 4% of the treatment group, compared to 11% of the control

group, experienced an influenza-like illness. Inactivated influenza vaccination is likely to have an even greater effect in epidemic years than seen in this review.

Even though the number of RCTs (and participants) was relatively small, the effectiveness of influenza vaccination seen in this review was consistent with that seen in large observational studies. In one of these, involving 1900 older people with chronic lung disease, those who were vaccinated had a halving of the risk of hospitalisation for pneumonia, and a 70% reduction in the risk of death during influenza seasons (Nichol 1999). A meta-analysis of 20 cohort studies of influenza vaccination in the older population showed a 56% reduction in respiratory illnesses and a 50% reduction in hospitalisation (Gross 1995). Most of these studies had been conducted in epidemic years.

AUTHORS' CONCLUSIONS

Implications for practice

There was RCT-based evidence that inactivated influenza vaccination had a clinically important and significant effect on influenza-related exacerbations, and probably an effect on the total of exacerbations in people with COPD. This effect is likely to be greater in epidemic years when the proportion of exacerbations due to influenza would be higher. The sizes of the effect were similar to those seen in cohort studies, and there was no evidence that inactivated virus vaccination caused exacerbations. The addition of intranasal live attenuated virus did not confer any added benefit.

While influenza vaccine was associated with significant reductions in exacerbation rates compared with placebo, it was associated with local adverse effects.

To reduce exacerbations in COPD overall would require a combination of approaches, including vaccination, as only a small percentage were caused by the influenza virus. In people with COPD, symptomatic influenza infections were difficult to diagnose clinically, with any certainty.

Implications for research

The evidence of effectiveness of influenza from observational studies has been viewed by many as sufficient for the strong recommendations in COPD guidelines. These studies may be biased, as there are potentially many differences between those who volunteer to be vaccinated and those who do not. Only some of the biases can be controlled for. These strong recommendations are now supported by some good quality RCT data. It is ethically difficult to conduct further large, randomised, placebo-controlled trials of influenza vaccination, even though it would appear desirable to do so. Any planned study would need to be large, since the incidence of influenza is low (particularly in non-epidemic years) and vaccine efficacy is less than 100% in older people. The effectiveness of influenza vaccination is best determined during epidemic years, with a good match between vaccine and circulating strains, yet this is not known until the influenza season starts, by which time trials have started. For studies conducted during non-epidemic times, results from participants who seroconvert may be used as a surrogate to determine the effectiveness of immunisation, however, clinical outcomes need to be reported, particularly if cost-effectiveness is to be studied.

There are still insufficient data from large enough RCTs to determine the effect of vaccination on rarer events in the trial period, such as hospitalisation or mortality. Measures of health status should be built into clinical studies of COPD as a matter of course.

Public health and policy approaches to increasing vaccine uptake need studying and incorporation into a systematic review, as do public health and other approaches to reducing the impact of influenza outbreaks. Studies should continue to look at ways to improve the effectiveness of vaccines, or combinations of vaccines. This might include adding new vaccine types, while administering the recommended inactivated virus vaccine, or conducting short term placebo-controlled studies, at the end of which all placebo recipients are vaccinated.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Cate 1977

Methods	Duration: about 7 months Withdrawals: 8 volunteers were lost but none had experienced vaccination-related complications. Follow-up schedule: adverse reactions recorded on days 1 and 2 post vaccination. HAI antibody titres at 4 weeks compared after re-vaccinations for a subgroup 5 months later.
Participants	Setting: June to Nov 1976, Texas Medical Centre, USA Number: 413; 8 withdrawals; 348 in combined vaccine groups Characteristics: all participants were ambulatory and either older (> 50 years) or high-risk adults. The average age was 64.3 (SD 7.3) years with 60.7% female participants. About 5% had lung disease, most of which was COPD. 35% were considered high-risk, due to cardiovascular complications, chronic and underlying disease. Baseline characteristics: no details Comorbidities: no details Diagnostic criteria: over the age of 50 years, or adults with a chronic disorder that placed them at high risk for serious complications of influenza infection. Exclusion criteria: no details
Interventions	Vaccination type: inactivated, bivalent influenza virus vaccine (A/New Jersey/76 and A/Victoria/75) in 200/200 or 400/400 CCA units, 0.5 mL dosage intramuscularly Vaccines were either subvirion or whole. Control: saline placebo, intramuscular, 0.5 mL dosage
Outcomes	Early: days 1 and 2 post vaccination. Adverse effects were recorded as symptom scores, including systemic and local reactions. Serology; HAI antibody titres were performed at 4 weeks

Cate 1977 (Continued)

Late: HAI antibody titres performed again after revaccination in a subgroup, about 5 months later.

Notes Not specifically people with COPD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quasi-randomised
Allocation concealment (selection bias)	Unclear risk	Vaccines and placebo provided in randomly arranged coded sets of 10 dose vials, with a rotating sequence of administration
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo controlled, but did not state if placebo identical-looking
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eight volunteers lost to follow-up reported as "none known to have had any unexpected complication from the vaccination." Further details were not provided
Selective reporting (reporting bias)	Unclear risk	No trial registry record available
Other bias	Unclear risk	Used volunteers and provided reimbursement to participants. None noted

Fell 1977

Methods Duration: 20 weeks
 Withdrawals: 1 (vaccinated participant developed pleuritic pain on day 14 of baseline)
 Follow-up schedule: during exacerbations

Participants Setting: Nov 1975, group practice; Deddington, Oxfordshire, UK (non-epidemic conditions)
 Number: 45 enrolled; 22 in vaccinated group, 23 in control. 1 vaccinated participant withdrew during baseline
 Characteristics: 28 men (64%) and the average age was 59.43 years.
 Baseline characteristics:
 The average age of the vaccinated group was 61 years and 58 years in the control group. The proportion of men in the vaccinated group was 57% but 70% in the control. Smoking histories were similar.
 Randomisation was unsuccessful in a number of areas; symptom scores of first 2 weeks after vaccination were used. The vaccinated group had greater symptom reports (not statistically significant) and lower mean PEF. 19% of the vaccinated group had histories of asthma and 30% were on digoxin at entry, while none in the control had either. Over 60% of the vaccinated group had circulating HAI antibody against the Wellcome Research Laboratories (WRL) 105 strain before vaccination while less than 35% of the control did.

Fell 1977 (Continued)

Comorbidities: past history of asthma in 19% and use of digoxin in 30 % of vaccinated

Diagnostic criteria: chronic bronchitis; 3 months productive cough annually for 3 years, MRC questionnaire completed. Severity of COPD unclear

Exclusion criteria: none described

Interventions	Vaccination type: live attenuated, WRL-105 (A/Finland/4/74-H3N2, A/Okuda/57-H2N2), intranasal, 0.5 mL carrier, 0.25 per nostril. Control: placebo, freeze-dried excipients of vaccine, indistinguishable by appearance or reconstitution
Outcomes	Early: adverse effects in Weeks 1 and 2 recorded by guided participant self-assessment, hospitalisation. Late: respiratory scores of adverse reactions greater than baseline, antibody responses to vaccination.
Notes	Prescribed use of live vaccination but was a small study, conducted in a non- epidemic setting

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation reported, however, no details regarding methods of randomisation reported
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled. "The freeze-dried excipients of the vaccine were used as placebo, which was indistinguishable from vaccine in appearance or reconstitution characteristics."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants completed self-assessments but were blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported exclusion of one participant from analyses
Selective reporting (reporting bias)	Unclear risk	No trial registry record available
Other bias	Unclear risk	Insufficient information to make determination

Gorse 1995

Methods	Duration: 4 weeks Withdrawals: no details Follow-up schedule: days 1 to 7 with immunological assays conducted on days 14 and 28
Participants	Setting: 1993 to 1994; Jefferson Barracks Division Nursing home, St Louis VA Medical Centre and at St Louis Altenheim nursing home, USA Number: 50; 25 in each of treatment and control groups

Gorse 1995 (Continued)

Characteristics: older adults, chronically ill nursing home residents, 86% male, average age 74.95 years

Baseline characteristics: generally comparable with average age in the treatment group being 74.3 (SE 1.6) years and 75.6 (SE 1.9) years in the control. 28% of the treatment group had lung conditions and 36% of the control. Levels of other Comorbidities, WBC counts, cholesterol, and pre-vaccination serum HAI antibodies were similar

Comorbidities: heart 64%, lung 32%, neurologic 84%, diabetes mellitus 40%, GI 30%, renal 24%, tobacco use 70%, alcohol use 62%

Diagnostic criteria: older adults > 60 years, (32% with lung disease)

Exclusion criteria: 1. history of hypersensitivity to influenza virus vaccines and eggs, 2. receipt of influenza vaccination less than 6 months prior to study, 3. incompetence to give written informed consent, 4. current administration of any antineoplastic chemotherapy, 5. hematologic malignancy not in remission, 6. blood haemoglobin levels less than 11 g/dL

Interventions	<p>Vaccination type:</p> <ol style="list-style-type: none"> 1. Bivalent live attenuated influenza A virus vaccine (CAV) derived from cold-adapted influenza A/Ann Arbor/6/60 (H2N2) and A/Kawasaki/9/86 (H1N1) and A/Beijing/353/89 (H3N2). Intranasal; 0.5 mL dose. 2. Trivalent inactivated subvirion influenza virus vaccine (TVV). The first 26 received A/Texas/36/91 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90. The next 26 received A/Texas/36/91 (H1N1), A/Beijing/32/92 (H3N2), and B/Panama/45/90 Intramuscular <p>Control:</p> <ol style="list-style-type: none"> 1. Saline placebo intranasal 2. Trivalent inactivated influenza virus vaccines (TVV), Intramuscular, identical to vaccinated group
Outcomes	<p>Early: adverse effects; mild upper respiratory symptoms, transient mild pain, malaise, febrile illness. Serology; virus titres determined and levels of anti-influenza A virus cytotoxic activity</p> <p>Late: serology, some adverse effects</p>
Notes	<p>Not specifically COPD participants. There is a possible advantage of administering live attenuated with inactivated virus because in frail older people who have decreased immune responsiveness due to underlying disease, there is evidence of increased memory of anti-influenza A virus cytotoxic T cell (CTL) activity.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Of each consecutive pair enrolled, one was assigned to intervention and one to control
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled. Same delivery method with participants and laboratory personnel blinded. See below — study nurse was unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	The nurse administering the immunisation was unblinded. This study nurse also "examined the vaccine injection site and evaluated the subjects for clinical signs and symptoms of influenza virus infection on 4 of the first 7 days, and 2 and 4 weeks after vaccination."

Gorse 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported that three participants could not be evaluated, but no further explanation given
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Gorse 1997

Methods	<p>Randomisation: no details</p> <p>Allocation concealment: participants and study personnel were blinded but not the study nurse administering vaccines</p> <p>Outcome assessment was conducted under blind conditions.</p> <p>Duration: unclear, more than 28 days</p> <p>Withdrawals: none reported</p> <p>Follow-up schedule: clinical evaluation 3 times between each of days 1 to 5, 7 to 10, 21 to 28 after immunisation</p>
Participants	<p>Setting: 1994 to 1995 Outpatient clinics of St Louis Department of Veterans Affairs Medical Centre, USA</p> <p>Number: 29; 16 in CAV/TVV group and 13 in TVV/placebo group</p> <p>Characteristics: the average age was 65.2 (SD 2.1) years. All male volunteers. Demographic characteristics and mean pre-vaccination clinical lab tests were comparable; mean total WBC was 7710 (SD 298) cells/microL. Mean lymphocytes were 22.7% (SD 1.4) of total WBC. Mean serum albumin was 4.3 (SD 0.07) g/dL. Mean total cholesterol was 222.8 (SD 12.4) mg/dL.</p> <p>Baseline characteristics: demographics and lab results largely comparable. Proportions of participants with underlying medical illnesses comparable with the exception of higher proportion of liver disease in CAV/TVV group</p> <p>Comorbidities: 32% of CAV/TVV participants had underlying liver disease. Overall, other diseases were comparable; 21% renal, 66% heart disease, 38% neurologic, 21% diabetes mellitus. 97% of the participants reported having smoked tobacco products in the past. 90% reported having consumed alcohol in the past.</p> <p>Diagnostic criteria: COPD with severe obstruction to airflow on average and FEV₁/FVC% < 70%. Medical history consisting of respiratory symptoms, physical examination and clinical lab tests were used.</p> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. History of hypersensitivity to influenza virus and eggs 2. Receipt of influenza vaccine < 6 months prior to enrolment 3. Incompetence to give written informed consent 4. Co-administration of immunosuppressive medication 5. Hematologic malignancy not in remission 6. Blood Hb concentration < 11g/dL
Interventions	<p>Vaccination type:</p> <ol style="list-style-type: none"> 1. Bivalent live attenuated influenza virus vaccine (CAV) derived from cold-adapted influenza A/Ann Arbor/6/60 (H2N2) and A/Kawasaki/9/86 (H1N1) and A/Beijing/353/89 (H3N2). Intranasal with 0.4 mL in each naris.

Gorse 1997 (Continued)

2. Trivalent inactivated subvirion influenza virus vaccine (TVV) — A/Texas/36/91 (H1N1), A/Shandong/9/93 (H3N2), B/Panama/47/90. Intramuscular, 15 µg of HA from each of 3 strains per 0.5 mL dose.

Control:

1. Saline placebo intranasal
2. TVV, intramuscular, identical to vaccinated group

Outcomes	<p>Early: all measured 7 to 10 days after immunisation.</p> <p>Clinical status; pulmonary function using basic spirometry, measuring FEV₁, FVC and FEV₁/FVC %. Adverse symptoms such as cough, nasal congestion, runny nose, etc. Serology; levels of anti-HA immunoglobulins in nasal washings</p> <p>Late: spirometry was repeated for those who reported changes in obstruction to airflow or respiratory symptoms at 7 to 10 days. Serology; cellular immune testing of in vitro levels of interleukins 2 and 4.</p>
Notes	To calculate standard deviations from continuous data, we assumed that only 1 exacerbation was experienced by each participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation reported, however, no details regarding methods of randomisation reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled. Same delivery method with participants and laboratory personnel blinded. Study nurse was unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The nurse administering the immunisation was unblinded. Unclear who did the follow-up checks on the days following vaccination
Incomplete outcome data (attrition bias) All outcomes	Low risk	All vaccinated participants were evaluated and reported in the study results
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Gorse 2003

Methods	<p>Duration: six + months</p> <p>Protocol: spirometry performed to check eligibility, then IM and intranasal vaccine given. Participants kept diary card for 7 days. Follow-up visit 3-4 weeks after vaccination, and antibody determination. Thereafter 2 weekly phone calls, and final follow-up visit at 6 months. Participants reported if developed respiratory illness.</p> <p>Dropouts: 90 in intervention (8.1%), 110 in control (9.9%). 64 deaths</p>
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Gorse 2003 (Continued)

Participants	<p>Setting: Winter; USA; 1998 to 1999; people with COPD meeting spirometric criteria for COPD from 20 VA Medical Centre sites</p> <p>Exclusion: allergic to vaccine components, received influenza vaccine less than six months previously, immunocompromised, cystic fibrosis, febrile illness 72 hours prior or exacerbation of COPD within 3 weeks prior, or history of Guillain-Barré syndrome</p> <p>Number: 2215; 1107 in intervention and 1108 in control group</p> <p>Age: 50 or over. Mean age 67.8 years, 98.2% male, 83.5% white, 95% had smoking history, 95% had comorbidity, mean FEV₁ 1.34 L, 42.6% predicted, FEV₁/FVC 0.53</p>
Interventions	<p>Trivalent inactivated influenza virus vaccine (TVV) -A/Beijing/262/95-like (H1N1), A/Sydney/5/97-like (H3N2), B/Beijing/184/93; intramuscular into deltoid; 0.5 mL dose. Same lot in all participants.</p> <p>On same day, participants also received either:</p> <p>Intervention: Trivalent, types A and B, live cold adapted influenza virus vaccine (CAIV-T) corresponding to the strains in the TVV, 0.25 mL per nostril, or</p> <p>Control: intranasal saline as a large particle aerosol</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> Added efficacy of CAIV-T as assessed by laboratory-documented influenza-caused illness (LDI). LDI defined as sudden onset of respiratory illness with one or both of (1) influenza A or B culture positivity from nasal or oropharyngeal swabs, (2) four-fold increase in antibody titre for influenza A or B <p>Secondary outcomes:</p> <ul style="list-style-type: none"> efficacy of CAIV-T on influenza-like illness (ILI) on influenza-like illness (ILI). ILI was defined as one of two definitions (i) febrile, 100 F° and influenza virus in the locality and 3/10 criteria met, or (ii) influenza virus not present in locality and 4/10 criteria met• Illness severity was documented• Lung function• VAS of overall sense of health <p>Adverse reactions: early reactions monitored for 7 days using diary</p> <p>Additional outcome of chronic lung disease severity index (CLDSI) was reported in Gorse 2003a.</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment 1:1, stratified by site
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, all participants received intramuscular vaccination; however, the method of intranasal delivery of intervention versus control was different
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination

Gorse 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make determination
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Govaert 1994

Methods	<p>Duration: 5 months</p> <p>Withdrawals: 47 incomplete questionnaires, none due to influenza-related morbidity or mortality</p> <p>Follow-up schedule: clinical assessments, questionnaire completed at 4, 10 and 23 weeks, serological tests at week 3 and 5 months</p>
Participants	<p>Setting: Winter 1991-92, 15 General Practices in Southern Netherlands</p> <p>Number: 1838; 927 vaccinated and 911 in the control</p> <p>Characteristics: Mean age 67 (SD5.6), 4 morbidity categories; heart, lung (9%), diabetes mellitus, and others, or healthy. 54% female</p> <p>Baseline characteristics: similar ages, sex ratios, risk status, previous vaccination rates. 13.5%heart, 11.3% lung, 2.3% diabetes mellitus in the vaccine group and 13.6% heart, 10.4% lung, 2.2% diabetes mellitus in the control. 54.7% female in the vaccine group compared to 50.7% in the control</p> <p>Comorbidities: cardiological, pulmonary, and other metabolic</p> <p>Diagnostic criteria: over 60 years of age, with conditions, if present, that were not severe enough to necessitate mandatory vaccination; not specifically COPD</p> <p>Influenza diagnosed serologically, by a physician or by International Classification of Health Problems in Primary Care 2nd Edition (ICHPPC-2) defined criteria</p> <p>Exclusion criteria: 1. Less than 60 years of age 2. High risk groups 3. Those in old people's or nursing homes</p> <p>Other reasons for non-participation included inability to consent and fear of injections</p>
Interventions	<p>Vaccination type: Purified, split virion vaccine (A/Singapore/6/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90, B/Beijing/1/87)</p> <p>Control: physiological saline placebo</p>
Outcomes	<p>Early: none</p> <p>Late: mortality, exacerbation rates in the form of occurrence of influenza or influenza-like illnesses, HAI antibody titres; adverse reactions assessed at week 4; local, systemic, subgroup analysis</p>
Notes	A subsequent report, Govaert 1994a was a sub-study of this trial reported the adverse reactions;

Risk of bias

Govaert 1994 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation schedule used with 4 strata according to each morbidity category
Allocation concealment (selection bias)	Low risk	At the vaccination session, the participant revealed a previously allocated study number to the vaccination team, which enabled allocation of the participant to the next consecutive number in the appropriate stratum.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled using a 'visually' identical syringe
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers blinded to vaccination status analysed questionnaires completed by the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate reporting of participants lost to follow-up. One death reported in the control group. Authors noted that participants with incomplete data were retained in the analyses where possible
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Howells 1961

Methods	<p>Duration: about 4 months</p> <p>Withdrawals: 1 (control group participant died during an acute exacerbation)</p> <p>Follow-up schedule: initially at week 2, then every 4 weeks by both observers</p>
Participants	<p>Setting: Winter 1960, NW Wolverhampton, UK</p> <p>Number: 55 enrolled; 26 in vaccinated group, 29 in control</p> <p>Characteristics: 37 men (67%) of average age 52.78 years (SD 12.51); overall average peak expiratory flow (PEF) was 270.09 L/min (SD111.88). The overall maximum breathing capacity was 64.33 L/min (SD 30.59)</p> <p>Baseline characteristics: The average age of the vaccinated group was 54.08 years (SD 14) and the control was 51.62 years (SD 11.12). 58% of the vaccinated group was male and 76% of the control. The vaccinated participants had an average duration of symptoms of around 17 years, while the control had around 20 years. The average PEF for the vaccinated group was 266.35 L/min (SD 101.12) and 273.45 L/min (SD 120.29) for the control. This difference could be attributed to 2 people with asthma who had relatively higher peak flows. The average maximum breathing capacity for the vaccinated group was 62.81 L/min (SD 28.66) and 65.75 L/min (SD 32.75) for the control. Comparable antibody levels to influenza viruses in all participants</p> <p>Comorbidities: 7% of control were asthmatics</p> <p>Diagnostic criteria: chronic bronchitis; "a minimum of 3 years' history of cough with phlegm on most days for at least 3 months of the year...". Participants were assessed to enable placement into Grades 1, 2 or 3 with increasing severity.</p>

Howells 1961 (Continued)

Exclusion criteria: people with Grade 4 bronchitis and TB

Interventions	Vaccination type: Flubron (A.A2 Asian-Formosa 7000, B England 5000), intramuscular Control: physiological saline solution
Outcomes	Early: exacerbations in weeks 1 to 3 recorded by clinical examination and measurement of PEF. Bacteriological and complement fixation results for cause of exacerbations. Late: hospitalisation, mortality, as well as all early outcomes.
Notes	We made an assumption for the number of early and late exacerbations per participant for the placebo group. We knew the total number of exacerbations was 24 experienced by 20 participants out of 29. Thus, there would have been at least 8 early and 10 late exacerbations, according to the numbers of participants experiencing exacerbations in the placebo group. We added 2 exacerbations to each group to make up the total of 24. We felt justified in doing so because the study stated that similar numbers of early exacerbations were recorded in both groups, which was the case using our assumption.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make determination
Allocation concealment (selection bias)	Low risk	A key was provided by the statistical advisor to the nursing staff administering injections.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; a nurse uninvolved in the conduct of the research study administered the vaccination
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No details of outcome assessment blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants described and accounted for in results. One death occurred in the control group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

MRC 1980

Methods	Duration: unclear; more than 3 weeks Withdrawals: 16 participants from the Sheffield centre had no baseline recordings. 15 participants failed to complete all records (reasons not discussed) Follow-up schedule: no details
Participants	Setting: no details

MRC 1980 (Continued)

Number: 86 to begin with, but 16 had no baseline data and 15 had incomplete records. Thus, only 55 included in final analysis, with 36 in the vaccinated group and 19 in the control

Characteristics: age range of 28 to 78 years

Baseline characteristics: none recorded

Comorbidities: no details

Diagnostic criteria: chronic bronchitis (MRC definition) and airways obstruction with an FEV₁ > 1 L

Exclusion criteria: cardiac disease symptoms and steroid treatment

Interventions	Vaccination type: live attenuated, RIT 4050 (H2N3) vaccine virus; having surface antigens of the A/Victoria/75 virus in a lyophilised preparation; intranasal; 0.5 mL volume Control: placebo preparation without virus
Outcomes	Early: 7 days post vaccination. Upper and lower respiratory symptoms, systemic symptoms Spirometry: MEFV curves used to determine V50, V75, EVC, PEFr, FEV ₁ Late: day 21; all self-assessments, spirometry of early outcomes, and serology; HAI tests
Notes	Standard errors of serologically negative and positive participants were averaged to calculate a standard deviation for all vaccinees according to the formula: SD = SE * square root of N.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make determination
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make determination
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	High risk	Eleven participants were vaccinated but excluded from the analyses; these originated from one study site
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Treanor 1992

Methods	<p>Duration: 3 years</p> <p>Withdrawals: 8; 7 from intranasal group; deaths due to unrelated causes, discharges from institutions</p> <p>Follow-up schedule: days 1 to 3 after each vaccination for adverse reactions and nasal sheddings; then daily staff nursing reports were used</p>
Participants	<p>Setting: 1987-90, 3 large nursing homes in Rochester, NY, USA; St Ann's Home, St John's Home and Monroe Community Hospital</p> <p>Number: 523; 345 participant years in the intranasal group and 346 participant years in the control</p> <p>Characteristics: older adults; Mean age of 84.2 years. 32% had cardiac or pulmonary conditions; 75% female</p> <p>Baseline characteristics: Relatively well matched for disabilities, age, sex ratios. Mean age in the vaccine group was 84.1 years with 26% of participants randomised to this group suffering either a cardiac or pulmonary condition; 4% of the vaccine group had both a cardiac and pulmonary condition. Mean age in the placebo group was 83.8 years with 23% of participants in this group suffering either a cardiac or pulmonary condition; 2% of participants in this group had both a cardiac and pulmonary condition</p> <p>Comorbidities: only details of cardiovascular and pulmonary complications</p> <p>Diagnostic criteria: none; all residents at these institutions were invited</p> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Acutely ill at time of enrolment 2. On current immunosuppressant therapy 3. Egg product allergy 4. Refusal of inactivated influenza vaccination
Interventions	<p>Vaccination type:</p> <ol style="list-style-type: none"> 1. Live attenuated, cold-adapted, monovalent influenza virus vaccination (A/Bethseda/1/85 (H3N2), A/Los Angeles/2 /87 (H3N2), A/Ann Arbor/6/60) intranasally in 0.5 mL doses 2. Inactivated, trivalent, subvirion influenza vaccine containing 9 different HAs intramuscular in 0.5 mL doses <p>Control:</p> <ol style="list-style-type: none"> 1. Intranasal placebo of sterile veal infusion broth 2. Trivalent inactivated subvirion influenza vaccine identical to treatment group
Outcomes	<p>Early: days 1 to 3 post vaccination; adverse effects</p> <p>Late: years 1, 2, 3: serum antibody responses measured and occurrence of respiratory and flu-like illnesses were measured to evaluate the efficacy of adding live intranasal vaccination to the inactivated type</p>
Notes	Not specifically people with COPD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details on randomisation sequence provided. Re-randomisation occurred every year

Treanor 1992 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail provided, although it is stated that this study was double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	A low number of dropouts reported per year, evenly across groups. Independent analysis each study year
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Treanor 1994

Methods	<p>Duration: at least 4 weeks</p> <p>Withdrawals: no details</p> <p>Follow-up schedule: early symptoms at days 3 to 4, serologic testing at 4 weeks post vaccination</p>
Participants	<p>Setting: outpatient clinics of Strong Memorial Hospital; Rochester, NY and a private practice, USA</p> <p>Number: 81; 34 in the live attenuated vaccination group, 30 in the inactivated vaccination group and 11 in the control</p> <p>Characteristics: older adults (> 65 years) and chronically ill, 65% female</p> <p>Baseline characteristics: distributions of chronic conditions, smokers and mean ages were roughly similar. 18% of the live vaccinated group had chronic lung disorders, and had a mean age of 68.9 years.</p> <p>Comorbidities: chronic cardiac, pulmonary, endocrine, hematologic conditions, 25% smokers</p> <p>Diagnostic criteria: ambulatory adults over 65 years, or with at least 1 high risk condition</p> <p>Exclusion criteria: no details</p>
Interventions	<p>Vaccination type:</p> <ol style="list-style-type: none"> 1. Cold-adapted, Live attenuated re-assortant influenza B virus vaccine (B/Ann Arbor/1/86 or B/Yamagata/16/88), intranasally in 0.5 mL doses with intramuscular placebo 2. Parenteral, trivalent, inactivated influenza vaccination (B/Ann Arbor/86 and B/Yamagata/88) intramuscularly, in 0.5 mL doses with intranasal placebo <p>Control: placebo; intramuscular saline and intranasal veal infusion broth</p>
Outcomes	<p>Early: 3 to 4 days post vaccination; pulse oximetry, spirometry, virus cultures and HAI tests; symptoms for 7 days (upper and lower respiratory tract symptoms, systemic)</p> <p>Late: serology repeated at week 4, hospitalisations</p>

Treanor 1994 (Continued)

Notes Cold adapted, live attenuated influenza B vaccines are safe but not as immunogenic as inactivated ones in chronically ill or older people. There were no significant differences between the groups in outcomes of spirometry and adverse effects. Author provided individual participant data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No further details other than 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This study was double-blind, however, methods were not described in any more detail.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data or withdrawals reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Wongsurakiat 2004a

Methods	<p>Duration: 1 year.</p> <p>Withdrawals: 3 dropouts (1 vaccine, 2 control). Deaths 8 (5 vaccine, 3 control) all died from causes not related to acute respiratory infection</p> <p>Follow-up schedule: reviewed monthly. Bloods taken at week 0, week 4, and 6 and 12 months; participants reported acute respiratory infections, and had extra visit for full assessment, including the taking of acute and convalescent serum 4 to 6 weeks later. If respiratory infection presented for less than 6 days, swabs taken</p>
Participants	<p>Setting: 1997-8. Thailand, university hospital, COPD outpatient clinic; non-influenza epidemic years in Thailand</p> <p>Number: 132 consecutive outpatients. 7 excluded as couldn't attend, making 125 in total, 62 in vaccine group and 63 in control group</p> <p>Inclusion: clinical COPD (COPD not defined although managed according to Thai guidelines), FEV₁ < 70% and < 15% increase after bronchodilator</p> <p>Exclusions: egg allergy, immunocompromised, immunosuppressive drugs (except corticosteroids), or if comorbidities expected to reduce survival to < 1 year</p>

Wongsurakiat 2004a (Continued)

Characteristics: mean age 68.3 years, 94% male, 96% smoking history, 37% FEV₁ < 50%, 44% FEV₁ > 70%, 33% with comorbidities

Interventions	Vaccination type: purified trivalent split-virus vaccine A/Texas/36/91 (H1N1), ANanchang/933/95 (H3N2), B/Harbin/07/94. 0.5 mL on Day 1 and a second dose at 4 weeks; two-dose schedule given as first time that influenza vaccine available in Thailand. Control was 0.5 mL of Vitamin B1
Outcomes	Acute respiratory infections, antibody responses to vaccination and to acute respiratory infections (by HAI test), allowing classification of whether the infection was influenza-related Clinical classification of ARI into common cold, acute exacerbation, influenza-like illness, or pneumonia. Severity recorded; hospitalisation, ventilation, and stratified by COPD severity Adverse effects recorded carefully for 4 weeks after vaccination
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants stratified based on disease severity and numbered consecutively. These numerical identifiers had been previously randomised to either intervention or placebo.
Allocation concealment (selection bias)	Low risk	A nurse not involved in participant care determined which numerical identifier was allocated to intervention or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo controlled. Both vaccine and placebo were same volume and quantity, administered to all participants.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study clearly outlines exclusions and dropouts; dropouts were very similar for both groups.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

ARI: acute respiratory infection; CAIV-T: live cold adapted influenza virus vaccine; CAV: live attenuated influenza A virus vaccine derived from cold-adapted influenza; CCA: chicken cell agglutinating; CLDSI: chronic lung disease severity index; COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; FVC: force vital capacity; HAI: hemagglutination inhibition; ICHPPC-2: International Classification of Health Problems in Primary Care; ILI: influenza-like illness; IM: intramuscular; LDI: laboratory-documented influenza; MD: mean difference; MEFV: maximum expiratory flow - volume curve; MRC: Medical Research Council; PEFR: peak expiratory flow rate; SD: standard deviation; TB: tuberculosis; TVV: trivalent inactivated influenza virus vaccine; USA: United States of America; UK: United Kingdom; VAS: visual analogue scale; V50: air flow rate at 50% vital capacity; V75: air flow rate at 75% vital capacity; WBC: white blood cells.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ambrosch 1979	Not placebo controlled and not COPD specific
Centanni 1997	Add-on benefit of bacterial immunostimulant is being assessed
Dorrell 1997	Not RCT, people with obstructive airways disease are only a small subgroup
Gorse 1986	Live and inactivated virus vaccines used without placebo as a control, not randomised
Gorse 1988	Serological results only; no primary outcomes suitable for this review
Gorse 1991	No randomisation of people with COPD.
Gorse 1996	Serological outcomes only, no primary outcomes suitable for this review
Howells 1975	No randomisation of older participants with lung disease
Keitel 1993	Healthy adults susceptible to virus vaccine were used
Lama 1998	Serological outcomes only; no primary outcomes suitable for this review, unclear if this is an RCT from the abstract. We were unable to retrieve the full paper.
Margolis 1990	Randomised survey with a lung disease component but not placebo controlled
MRC 1959	3 inactivated vaccines used without placebo as a control
MRC 1984	Not randomised for people with COPD.
Paul 1988	Not RCT
Portari 1998	Not RCT, serological outcomes only; no primary outcomes suitable for this review
Powers 1991	Healthy older adults used
Prevost 1975	Not RCT
Saah 1986	Retrospective cohort study , not COPD
Teanor 1998	Older and high risk participants but no details of COPD or any other lung disease
Winson 1977	No randomisation of chronic bronchitis

DATA AND ANALYSES

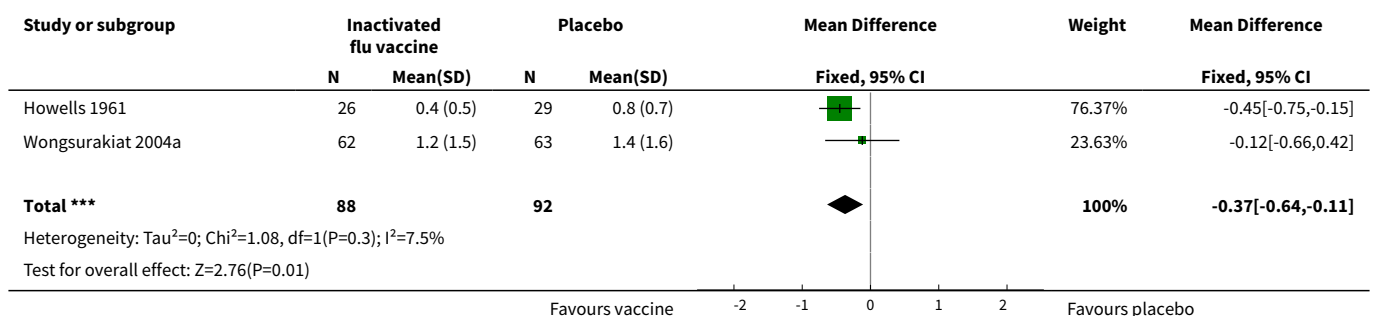
Comparison 1. Inactivated influenza vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total exacerbations per participant	2	180	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.64, -0.11]

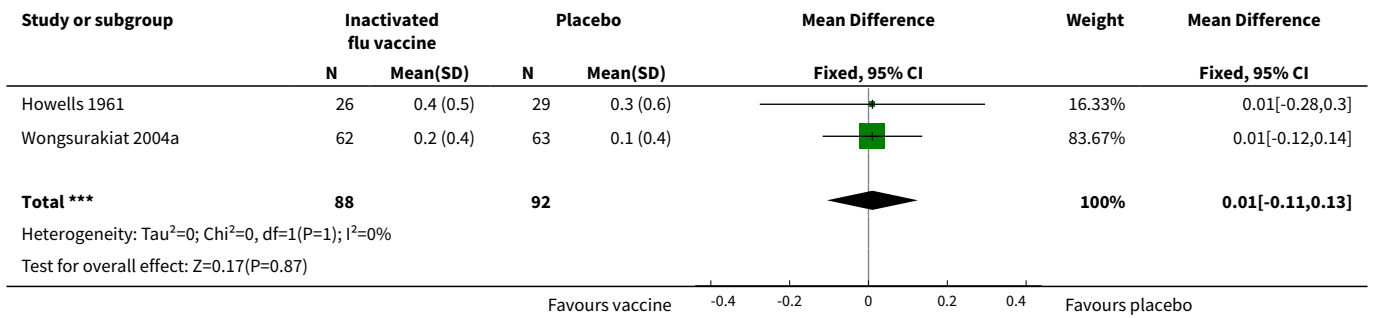
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Early exacerbations per participant	2	180	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.13]
3 Late exacerbations per participant	2	180	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.61, -0.18]
4 Participants with at least one exacerbation or acute respiratory illness	3	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.44, 1.48]
4.1 Clinical exacerbations	2	97	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.48, 2.33]
4.2 Any acute respiratory illness	1	125	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.22, 1.42]
5 Participants with early exacerbations	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.52, 2.26]
6 Participants with late exacerbations	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Hospital admissions	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.09, 1.24]
7.1 Clinical exacerbations	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.39]
7.2 Influenza-related exacerbations	1	125	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.09, 1.89]
8 Mortality (all cause)	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.28, 2.70]
9 Mortality (acute respiratory illness-related)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Overall change in lung function (FEV ₁ , L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Change in early lung function (FEV ₁ , L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Systemic adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Local effects at injection site	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Participants with early breathlessness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
15 Participants with early tightness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Participants with early wheeze	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
17 Participants with early cough	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
18 Acute respiratory illness subsequently documented as influenza-related	2	180	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.07, 0.48]
18.1 FEV ₁ ≥ 70% predicted	1	45	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 1.11]
18.2 Participants with chronic bronchitis	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.96]
18.3 FEV ₁ < 50% predicted	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.99]
18.4 FEV ₁ 50% to 69% predicted	1	33	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.07, 2.98]
19 Early acute respiratory illness (ARI)	1	250	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.34, 1.50]
19.1 ARI within 1 week of vaccination	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.24, 4.26]
19.2 ARI between 1 and 4 weeks after vaccination	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.27, 1.50]
20 Participants with early sputum production	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

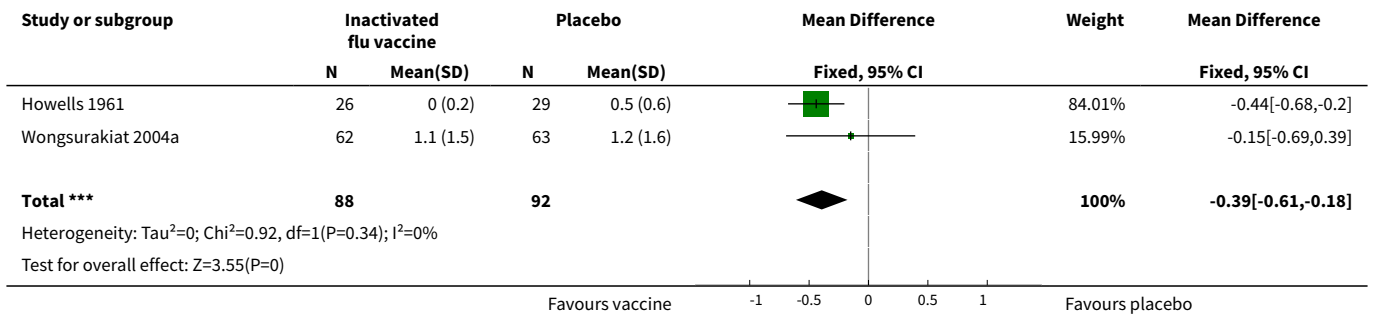
Analysis 1.1. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 1 Total exacerbations per participant.



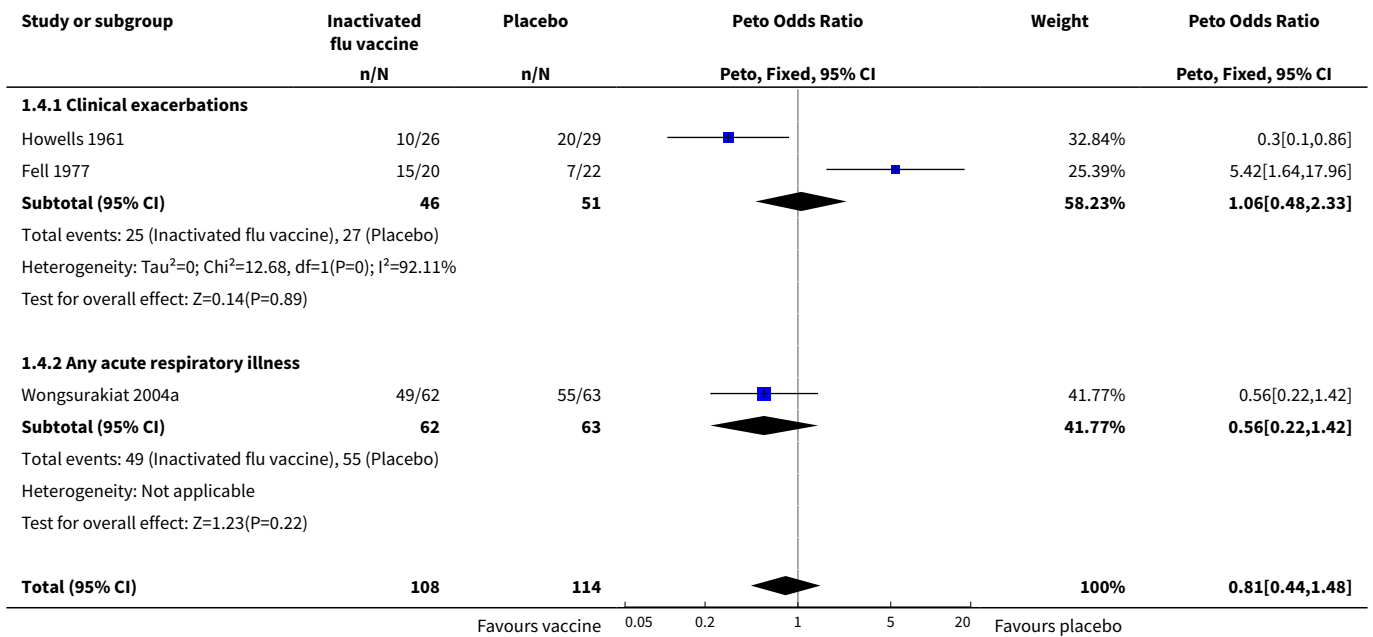
Analysis 1.2. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 2 Early exacerbations per participant.

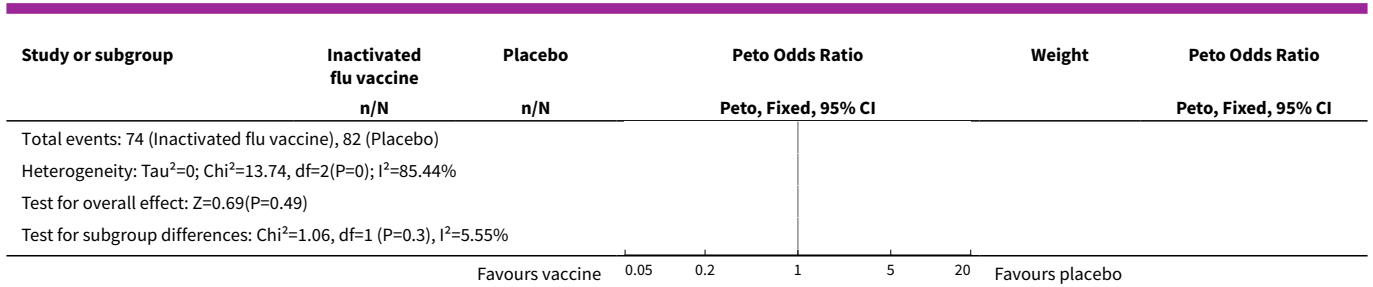


Analysis 1.3. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 3 Late exacerbations per participant.

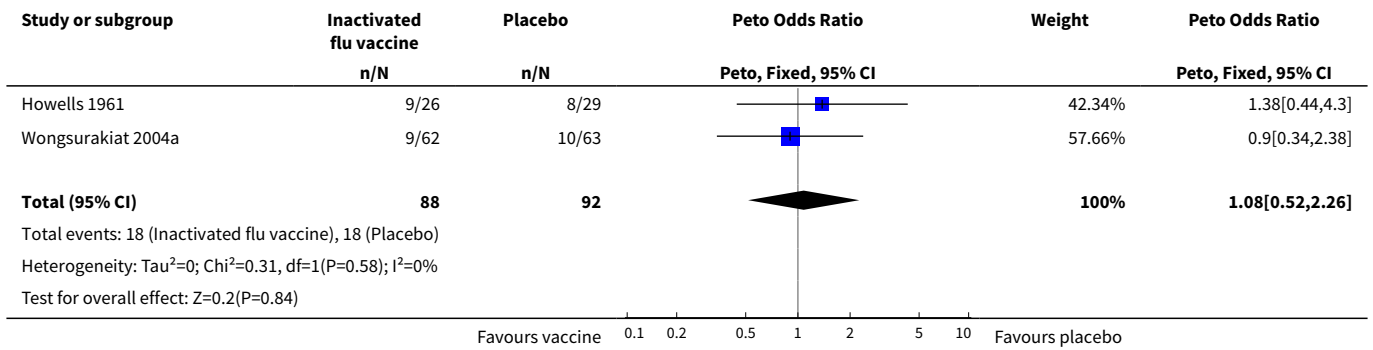


Analysis 1.4. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 4 Participants with at least one exacerbation or acute respiratory illness.

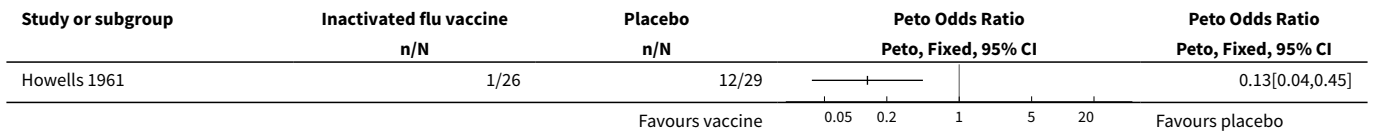




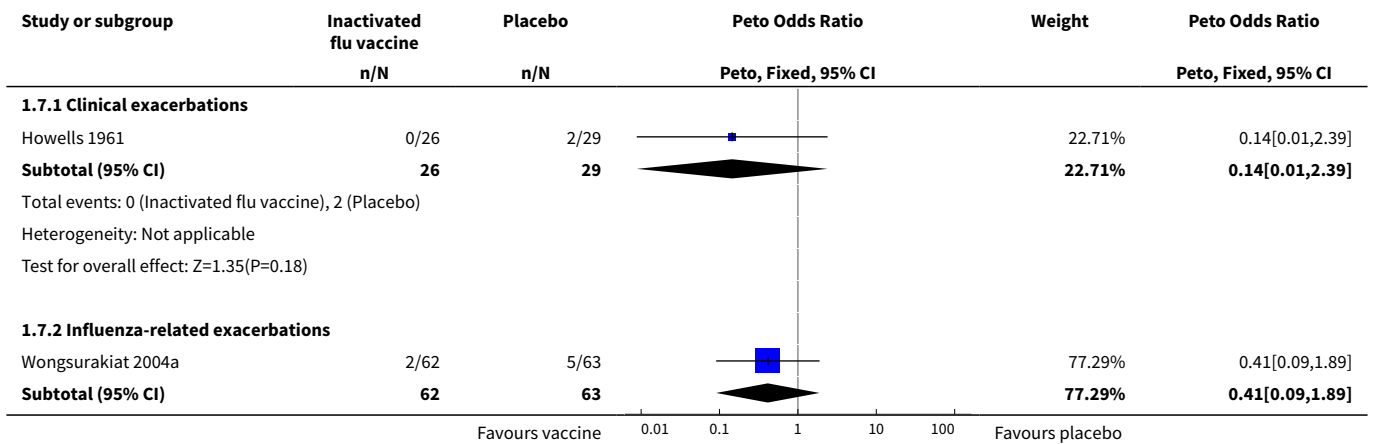
Analysis 1.5. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 5 Participants with early exacerbations.

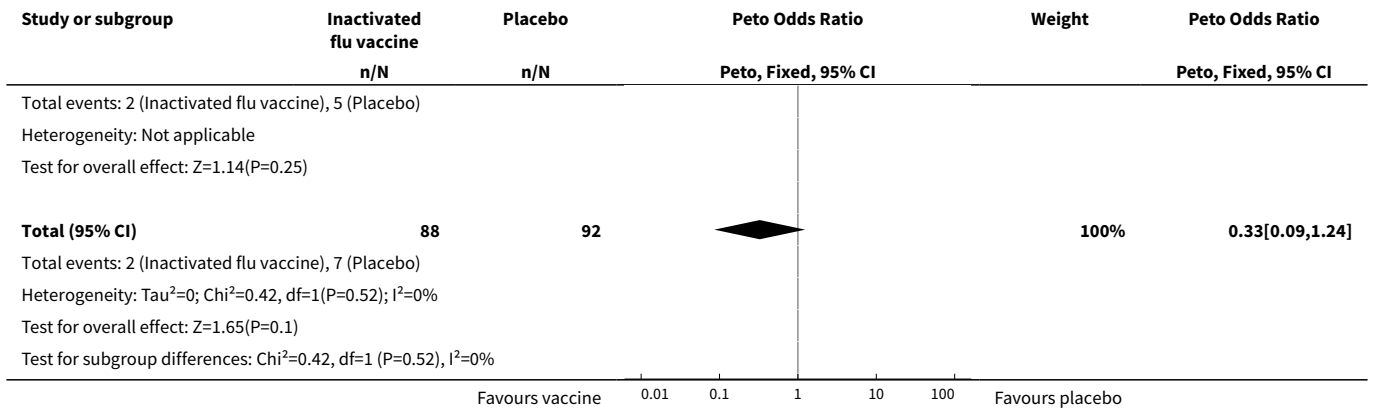


Analysis 1.6. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 6 Participants with late exacerbations.

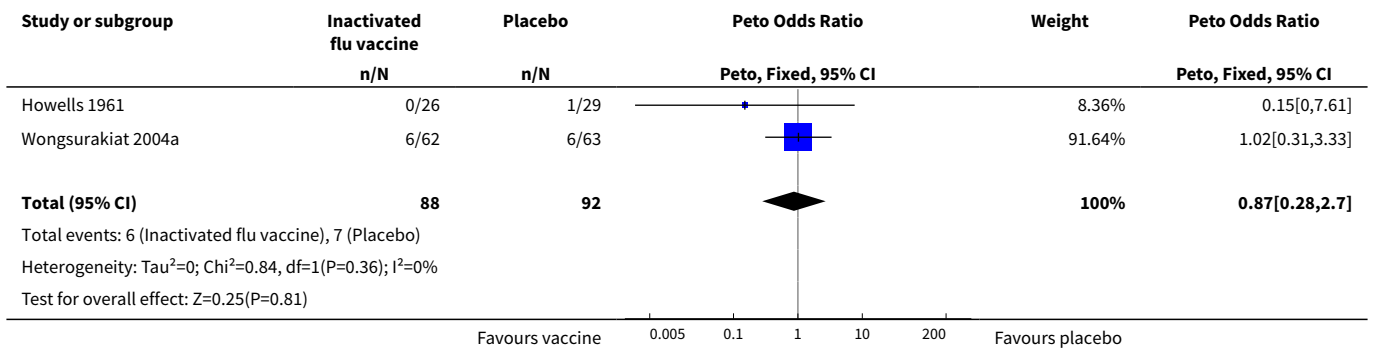


Analysis 1.7. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 7 Hospital admissions.

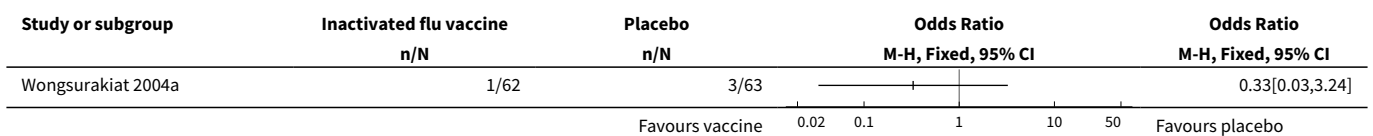




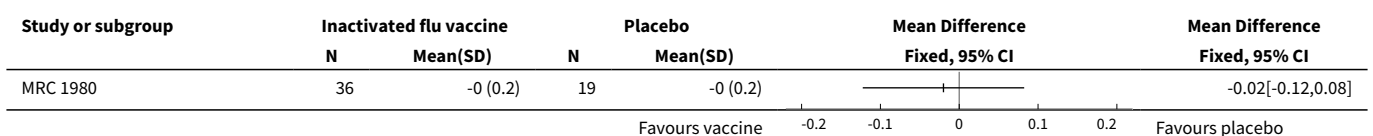
Analysis 1.8. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 8 Mortality (all cause).



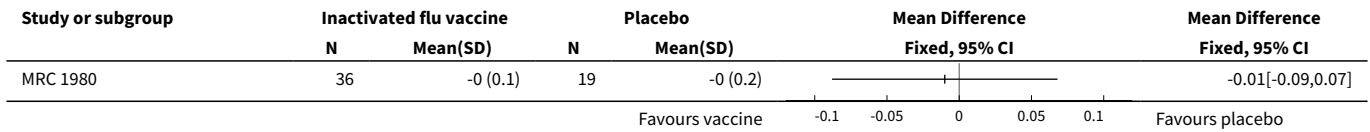
Analysis 1.9. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 9 Mortality (acute respiratory illness-related).



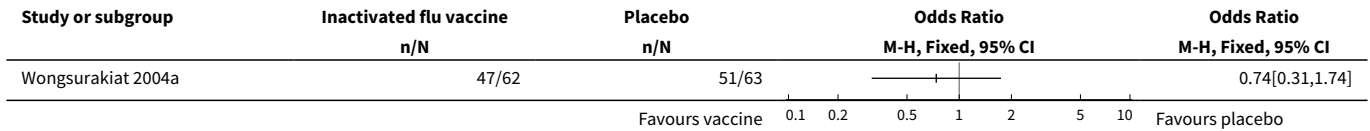
Analysis 1.10. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 10 Overall change in lung function (FEV₁, L).



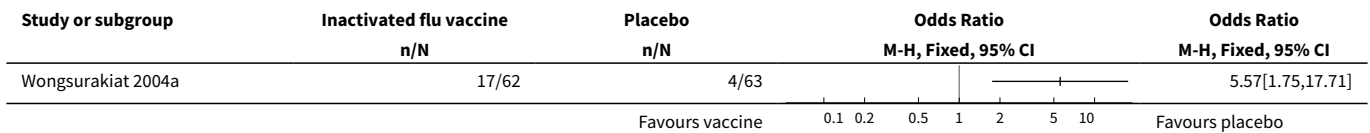
Analysis 1.11. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 11 Change in early lung function (FEV₁, L).



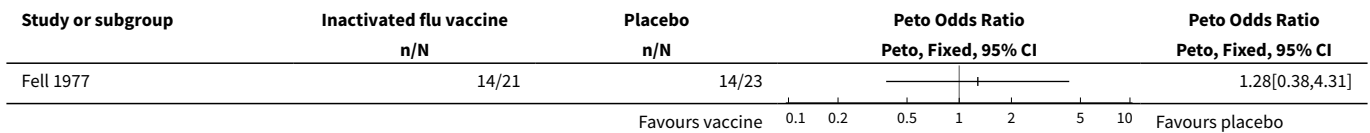
Analysis 1.12. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 12 Systemic adverse effects.



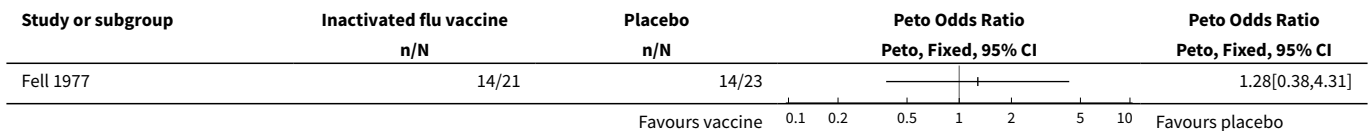
Analysis 1.13. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 13 Local effects at injection site.



Analysis 1.14. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 14 Participants with early breathlessness.



Analysis 1.15. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 15 Participants with early tightness.



Analysis 1.16. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 16 Participants with early wheeze.

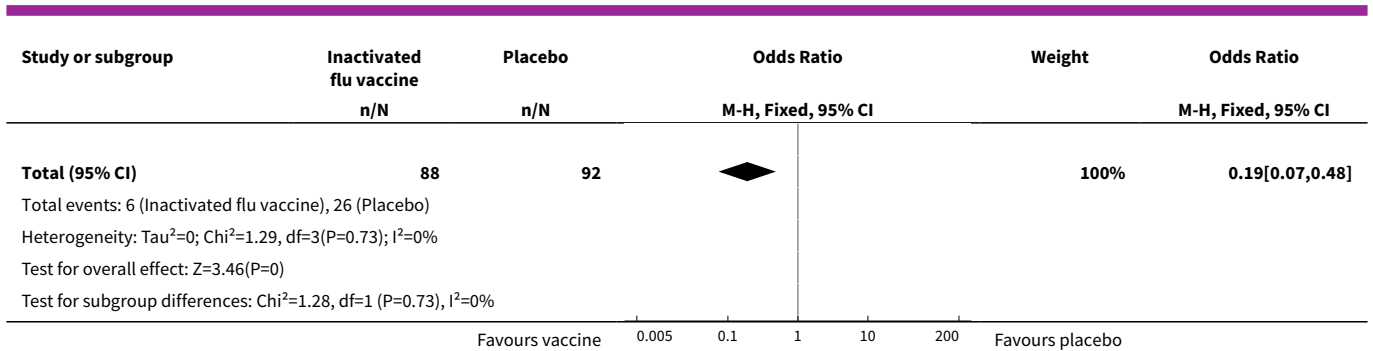
Study or subgroup	Inactivated flu vaccine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fell 1977	15/21	9/23		3.57[1.1,11.56]

Analysis 1.17. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 17 Participants with early cough.

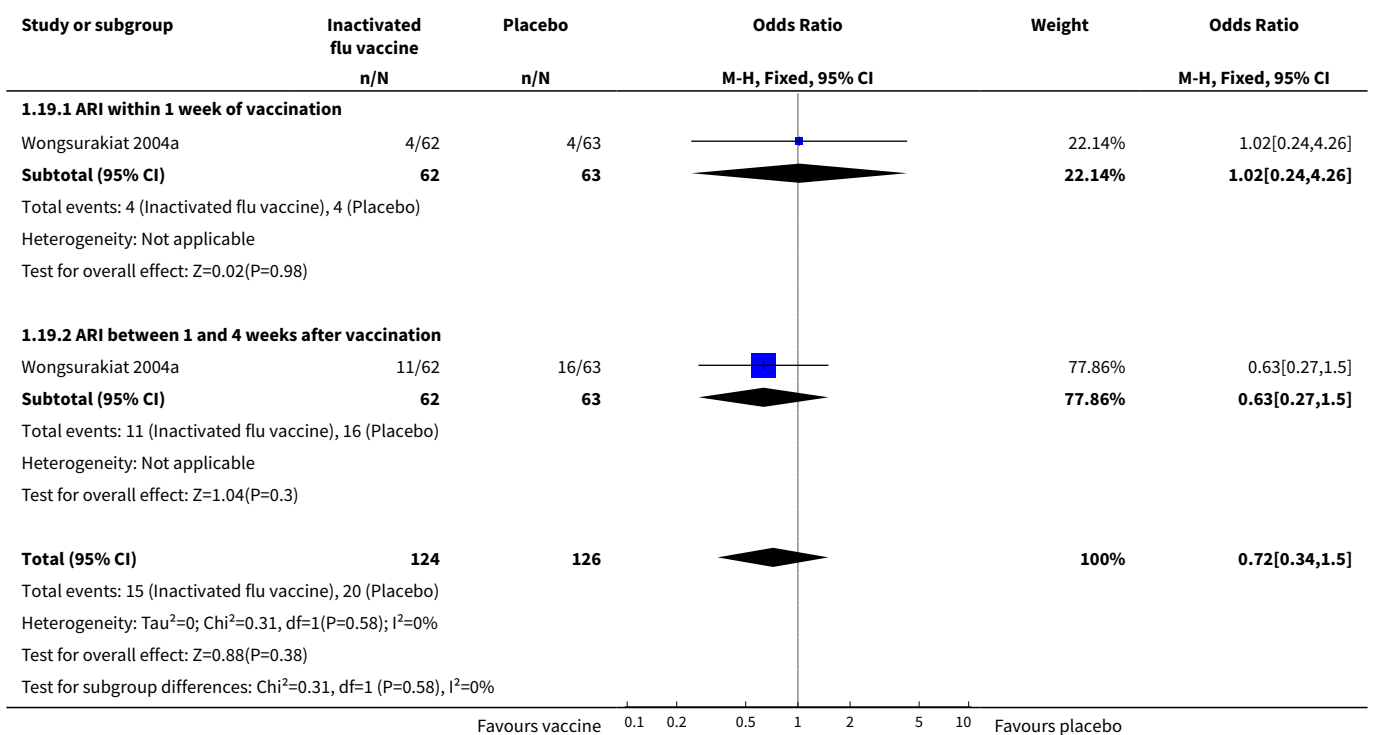
Study or subgroup	Inactivated flu vaccine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fell 1977	20/21	18/23		4.09[0.74,22.49]

Analysis 1.18. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 18 Acute respiratory illness subsequently documented as influenza-related.

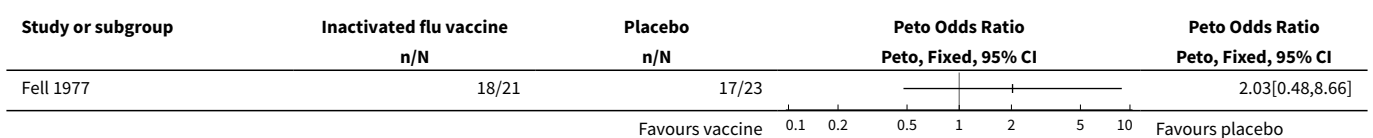
Study or subgroup	Inactivated flu vaccine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.18.1 FEV¹ ≥ 70% predicted					
Wongsurakiat 2004a	1/23	6/22		24.79%	0.12[0.01,1.11]
Subtotal (95% CI)	23	22		24.79%	0.12[0.01,1.11]
Total events: 1 (Inactivated flu vaccine), 6 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0, df=0(P<0.0001); I ² =100%					
Test for overall effect: Z=1.87(P=0.06)					
1.18.2 Participants with chronic bronchitis					
Howells 1961	2/26	9/29		33.19%	0.19[0.04,0.96]
Subtotal (95% CI)	26	29		33.19%	0.19[0.04,0.96]
Total events: 2 (Inactivated flu vaccine), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.01(P=0.04)					
1.18.3 FEV¹ < 50% predicted					
Wongsurakiat 2004a	1/23	7/24		27.69%	0.11[0.01,0.99]
Subtotal (95% CI)	23	24		27.69%	0.11[0.01,0.99]
Total events: 1 (Inactivated flu vaccine), 7 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0, df=0(P<0.0001); I ² =100%					
Test for overall effect: Z=1.97(P=0.05)					
1.18.4 FEV¹ 50% to 69% predicted					
Wongsurakiat 2004a	2/16	4/17		14.34%	0.46[0.07,2.98]
Subtotal (95% CI)	16	17		14.34%	0.46[0.07,2.98]
Total events: 2 (Inactivated flu vaccine), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.81(P=0.42)					



Analysis 1.19. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 19 Early acute respiratory illness (ARI).



Analysis 1.20. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 20 Participants with early sputum production.

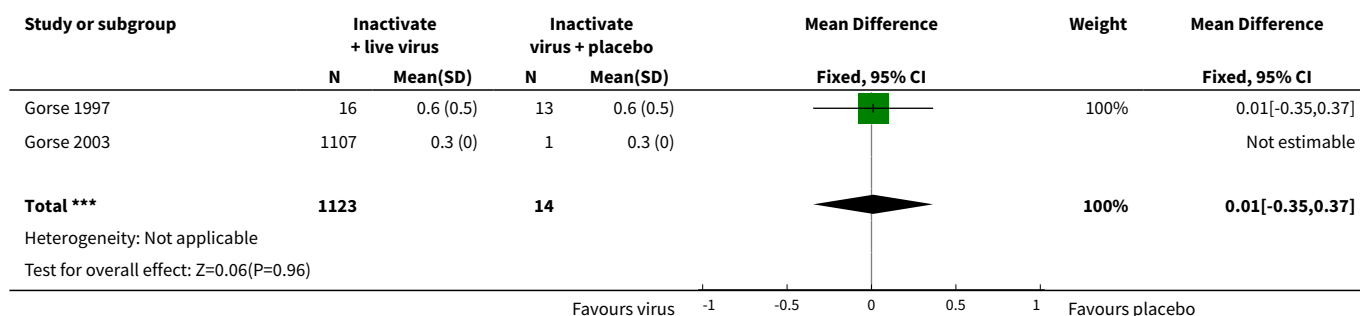


Comparison 2. Inactivated + live virus versus inactivated virus + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total exacerbations per participant	2	1137	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.35, 0.37]
2 Early exacerbations per participant	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Late exacerbations per participant	1	29	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.08, 0.54]
4 Participants with improvement in exacerbations	1	29	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.30, 7.42]
5 Participants with early improvements	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
6 Participants with late improvements	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Early changes in lung function (% predicted FEV ₁)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Early changes in lung function (FEV ₁ /FVC %)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Post immunisation lung function (FEV ₁)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Participants with increased lung function (1 category)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
12 Participants with decreased lung function	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
13 FEV ₁ at end of study	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Participants with adverse effects (new upper respiratory tract symptoms)	1	29	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [0.45, 8.04]
15 Participants with early adverse effects	2	2244	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.63, 1.17]
16 Number of days with early symptoms and signs	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17 Number of participants with early adverse effects (by type)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 COPD	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 Dyspnoea	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.60, 5.41]
17.3 Pharyngitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.86]
17.4 Flu syndrome	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.20, 1.91]
17.5 Rhinitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.34]
17.6 Bronchitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.50, 8.05]
17.7 Increased cough	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.51]
17.8 Myalgia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.51 [0.49, 12.96]
17.9 Increased sputum	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.36]
17.10 Pneumonia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.97]
17.11 Asthenia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.97]
17.12 Guillain-Barré syndrome	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.19]
17.13 Other	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.26, 0.92]
18 Participants with late adverse effects	2	2244	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.33 [1.22, 4.46]
19 Acute respiratory illness subsequently documented as influenza-related	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
20 Participants with at least one influenza-like illness	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 1 Total exacerbations per participant.



Analysis 2.2. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 2 Early exacerbations per participant.

Study or subgroup	Inactivate + live virus		Inactivate virus + placebo		Mean Difference		Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Gorse 1997	16	0.3 (0.4)	13	0.5 (0.5)			-0.21[-0.55,0.13]

Analysis 2.3. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 3 Late exacerbations per participant.

Study or subgroup	Inactivate + live virus		Inactivate virus + placebo		Mean Difference		Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI			
Gorse 1997	16	0.4 (0.5)	13	0.2 (0.4)			100%	0.23[-0.08,0.54]
Total ***	16		13				100%	0.23[-0.08,0.54]

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%
Test for overall effect: Z=1.47(P=0.14)

Analysis 2.4. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 4 Participants with improvement in exacerbations.

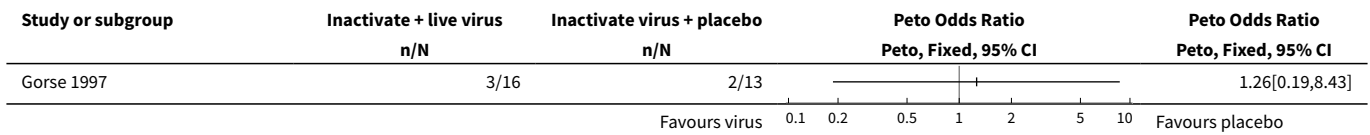
Study or subgroup	Inactivate + live virus		Inactivate virus + placebo		Peto Odds Ratio		Weight	Peto Odds Ratio
	n/N	n/N	n/N	n/N	Peto, Fixed, 95% CI			
Gorse 1997	5/16	3/13					100%	1.48[0.3,7.42]
Total (95% CI)	16	13					100%	1.48[0.3,7.42]

Total events: 5 (Inactivate + live virus), 3 (Inactivate virus + placebo)
Heterogeneity: Not applicable
Test for overall effect: Z=0.48(P=0.63)

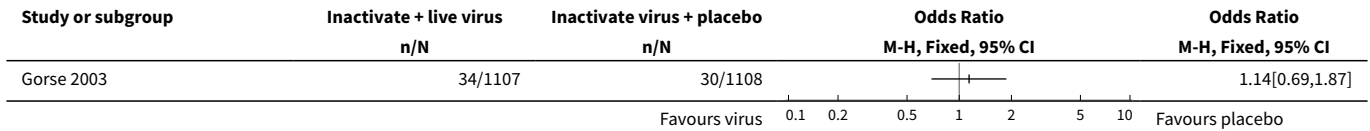
Analysis 2.5. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 5 Participants with early improvements.

Study or subgroup	Inactivate + live virus		Inactivate virus + placebo		Peto Odds Ratio		Peto Odds Ratio
	n/N	n/N	n/N	n/N	Peto, Fixed, 95% CI		
Gorse 1997	2/16	1/13					1.65[0.16,17.49]

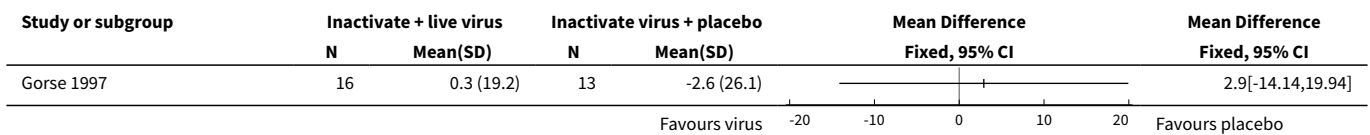
Analysis 2.6. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 6 Participants with late improvements.



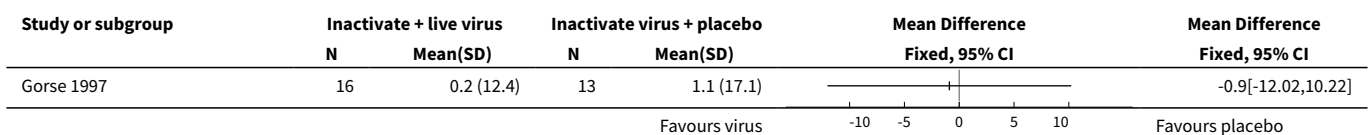
Analysis 2.7. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 7 Mortality.



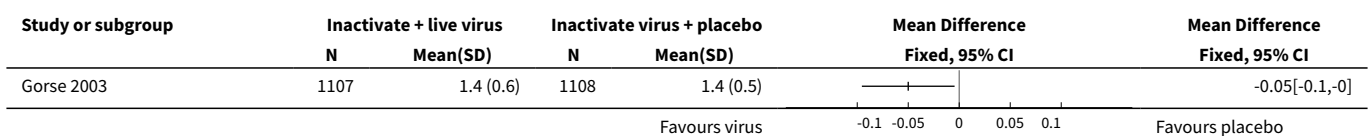
Analysis 2.8. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 8 Early changes in lung function (% predicted FEV₁).



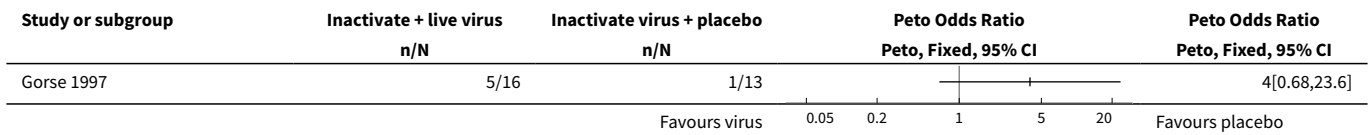
Analysis 2.9. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 9 Early changes in lung function (FEV₁/FVC %).



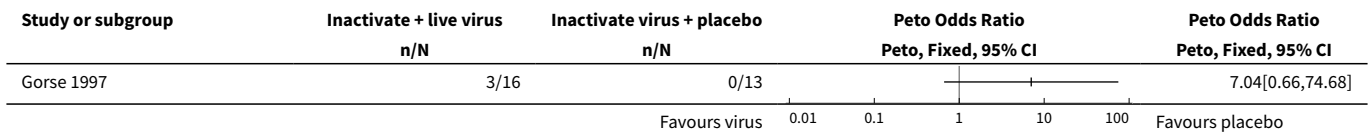
Analysis 2.10. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 10 Post immunisation lung function (FEV₁).



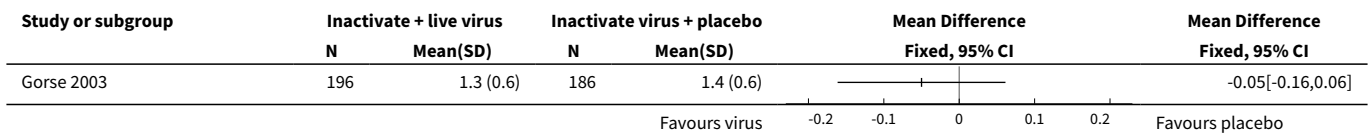
Analysis 2.11. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 11 Participants with increased lung function (1 category).



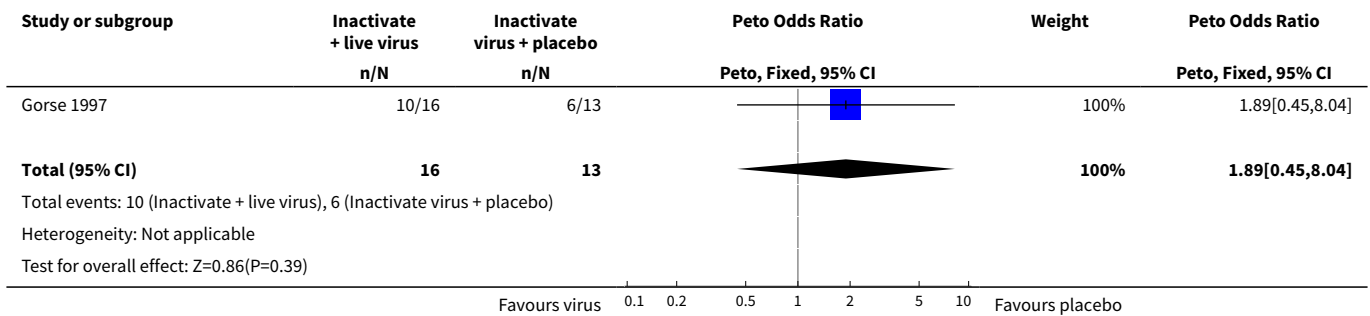
Analysis 2.12. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 12 Participants with decreased lung function.



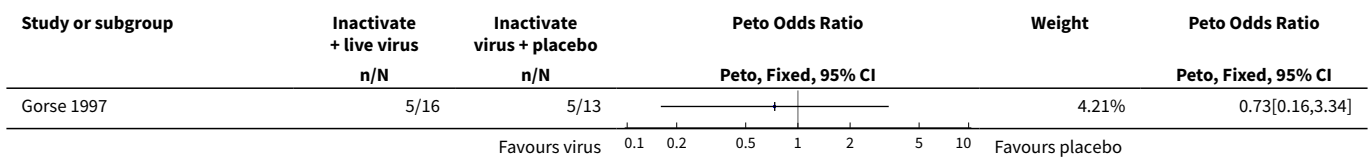
Analysis 2.13. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 13 FEV₁ at end of study.

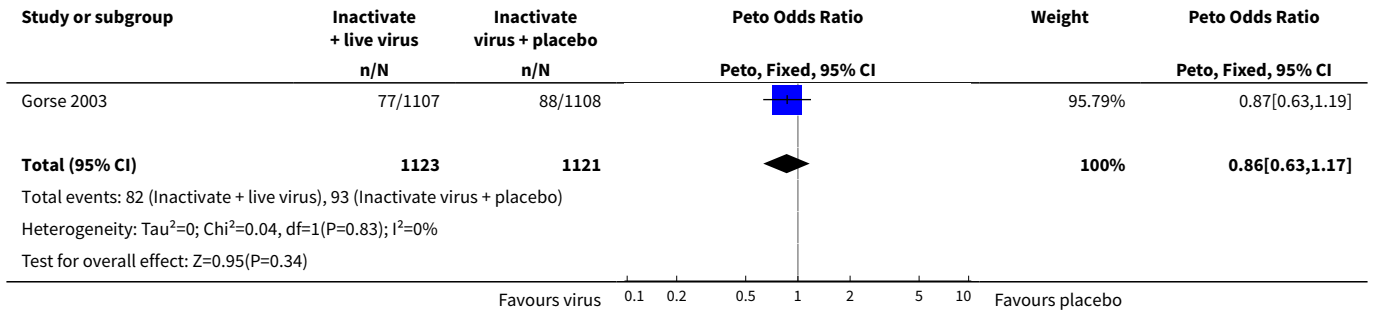


Analysis 2.14. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 14 Participants with adverse effects (new upper respiratory tract symptoms).

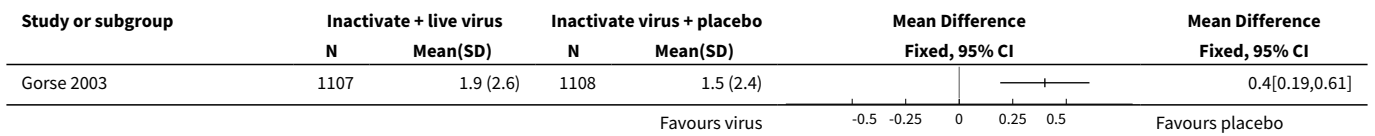


Analysis 2.15. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 15 Participants with early adverse effects.

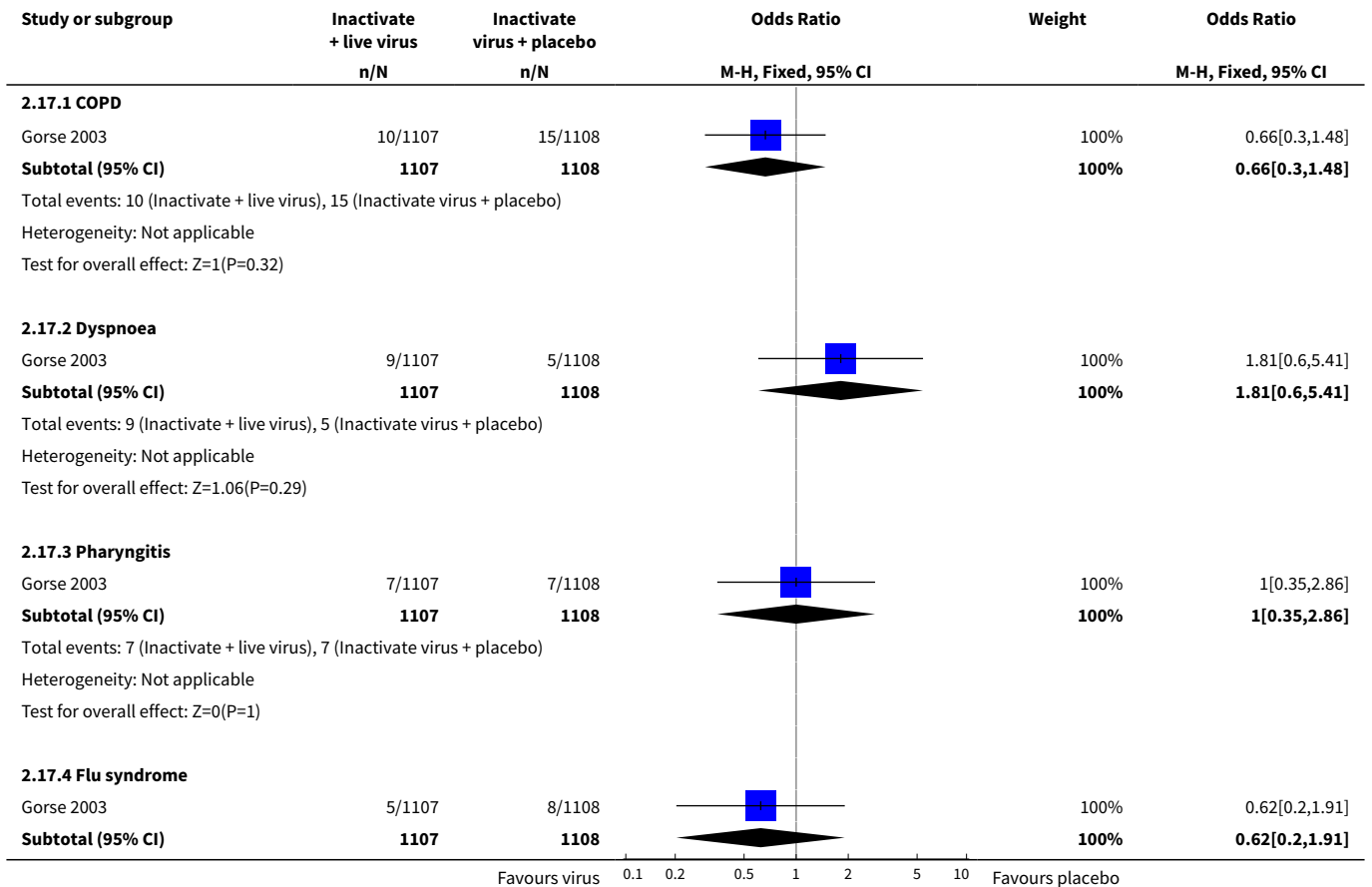


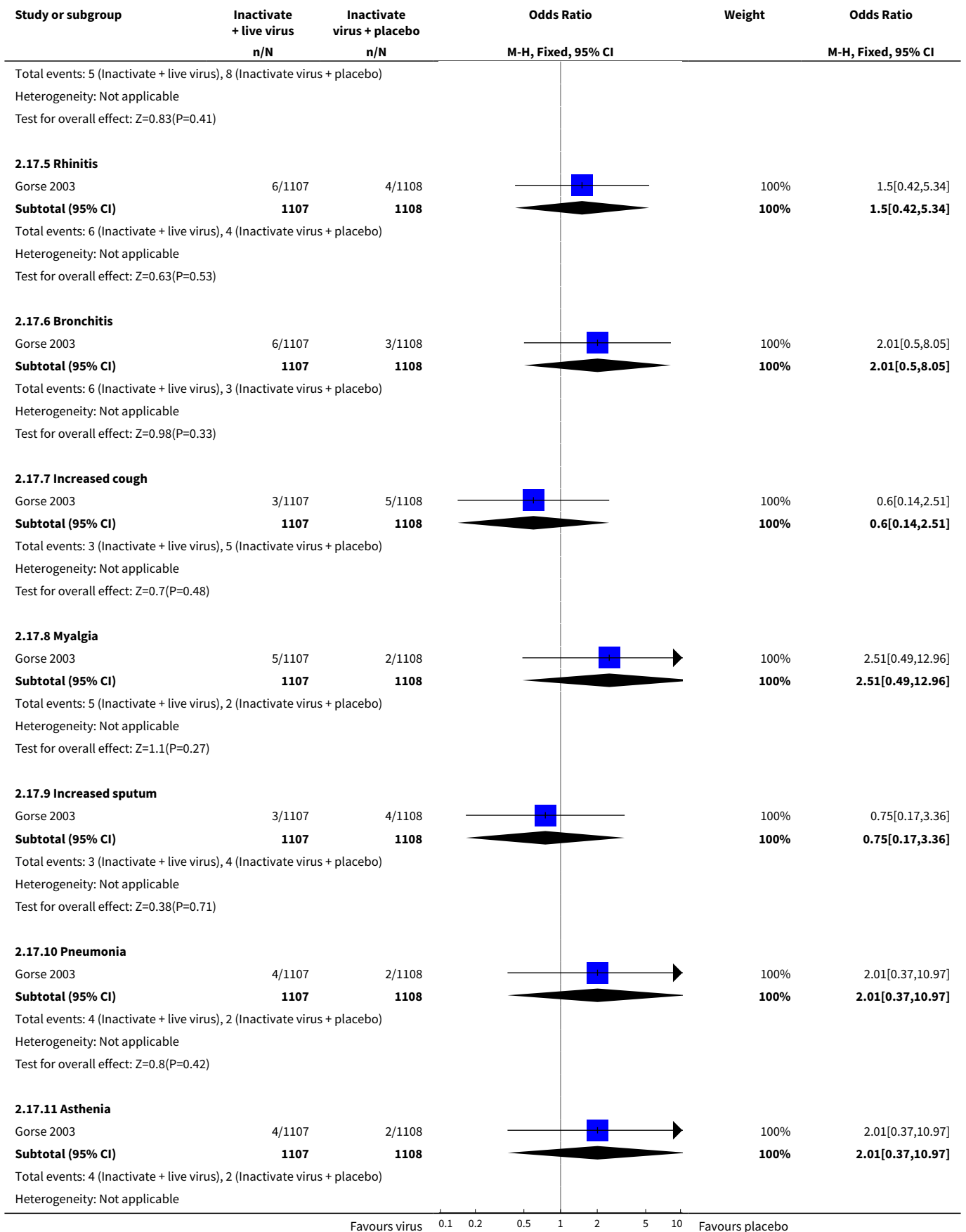


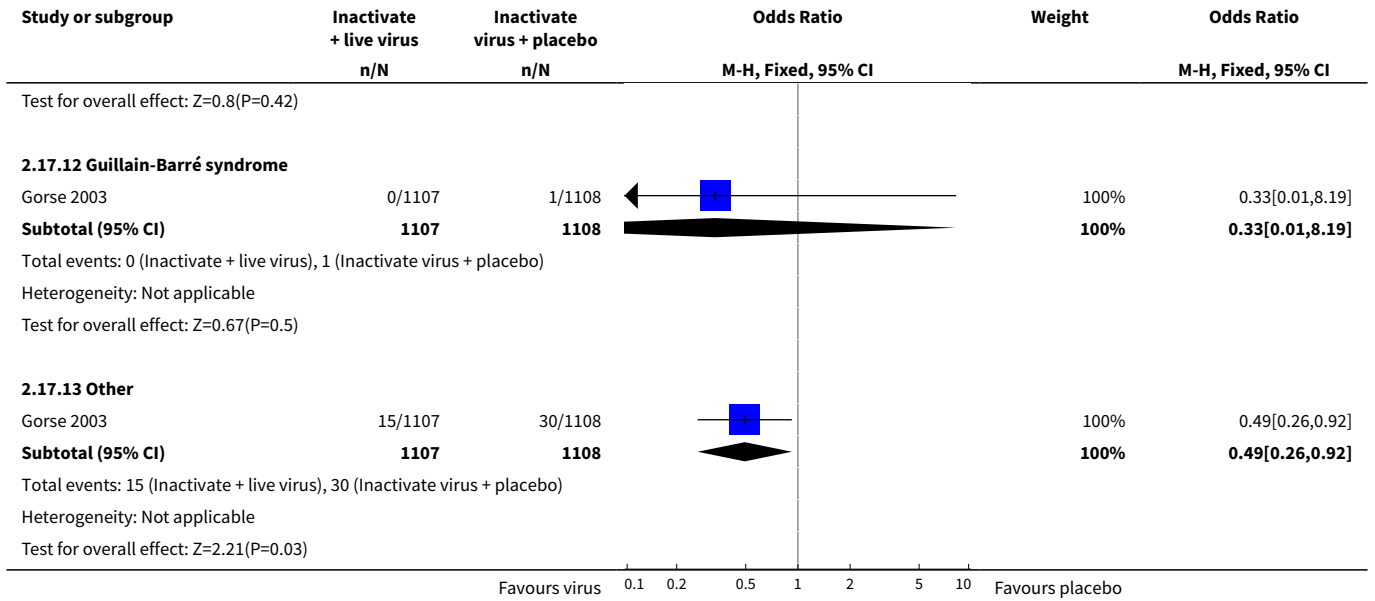
Analysis 2.16. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 16 Number of days with early symptoms and signs.



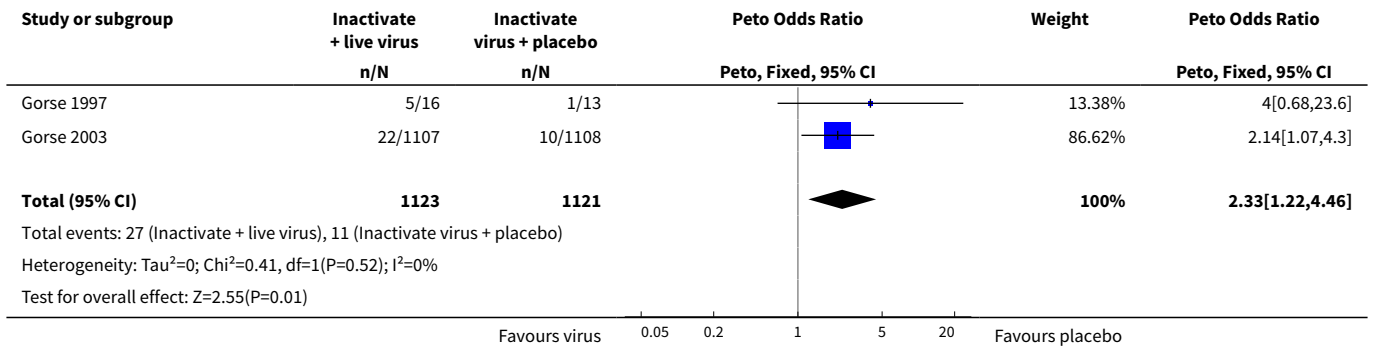
Analysis 2.17. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 17 Number of participants with early adverse effects (by type).



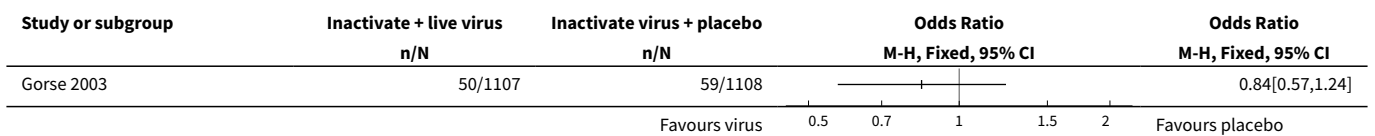




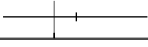
Analysis 2.18. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 18 Participants with late adverse effects.



Analysis 2.19. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 19 Acute respiratory illness subsequently documented as influenza-related.



Analysis 2.20. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 20 Participants with at least one influenza-like illness.

Study or subgroup	Inactivate + live virus	Inactivate virus + placebo	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gorse 2003	196/1107	186/1108		1.07[0.86,1.33]
		Favours virus	1	Favours placebo

APPENDICES
Appendix 1. Sources and search methods for the Cochrane Airways Trials Register
Electronic searches: core databases

Database	Frequency of search
CENTRAL (<i>the Cochrane Library</i>)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the Cochrane Airways Trials Register

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema\$.mp.
4. (chronic\$ adj3 bronchiti\$).mp.
5. (obstruct\$ adj3 (pulmonary or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

Search via Cochrane Register of Studies (CRS Web)

- #1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
- #2 MeSH DESCRIPTOR Bronchitis, Chronic
- #3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
- #4 COPD:MISC1
- #5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 MeSH DESCRIPTOR Influenza Vaccines
- #8 MeSH DESCRIPTOR Vaccines
- #9 (influenza* or flu*) NEAR (vaccin* or immuni* or inoculat*)
- #10 flumist
- #11 trivalent
- #12 CAIV
- #13 LAIV

Influenza vaccine for chronic obstructive pulmonary disease (COPD) (Review)

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#14 medimmune
 #15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
 #16 #6 AND #15

WHAT'S NEW

Date	Event	Description
5 December 2017	New search has been performed	Literature search keywords updated and search re-run
5 December 2017	New citation required but conclusions have not changed	No new studies included. Updated to current review format including summary of findings table and risk of bias.

HISTORY

Protocol first published: Issue 2, 1999
 Review first published: Issue 3, 2000

Date	Event	Description
11 June 2010	New search has been performed	Literature search re-run; no new studies found.
23 June 2009	New search has been performed	Literature search re-run; no new studies found.
28 July 2008	Amended	Converted to new review format.
14 May 2007	New search has been performed	Literature search conducted, no new studies found. Second published report of Gorse 2003 located via searching added, and consequential text changes made.
15 August 2006	New citation required and conclusions have changed	<p>There are two new trials (five reports). Gorse 2003 included 2215 people with COPD and Wongsurakiat 2004 included 132 people with COPD.</p> <p>New outcomes have been included: *Acute infection subsequently documented as influenza-related *Cost effectiveness *Number of people with exacerbations</p> <p>A significant protective effect has now been shown of influenza vaccine on exacerbations of COPD.</p>

CONTRIBUTIONS OF AUTHORS

Kopsaftis Z: conducted 2018 update: updated search terms, assessed search results, led write up.

Wood-Baker R: protocol, literature search, reviewed papers for inclusion, format of data extraction sheet, analyses, and discussion.

Poole PJ: initial protocol, literature search, reviewed papers for inclusion, contributed to format of data extraction sheet, review write up, analyses, and discussion. Conducted 2006 update. Assessed results from 2007, 2009, and 2018 search updates and contributed to writing each version. Remains the senior and contact author.

DECLARATIONS OF INTEREST

Kopsaftis Z: none known

Wood-Baker R: none known

Poole PJ: none known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Update in 2018 included a change in format to reflect current Cochrane practice; including a revision of risk of bias assessment for all included studies and development of a 'Summary of findings' table; split outcomes into primary and secondary; searched clinical trials registries; added all required headings for methods and used either existing, revised, or standard text provided by Cochrane Airways.

Major update 2004-5, following searches in 2003 and 2004, located two further trials (5 reports).

New outcomes have been included:

- Acute infection subsequently documented as influenza-related
- Cost effectiveness
- Number of people with exacerbations

INDEX TERMS

Medical Subject Headings (MeSH)

Disease Progression; Influenza Vaccines [adverse effects] [*therapeutic use]; Influenza, Human [*prevention & control]; Lung Diseases, Obstructive [*complications]; Randomized Controlled Trials as Topic; Vaccines, Attenuated [adverse effects] [therapeutic use]; Vaccines, Inactivated [adverse effects] [therapeutic use]

MeSH check words

Aged; Humans