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Influenza vaccine for patients with chronic obstructive pulmonary disease (Review)

Poole P, Chacko EE, Wood-Baker R, Cates CJ

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[Intervention Review]

Influenza vaccine for patients with chronic obstructive pulmonary disease

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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 COPD patients but there is also the potential for influenza vaccination to cause adverse effects or not to be cost effective.

Objectives

To evaluate the evidence from RCTs for a treatment effect of influenza vaccination in COPD subjects. Outcomes of interest were exacerbation rates, hospitalisations, mortality, lung function and adverse effects.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials, and reference lists of articles. References were also provided by a number of drug companies we contacted. The latest search was carried out in May 2010.

Selection criteria

RCTs that compared live or inactivated virus vaccines with placebo, either alone or with another vaccine in persons with COPD. Studies of people with asthma were excluded.

Data collection and analysis

Two reviewers extracted data. All entries were double checked. Study authors and drug companies were contacted for missing information.

Main results

Eleven trials were included but only six of these were specifically performed in COPD patients. The others were conducted on elderly and high-risk individuals, some of whom had chronic lung disease. Inactivated vaccine in COPD patients resulted in a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo (weighted mean difference (WMD) -0.37, 95% confidence interval -0.64 to -0.11, P = 0.006). This was due to the reduction in "late" exacerbations

occurring after three or four weeks (WMD -0.39, 95% CI -0.61 to -0.18, P = 0.0004). In Howells 1961, the number of patients experiencing late exacerbations was also significantly less (odds ratio 0.13, 95% CI 0.04 to 0.45, P = 0.002). Both Howells 1961 and Wongsurakiat 2004 found that inactivated influenza vaccination reduced influenza -related respiratory infections (WMD 0.19, 95% CI 0.07 to 0.48, P = 0.0005). In both COPD patient and in elderly patients (only a minority of whom had COPD), there was a significant increase in the occurrence of local adverse reactions in vaccinees, 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. The studies are too small to have detected any effect on mortality.

An updated search conducted in September 2001did not yield any further studies. A search in 2003 yielded two further reports of the same eligible study Gorse 2003. A search in 2004 yielded two reports of the another eligible study Wongsurakiat 2004. The author informed us of another report of the same study Wongsurakiat 2004/2. An update search in May 2010 did not identify any new studies for consideration.

Authors' conclusions

It appears, from the limited number of studies performed, that inactivated vaccine reduces exacerbations in COPD patients. 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 is a mild increase in transient local adverse effects with vaccination, but no evidence of an increase in early exacerbations.

PLAIN LANGUAGE SUMMARY

Influenza vaccine for patients with chronic obstructive pulmonary disease

Despite the almost universal recommendation that people with chronic obstructive pulmonary disease (COPD) should receive an annual influenza vaccination, very few randomised controlled trials have evaluated the effect of influenza vaccination in these patients. This review looks at six studies in COPD patients and a further five in elderly or high risk patients, a proportion of whom had chronic lung disease. It shows that there is now some evidence from randomised trials that inactivated influenza vaccine indeed decreases "flare ups" of COPD, especially those that are related to the influenza virus itself. The inactivated influenza virus vaccine is given intramuscularly and is associated with an increase in local side effects such as pain at the site of injection. This is short-lived, not serious and is outweighed by the long term benefit of the vaccine. The inactivated virus vaccine does not cause influenza or any significant worsening of COPD.

BACKGROUND

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 can occur several times per year, and may require hospital admission. These exacerbations can take several weeks to resolve, during which time considerable morbidity can occur and result in significant health care costs. Infection with influenza is an important cause of excess mortality and morbidity in COPD (Rothbart 1995), and may affect the progression of the disease (Centanni 1997). Patients with COPD are at an increased risk for respiratory illness-related hospitalisation during influenza outbreaks irrespective of age and degree of morbidity (Monto 1987). Medicines have a very limited role in the management of acute exacerbations and in altering the natural history of the disease. Strategies that prevent exacerbations are, therefore, very appealing.

Annual influenza vaccination is recommended almost universally in COPD guidelines (Siafakas 1995; BTS 1997; ATS 1995). The largest body of evidence to support this recommendation comes from observational studies in the elderly. In a large, serial cohort study of nearly 150,000 elderly patients, 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 those subjects with chronic lung disease, vaccinated subjects 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 the elderly 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 co-workers estimated that vaccination was associated with a reduction in health care costs of about $US 171 per year per high risk person vaccinated (Nichol 1998).

The effectiveness of the vaccine depends on the immuno competence of the vaccine recipient and the degree of similarity between virus strains in the vaccine and those in circulation (ACIP 1999). Most vaccine programmes currently 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). The elderly in general 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, Igs and anti-influenza A virus cytotoxic T-cell responses were better in COPD patients after immunisation with monovalent live attenuated vaccine than with inactivated influenza A virus vaccines (Gorse 1991; Gorse 1996; Gorse 1995). 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 COPD patients (Gorse 1997).

Despite the recommendations in the guidelines, vaccination in the elderly (the age group that includes most COPD patients) is not universal. In USA in 1997, only 65.5% of the elderly were vaccinated in the previous year (BRFSS 1998). 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 elderly and concern about adverse effects (Patriarca 1994). Patients and their doctors often express concern that vaccination precipitates exacerbations despite the fact that is not possible to contract influenza from inactivated virus. Adverse effects usually become 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 vaccinated patients than in those given placebo (Govaert 1993; 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 for developing vaccine-associated GBS (ACIP 1999).

This systematic review evaluates the evidence from RCTs that have studied the effect of influenza vaccination in people with COPD.

OBJECTIVES

To determine whether influenza vaccination:

1. reduces respiratory illness in people with COPD;
2. reduces mortality in people with COPD;
3. is associated with excess adverse events in people with COPD;
4. is cost effective in people with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adults with COPD defined by the American Thoracic Society (ATS 1995) or European Respiratory Society (Siafakas 1995). Participants defined as having chronic bronchitis were also included.

Types of interventions

At least one annual influenza vaccination. Influenza vaccination was of one of the following types: live attenuated whole virus, inactivated, or a split-virus type vaccine, and administered by either intramuscular or intranasal routes.

Types of outcome measures

1. The number of acute exacerbations of COPD, defined as an increase in breathlessness and/or the volume and/or purulence of sputum;
2. The number of days of disability from respiratory illness variously defined as days in bed, days off work or days where the person was unable to undertake normal activities;
3. The number of hospital admissions;
4. Mortality in the year following vaccination. This may include mortality from respiratory disease, all causes, and causes other than respiratory disease;
5. Change in lung function from baseline at the end of the study period;
6. Other adverse effects of treatment.

For the 2005 update, the following categories were added:

1. Number of acute respiratory illnesses subsequently proven to be influenza-related;
2. Number of patients who developed an exacerbation/acute respiratory infection;
3. Cost effectiveness of vaccination.

Outcomes were classified as early or late. "Early" referred to the early post vaccination period when immunity may not have developed but adverse effects may have occurred

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group Module for further details). All records in the Register coded as 'COPD' were searched using the following terms:

((vaccin* or immuni*) and (influenza* or flu*)) or (flumist or trivalent or CAIV or LAIV or medimmune)

The most recent serach was conducted in May 2010.

Searching other resources

From the full text papers obtained, the bibliographic lists were searched for additional articles. 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, we contacted pharmaceutical companies who had been involved in conduct of vaccine trials and/or manufacture of vaccines. The companies we contacted were Smith Kline Beecham, Glaxo-Wellcome, Merck Sharp and Dohme, Astra, Parke Davis, Wyeth, Pasteur Merieux, and Commonwealth Serum Laboratories. 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.

Data collection and analysis

Selection of studies

Abstracts of articles containing the words "controlled" or "randomised" and "chronic obstructive pulmonary disease" or "chronic airways limitation" or "chronic obstructive airways disease" or "chronic bronchitis" or "emphysema" and "influenza" and "vaccine*" were reviewed, and articles that potentially fulfilled the inclusion criteria were retrieved in full as well as those that were doubtful. For the original review, three reviewers (PJP, RWB, EC) independently established whether each study met the inclusion criteria as an RCT of influenza vaccination in COPD with suitable outcome measures. For the update this was done by two reviewers (PJP, EC). Disagreements were resolved by discussion between the reviewers.

Data extraction and management

Data extraction sheets were of a format agreed by the three reviewers. Data were extracted independently by two reviewers, and entered by one reviewer onto data extraction sheets before being entered into RevMan 4.0.4. Each entry was double-checked by a second reviewer. Versions of this review published after the 2005 update have been performed using Review Manager 5.

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

Data synthesis

Only RCTs were included. For continuous outcomes, the weighted mean difference (WMD) and 95% confidence intervals were calculated. For dichotomous outcomes, the Peto odds ratio was used. If there had been significant heterogeneity, we had intended to conduct a sensitivity analysis using study quality as a categorising variable.

It had been 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 studies become available, it may be necessary to annualise the event rate, particularly if follow-up periods vary.

Subgroup analysis and investigation of heterogeneity

If any heterogeneity could not be explained in terms of study quality, the following sub-group analyses were planned:

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 patients

RESULTS

Description of studies

Results of the search

We screened 105 abstracts of papers from the initial searches. After excluding those that were clearly ineligible we obtained full texts for 25 of them. An additional 40 articles were identified from bibliographies and references provided by pharmaceutical companies. Commonwealth Serum Laboratories provided us with another 70 references from an independent search. Full text articles were obtained when the title and abstract indicated the study was possibly eligible. A total of 70 full texts were read by the reviewers.

The 2003 search revealed four new abstracts, yielding two reports of the same eligible study (Gorse 2003; Neuzil 2003). The 2004 search revealed a further five abstracts, yielding two reports of the same eligible study (Wongsurakiat 2003; Wongsurakiat 2004). Dr Wongsurakiat told us of a further study Wongsurakiat 2004/2 published after our search. The main reasons for study exclusion were a lack of randomisation and absence of primary outcome data (Gorse 1988; Gorse 1996; Lama 1998). Another two studies were excluded because they lacked a placebo control (Ambrosch 1979; MRC 1959). The studies that meet the inclusion criteria of this review have been identified from literature searches up to May 2006. No new eligible studies have been identified from literature searches conducted between 2007 and 2010.

Eleven studies (reported in 15 publications) are included in this review. We wrote requesting more information on six of them (Cate 1977; Gorse 1995; Govaert 1993/Govaert 1994; Treanor 1992; Treanor 1994; Wongsurakiat 2004). Dr Treanor and Dr Cate kindly supplied individual patient data. We received a reply from Dr Gorse but he was unable to supply us with further data. Dr Wongsurakiat kindly provided very useful further information.

Included studies

Eleven studies met the entry criteria. All were randomised, controlled studies using a parallel group design. All studies except two (Gorse 1997; Gorse 1995) were double-blinded and placebo-controlled. These two studies were single-blinded and both the treatment and the control group were given intra-muscular inactivated vaccine. The treatment group received intranasal live attenuated vaccine in addition to the inactivated vaccine while the control group received intranasal placebo. Because these studies assessed the additional benefit of a second vaccine, in addition to the inactivated vaccine, they are assessed separately in this review.

Six of the 11 trials in this review studied COPD or chronic bronchitis subjects alone (Gorse 1997; Fell 1977; Howells 1961; MRC 1980; Wongsurakiat 2004; Gorse 2003). These studies ranged in size from 29 (Gorse 1997) to 2215 (Gorse 2003), making a total of 2469 subjects. The other five trials were conducted in elderly and/or chronically ill subjects of whom a proportion had chronic lung disease. In these studies, the percentage of subjects with chronic lung diseases varied from 32% in Gorse 1995 to 5% in Cate 1977. From these authors, we sought individual patient 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 patients with chronic lung disease are described in the discussion section for comparison with the six studies carried out in exclusively COPD patients.

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

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

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

Duration: This varied from as little as three weeks (MRC 1980) to one year (Wongsurakiat 2004).

Inclusion and Exclusion criteria: Howells 1961; MRC 1980 and Fell 1977 studied patients with chronic bronchitis. Gorse 1997; Gorse 2003; Wongsurakiat 2004; specifically studied patients with pre-existing COPD categorised by FEV1/FVC% < 70%. Exclusion criteria were varied. They were explicit in Gorse 1997; Gorse 2003; Wongsurakiat 2004 and MRC 1980 but limited to Grade 4 bronchitics in Howells 1961 and were not reported at all in Fell 1977.

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

Co-morbidities: 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 were on digoxin and 8% had coexistent asthma and chronic bronchitis. In Gorse 2003, 95%

had co morbidities, and in Wongsurakiat 2004 this 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 2004.
Lung Function: The mean peak flow was 280 L/min from the two studies that reported these measurements. Wongsurakiat 2004 stratified the participants in the study by baseline FEV1. Thirty-six per cent of subjects had FEV1 >= 70% predicted, 26% FEV1 50%-69%, and 38% an FEV1 < 50%. The mean baseline FEV1 in Gorse 2003 was 1.38 L (43.5% predicted).
The treatment and control populations 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 co-morbidities. No details of baseline characteristics were provided by one study (MRC 1980).
Vaccination Type: Two studies used inactivated virus (Howells 1961; Wongsurakiat 2004). 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 since both treatment and control groups received inactivated virus vaccine intramuscularly. These studies are examined 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 2004 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 2004), 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 1-2 weeks after vaccination, but Howells 1961 used a period of three weeks, and Wongsurakiat 2004, four weeks. Wongsurakiat 2004 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). Health status as assessed by the chronic lung disease index (CLDI) was reported by vaccination status in Gorse 2006.
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 patients from one centre had no baseline data and 15 had incomplete records. In the largest study (Gorse 2003) with 2215 subjects, 9% of patients dropped out. In Wongsurakiat 2004, three out of 125 subjects dropped out.

Risk of bias in included studies

For the 11 studies in the review, quality was assessed using two methods:
1. Adequacy of concealment:
Three studies, Howells 1961; Govaert 1994/Govaert 1993 and Treanor 1994 had adequate concealment (Grade A). Treanor 1992; Cate 1977; MRC 1980; Fell 1977 and provided minimal details of blinding (Grade B). The Gorse 1997; Gorse 1995; Gorse 2003; Wongsurakiat 2004 studies were considered inadequate because the study nurse who administered the vaccines was not blinded (Grade C).
2. Jadad Score:
Each study was assessed using a 0 to 5 scale described by Jadad 1996 and summarised as follows:

1. Was the study described as randomised? (1 = yes; 0 = no)
2. Was the study described as double-blind? (1 = yes; 0 = no)
3. Was there a description of withdrawals and dropouts? (1 = yes; 0 = no)
4. Was the method of randomisation well described and appropriate? (1 = yes; 0 = no)
5. Was the method of double blinding well described and appropriate? (1 = yes; 0 = no)
6. Deduct 1 point if methods for randomisation or blinding were inappropriate.

Two studies (Govaert 1994/Govaert 1993; Howells 1961) had a Jadad score of 4/5. Jadad scores were 3 or more for 8/11 studies. A modified Jadad Scale with a total out of 4 was also used. This followed the recommendations of Clark 1999, showing a substantial improvement in inter-rater agreement with the removal of the third item of the Jadad scale (explanation of withdrawals). Seven studies (Cate 1977; Fell 1977; Gorse 1995; Gorse 1997; Gorse 2003; Treanor 1992; Wongsurakiat 2004) had a modified Jadad score of 2/4.

Effects of interventions

Influenza vaccination versus placebo

Exacerbations

Only two studies in COPD / chronic bronchitis patients (both using inactivated virus vaccination) reported continuous data for exacerbation rates (Howells 1961; Wongsurakiat 2004). Vaccination significantly reduced the number of exacerbations per patient during the follow up period (WMD -0.37, 95% CI -0.64 to -0.11, P = 0.006). It was possible to determine the number of early or late exacerbations per patient by further interpretation of the data. For the placebo group of Howells 1961 20 patients experienced 24 exacerbations. Since there were eight patients experiencing early exacerbations there would have been at least eight early exacerbations. Similarly, since there were 12 patients 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 2004 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 patients, and the SD calculated accordingly. We allocated the SD of the "total exacerbations" per patient provided by the author to the "late exacerbations".

While there was no statistically significant effect of vaccination on early exacerbation rates (WMD 0.01, 95% CI -0.11 to 0.13, P = 0.87), inactivated influenza vaccination significantly reduced late exacerbation rates (WMD -0.39, 95% CI -0.61 to -0.18, P = 0.0004).

The two studies each assessed the clinical presentations to see if they were related to influenza virus infection. Howells used serology (HAI test) and Wongsurakiat used both serology (HI) 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 = 0.0005). The effect was similar whether in patients with mild, moderate and severe COPD, or chronic bronchitis (test for heterogeneity P = 0.73). Influenza accounted for 8% (13/161) of the acute exacerbations in the Wongsurakiat study.

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

Patients with at least one exacerbation / acute respiratory illness in the study period

Three studies contributed to this outcome. There was no difference between vaccination and placebo-treated subjects with respect to the number of patients having at least one exacerbation or acute respiratory illness (OR 0.89, 95% CI 0.49 to 1.62, P = 0.7). There was, however, significant heterogeneity in this result (P = 0.001), so it must be treated with caution. A sensitivity analysis by vaccine type shows that if only the two studies that used inactivated virus vaccine are included this heterogeneity is removed. There is a significant reduction in the number of patients 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).

Results from Howells 1961 showed no significant difference in the number of individual patients with early exacerbations, but it did show a significant reduction in the number of patients with late exacerbations (OR 0.13, 95% CI 0.04 to 0.45, P = 0.002). In Wongsurakiat 2004 there was a total of 76 exacerbations in the vaccination group and 85 in the placebo group, of which 9 and 10 respectively were early exacerbations. We have assumed that they each occurred in a different patient. Clearly, over the course of the study there were some patients who had more than one exacerbation, and the numbers of individual patients in each group who had late exacerbations was not reported.

Hospitalisations

Two studies reported data on this outcome. There is no significant effect of vaccination over placebo on hospitalisation (OR 0.33, 95% CI 0.09 to 1.24, P = 0.52). In Howells 1961 there were no hospitalised subjects in the treatment group, and only two in the control group. Wongsurakiat 2004 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 difference in the severity of acute respiratory infections between groups, including no difference in the chance of being hospitalised (P = 0.2 by log rank test). None of the vaccinated patients required mechanical ventilation for acute respiratory infection, whereas five in the placebo group did.

Mortality

Two studies reported mortality, although there was a total of only thirteen deaths. There was no significant difference between vaccine and placebo-treated groups (OR = 1.30, 95% CI 0.34 to 4.97, P = 0.7). The one control patient died during an acute exacerbation (Howells 1961). In the largest study (Gorse 2003) with 2215 subjects, there were 64 deaths (3%), reportedly not different in number between the intervention and control groups. In Wongsurakiat 2004 with 125 subjects there were 12 deaths (8 of which were unrelated to acute respiratory infection).

Lung Function

There were very small and insignificant decreases in lung function tests one and three weeks following live vaccination in one COPD study (MRC 1980) compared with placebo. Wongsurakiat 2004/2 reported no difference in lung function between groups at one

and four weeks after vaccination. They also confirmed that there was no adverse effect on maximum inspiratory pressure, or pre- and post-exercise SaO2 regardless of severity of baseline airways obstruction. There was also no negative effect on exercise capacity judged by the six minute walk test with vaccination.

Adverse effects

Fell 1977 reported early (within two weeks of vaccination) upper respiratory tract symptoms. One vaccinated patient also developed pleuritic pain. There was no difference between vaccinated and control patients in terms of breathlessness and tightness (OR 1.28, 95% CI 0.38 to 4.31, P = 0.696), cough (OR 4.09, 95% CI 0.74 to 22.49, P = 0.106), or sputum production (OR 2.03, 95% CI 0.48 to 8.66, P = 0.338). The occurrence of wheeze within the first two weeks was greater in vaccinated patients (OR 3.57, 95% CI 1.10 to 11.56, P = 0.034). Breathlessness was recorded significantly less often (P < 0.05) in the 5 of 21 patients who had a serological response to vaccination than in the placebo group.
Wongsurakiat 2004/2 evaluated local and systemic symptoms in the weeks following vaccination. There was no significant difference in the incidence of acute respiratory infection, or dyspnoea between the treated and placebo groups either at one or four weeks. 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 (P = 0.002).
In Treanor 1994 12% of the elderly patients vaccinated with live attenuated virus reported systemic symptoms of malaise and myalgias as did 10% of inactivated virus vaccinees. The placebo group reported none. 26% of the live virus vaccinees had lower respiratory tract symptoms of hoarseness and non-productive cough, as did 13% of inactivated virus vaccinees and 9% of placebo. 29% of live virus vaccinees had upper respiratory tract symptoms of sneezy, runny or stuffy nose or sore throat as did 37% of the inactivated virus vaccinees and 18% of placebo. Six per cent of live virus vaccinees experienced fever as did 2.5% of the inactivated virus vaccinees. None of the placebo group had any febrile illness. In the subgroup of patients with chronic lung disease in this study, the patients who received some form of influenza vaccination (n = 20) had a total of 20 adverse effects in 11 patients, and in the placebo recipients (n = 2), there were two adverse effects in one patient.
In Govaert 1993 25% of high risk vaccinees experienced one or more adverse reactions compared to 16% of placebo recipients, however effects if any appeared to have been mild and transitory. Eleven percent 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.
In Cate 1977 7.8% of inactivated virus vaccinees 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 patients experienced erythema (local redness) with or without induration (hardening) at the injection site, compared to none in the control group.

Cost effectiveness

Wongsurakiat 2003 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 published by Wongsurakiat 2004. 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 ARI were costs of hospitalisation. In patients 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, with vaccination costing 248.40 baht. He concluded that for every 100 patients with mild, moderate, or severe COPD vaccinated, the cost savings would be 125,629, 538,184 and 680,647 baht respectively, i.e. vaccination was very cost effective, but more so in those with more severe COPD.

Live attenuated, intranasal/inactivated, intramuscular versus placebo/inactivated, intramuscular vaccination

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

Exacerbations

There were no significant differences in the number of exacerbations per patient between the two groups in the Gorse 1997 study, or in the number of patients with an acute respiratory illness in the Gorse 2003 study. In the former, exacerbations were defined as the occurrence of increased cough, shortness of breath and/or sputum production. There was a trend towards a lower early exacerbation rates per patient in the control group (WMD -0.21, 95% CI -

0.554 to 0.134, P = 0.23), but a trend towards fewer late exacerbations in the treatment group (WMD -0.23, 95% CI -0.076 to 0.536, P = 0.142). In the latter, patients were asked to report any febrile influenza-like illness (ILI). This was then investigated by serology and/or swabs to determine if it was influenza-related. A total of 196 patients in the treatment group had at least one ILI, and 186 in the control group (OR 1.07, 95% CI 0.86 to 1.33, P = 0.57).

There was no difference in the number of patients who reported improvements in their exacerbations (OR 1.48, CI 0.30 to 7.42, P = 0.632).

Gorse 2006 performed a univariate and stepwise multivariate logistic regression analysis of associations 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 prevaccine status, compared with 163 (16%) in the control group that had received inactivated virus vaccine alone. (OR 1.39, CI 1.10-1.74).

Lung Function

There was no consistent effect on lung function in Gorse 1997. The results from Gorse 2003 suggest an early significant effect on lung function in favour of the control, however, there was a significant difference between the two study groups at baseline 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. Treanor 1994 reported no significant differences in lung function between groups. From data supplied by the author, for the subgroup with underlying chronic lung disease, those 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. There were no statistically significant differences between treatment and control for any adverse effects (OR 1.89, 95% CI 0.45 to 8.04, P = 0.39), early adverse effects (OR 0.73, 95% CI 0.16 to 3.34, P = 0.69) or late adverse effects (OR 4.00, 95% CI 0.68 to 23.60, P = 0.126). In Gorse 2003 the proportion of patients with adverse effects at least possibly related to immunisation was said to not differ between groups. There were, however, significantly fewer patients with early signs and symptoms in the group receiving inactivated virus vaccine only, as well as a smaller number of patients with late adverse effects. In this group there was a total number of 99 events in 88 patients (7.9% of total).

In Treanor 1992, which was a study with a lung disease subgroup, 24% of the treatment group experienced respiratory illness 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 controls. Of the control group, 1.1% reported fever and 2.7% of them had respiratory symptoms consisting of rhinitis or pharyngitis. However, 2.2% of the treatment group had fever and 6.7% had respiratory symptoms. Five per cent of the live virus vaccinees experienced sore arms, compared to 18% of inactivated virus vaccinees. None in the placebo group reported sore arms. The tendency for inactivated virus to cause local side effects to a greater extent than live virus is statistically significant in this study (P = 0.02).

In Gorse 1995, 12% of all patients experienced transient, mild pain at the site of local intramuscular injection.

Mortality

Of the 64 patients who died in the Gorse 2003 study, five patients in the treatment group and two subjects in the placebo group had influenza-like illnesses, four of which were laboratory documented.

DISCUSSION

This systematic review evaluates the few RCTs that have been reported on the effects of influenza vaccination in people with COPD. Despite exhaustive searches, only 15 reports (from 11 studies) were identified that met inclusion criteria, with only six of these having been performed solely on subjects with COPD or chronic bronchitis. The entry criteria for these studies were variously reported but, where reported, they showed that the majority of patients had a smoking history and airways obstruction. The earlier studies enrolled younger subjects than the more recent studies. The other studies in the review were of elderly and /or chronically ill patients of whom a subset had chronic lung disease. There was a total of 2469 subjects in the six COPD or chronic bronchitis trials.

In the original Cochrane review in 2001 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 2004). 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 patients over one year following vaccination, with only three dropouts. An analysis with the results from another carefully conducted RCT (Howells 1961) shows that inactivated influenza vaccine significantly reduces COPD exacerbations with an effectiveness ((1-RR) x 100%) of over 60%. Moreover, inactivated influenza vaccination has an effectiveness of over 80% in reducing influenza-related acute respiratory infections (ARIs).

The effectiveness of vaccination is confined to late exacerbations i.e. those occurring more than three to four weeks after vaccination. The investigators chose to study this time period specifically in order to allow time for immunity to develop. The authors of Wongsurakiat 2004 and others make the point that the effectiveness of the vaccine in reducing exacerbations will depend on how much influenza-related ARI is present, i.e. whether there is an epidemic or not. Fell 1977 and Wongsurakiat 2004 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 2004, but was responsible for 37% of the acute exacerbations in Howells 1961.

To further emphasise this point, the findings of Howells 1961 and Wongsurakiat 2004 are both consistent with one large (n = 1906), high quality RCT trial (Govaert 1994) conducted on elderly patients, 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 patients 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 elderly patients who were in institutions where laboratory-documented outbreaks of influenza A occurred, only 8% of the treatment group compared to 20% of the controls had respiratory illness. 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 patients) is relatively small, the effectiveness of influenza vaccination seen in this review is consistent with that seen in large observational studies. In one of these, in 1900 elderly subjects with chronic lung disease, those 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 elderly showed a 56% reduction in respiratory illness and a 50% reductions in hospitalisation (Gross 1995). Most of these studies had been conducted in epidemic years.

Because of the risk of influenza and the lesser immunogenicity of vaccines in the elderly (including COPD patients), 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 patients are needed if the study is to have sufficient power to detect an effect. The studies in this review show 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 one study (Gorse 2003) and the investigators did not regard it as significant.

One of the main barriers to increasing vaccination rates in COPD patients is the concern of both health professionals and patients that vaccination may increase early exacerbations before immunity has developed. The evidence in this review shows that inactivated virus vaccination does not have a significant effect on the number, or the number of patients with early exacerbations or early acute respiratory illnesses.

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 appear to be mild and transitory. These findings are consistent with results from a large, well conducted randomised placebo-controlled trial (Nichol 1994) of influenza vaccination in healthy adults where no significant side effects of vaccination were observed, except for arm soreness (63.8% of vaccinees compared to 24.1% placebo, P = 0.001).

There is no evidence of any significant effect on hospitalisations, mortality rates, lung function decline or exercise tolerance between the vaccine and placebo groups. For the infrequent outcomes of hospitalisation and mortality, the studies are probably too small to show any difference. Interestingly one subject in the control group in Gorse 2003 developed Guillain Barre syndrome, although further details of severity and outcome were not provided.

We did not intend to evaluate serological outcomes such as a significant rise in antibody titre in this review. However, some au-

thors looked at outcomes in the subgroup with a serological response to vaccination. The limited data from these comparisons is consistent with that of the clinical outcomes alone. It also suggests that if subjects seroconvert, they have fewer adverse effects.

Two authors (Neuzil 2003; Wongsurakiat 2004) studied the clinical presentation of symptomatic laboratory-documented influenza (LDI). Neuzil 2003 found, using stepwise logistic regression, 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 2004, the most specific presentation of LDI was "influenza-like illness" (namely generalised aches, fever, headache +/- respiratory tract symptoms). LDI occurred in only 10% of these patients, however, indicating a low positive predictive value of this symptom complex for LDI. The conclusion is that it is difficult to diagnose influenza infection clinically with certainty in patients with COPD.

The one cost effectiveness analysis that has been conducted based on an RCT suggests that inactivated virus vaccination is highly cost effective in COPD patients, 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 COPD patients living longer. It was conducted in a non-epidemic year, and therefore will underestimate the benefits that would be gained in an epidemic year.

Methodological limitations

The main issue is that there are few RCTs of influenza vaccinations in COPD and data were generally not reported in the same way. However, the studies that were found were of satisfactory quality (8/11 studies had Jadad scores of 3 or more out of 5). The effects observed in RCTS are internally consistent, biologically plausible, and supported by observational studies.

AUTHORS' CONCLUSIONS

Implications for practice

There is RCT evidence that inactivated influenza vaccination has a clinically important and significant effect on influenza-related exacerbations, and probably an effect on the total of exacerbations in COPD patients. This effect is likely to be greater in epidemic years when the proportion of exacerbations due to influenza will be higher. The size of the effect is similar to those seen in cohort studies and there is no evidence that inactivated virus vaccination causes exacerbations. The addition of intranasal live attenuated virus does not confer any added benefit.

There are significantly more local side-effects reported with intramuscular influenza vaccine than with placebo, however these effects are self limiting and are far outweighed by the longer term benefits of the vaccination.

To reduce exacerbations in COPD overall will require a combination of approaches, including vaccination, as only a small percentage are caused by influenza virus.

In COPD patients symptomatic influenza infections are 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 don't. 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 the elderly. 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 patients 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 is still not enough 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 in to 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 heath and other approaches to reducing the impact of influenza outbreaks. Studies should continue to look at ways to improve the effectiveness of the vaccine, or combination of vaccines. This might include adding in 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	Randomisation: Quasi-randomised; vaccines/ placebo provided in randomly arranged coded sets of 10 dose vials, with a rotating sequence of administration. Allocation concealment: double-blind but no details. Duration: about 7 months Withdrawals: 8 volunteers were lost but none had experienced vaccination-related complications. Review: 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. Jadad Score: 3 Modified Jadad Score: 2
Participants	Setting: June-Nov 1976, Texas Medical Centre Number: 413; 8 withdrawals; 348 in combined vaccine groups. Characteristics: All subjects were ambulatory and either elderly (>50 years) or high-risk adults. The average age was 64.3 (SD7.3) years with 60.7% female participants. About 5% had lung disease of which most were COPD. 35% were considered high-risk due to cardiovascular complications, chronic and underlying disease. Baseline characteristics: no details Co-morbidities: 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 (PD) or whole (MSD, MD). Control: Saline placebo, intramuscular, 0.5 ml dosage.
Outcomes	Early: days 1and 2 post vaccination. Adverse effects recorded as symptom scores including systemic and local reactions. Serology; HAI antibody titres were performed at 4 weeks Late: HAI antibody titres performed again after revaccination in a subgroup after about 5 months
Notes	not specifically COPD patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Quasi-randomised; vaccines/ placebo provided in randomly arranged coded sets of 10 dose vials, with a rotating sequence of administration

Fell 1977

Methods	Randomisation: no details Allocation concealment: double blind conditions but not described. No details of outcome assessment blinding so detection bias possible. Duration: 20 weeks Withdrawals: 1 (vaccinated patient developed pleuritic pain on day 14 of baseline.) Review: during exacerbations Jadad score: 3 Modified Jadad Score: 2
Participants	Setting: Nov 1975, Group Practice; Deddington, Oxfordshire (Non epidemic conditions) Number: 45 enrolled; 22 in vaccinated group,23 in control. 1 vaccinated patient withdrew during baseline. Characteristics: There were 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 Peak Expiratory Flow-Rates. 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 WRL105 strain before vaccination while less than 35% of the control did. Co-morbidities: 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 patient self-assessment, hospitalization. Late: Respiratory scores of adverse reactions greater than baseline, antibody responses to vaccination
Notes	proscribes use of live vaccination but is a small study , conducted in a non- epidemic setting

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Information not available

Gorse 1995

Methods	Randomisation: in each consecutive pair 1 was assigned to treatment and 1 to control. Allocation concealment: Subjects and study personnel were blinded but not the study nurse administering the vaccines. Duration: 4 weeks Withdrawals: no details Review: Days 1-7 with immunological assays conducted on days 14 and 28. Jadad Score: 2 Modified Jadad Score: 2
Participants	Setting: 1993-1994 Jefferson Barracks Division Nursing home, St Louis VA Medical Centre and at St Louis Altenheim nursing home Number: 50; 25 in each of treatment and control groups. Characteristics: Elderly, chronically ill nursing home residents, 86% male , and of average age 74.95 years. Baseline Characteristics: Generally comparable with average age in the treatment group being 74.3 (SE1. 6) years and 75.6 (SE1.9) years in the control. 28% of the treatment group had lung conditions and 36% of the control. Levels of other co-morbidities, WBC counts, cholesterol and pre-vaccination serum HAI antibodies were similar. Co-morbidities: Heart 64%, Lung 32%, Neurologic 84%, Diabetes mellitis 40%, GI 30%, Renal 24%, Tobacco use 70%, Alcohol use 62% Diagnostic Critieria: Elderly >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 hemoglobin levels less than 11g/dL
Interventions	Vaccination Type: 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/texaz/36/91 [H1N1], A/Beijing/32/92 [H3N2], and B/Panama/45/90 Intramuscular, Control: 1. Saline Placebo intranasal. 2. Trivalent inactivated influenza virus vaccines (TVV), Intramuscular, identical to vaccinated group
Outcomes	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 . Late: serology, some adverse effects.
Notes	not specifically COPD patients. There is a possible advantage of administering live attenuated with inactivated virus because in the frail elderly who have decreased immune responsiveness due to underlying disease, there is evidence of increased memory of anti-influenza A virus CTL activity

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	In each consecutive pair 1 was assigned to treatment and 1 to control

Gorse 1997

Methods	Randomisation: no details Allocation Concealment: Subjects and study personnel were blinded but not the study nurse administering vaccines. Outcome assessment was conducted under blind conditions. Duration: Unclear, more than 28 days Withdrawals: none reported Review: Clinical evaluation 3 times between each of days 1-5, 7-10, 21-28 after immunisation. Jadad score: 2 Modified Jadad Score: 2
Participants	Setting: 1994-1995 Outpatient clinics of St Louis Department of Veterans Affairs Medical Centre. Number: 29; 16 in CAV/TVV group and 13 in TVV/placebo group. 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. Baseline Characteristics: Demographics and lab results largely comparable. Proportions of subjects with underlying medical illnesses comparable with the exception of higher proportion of liver disease in CAV/TVV group. Co-morbidities: 32% of CAV/TVV patients had underlying liver disease. Overall, other diseases were comparable; 21% renal, 66% heart disease, 38% neurologic, 21% diabetes mellitus. 97% of the subjects reported having smoked tobacco products in the past. 90% reported having consumed alcohol in the past. 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. Exclusion Criteria: 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	Vaccination Type: 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. 2.Trivalent inactivated subvirion influenza virus vaccine (TVV) -A/Texas/36/91 (H1N1), A/Shandong/9/93 (H3N2), B/Panama/4?/90. Intramuscular, 15 microg of HA from each of 3 strains per 0.5 ml dose. Control: 1. Saline Placebo intranasal. 2. Trivalent inactivated influenza virus vaccine (TVV), Intramuscular, identical to vaccinated group
Outcomes	Early: All measured 7-10 days after immunisation. 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. Late: Spirometry was repeated for those who reported changes in obstruction to airflow or respiratory symptoms at 7-10 days. Serology; Cellular immune testing of in vitro levels of interleukins 2 and 4

Gorse 1997 (*Continued*)

Notes	To calculate standard deviations from continuous data we assumed that only 1 exacerbation was experienced by each patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Gorse 2003

Methods	Randomisation: stratified by site, no other details Allocation Concealment: Subjects and study personnel were blinded - no details as to how Duration: Six + months Protocol: spirometry performed to check eligibility, Then IM and intranasal vaccine given. Subjects 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. Subjects reported if developed resp illness Dropouts: 90 in intervention (8.1%), 110 in control (9.9%). 64 deaths. Jadad score: 2 Modified Jadad Score: 2
Participants	Setting: Winter USA 1998-1999. COPD patients meeting spirometric criteria for COPD from 20 VA Medical Centre sites Exclusion: allergic to vaccine components, received influenza vaccine less than six months previously, immunocompromise, cystic fibrosis, febrile illness 72 hours prior or exacerbation of COPD within 3 weeks prior, or history of Guillain Barre Number: 2215, 1107 in intervention and 1108 in control group. 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 litres, 42.6% predicted, FEV1/FVC 0.53
Interventions	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 subjects. On same day subjects also received either: Intervention: Trivalent, Types A and B, live cold adapted influenza virus vaccine (CAIV-T) corresponding to the strains in the TVV, 0.25ml per nostril, or Control: intranasally as a large particle aerosol
Outcomes	Primary outcome-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. Secondary outcome-efficacy of CAIV-T on influenza-like illness (ILI). ILI This was defined as one of two definitions (i) febrile, 100 degrees 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.

Gorse 2003 (*Continued*)

	Lung function, VAS of overall sense of health Adverse reactions : Early reactions monitored for 7 days using diary
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Information not available

Gorse 2006

Methods	As above
Participants	As above
Interventions	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 subjects. On same day subjects also received either: Intervention: Trivalent, Types A and B, live cold adapted influenza virus vaccine (CAIV-T) corresponding to the strains in the TVV, 0.25ml per nostril, or Control: intranasally as a large particle aerosol
Outcomes	Additional outcome of relevance to this review was the reporting of CLDSI (chronic lung disease severity index) for patients in the two intervention groups. Secondary outcome
Notes	Same study as Gorse 2003. Reported impact of one influenza season on all study participants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	See Gorse 2003

Govaert 1993

Methods	Randomisation: Stratified randomisation schedule used with 4 strata according to each morbidity category. Allocation Concealment: Double blind with outcome assessment blinding. Duration: 4 weeks. Withdrawals: 32 incomplete questionnaires. Review: Questionnaire completed at 4 weeks. Jadad Score: 4 Modified Jadad Score: 4
Participants	Setting: Winter 1991-92, 15 General Practices in Southern Netherlands. Number: 1806; 904 vaccinated and 902 in the control. Characteristics: Mean age 67 (SD5.6), 4 morbidity categories; heart, lung (9%), diabetes mellitus, and others/healthy. 54% female. 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. Comorbidities: cardiological, pulmonary and other metabolic. Diagnostic Criteria: over 60 years of age, with conditions if present that were not severe enough to necessitate mandatory vaccination. Exclusion criteria: 1. less than 60 years of age 2. high risk groups 3. those in old people's or nursing homes.
Interventions	Vaccination Type: Purified, split virion vaccine (A/Singapore/6/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90, B/Beijing/1/87). Control: Physiological saline placebo.
Outcomes	Early: none Late: adverse reactions assessed at week 4; local, systemic, sub group analysis
Notes	Sub-Study of Govaert 1994; not specifically COPD patients. only adverse reactions.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Stratified randomisation schedule used with 4 strata according to each morbidity category

Govaert 1994

Methods	Randomisation: Stratified randomisation schedule used with 4 strata according to each morbidity category Allocation Concealment: Double blind with outcome assessment blinding. Duration: 5 months Withdrawals: 47 incomplete questionnaires, none due to influenza related morbidity or mortality. Review: Clinical assessments, questionnaire completed at weeks 10 and 23, serological tests at week 3 and at 5 months. Jadad Score: 4 Modified Jadad Score: 3
Participants	Setting: Influenza season 1991-92, 15 General Practices in Southern Netherlands. Number: 1838; 927 vaccinated and 911 in the control. Characteristics and Comorbidities same as those described in Govaert 1993. Diagnostic Criteria: not COPD specifically; over 60 years, not belonging to a pre-vaccinated high-risk group. Influenza diagnosed serologically, by physician or by ICHPPC-2-defined criteria. Exclusion Criteria: reasons for non- participation included inability to give consent and fear of injections
Interventions	Vaccination Type: Purified, split virion vaccine (A/Singapore/6/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90, B/Beijing/1/87). Control: Physiological saline placebo.
Outcomes	Early: none Late: mortality, exacerbation rates in the form of occurrence of influenza or influenza -like illnesses, HAI antibody titres
Notes	not specifically COPD patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Stratified randomisation schedule used with 4 strata according to each morbidity category

Howells 1961

Methods	Randomisation: no details Allocation concealment: double blinded. A key was provided to the nursing staff administering injections by the statistical advisor. No details of outcome assessment blinding. Duration: about 4 months Withdrawals: 1(control group patient died during an acute exacerbation.) Review: Initially at week 2, then every 4 weeks by both observers. Jadad Score: 4 Modified Jadad Score: 3

Howells 1961 (*Continued*)

Participants	Setting: Winter 1960, NW Wolverhampton. Number: 55 enrolled; 26 in vaccinated group, 29 in control. Characteristics: 37 men (67%) of average age 52.78 (SD 12.51)years; overall average Peak Expiratory Flow was 270.09 (SD111.88) l/min. The overall Maximum Breathing Capacity was 64.33 (SD 30.59) l/min. Baseline characteristics: The average age of the vaccinated group was 54.08 (SD14)years and the control was 51.62 (SD11.12) years. 58% of the vaccinated group was male and 76% of the control. The vaccinated patients had an average duration of symptoms of around 17 years, while the control had around 20 years. The average Peak Expiratory Flow for the vaccinated group was 266.35(SD101.12) l/min and 273.45(SD120.29) l/min for the control. This difference could be attributed to the 2 asthmatics who had relatively higher peak flows. The average Maximum Breathing Capacity for the vaccinated group was 62.81(SD28.66) l/min and 65.75(SD32.75) l/min for the control. Comparable antibody levels to influenza viruses in all patients. Co-morbidities: 7% of control were asthmatics. 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..." Patients were assessed to enable placement into Grades 1, 2 or 3 with increasing severity. Exclusion Criteria: Grade 4 Bronchitis and TB patients.
Interventions	Vaccination Type: Flubron (A.A2 Asian-Formosa 7000, B England 5000), Intramuscular Control: Physiological saline solution.
Outcomes	Early: Exacerbations in weeks 1-3 recorded by clinical examination and measurement of Peak Expiratory Flow. Bacteriological and Complement Fixation results for cause of exacerbations. Late: Hospitalization, mortality, as well as all early outcomes
Notes	We made an assumption for the number of early and late exacerbations per patient for the placebo group. We knew the total number of exacerbations was 24 experienced by 20 patients out of 29. Thus, there would have been at least 8 and 10 exacerbations for early and late respectively according to the numbers of patients 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**
Allocation concealment?	Low risk	Information not available

MRC 1980

Methods	Randomisation: no details Allocation Concealment: clinician blinded. No details of outcome assessment blinding. Duration: unclear; more than 3 weeks. Withdrawals: 16 patients from the Sheffield centre had no baseline recordings. 15 patients failed to complete all records (reasons not discussed). Review: no details Jadad Score: 2 Modified Jadad Score: 1
Participants	Setting: no details. 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 28-78 years. Baseline Characteristics: none recorded. Comorbidities: no details. Diagnostic Criteria: Chronic Bronchitis (MRC definition) and airways obstruction with an FEV1 > 1L. 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, PFR, FEV1. Late; day 21; all self assessments and spirometry of early outcomes and also serology; HAI tests
Notes	Standard errors of serologically negative and positive patients 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**
Allocation concealment?	Unclear risk	Information not available

Neuzil 2003

Methods	See Gorse 2003
Participants	See Gorse 2003
Interventions	See Gorse 2003
Outcomes	See Gorse 2003
Notes	Substudy of Gorse 2003

Neuzil 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	See Gorse 2003

Treanor 1992

Methods	Randomisation: re-randomisation every year Allocation Concealment: double blinded but no details of outcome assessment blinding. Duration: 3 years Withdrawals: 8; 7 from intranasal group; deaths due to unrelated causes, discharges from institutions. Review: days 1-3 after each vaccination for adverse reactions and nasal sheddings. Then daily staff nursing reports were used. Jadad Score: 3 Modified Jadad Score: 2
Participants	Setting: 1987-90, 3 large nursing homes in Rochester, NY; St Ann's Home, St John's Home and Monroe Community Hospital. Number: 523; 345 subject years in the intranasal group and 346 subject years in the control. Characteristics: Elderly; Mean age of 84.2 years. 32% had cardiac or pulmonary conditions; 75% female. Baseline Characteristics: Relatively well matched for disabilities, age, sex ratios. Mean age in the intranasal group was 84.1 years with 26% cardiac/pulmonary patients. Mean age in the vaccinated group was 83.8 years with 23% cardiac/pulmonary complications. Co-morbidities: only details of cardiovascular and pulmonary complications. Diagnostic Criteria: none; all residents at these institutions were invited. Exclusion Criteria: 1. acutely ill at time of enrolment 2. concurrent immunosuppressant therapy 3. egg product allergy 4. refusal of inactivated influenza vaccination
Interventions	Vaccination Type: 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 0.5ml doses. 2. Inactivated, trivalent, subvirion influenza vaccine containing 9 different HAs intramuscular in 0.5 ml doses. Control: 1. Intranasal placebo of sterile veal infusion broth. 2. Trivalent inactivated subvirion influenza vaccine identical to treatment group
Outcomes	Early: days 1-3 post-vaccination; adverse effects 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
Notes	not specifically COPD patients

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Treanor 1992 (*Continued*)

Allocation concealment?	Unclear risk	Information not available

Treanor 1994

Methods	Randomisation: no details Allocation Concealment: Double blinded, intranasal and intramuscular placebo given to treatment groups. Duration: at least 4 weeks Withdrawals: no details Review: Early symptoms at days 3-4, serologic testing at 4 weeks post- vaccination Jadad Score:3 Modified Jadad Score: 3
Participants	Setting: Outpatient clinics of Strong Memorial Hospital; Rochester, NY and a private practice. Number: 81; 34 in the live attenuated vaccination group, 30 in the inactivated vaccination group and 11 in the control. Characteristics: Elderly (> 65 years) and chronically ill, 65% female. 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. Comorbidities: chronic cardiac, pulmonary, endocrine, hematologic conditions, 25% smokers. Diagnostic Criteria: Ambulatory adults over 65 years or with at least 1 high risk condition. Exclusion Criteria: no details
Interventions	Vaccination Type: 1. Cold-adapted, Live attenuated reassortant influenza B virus vaccine (B/Ann Arbor/1/86 or B/Yamagata/16/88) , intranasally in 0.5ml 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. Control: Placebo; Intramuscular saline and Intranasal veal infusion broth
Outcomes	Early: 3-4 days post vaccination. Pulse oximetry, Spirometry, Virus cultures and HAI tests, Symptoms for 7 days (Upper and Lower Respiratory Tract Symptoms, Systemic) Late: Serology repeated at week 4 , hospitalisations.
Notes	Cold adapted, live attenuated influenza B vaccines are safe but not as immunogenic as inactivated ones in chronically ill or elderly patients. There were no significant differences between the groups in outcomes of spirometry and adverse effects. Author provided individual patient data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Information not available

Wongsurakiat 2003

Methods	See Wongsurakiat 2004
Participants	See Wongsurakiat 2004
Interventions	See Wongsurakiat 2004
Outcomes	See Wongsurakiat 2004
Notes	Substudy of Wongsurakiat 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	See Wongsurakiat 2004

Wongsurakiat 2004

Methods	Randomisation: stratified, randomised Allocation concealment: No details of how investigators blinded although nurse giving injection did not participate in care. No details of how the allocation key concealed. No details of outcome assessment blinding. Duration: 1 year. Withdrawals: 3 dropouts (1 vaccine, 2 control). Deaths 8 (5 vaccine, 3 control) all died from causes not related to acute respiratory infection. Review: Reviewed monthly. Bloods taken at week 0, week 4, and 6 and 12 months. Subjects reported acute resp infections, and had extra visit for full assessment, including the taking of acute and convalescent serum 4-6 weeks later. If resp infection present for less than 6 days, swabs taken Jadad Score: 3 Modified Jadad 2
Participants	Setting: 1997-8. Thailand, university hospital COPD outpatient clinic. Non-influenza epidemic years in Thailand. Number: 132 consecutive outpatients. 7 excluded a couldn't attend making 125 in total, 62 in vaccine group and 63 in control group. Inclusion: Clinical COPD (COPD not defined although managed according to Thai guidelines), FEV1<70% and <15% increase after bronchodilator. Exclusions: Egg allergy, immunocompromise, immunosuppressive drugs (except corticosteroids), or if comorbidities expected to reduce survival to < 1 year. 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. 0.5mL 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 0.5mL of Vitamin B1
Outcomes	Acute respiratory infections, antibody responses to vaccination and to acute respiratory infections (by HI test) allowing classification of whether the infection was influenza-related. Clinical classification of acute resp infections (ARI) into common cold, acute exacerbation, influenza-like illness, or pneumonia. Severity recorded-hospitalisation, ventilation, and stratified by COPD severity.

Wongsurakiat 2004 (*Continued*)

	Adverse effects recorded carefully for 4 weeks after vaccination	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	Information not available

Wongsurakiat 2004/2

Methods	See Wongsurakiat 2004	
Participants	See Wongsurakiat 2004	
Interventions	See Wongsurakiat 2004	
Outcomes	See Wongsurakiat 2004	
Notes	Substudy of Wongsurakiat 2004	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	See Wongsurakiat 2004

Modified Jadad Score- the 1999 Clark study showed a substantial improvement in interrater agreement with the removal of the third item of the Jadad scale (an explanation of withdrawals) . Thus, this score is out of only 4.

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, obstructive airways disease patients are only a small subgroup
Gorse 1986	Live and inactivated virus vaccines used without placebo as a control, not randomised

(*Continued*)

Gorse 1988	serological results only; no primary outcomes suitable for this review
Gorse 1991	no randomisation of COPD patients
Gorse 1996	serological outcomes only, no primary outcomes suitable for this review
Howells 1975	no randomisation of elderly patients 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 Chronic Airways Disease patients
Paul 1988	not RCT
Portari 1998	not RCT, serological outcomes only; no primary outcomes suitable for this review
Powers 1991	healthy elderly used
Prevost 1975	not RCT
Saah 1986	retrospective cohort study , not COPD
Treanor 1998	Elderly and high risk patients but no details of COPD or any other lung disease
Winson 1977	No randomisation of chronic bronchitics

DATA AND ANALYSES

Comparison 1. Influenza vaccination versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total exacerbations per patient	2	180	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.64, -0.11]
2 Early exacerbations per patient	2	180	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.13]
3 Late exacerbations per patient	2	180	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.61, -0.18]
4 Patients with at least one exacerbation / 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 Patients with early exacerbations	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.52, 2.26]
6 Patients with late exacerbations	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Acute respiratory illness subsequently documented as influenza-related	2	180	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.07, 0.48]
7.1 FEV1>=70% predicted	1	45	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 1.11]
7.2 FEV150-69% predicted	1	33	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.07, 2.98]
7.3 FEV1<50% predicted	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.99]
7.4 Chronic bronchitis patients	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.96]
8 Early acute respiratory illness	1	250	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.34, 1.50]
8.1 ARI within 1 week of vaccination	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.24, 4.26]
8.2 ARI between 1 and 4 weeks after vaccination	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.27, 1.50]
9 Hospitalisations	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.09, 1.24]
9.1 Clinical exacerbations	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.39]
9.2 Influenza-related exacerbations	1	125	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.09, 1.89]
10 Mortality	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.28, 2.70]
11 Mortality related to acute respiratory infection	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12 Overall change in lung function (FEV1 in litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Change in early lung function (FEV1 in litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Local effects at Injection Site	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15 Systemic adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16 Patients with early breathlessness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
17 Patients with early tightness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
18 Patients with early wheeze	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
19 Patients with early cough	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

20 Patients with early sputum production	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Comparison 2. Inactivated/ Live versus Inactivated/Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total exacerbations per patient	2	1137	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.35, 0.37]
2 Early exacerbations per patient	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Late exacerbations per patient	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Acute respiratory illness subsequently documented as influenza-related	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Patients with at least one influenza-like illness	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Patients with improvement in exacerbations	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Patients with early improvements	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
8 Patients with late improvements	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
9 Early changes in lung function (% predicted FEV1)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Early changes in lung function (FEV1/FVC %)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Post immunisation lung function (FEV1)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Patients with increase in lung function (1 category)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
13 Patients with a decrease in lung function	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
14 FEV1 at end of study	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Patients with adverse effects (new upper respiratory tract symptoms)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
16 Patients with early adverse effects	2	2244	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.63, 1.17]
17 Days with early symptoms and signs	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18 No of subjects, and nature of, early adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 COPD	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.48]
18.2 Dyspnea	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.60, 5.41]
18.3 Pharyngitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.86]
18.4 Flu syndrome	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.20, 1.91]
18.5 Rhinitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.34]
18.6 Bronchitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.50, 8.05]
18.7 Increased cough	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.51]
18.8 Myalgia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.51 [0.49, 12.96]
18.9 Increased sputum	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.36]

18.10 Pneumonia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.97]
18.11 Asthenia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.97]
18.12 Guillain - Barre syndrome	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.19]
18.13 Other	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.26, 0.92]
19 Patients with late adverse effects	2	2244	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.33 [1.22, 4.46]
20 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Influenza vaccination versus placebo, Outcome 1 Total exacerbations per patient.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

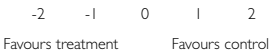
Outcome: 1 Total exacerbations per patient

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howells 1961	26	0.38 (0.49)	29	0.83 (0.65)		76.4 %	-0.45 [-0.75, -0.15]
Wongsurakiat 2004	62	1.23 (1.5)	63	1.35 (1.6)		23.6 %	-0.12 [-0.66, 0.42]
Total (95% CI)	**88**		**92**			**100.0 %**	**-0.37 [-0.64, -0.11]**

Heterogeneity: Chi^2 = 1.08, df = 1 (P = 0.30); I^2 =8%

Test for overall effect: Z = 2.76 (P = 0.0058)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Influenza vaccination versus placebo, Outcome 2 Early exacerbations per patient.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

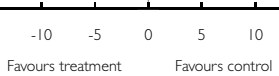
Outcome: 2 Early exacerbations per patient

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howells 1961	26	0.35 (0.48)	29	0.34 (0.6)		16.3 %	0.01 [-0.28, 0.30]
Wongsurakiat 2004	62	0.15 (0.37)	63	0.14 (0.35)		83.7 %	0.01 [-0.12, 0.14]
Total (95% CI)	**88**		**92**			**100.0 %**	**0.01 [-0.11, 0.13]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Influenza vaccination versus placebo, Outcome 3 Late exacerbations per patient.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

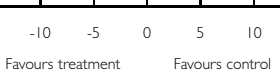
Outcome: 3 Late exacerbations per patient

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Howells 1961	26	0.04 (0.19)	29	0.48 (0.62)		84.0 %	-0.44 [-0.68, -0.20]
Wongsurakiat 2004	62	1.06 (1.5)	63	1.21 (1.6)		16.0 %	-0.15 [-0.69, 0.39]
Total (95% CI)	**88**		**92**			**100.0 %**	**-0.39 [-0.61, -0.18]**

Heterogeneity: $Chi^2 = 0.92$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 3.55 (P = 0.00039)

Test for subgroup differences: Not applicable

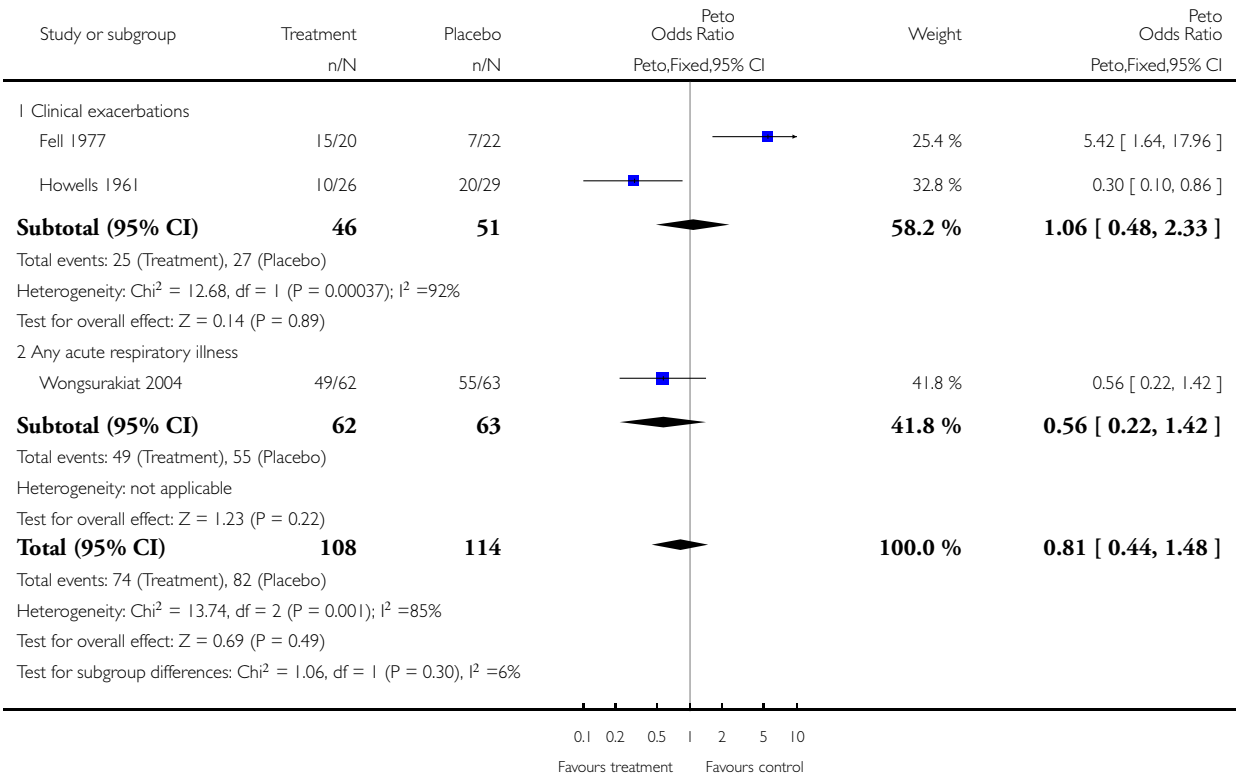


Analysis 1.4. Comparison 1 Influenza vaccination versus placebo, Outcome 4 Patients with at least one exacerbation / acute respiratory illness.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 4 Patients with at least one exacerbation / acute respiratory illness



Analysis 1.5. Comparison 1 Influenza vaccination versus placebo, Outcome 5 Patients with early exacerbations.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 5 Patients with early exacerbations

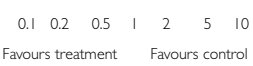
Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Howells 1961	9/26	8/29		42.3 %	1.38 [0.44, 4.30]
Wongsurakiat 2004	9/62	10/63		57.7 %	0.90 [0.34, 2.38]
Total (95% CI)	**88**	**92**		**100.0 %**	**1.08 [0.52, 2.26]**

Total events: 18 (Treatment), 18 (Placebo)

Heterogeneity: $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable



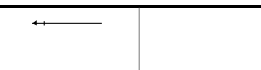
Analysis 1.6. Comparison 1 Influenza vaccination versus placebo, Outcome 6 Patients with late exacerbations.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 6 Patients with late exacerbations

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Howells 1961	1/26	12/29		0.13 [0.04, 0.45]

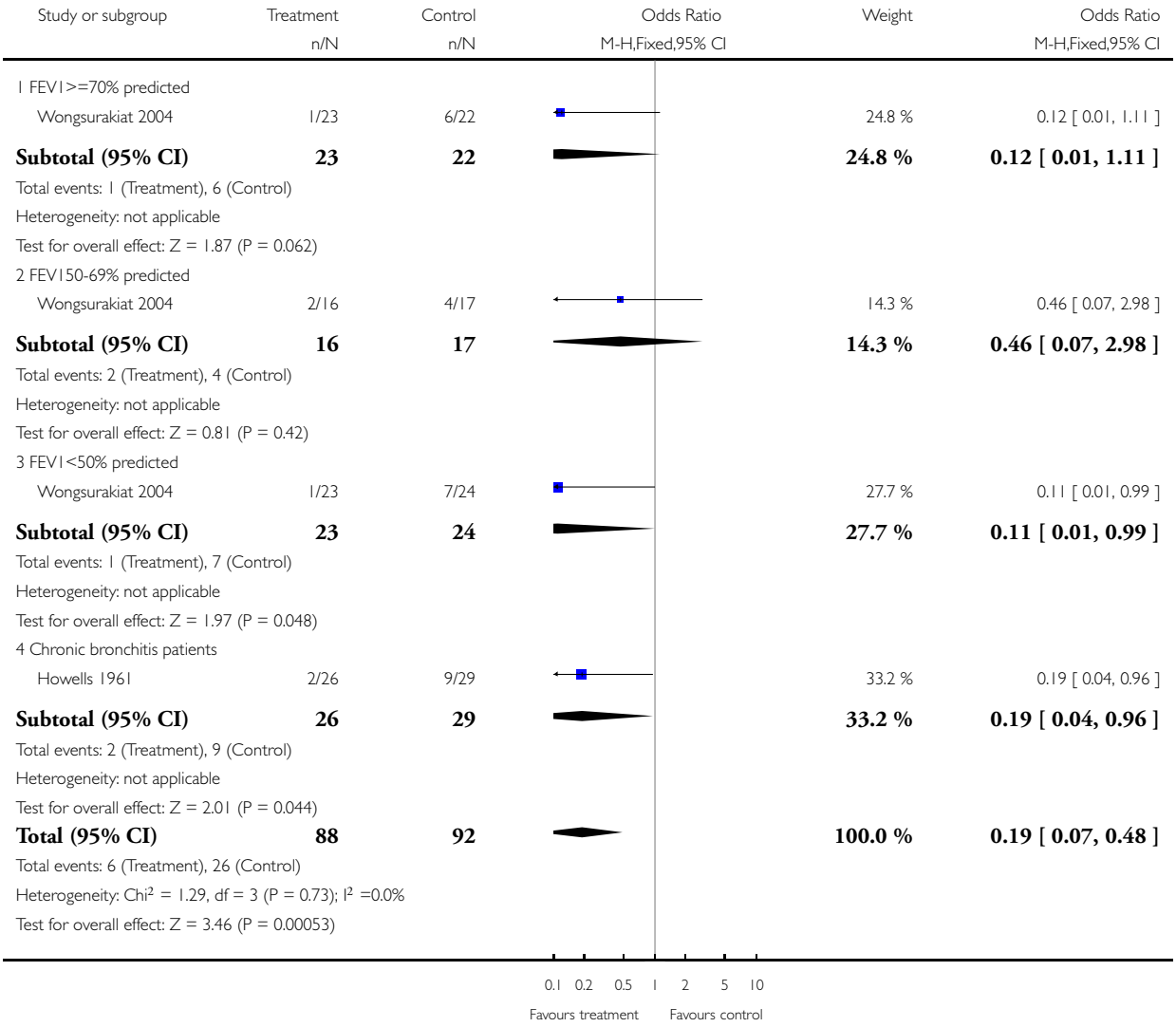


Analysis 1.7. Comparison 1 Influenza vaccination versus placebo, Outcome 7 Acute respiratory illness subsequently documented as influenza-related.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 7 Acute respiratory illness subsequently documented as influenza-related

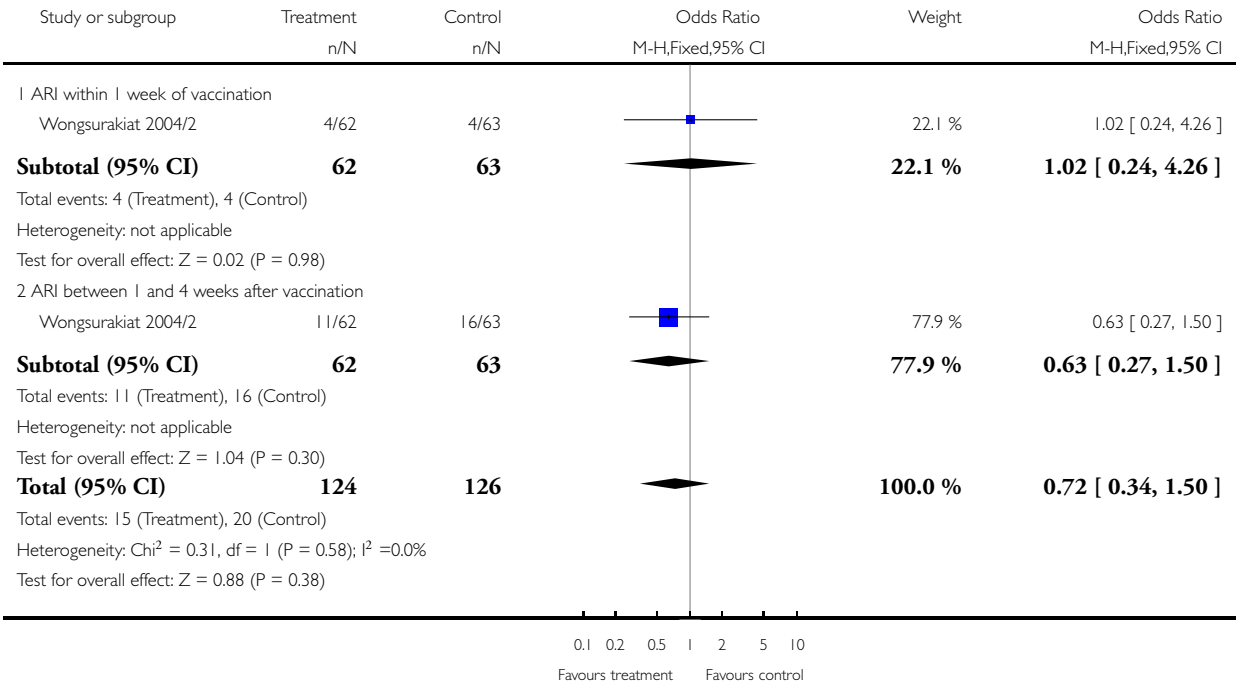


Analysis 1.8. Comparison 1 Influenza vaccination versus placebo, Outcome 8 Early acute respiratory illness.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 8 Early acute respiratory illness

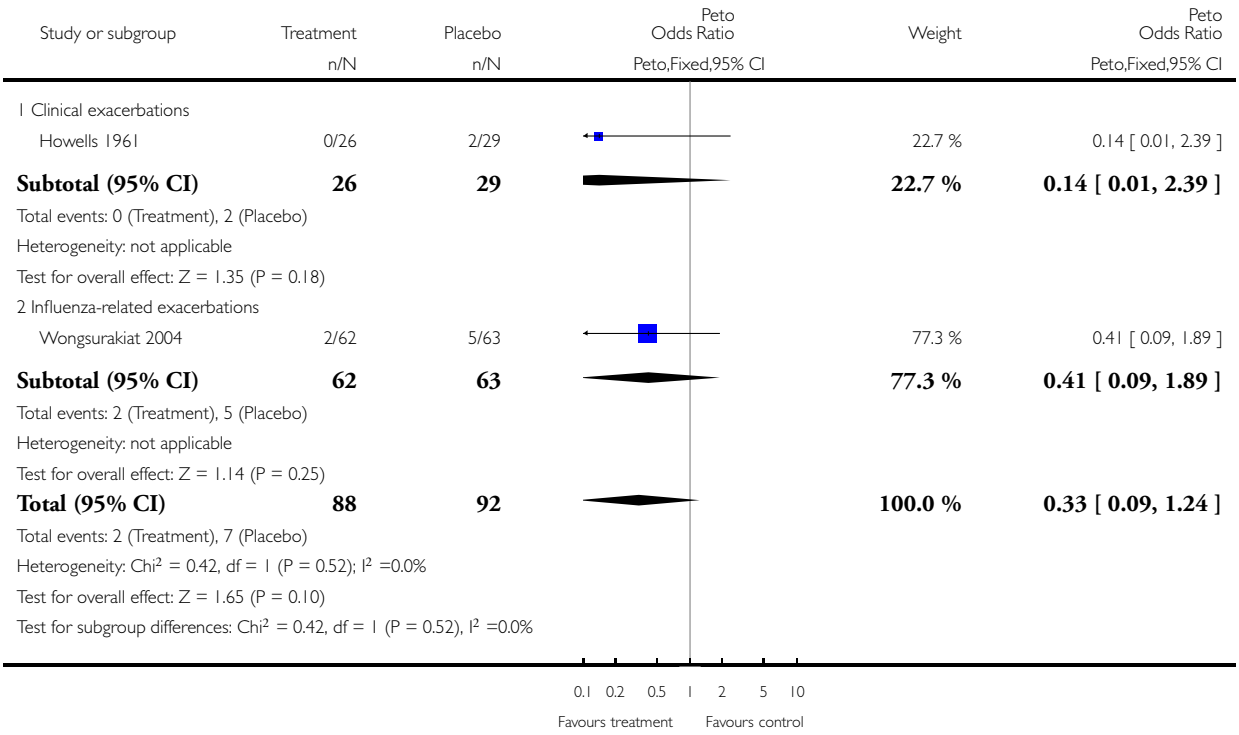


Analysis 1.9. Comparison 1 Influenza vaccination versus placebo, Outcome 9 Hospitalisations.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 9 Hospitalisations



Analysis 1.10. Comparison 1 Influenza vaccination versus placebo, Outcome 10 Mortality.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 10 Mortality

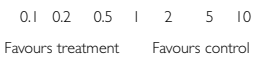
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Howells 1961	0/26	1/29		8.4 %	0.15 [0.00, 7.61]
Wongsurakiat 2004	6/62	6/63		91.6 %	1.02 [0.31, 3.33]
Total (95% CI)	**88**	**92**		**100.0 %**	**0.87 [0.28, 2.70]**

Total events: 6 (Treatment), 7 (Control)

Heterogeneity: Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%

Test for overall effect: Z = 0.25 (P = 0.81)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Influenza vaccination versus placebo, Outcome 11 Mortality related to acute respiratory infection.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 11 Mortality related to acute respiratory infection

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Wongsurakiat 2004	1/62	3/63		0.33 [0.03, 3.24]

Analysis 1.12. Comparison 1 Influenza vaccination versus placebo, Outcome 12 Overall change in lung function (FEV1 in litres).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 12 Overall change in lung function (FEV1 in litres)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
MRC 1980	36	-0.04 (0.15)	19	-0.02 (0.2)		-0.02 [-0.12, 0.08]

Analysis 1.13. Comparison 1 Influenza vaccination versus placebo, Outcome 13 Change in early lung function (FEV1 in litres).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 13 Change in early lung function (FEV1 in litres)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
MRC 1980	36	-0.04 (0.12)	19	-0.03 (0.15)		-0.01 [-0.09, 0.07]

Analysis 1.14. Comparison 1 Influenza vaccination versus placebo, Outcome 14 Local effects at Injection Site.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 14 Local effects at Injection Site

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Wongsurakiat 2004/2	17/62	4/63		5.57 [1.75, 17.71]

Analysis 1.15. Comparison 1 Influenza vaccination versus placebo, Outcome 15 Systemic adverse effects.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 15 Systemic adverse effects

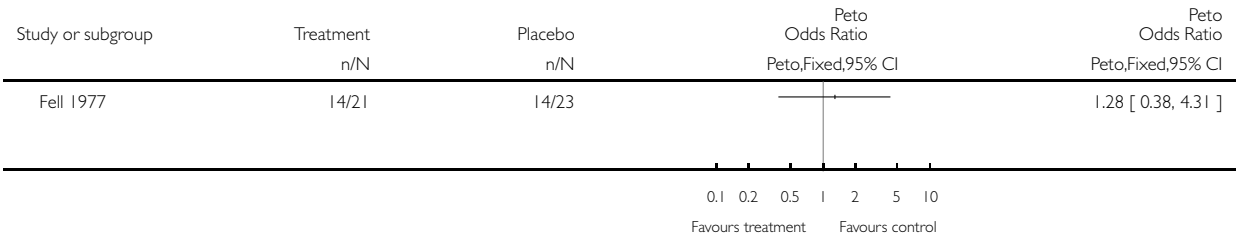
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Wongsurakiat 2004/2	47/62	51/63		0.74 [0.31, 1.74]

Analysis 1.16. Comparison 1 Influenza vaccination versus placebo, Outcome 16 Patients with early breathlessness.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 16 Patients with early breathlessness

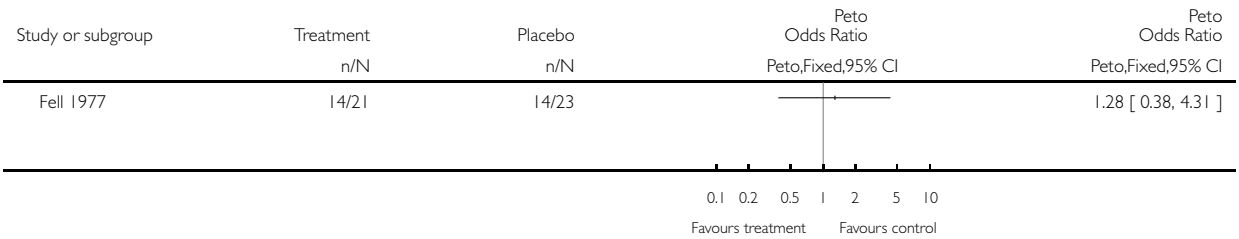


Analysis 1.17. Comparison 1 Influenza vaccination versus placebo, Outcome 17 Patients with early tightness.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 17 Patients with early tightness

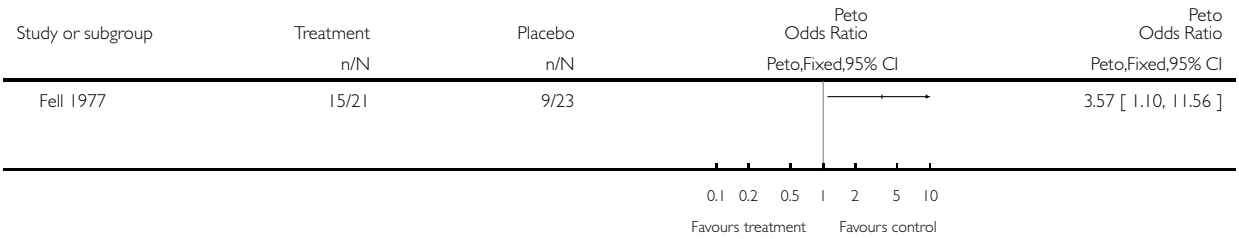


Analysis 1.18. Comparison 1 Influenza vaccination versus placebo, Outcome 18 Patients with early wheeze.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 18 Patients with early wheeze

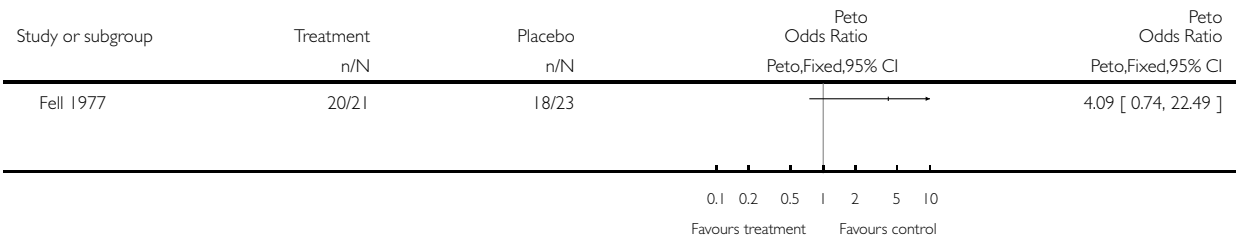


Analysis 1.19. Comparison 1 Influenza vaccination versus placebo, Outcome 19 Patients with early cough.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 19 Patients with early cough

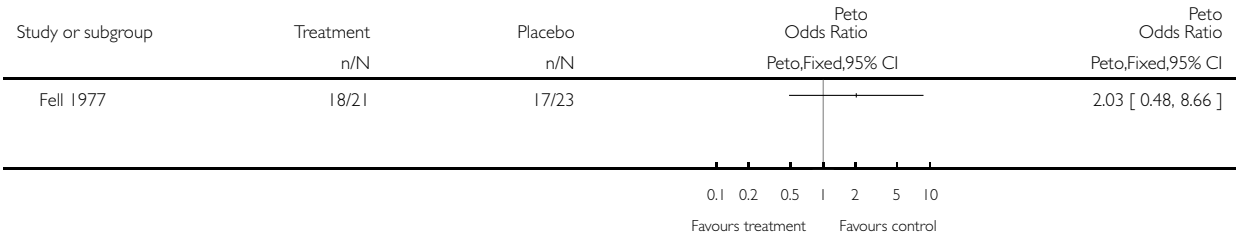


Analysis 1.20. Comparison 1 Influenza vaccination versus placebo, Outcome 20 Patients with early sputum production.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 1 Influenza vaccination versus placebo

Outcome: 20 Patients with early sputum production

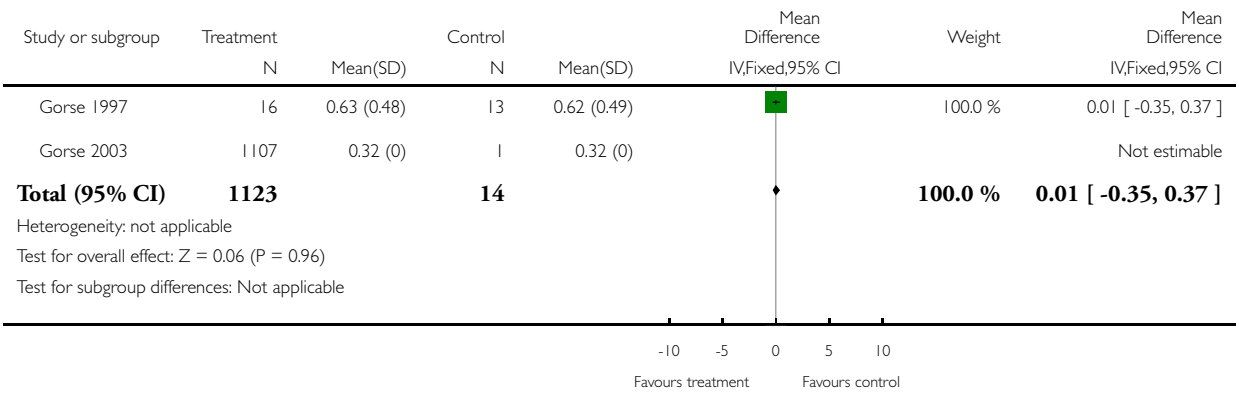


Analysis 2.1. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 1 Total exacerbations per patient.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 1 Total exacerbations per patient



Analysis 2.2. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 2 Early exacerbations per patient.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 2 Early exacerbations per patient

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 1997	16	0.25 (0.43)	13	0.46 (0.5)		-0.21 [-0.55, 0.13]

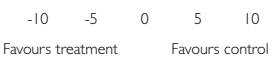
Analysis 2.3. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 3 Late exacerbations per patient.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 3 Late exacerbations per patient

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 1997	16	0.38 (0.48)	13	0.15 (0.36)		0.23 [-0.08, 0.54]



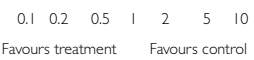
Analysis 2.4. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 4 Acute respiratory illness subsequently documented as influenza-related.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 4 Acute respiratory illness subsequently documented as influenza-related

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Gorse 2003	50/1107	59/1108		0.84 [0.57, 1.24]



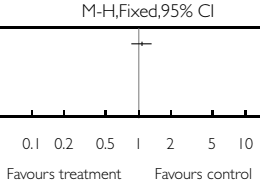
Analysis 2.5. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 5 Patients with at least one influenza-like illness.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 5 Patients with at least one influenza-like illness

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Gorse 2003	196/1107	186/1108		1.07 [0.86, 1.33]

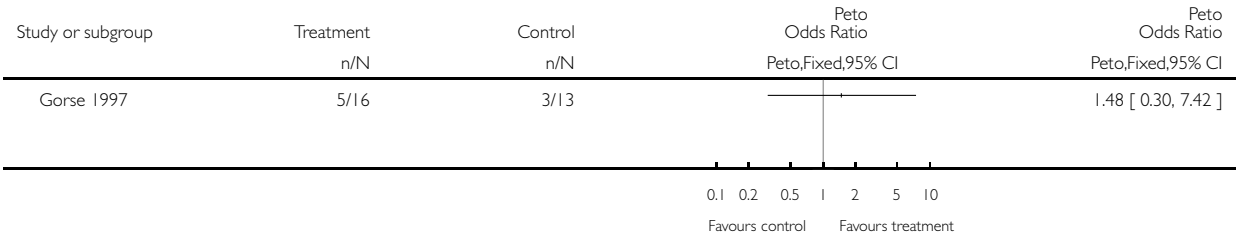


Analysis 2.6. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 6 Patients with improvement in exacerbations.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 6 Patients with improvement in exacerbations

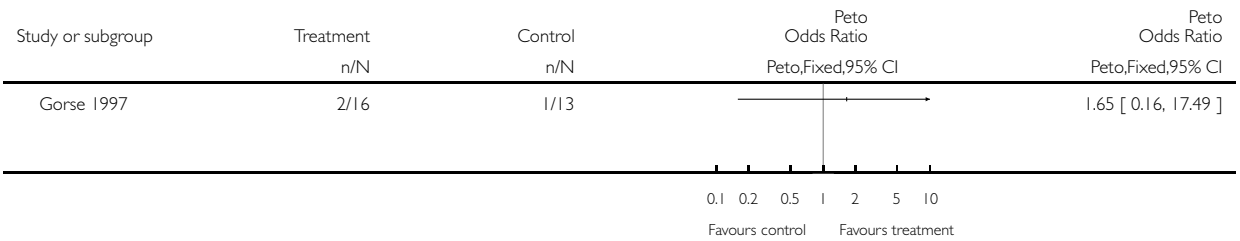


Analysis 2.7. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 7 Patients with early improvements.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 7 Patients with early improvements



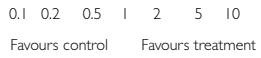
Analysis 2.8. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 8 Patients with late improvements.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 8 Patients with late improvements

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Gorse 1997	3/16	2/13		1.26 [0.19, 8.43]



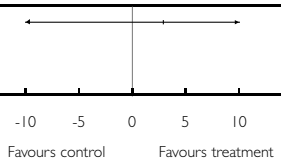
Analysis 2.9. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 9 Early changes in lung function (% predicted FEV1).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 9 Early changes in lung function (% predicted FEV1)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 1997	16	0.3 (19.2)	13	-2.6 (26.14)		2.90 [-14.14, 19.94]



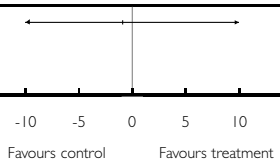
Analysis 2.10. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 10 Early changes in lung function (FEV1/FVC %).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 10 Early changes in lung function (FEV1/FVC %)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 1997	16	0.2 (12.4)	13	1.1 (17.13)		-0.90 [-12.02, 10.22]



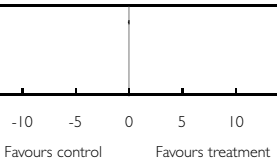
Analysis 2.11. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 11 Post immunisation lung function (FEV1).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 11 Post immunisation lung function (FEV1)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 2003	1107	1.36 (0.57)	1108	1.41 (0.52)		-0.05 [-0.10, 0.00]

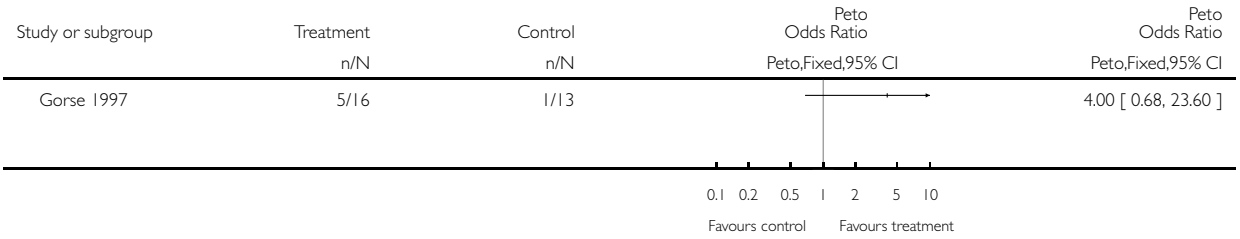


Analysis 2.12. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 12 Patients with increase in lung function (1 category).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 12 Patients with increase in lung function (1 category)

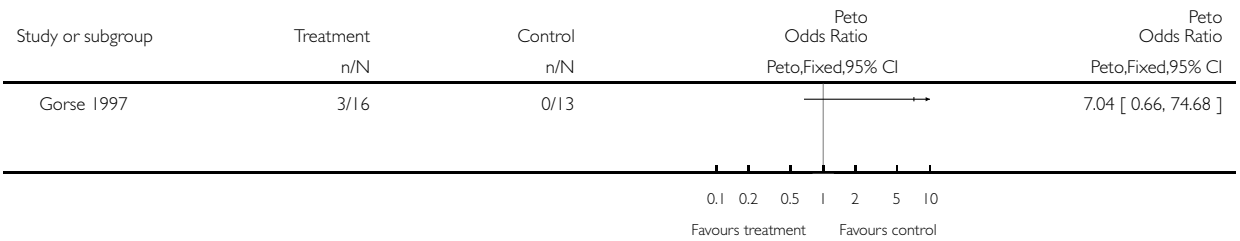


Analysis 2.13. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 13 Patients with a decrease in lung function.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 13 Patients with a decrease in lung function



Analysis 2.14. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 14 FEV1 at end of study.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 14 FEV1 at end of study

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 2003	196	1.34 (0.56)	186	1.39 (0.55)		-0.05 [-0.16, 0.06]

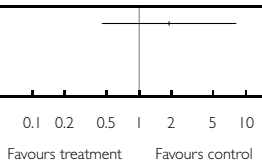
Analysis 2.15. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 15 Patients with adverse effects (new upper respiratory tract symptoms).

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 15 Patients with adverse effects (new upper respiratory tract symptoms)

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Gorse 1997	10/16	6/13		1.89 [0.45, 8.04]



Analysis 2.16. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 16 Patients with early adverse effects.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 16 Patients with early adverse effects

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Gorse 1997	5/16	5/13		4.2 %	0.73 [0.16, 3.34]
Gorse 2003	77/1107	88/1108		95.8 %	0.87 [0.63, 1.19]
Total (95% CI)	**1123**	**1121**		**100.0 %**	**0.86 [0.63, 1.17]**

Total events: 82 (Treatment), 93 (Control)

Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable

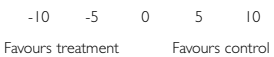
Analysis 2.17. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 17 Days with early symptoms and signs.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 17 Days with early symptoms and signs

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gorse 2003	1107	1.9 (2.6)	1108	1.5 (2.4)		0.40 [0.19, 0.61]

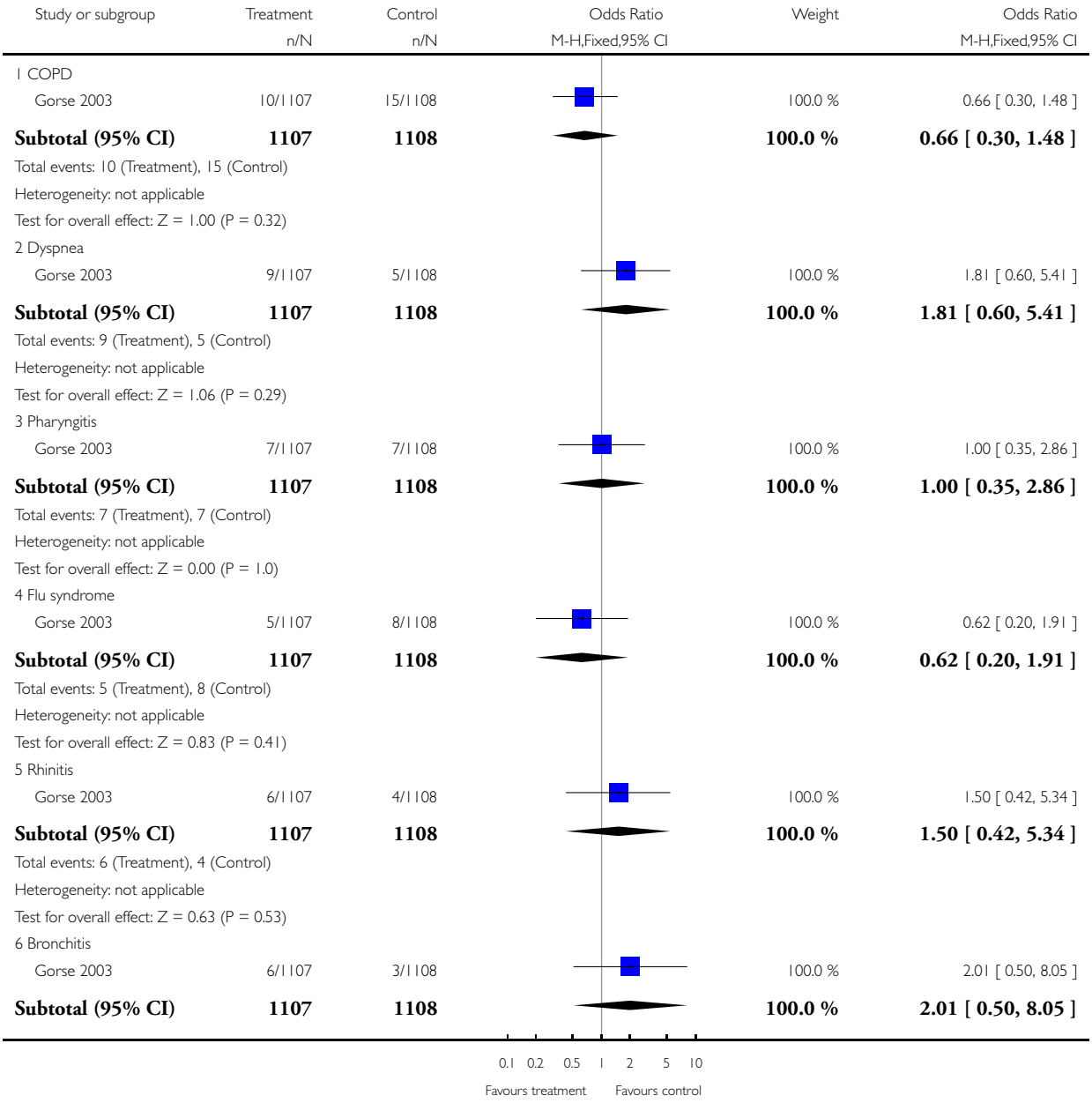


Analysis 2.18. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 18 No of subjects, and nature of, early adverse effects.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 18 No of subjects, and nature of, early adverse effects



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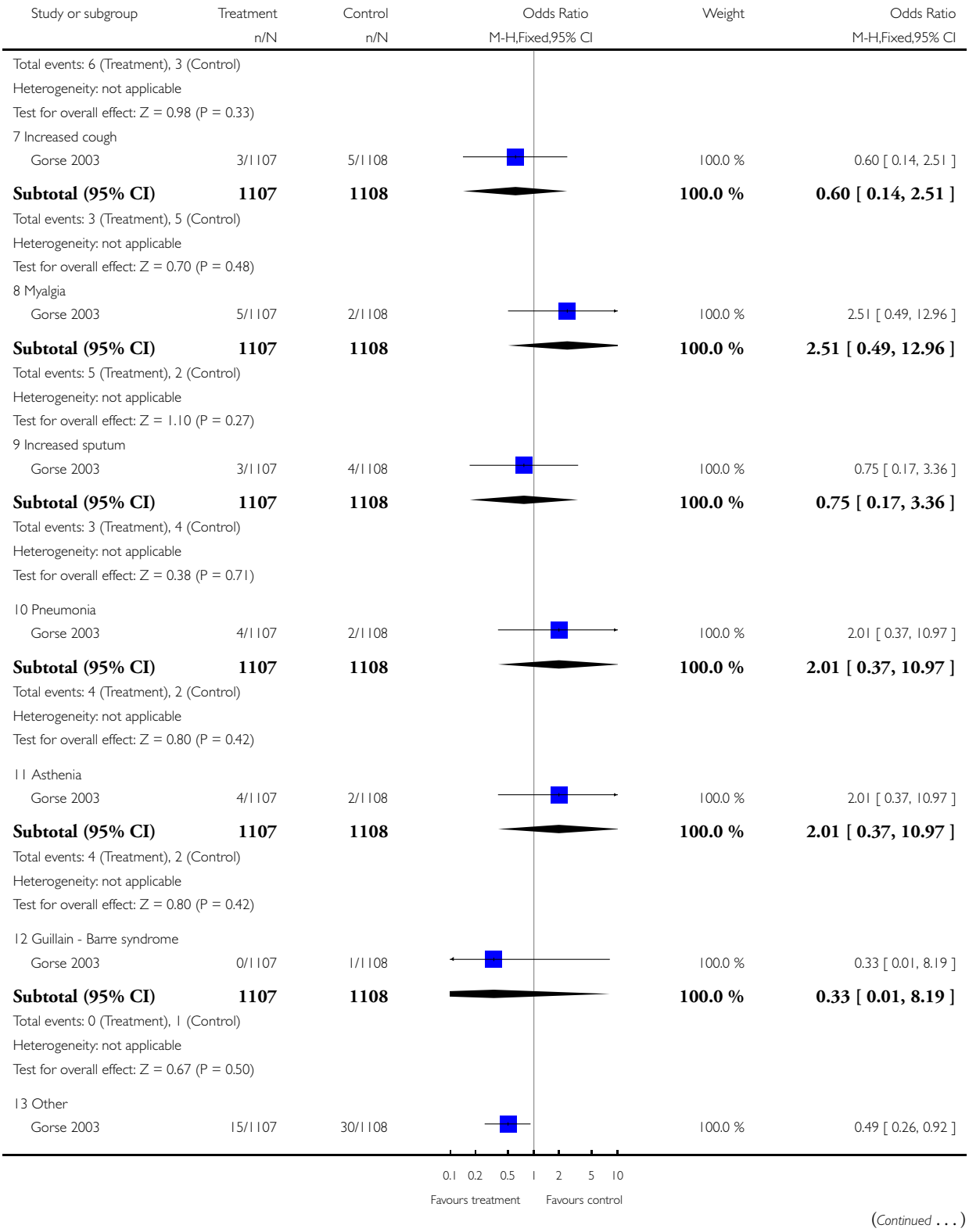

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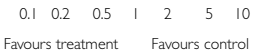
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**1107**	**1108**		**100.0 %**	**0.49 [0.26, 0.92]**
Total events: 15 (Treatment), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.21 (P = 0.027)					



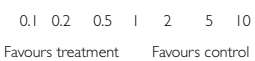
Analysis 2.19. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 19 Patients with late adverse effects.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 19 Patients with late adverse effects

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Gorse 1997	5/16	1/13		13.4 %	4.00 [0.68, 23.60]
Gorse 2003	22/1107	10/1108		86.6 %	2.14 [1.07, 4.30]
Total (95% CI)	**1123**	**1121**		**100.0 %**	**2.33 [1.22, 4.46]**
Total events: 27 (Treatment), 11 (Control)					
Heterogeneity: Chi^2 = 0.41, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 2.55 (P = 0.011)					
Test for subgroup differences: Not applicable					

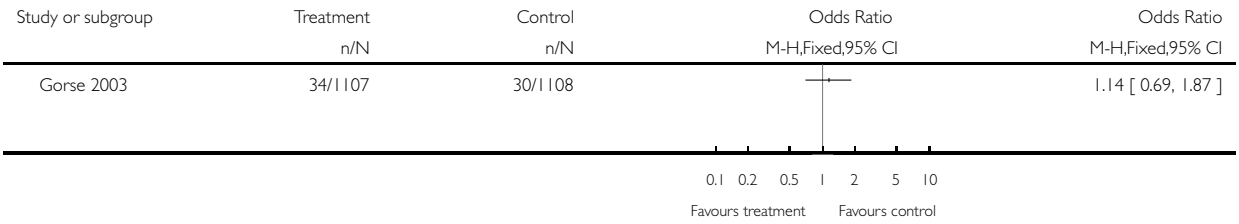


Analysis 2.20. Comparison 2 Inactivated/ Live versus Inactivated/Placebo, Outcome 20 Mortality.

Review: Influenza vaccine for patients with chronic obstructive pulmonary disease

Comparison: 2 Inactivated/ Live versus Inactivated/Placebo

Outcome: 20 Mortality



WHAT'S NEW

Last assessed as up-to-date: 10 June 2010.

Date	Event	Description
11 June 2010	New search has been performed	Literature search re-run; no new studies found.

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 3, 2000

Date	Event	Description
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	There are two new trials (five reports). Gorse 2003 included 2215 patients and Wongsurakiat 2004 included 132 patients.

(*Continued*)

		New outcomes have been included: *Acute infection subsequently documented as influenza-related *Cost effectiveness *Number of patients with exacerbations A significant protective effect has now been shown of influenza vaccine on exacerbations of COPD

CONTRIBUTIONS OF AUTHORS

Poole PJ:

Protocol, literature search, reviewed papers for inclusion, format of data extraction sheet, review write up, analyses and discussion.

Conducted 2004/5 update. Assess search results for 2007 & 2009 versions.

Chacko E:

Literature search, reviewed papers for inclusion, format of data extraction sheet , data extraction, review write up, analyses and discussion. Collaborated on 2004/5 update.

Wood-Baker R:

Protocol, literature search, reviewed papers for inclusion, format of data extraction sheet, analyses and discussion.

Cates CJ:

Protocol and review editor, statistical advice, difficult questions. Edited 2004/5 review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- Health Research Council of New Zealand Summer Studentship, New Zealand.
- NHS Executive Eastern Region, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

New outcomes have been included:

*Acute infection subsequently documented as influenza-related

*Cost effectiveness

*Number of patients with exacerbations

INDEX TERMS

Medical Subject Headings (MeSH)

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