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Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease (Review)

Walters JAE, Tang JNQ, Poole P, Wood-Baker R

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[Intervention Review]

Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

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ABSTRACT

Background

People with chronic obstructive pulmonary disease (COPD) are at increased risk of pneumococcal disease, especially pneumonia, as well as acute exacerbations with associated morbidity and healthcare costs.

Objectives

To determine the efficacy of injectable pneumococcal vaccination for preventing pneumonia in persons with COPD.

Search methods

We searched the Cochrane Airways COPD Trials Register and the databases CENTRAL, MEDLINE and Embase, using prespecified terms. Searches are current to November 2016.

Selection criteria

We included randomised controlled trials (RCT) comparing injectable pneumococcal polysaccharide vaccine (PPV) or pneumococcal conjugated vaccine (PCV) versus a control or alternative vaccine type in people with COPD.

Data collection and analysis

We used standard Cochrane methodological procedures. For meta-analyses, we subgrouped studies by vaccine type.

Main results

For this update, we added five studies (606 participants), meaning that the review now includes a total of 12 RCTs involving 2171 participants with COPD. Average age of participants was 66 years, male participants accounted for 67% and mean forced expiratory volume in one second (FEV_1) was 1.2 L (five studies), 54% predicted (four studies). We assessed risks of selection, attrition and reporting bias as low, and risks of performance and detection bias as moderate.

Compared with control, the vaccine group had a lower likelihood of developing community-acquired pneumonia (CAP) (odds ratio (OR) 0.62, 95% confidence interval (CI) 0.43 to 0.89; six studies, n = 1372; GRADE: moderate), but findings did not differ specifically

for pneumococcal pneumonia (Peto OR 0.26, 95% CI 0.05 to 1.31; three studies, n = 1158; GRADE: low). The number needed to treat for an additional beneficial outcome (NNTB) (preventing one episode of CAP) was 21 (95% CI 15 to 74). Mortality from cardiorespiratory causes did not differ between vaccine and control groups (OR 1.07, 95% CI 0.69 to 1.66; three studies, n = 888; GRADE: moderate), nor did all-cause mortality differ (OR 1.00, 95% CI 0.72 to 1.40; five studies, n = 1053; GRADE: moderate). The likelihood of hospital admission for any cause, or for cardiorespiratory causes, did not differ between vaccine and control groups. Vaccination significantly reduced the likelihood of a COPD exacerbation (OR 0.60, 95% CI 0.39 to 0.93; four studies, n = 446; GRADE: moderate). The NNTB to prevent a patient from experiencing an acute exacerbation was 8 (95% CI 5 to 58). Only one study (n = 181) compared the efficacy of different vaccine types - 23-valent PPV versus 7-valent PCV - and reported no differences for CAP, all-cause mortality, hospital admission or likelihood of a COPD exacerbation, but investigators described a greater likelihood of some mild adverse effects of vaccination with PPV-23.

Authors' conclusions

Injectable polyvalent pneumococcal vaccination provides significant protection against community-acquired pneumonia, although no evidence indicates that vaccination reduced the risk of confirmed pneumococcal pneumonia, which was a relatively rare event. Vaccination reduced the likelihood of a COPD exacerbation, and moderate-quality evidence suggests the benefits of pneumococcal vaccination in people with COPD. Evidence was insufficient for comparison of different pneumococcal vaccine types.

PLAIN LANGUAGE SUMMARY

Do injectable pneumococcal vaccines prevent pneumonia in people with COPD?

We wanted to find out if pneumococcal vaccination for people with chronic obstructive pulmonary disease (COPD) reduces the risk of pneumonia and associated mortality. We found a total of 12 studies including 2171 participants. Evidence gathered in this review is current to December 2015.

Background

People with COPD are at increased risk of respiratory illness such as pneumonia due to a bacterium called *Streptococcus pneumonia*e, other community-acquired pneumonias and acute COPD exacerbations. These illnesses increase mortality and are associated with increased healthcare costs.

Study characteristics

For this updated review, we identified five new studies (606 participants), bringing the total number of studies to 12, involving 2171 participants with COPD. The average age of participants was 66 years, 67% were male and participants had received a diagnosis of moderate to severe COPD. Eleven studies compared an injectable vaccine versus a control, and one study compared two different types of injectable vaccine.

Key results

People who were vaccinated were less likely to experience an episode of community-acquired pneumonia; 21 people with COPD (95% confidence interval (CI) 15 to 74) would have to be vaccinated to prevent one episode of pneumonia. Vaccination made no difference in the risk of pneumococcal pneumonia due to *S pneumonia*e or in the chance of dying or of being admitted to hospital. People who were vaccinated were less likely to experience a COPD exacerbation; eight people with COPD (95% CI 5 to 58) would have to be vaccinated to prevent one person from having an acute exacerbation. We found no difference in effectiveness between the two types of injectable vaccine.

Quality of the evidence

Evidence in this review is generally independent and reliable, and we are moderately certain about the results.

Conclusions

In line with current guidance, this review suggests that all people with COPD should be given pneumococcal vaccination to provide some protection against community-acquired pneumonia, and to reduce the chance of an acute exacerbation.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Is pneumococcal vaccination effective in preventing pneumonia in chronic obstructive pulmonary disease?

Patient or population: patients with COPD
Setting: community
Intervention: pneumococcal vaccine
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with pneumococcal vaccine				
Pneumonia, community acquired, at least 1 episode Follow-up: range 6 to 36 months	143 per 1000	94 per 1000 (67 to 129)	OR 0.62 (0.43 to 0.89)	1372 (6 RCTs)	⊕⊕⊕◯ Moderate[a]	Study limitations with lack of participant blinding and no use of placebo in 3 studies. NNTB to prevent 1 episode of CAP = 21 (95% CI 15 to 74)
Pneumococcal pneumonia, at least 1 episode Follow-up: range 6 to 36 months	11 per 1000	3 per 1000 (1 to 14)	OR 0.26 (0.05 to 1.31)	1158 (3 RCTs)	⊕⊕◯◯ Low[b,c]	Very few confirmed episodes of pneumococcal pneumonia. Rate of pneumococcal CAP to total CAP from 2008 to 2013 varied from 17.1% to 37.3% of cases (Rodrigo 2015).
Death from cardiorespiratory causes Follow-up: range 24 to 48 months	98 per 1000	104 per 1000 (70 to 153)	OR 1.07 (0.69 to 1.66)	888 (3 RCTs)	⊕⊕⊕◯ Moderate[d]	

Death from all causes Follow-up: range 12 to 48 months	165 per 1000	165 per 1000 (125 to 217)	OR 1.00 (0.72 to 1.40)	1053 (5 RCTs)	⊕⊕⊕◯ Moderate[d]	
Hospital admission: any cause, at least 1 episode Follow-up: range 6 to 12 months	86 per 1000	65 per 1000 (29 to 140)	OR 0.74 (0.32 to 1.74)	391 (3 RCTs)	⊕⊕⊕◯ Moderate[d]	
COPD exacerbation: at least 1 episode Follow-up: range 6 to 24 months	608 per 1000	482 per 1000 (377 to591)	OR 0.60 (0.39 to 0.93)	446 (4 RCTs)	⊕⊕⊕◯ Moderate[a]	Study limitations with lack of or unclear participant blinding in 3 studies. NNTB = 8 (95% CI 5 to 58); see Figure 1
Lung function: FEV_1 (L) Follow-up: 12 months	Mean lung function: FEV_1 (L) was 1.43 L	Mean lung function: FEV_1 (L) in the intervention group was 0.12 L lower (7.17 lower to 6.93 greater)	-	142 (1 RCT)	⊕⊕◯◯ Low[d,e]	No difference in lung function seen at 3 or 24 months in 1 study

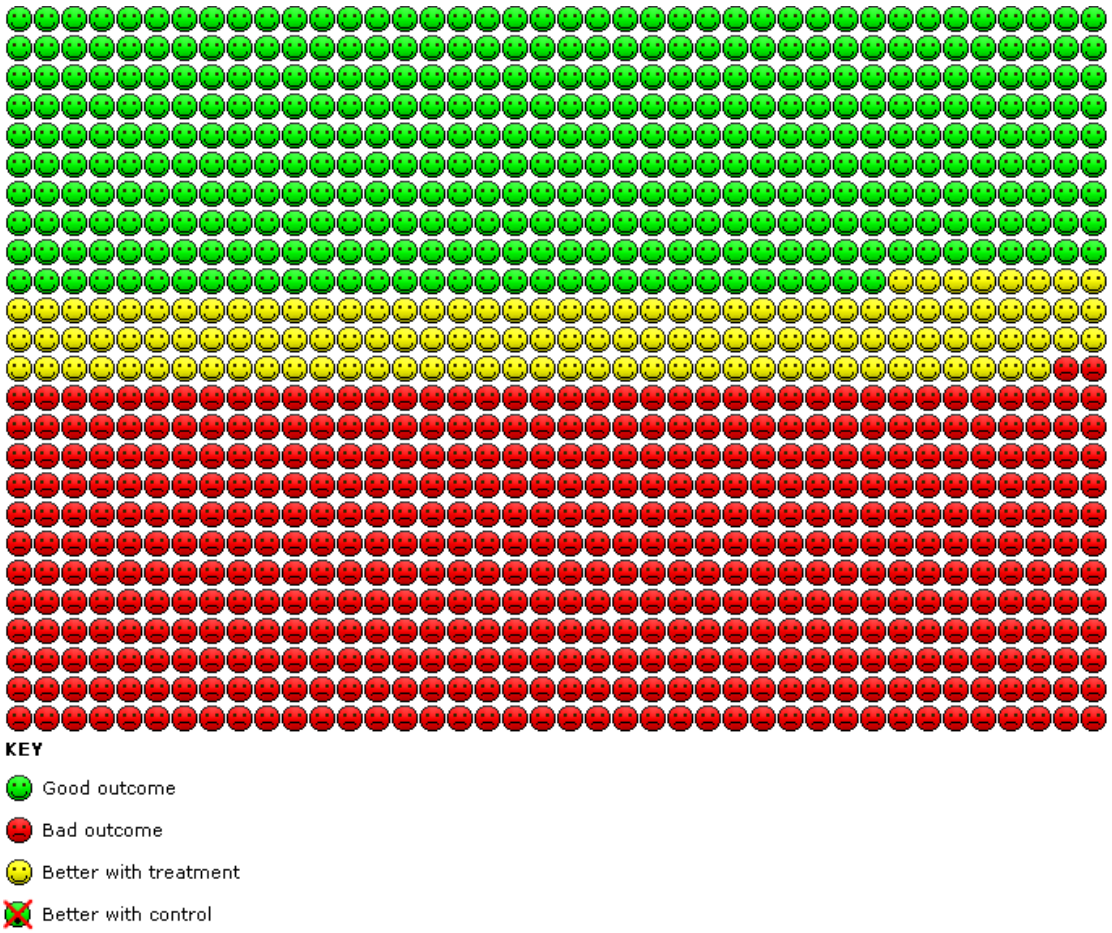
*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome; OR: odds ratio

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Study limitations increase risk of performance and detection bias.
[b] substantial heterogeneity present.
[c] Wide confidence interval; few events in 2 studies, no events in 1 study.
[d] Wide confidence interval; effect size includes the null.
[e] Single study.

Figure 1. In the control group, 608 out of 1000 people had one or more exacerbations over 6 to 24 months, compared with 482 (95% CI 377 to 591) out of 1000 for the active treatment group.



BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is not fully reversible. Data from 12 countries in the Burden of Lung Disease (BOLD) initiative show that more than 10% of adults have COPD at Stage II or higher, as defined by GOLD 2016. Prevalence and staging vary across countries between men and women (Buist 2007) and increase with age. Worldwide, COPD was the fifth- leading cause of death in 2011, and it was the seventh-leading cause of lost disability-adjusted life years (DALYs) (WHO 2013).

Exacerbations and comorbidities contribute to the variable natural history of COPD in individual patients (GOLD 2016). Exacerbations contribute to long-term decline in lung function (Donaldson 2002) and reduced physical activity (Donaldson 2005). They have a profound and long-lasting effect on quality of life (Groenewegen 2001; Seemungal 1998) and contribute to increased risk of death (Soler-Cataluna 2005). Exacerbations are a major contributor to healthcare costs, especially for hospital admission (Wedzicha 2003).

The clinical onset of an acute exacerbation is defined according to symptoms, although definitions vary (Rodriguez-Roisin 2000). Anthonisen defined type 1 exacerbations on the basis of three major symptoms: increased dyspnoea, sputum volume and sputum purulence. Type 2 exacerbations required two major symptoms, and type 3 exacerbations required one major symptom plus cough, wheeze or symptoms of an upper respiratory tract infection (Anthonisen 1987). A later definition required an increase in two 'major symptoms' of dyspnoea - sputum volume and sputum purulence - or an increase in one major symptom and in one 'minor symptom' for two days (wheeze, sore throat, cough or common cold symptoms) (Seemungal 2000). Researchers recently developed a standardised measure for assessing the frequency, severity and duration of exacerbations of COPD using patient-reported outcomes as described in clinical studies (Leidy 2010).

Patients with COPD with persistent lower airway bacterial colonisation when stable are at increased risk of exacerbations (Bogaert 2004; Patel 2002). Infection is frequently detected during exacerbations; one study found that 48.4% of participants had viral causes and 54.7% had bacterial causes of infection (Papi 2006). Infection-associated exacerbations required longer hospitalisation and resulted in greater impairment of lung function than exacerbations in which no infection was present (Papi 2006). Investigators in one study (Patel 2002) recovered *Streptococcus pneumoniae* (*S pneumoniae*) from the sputum of 33% of participants. Risk of exacerbations of COPD is increased among patients with pneumococcal colonisation (Bogaert 2004). Researchers have discovered an association between detection of *S pneumoniae* as a new organism in the sputum of patients with COPD and significantly increased risk of an exacerbation (Sethi 2002).

Pneumonia is usually a serious illness, and diagnosis is based on the presence of radiological infiltrates, symptoms (cough, expectoration, fever, dyspnoea, pleuritic pain, altered mental status), signs of pulmonary consolidation on auscultation and leukocytosis (Ochoa-Gondar 2008). Community-acquired pneumonia (CAP) is a major health problem among adults over 65 years of age (Welte 2009), and prevalence of 14 cases per 1000 person-years (95% confidence interval (CI) 12.7 to 15.3) has been reported. Hospitalisation rate is high (75%), and in-patient stays are often lengthy (mean 10.4 days) (Ochoa-Gondar 2008). Overall mortality estimates are high: 6% in Canada, 20% in the USA and Spain, 13% in the UK and 8% in Sweden (File 2003; Mandell 2007). Patients with COPD who develop CAP have more severe pneumonia, are admitted to the intensive care unit more frequently and have significantly higher 30- and 90-day mortality than non-COPD patients (Molinos 2009; Restrepo 2006). *S pneumoniae* is the predominant pathogen among all patients with CAP (Mandell 2007) and among patients with COPD and CAP, for whom a 43% pneumococcal aetiology has been found (Lieberman 2002; Torres 1996). Progression from COPD to CAP has been shown to be strongly associated with the presence of *S pneumoniae* (57.3%), and other pathogens were predominant among exacerbations that did not progress to CAP (61.7%) (File 2009).

Description of the intervention

On the basis of differences in polysaccharide capsules, investigators have identified 91 different serotypes of *S pneumoniae*. Capsule polysaccharides have antiphagocytic activity, which affects the pathogenesis of invasive pneumococcal disease (IPD), including CAP (Postma 2012), and the incidence of IPD differs between serotypes. In the late 1970s, a 14-valent pneumococcal polysaccharide vaccine (PPV-14) was registered in the United States; this was replaced in the 1980s by a 23-valent pneumococcal polysaccharide vaccine (PPV-23) (Pneumovax/Pneumo 23) in the USA and Europe. This vaccine contains purified capsular antigens from 23 serotypes that cover 85% to 90% of cases of invasive pneumococcal disease among adults (ERS 2014). The vaccine induces T-cell-independent short-lived B-cell immune responses by causing B cells to differentiate into plasma cells, producing antibodies without producing memory B cells. The immunological antibody response is age- and serotype-dependent and generally is lower among elderly people than in younger adults. A booster vaccination produces no memory response.

To enhance the immunogenicity of pneumococcal vaccines, researchers have developed conjugate vaccines. Polysaccharide antigens are chemically joined to a highly immunogenic protein carrier (such as tetanus or diphtheria toxoid). This process leads to the induction of B cell-dependent and T cell-dependent responses as well as a memory response to a booster dose of the vaccine. Healthcare providers have administered pneumococcal conjugate vaccine containing capsular polysaccharides from seven pneumococcal serotypes (PCV-7) to young children since the 2000s, with a resulting striking decrease in invasive pneumococcal disease caused by vaccine serotypes. As children are the main reservoir of *S pneumoniae* (60% are carriers), a reduction in the carrier rate has had beneficial effects among children and a protective herd effect in adults (Moseley 2013).

Investigators are evaluating new conjugate vaccines, including 7-valent (PCV-7), 10-valent (PCV-10) and 13-valent (PCV-13) vaccines, for use in children and adults, although respiratory guidelines in Europe (ERS 2014) and Australia (COPDX 2016) recommend immunisation with the PPV-23 polysaccharide pneumococcal vaccine for adults at risk of pneumococcal disease, including those with COPD. The PCV-13 and the PCV-10 are not recommended for patients with COPD in Australia (NHMRC 2013). Recommendations for age at immunisation and at revaccination vary depending on the guideline, with some recommending vaccination only for patients who are over 64 years of age, or for younger patients with severe COPD or comorbid conditions (GOLD 2016), and others recommending vaccination for all patients 50 years of age and older, along with revaccination five years later (NHMRC 2013).

How the intervention might work

Patients with COPD are able to mount a significant immune response to pneumococcal infection (Bogaert 2004); thus immunisation against pneumococcal infection may be effective in preventing bacterial growth in the airways of patients with COPD, in turn decreasing the occurrence of exacerbations and pneumonia.

Why it is important to do this review

Major COPD guidelines (COPDX 2016; ERS 2014; GOLD 2016; NICE 2010) have recommended pneumococcal vaccination, largely on the basis of results showing the efficacy of pneumococcal vaccination as reported by observational studies in general populations and by randomised controlled trials (RCTs) in people without COPD. Both a large indirect cohort study (Butler 1993) and a meta-analysis (Fine 1994) of pneumococcal vaccination have confirmed protection against invasive bacteraemic disease, but efficacy remains to be assessed in the population with COPD, for which risks of CAP and of deterioration may be higher owing to exacerbations of the disease.

OBJECTIVES

To determine the efficacy of injectable pneumococcal vaccination for preventing pneumonia in persons with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included in this review only RCTs using injectable pneumococcal vaccines.

Types of participants

We included studies if participants were adults with a diagnosis of COPD, preferably based on objective diagnostic criteria: demonstration of airflow obstruction on spirometry, generally forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio less than 0.7 (GOLD 2016) and a significant smoking history. We included studies in which the proportion of participants with COPD was at least 80%, if the age of other participants matched that of participants with COPD.

Types of interventions

At least one injectable pneumococcal vaccine - a pneumococcal polysaccharide vaccine or a pneumococcal conjugate vaccine or other vaccine type. The control group could be given placebo or no vaccination, or different types of pneumococcal vaccine for comparison.

Types of outcome measures

Primary outcomes

1. Pneumonia
2. Mortality, respiratory-related and all-cause
3. Healthcare utilisation, including hospital admissions and emergency department visits

Secondary outcomes

1. Acute exacerbations of COPD
2. Days of disability from respiratory illness variously defined as days in bed, days off work or days when the participant was unable to undertake normal activities
3. Lung function
4. Adverse effects of vaccination
5. Cost-effectiveness of pneumococcal vaccination
6. Quality of life

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Specialised Register up to 25 November 2016. The Information Specialist for the Group maintains the Cochrane Airways Specialised Register, which contains studies identified from several sources.

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

We identified studies included in the Trials Register by applying search strategies based on the scope of the Cochrane Airways Review Group. We have provided details of these strategies, as well

as a list of handsearched conference proceedings, in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We carried out additional searches of CENTRAL CRSO (searched 25 November 2016), MEDLINE Ovid (1946 to 23 November 2016) and Embase Ovid (1974 to 23 November 2016). We have listed in Appendix 3 the search strategies used for these databases. We applied no restrictions on language of publication.

Searching other resources

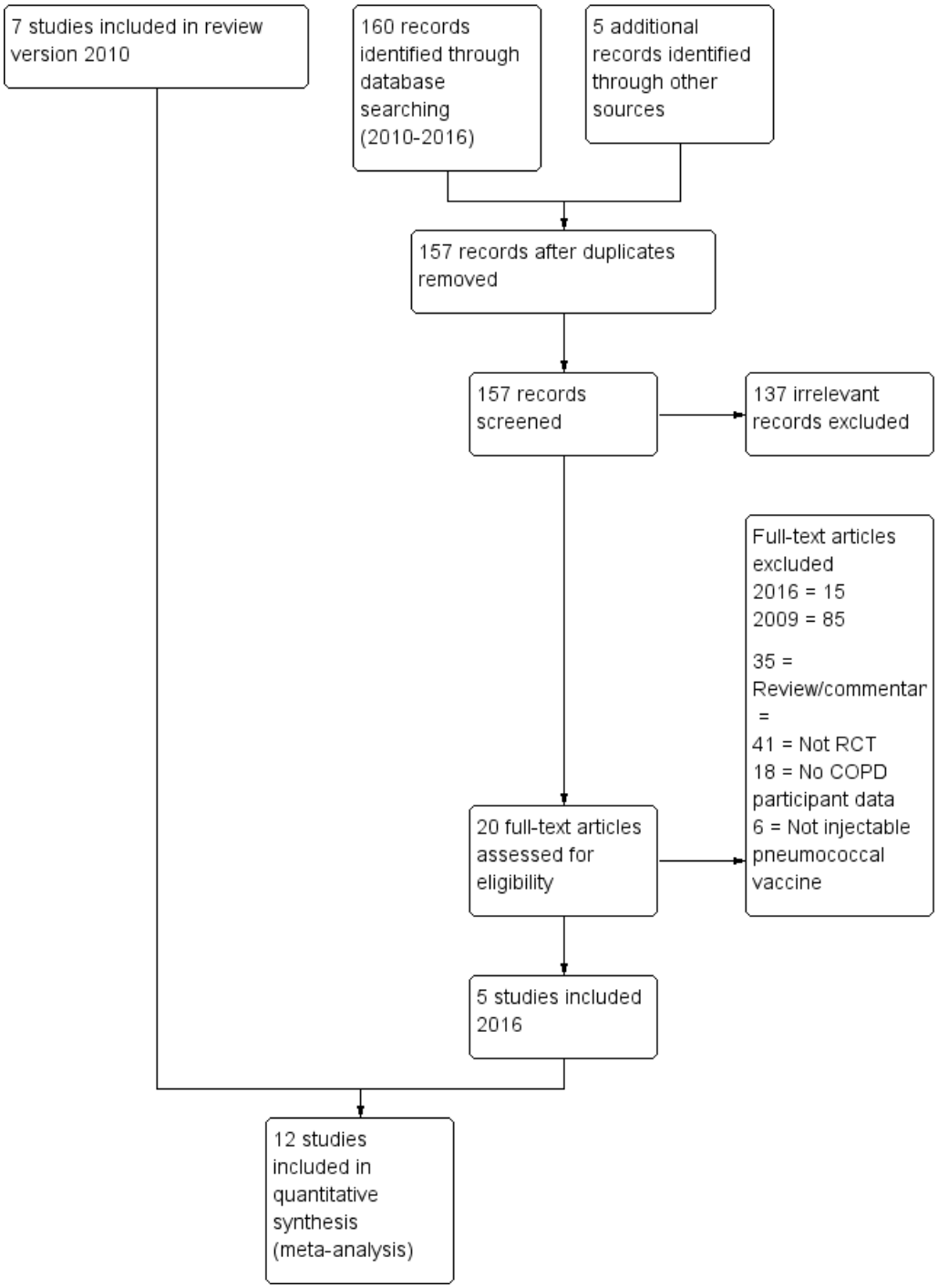
From full-text papers obtained, we searched the bibliographic lists for additional articles. We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) up to 25 November 2016 and pharmaceutical company clinical trial databases of companies manufacturing pneumococcal vaccines.

Data collection and analysis

Selection of studies

At least two review authors (JW, JT or RWB) assessed all potentially relevant trials for relevance by screening the full texts to independently select studies for inclusion and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion or, if required, we consulted a third review author. We identified and excluded duplicates and collated multiple reports of the same study, so that each study (rather than each report) was the unit of interest in the review. We recorded the selection process via a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 2).

Figure 2. Study flow diagram.



Data extraction and management

Two review authors (JT, JW) independently extracted study details and used a data collection form to record the following study characteristics and outcome data.

1. Methods: study design, total duration of study, number of study centres and locations, study setting, duration and date of study.
2. Participants: N, mean age, age range, gender, withdrawals, inclusion criteria and exclusion criteria.
3. Interventions: study treatment, comparison, cointerventions.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, trial registration, notable conflicts of interest of trial authors.

The first review author entered data into Review Manager (version 5.3) (RevMan 2014), and a second review author double-checked the data. We checked that data were entered correctly by comparing data presented in the systematic review against information provided in the study reports.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study (JW, JT), using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook). We resolved disagreements by discussion or by consultation with another review author. We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias(es).

We graded each potential source of bias as high, low or unclear and provided a quote from the study report, together with a justification for our judgement, in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. When information on risk of bias was related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contributed to those outcomes.

Measures of treatment effect

We analysed dichotomous outcomes by using Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CIs). When events were rare, we employed the Peto odds ratio. We entered scale data with a consistent direction of effect.

For continuous variables, we analysed data as mean differences (MDs) with 95% CIs. We used standardised mean differences (SMDs) with 95% CIs if investigators had used different scales of measurement for a specific outcome. The SMD is a statistic that expresses differences in means between treatment groups in units of the pooled standard deviation.

We undertook meta-analyses only when this was meaningful, that is, when treatments, participants and the underlying clinical question were similar.

When skewed data were available (reported as medians and interquartile ranges), we described them narratively.

For 'time-to-event' outcomes such as log hazard ratios, we used the fixed-effect generic inverse variance outcome to combine results. This method yields a weighted average of effect estimates of separate studies (Cochrane Handbook, Chapter 9). We calculated the number needed to treat for an additional beneficial outcome from the pooled OR and its CI, using baseline risk in the control group.

Unit of analysis issues

We used participants as the unit of analysis when analysing dichotomous data.

Dealing with missing data

We contacted investigators to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only).

When this was not possible, and missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing a sensitivity analysis**.**

Assessment of heterogeneity

We used a Breslow-Day test to assess heterogeneity for pooled effects when the null hypothesis was that all studies were evaluating the same effect; we considered a P value > 0.05 to indicate significant differences between studies.

In addition, we used the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than to chance (Higgins 2003). We interpreted statistical heterogeneity as follows: 0% to 40% might not be important, 30% to

60% may represent moderate heterogeneity and 50% to 90% may represent substantial heterogeneity (Cochrane Handbook).
We assessed clinical and methodological heterogeneity by recording differences in study design and participant characteristics between individual studies. When we found substantial heterogeneity. we reported this and explored possible causes by conducting prespecified subgroup analyses.

Assessment of reporting biases

We tried to minimise reporting bias resulting from non-publication of studies or from selective outcome reporting by using a broad search strategy, checking references of included studies and relevant systematic reviews and contacting study authors to ask for additional outcome data. We visually inspected funnel plots when 10 or more studies contributed to the analysis for a specific outcome.

Data synthesis

We combined studies to compare the following.

1. Comparison 1: pneumococcal polysaccharide vaccine, 23-valent (PPSV-23) OR 14-valent (PPV-14), versus control.
2. Comparison 2: 23-valent pneumococcal polysaccharide vaccine (PPV-23) versus 7-valent diphtheria-conjugated pneumococcal polysaccharide vaccine (PCV-7).

We used a fixed-effect model, but we performed a sensitivity analysis by using a random-effects model if we detected unexplained heterogeneity. We presented the findings of our primary outcomes in a 'Summary of findings' table according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook) (generated with the use of GradePro software).

Subgroup analysis and investigation of heterogeneity

If heterogeneity was not sufficiently accounted for by study quality, we specified the following subgroup analyses a priori.

1. Vaccine type - the number of capsular polysaccharide antigens used in the vaccine (more than 14 vs 14 or fewer).
2. Severity of COPD (assessed by lung function: mild = FEV_1 50% to 79% predicted, moderate = FEV_1 35% to 49% predicted, severe = FEV_1 < 35% predicted).
3. Setting of the study.
4. Match between strain of vaccine and infecting strains.
5. Age of participants.

Sensitivity analysis

In assessing heterogeneity, we considered possible causes associated with details of study design.

We performed sensitivity analyses using random-effects models versus a fixed-effect model to examine risk of bias and other potential confounders, and to evaluate studies published only as abstracts.

RESULTS

Description of studies

Results of the search

From searches for the original 2004 review, we included two studies (Davis 1987; Leech 1987), and in 2010, we included five additional studies (Alfageme 2006; Furumoto 2008; Steentoft 2006; Teramoto 2007 (published conference abstract); Ya Tseimakh 2006 (published conference abstract)). Through searches conducted for this 2016 review (current to 25 November 2016) (Figure 2), we identified 157 unique new citations, assessed 20 for eligibility, and added five to this review (Dransfield 2009; Kostinov 2014; Lin 2013; Trofimov 2010 (published conference abstract); Yilmaz 2013).
We have listed the reasons for exclusion of studies in the Characteristics of excluded studies table.

Included studies

For specific details of each study included in the review, see the Characteristics of included studies table.
We included in this review 12 RCTs of pneumococcal vaccines for a total of 2171 participants that provided outcome data for COPD. When studies included participants with other diagnoses, such as Furumoto 2008, we included only data for participants with COPD. Average duration of follow-up was 14 months. Two studies (Steentoft 2006; Trofimov 2010) reported follow-up for six months; three studies (Kostinov 2014; Lin 2013; Ya Tseimakh 2006) follow-up for 12 months; four studies (Furumoto 2008; Leech 1987; Teramoto 2007; Yilmaz 2013) follow-up for 24 months; two studies (Alfageme 2006; Davis 1987) follow-up for 32 months and one study (Dransfield 2009) follow-up for 48 months.

Study setting and participants

All studies were conducted in a community setting and were randomised, parallel-group trials (Table 1). Participants (n = 2171) had a diagnosis of COPD that was based on spirometric criteria (Alfageme 2006; Dransfield 2009; Kostinov 2014; Steentoft 2006);clinical or spirometric criteria (Davis 1987); a clinical diagnosis of COPD (Furumoto 2008; Lin 2013; Teramoto 2007; Ya Tseimakh 2006; Yilmaz 2013); or a diagnosis not specified

(Trofimov 2010). A common exclusion criterion was previous pneumococcal vaccination. The average age of study participants was 66 years, and the percentage of male participants was 67%(range 36% to 98%). When data could be extracted, the mean FEV_1 was 1.2 L (five studies), 54% of predicted (four studies). Information on participants' treatment with inhaled corticosteroids was available only for Dransfield 2009 (65%) and Lin 2013 (100%); in Steentoft 2006, 24% of participants were taking oral corticosteroids.

Intervention and comparison

Vaccine type

Investigators used a 23-valent pneumococcal polysaccharide vaccine in Alfageme 2006, Dransfield 2009, Kostinov 2014, Lin 2013, Steentoft 2006, Teramoto 2007, Trofimov 2010, Ya Tseimakh 2006 and Yilmaz 2013, and a 14-valent pneumococcal polysaccharide vaccine in Davis 1987, Furumoto 2008 and Leech 1987.

Treatment groups in Leech 1987 and Furumoto 2008 also received influenza vaccine.

Comparison

Control groups in Leech 1987 and Furumoto 2008 received the same influenza vaccine as the intervention group.

Control groups in Davis 1987, Lin 2013 and Yilmaz 2013 received a placebo injection.

Researchers in Alfageme 2006, Kostinov 2014, Steentoft 2006, Teramoto 2007, Trofimov 2010 and Ya Tseimakh 2006, withheld vaccine from the control group and did not administer a placebo. Dransfield 2009 used a different vaccine in the comparison group - a 7-valent diphtheria-conjugated pneumococcal polysaccharide vaccine.

In all studies, investigators administered injections subcutaneously.

Outcome measurement

Eight studies reported data on participants experiencing one or more episodes of pneumonia - but not all episodes were confirmed as due to pneumococcal infection (Alfageme 2006; Davis 1987; Dransfield 2009; Furumoto 2008; Leech 1987; Lin 2013; Steentoft 2006; Teramoto 2007). The basis for the diagnosis of pneumonia was radiological AND included clinical symptoms/signs in Alfageme 2006, Davis 1987, Leech 1987 and Steentoft 2006; was radiological OR included clinical symptoms/signs in Furumoto 2008 and Lin 2013; and was self-reported by participants in Dransfield 2009.

Excluded studies

Of 100 excluded citations, 35 were reviews/commentary articles, 41 were not of RCT design, 18 included non-COPD participants or did not provide their data separately and six provided an intervention that was not an injectable pneumococcal vaccine. Individual reasons for exclusion of studies are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

Review authors assessed the quality of the 12 studies included in the review against six criteria and provide a summary of results in Figure 3 and Figure 4.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

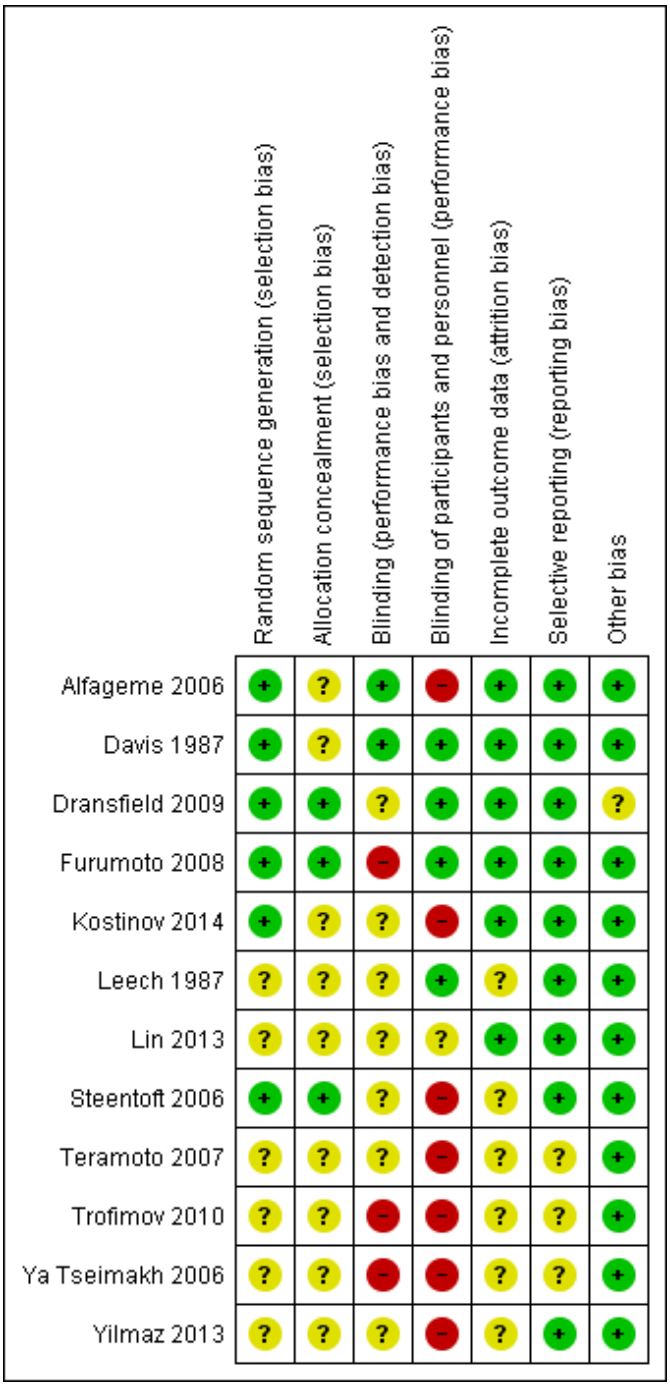
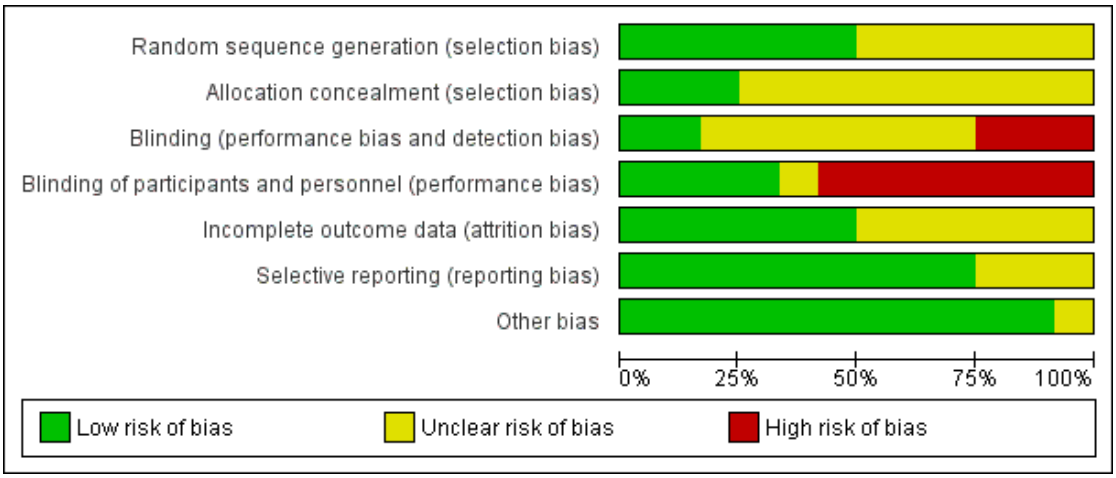


Figure 4. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Allocation generation

Overall risk of selection bias due to allocation generation was moderate. Six of the 12 studies did not report their methods for random sequence generation (Leech 1987; Lin 2013; Teramoto 2007; Trofimov 2010; Ya Tseimakh 2006; Yilmaz 2013). All of the remaining trials had low risk of bias. Methods for random sequence generation varied by study. Four studies used random number tables, one performed random number generation in blocks of 10 (Alfageme 2006) and another conducted randomisation centrally online (Dransfield 2009).

Allocation concealment

Overall risk of selection bias due to allocation concealment was moderate. However, nine of the 12 studies did not report their methods for allocation concealment (Alfageme 2006; Davis 1987; Kostinov 2014; Leech 1987; Lin 2013; Teramoto 2007; Trofimov 2010; Ya Tseimakh 2006; Yilmaz 2013). The remaining three had low risk of bias. Allocation concealment methods included third party randomisation and sequentially numbered, opaque, sealed envelopes.

Blinding

Overall risk of performance bias and detection bias was moderate, with three studies at particularly high risk of bias (Furumoto 2008; Trofimov 2010; Ya Tseimakh 2006). Two had low risk of bias (Alfageme 2006; Davis 1987), and nine could not be adequately assessed for risk.

Of the 12 studies, two were double-blind (Davis 1987; Leech 1987), three were single-blind (Alfageme 2006; Leech 1987; Yilmaz 2013), two were open-label (Dransfield 2009; Trofimov 2010) and five did not describe the use of blinding. Among double-blind trials, only Davis 1987 adequately described the method of blinding used. Of three single-blind trials, Leech 1987 blinded participants, Alfageme 2006 blinded assessors and Yilmaz 2013 did not indicate who was blinded. We could not perform sensitivity analysis for Dransfield 2009, as it was the only study that compared PPSV-23 versus PCV-7. However, sensitivity analysis for the outcome of acute COPD exacerbation for Trofimov 2010 showed little change in the direction of effect.

Six of the 12 studies (Alfageme 2006; Kostinov 2014; Steentoft 2006; Teramoto 2007; Trofimov 2010; Ya Tseimakh 2006) did not use any form of placebo; Dransfield 2009 used PCV-7 as a comparator. Sensitivity analysis for the primary outcome of pneumonia with exclusion of these studies showed a shift in effect direction, although the OR remained of no statistical significance (OR 0.78, 95% CI 0.16 to 3.68). For acute exacerbations of COPD, data showed no shift in effect direction nor in OR significance,

with a wider CI (OR 0.41, 95% CI 0.18 to 0.92). We noted similar findings for all-cause mortality (OR 0.95, 95% CI 0.48 to 1.86) and all-cause hospital admissions (OR 0.80, 95% CI 0.21 to 3.13).

Incomplete outcome data

Overall risk of attrition bias was low. Six of the 12 studies managed to adequately address incomplete outcomes, with no unequal rates across groups and with adequate reasons provided for drop-outs and losses to follow-up (Alfageme 2006; Davis 1987; Dransfield 2009; Furumoto 2008; Kostinov 2014; Lin 2013).

Selective reporting

Overall risk of reporting bias was very low. Nine of the 12 studies adequately addressed all primary and secondary outcomes (Alfageme 2006; Davis 1987; Dransfield 2009; Furumoto 2008; Kostinov 2014; Leech 1987; Lin 2013; Steentoft 2006; Yilmaz 2013).

Other potential sources of bias

Of the 12 studies, 11 did not display other types of bias (Alfageme 2006; Davis 1987; Furumoto 2008; Kostinov 2014; Leech 1987; Lin 2013; Steentoft 2006; Teramoto 2007; Trofimov 2010; Ya Tseimakh 2006; Yilmaz 2013). The only study that displayed unclear risk was Dransfield 2009. As this study relied in part on self-reported vaccination, some participants may have been misclassified as vaccine-naive or previously vaccinated; or may have been enrolled within five years after the previous vaccination dose.

Effects of interventions

See: **Summary of findings for the main comparison** Pneumoccocal vaccination to prevent pneumonia in chronic obstructive pulmonary disease?

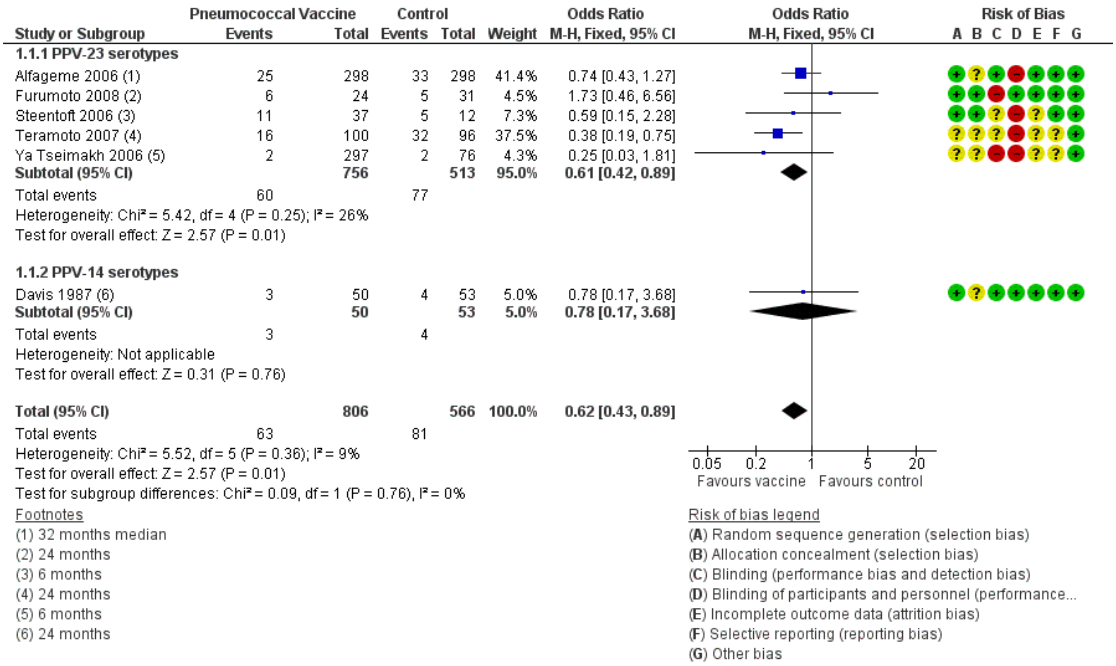
Comparison 1: pneumococcal polysaccharide vaccine, 23-valent (PPSV-23) OR 14-valent (PPV-14), versus control (11 studies; N = 2125)

Primary outcomes

Pneumonia

Analysis 1.1: likelihood of at least one episode of community-acquired pneumonia (CAP): We found six relevant studies (n = 1372) with follow-up ranging from six to 36 months. Results showed a statistically significant difference with lower likelihood for vaccine compared with control (subgrouped by vaccine number of serotypes) (OR 0.62, 95% 0.43 to 0.89) and no heterogeneity (Figure 5). Subgroup analysis of likelihood of CAP by lung function was possible only with data from Alfageme 2006 (Analysis 3.1) for participants with FEV_1 < 40% predicted at baseline (OR 0.48, 95% CI 0.23 to 1.00) and for participants with $FEV_1 \geq 40\%$ predicted (OR 1.12, 95% CI 0.50 to 2.48). A test for subgroup differences was not statistically significant: $Chi^2 = 2.36$, df = 1 (P = 0.12), $I^2 = 57.6\%$.

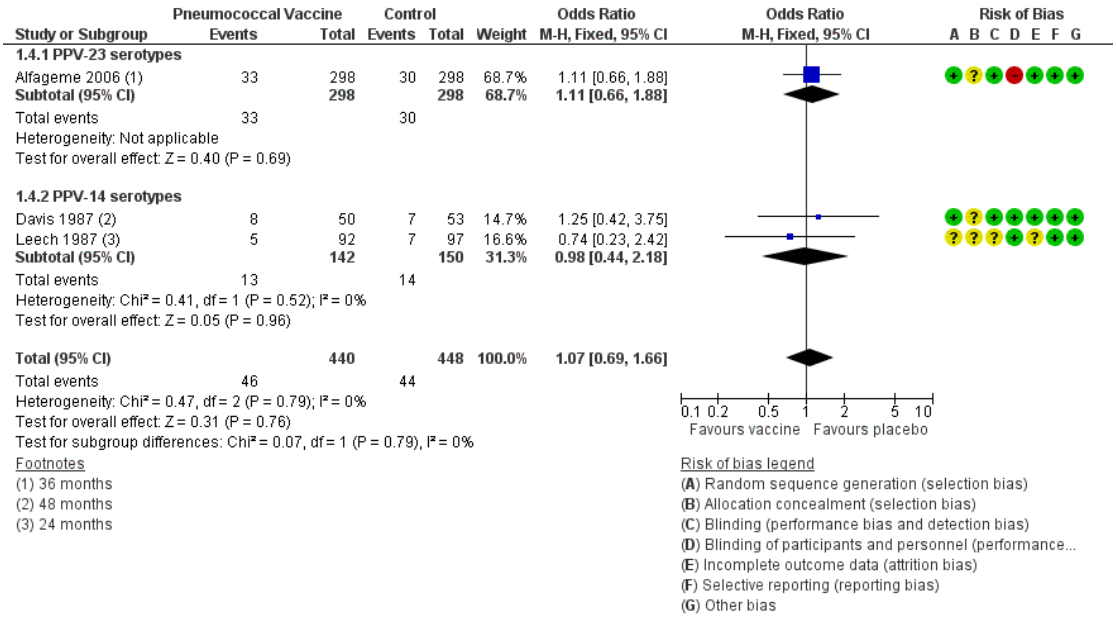
Figure 5. Forest plot of comparison: 1 Pneumococcal vaccine versus control, outcome: 1.1 Community-acquired pneumonia: at least 1 episode.



Analysis 1.2: rate of CAP per person-year: For this outcome, we found one relevant trial with 12 months of follow up (n = 36). Investigators reported no significant differences between vaccine and control groups (risk ratio (RR) 0.37, 95% CI 0.12 to 1.14).

Analysis 1.3: likelihood of at least one episode of pneumococcal pneumonia: We found three relevant trials with follow-up ranging from six to 36 months (n = 1158). Results showed no significant differences between vaccine and control groups (subgrouped by vaccine number of serotypes) (Peto OR 0.26, 95% CI 0.05 to 1.31) (Figure 6). Heterogeneity was substantial: $Chi^2 = 3.44$, df = 1 (P = 0.06), $I^2 = 71\%$; and the test for subgroup differences approached significance: $Chi^2 = 3.44$, df = 1 (P = 0.06), $I^2 = 70.9\%$.

Figure 6. Forest plot of comparison: 1 Pneumococcal vaccine versus control, outcome: 1.4 Death from cardiorespiratory causes.



Mortality

Analysis 1.4: death from cardiorespiratory causes: We found three relevant studies, with follow-up ranging from 24 to 48 months (n = 888). Results showed no significant differences in likelihood between vaccine and control groups (subgrouped by vaccine number of serotypes) (OR 1.07, 95%CI 0.69 to 1.66) (Figure 6) and no heterogeneity.

Analysis 1.5: death from all causes: We found five relevant trials with follow-up ranging from 12 to 48 months (n = 1053). Results revealed no significant differences in likelihood between vaccine and control groups (subgrouped by vaccine number of serotypes) (OR 1.00, 95% CI 0.72 to 1.40) and no heterogeneity.

Healthcare utilisation

Analysis 1.6: likelihood of at least one episode of hospital admission for any cause: We found three relevant studies with follow-up ranging from three to 12 months (n = 391). Results showed no significant differences in likelihood between vaccine and control groups (OR 0.74, 95% CI 0.32 to 1.74) and no heterogeneity. When we included the 24-month follow-up period for Yilmaz 2013, which was affected by a greater number of withdrawals (Analysis 3.2), the result was similar (OR 0.54, 95% 0.23 to 1.22).

Analysis 1.7: rate of cardiorespiratory-related hospital admissions: We found one relevant study (Leech 1987; n = 160) that reported no significant differences between vaccine and control groups for follow-up between seven and 12 months (RR 0.89, 95% CI 0.51 to 1.58) nor any differences for longer follow-up periods of 13 to 18 months and 19 to 24 months (Analysis 3.3).

Analysis 1.8: rate of all-cause hospital admissions: We found one relevant study with 12 months of follow-up (n = 36). Results showed no significant differences between vaccine and control groups (RR 0.84, 95% CI 0.26 to 2.71).

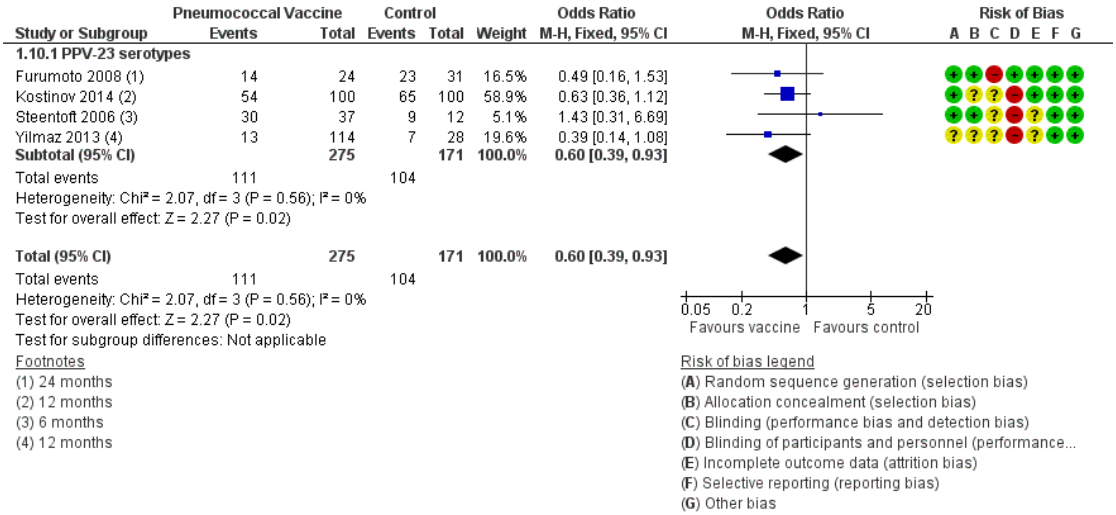
Analysis 1.9: likelihood of at least one emergency department (ED) visit for any cause: We found one relevant study (Yilmaz 2013) with follow-up between three and 12 months (n = 142). Results showed statistically significant differences, with lower likelihood for vaccine compared with control (OR 0.26, 95% CI 0.07 to 0.91); results for a long-term follow-up period of 12 to 24 months were similar (Analysis 3.4). Another single study (Leech 1987) reported ED visits due to respiratory causes, upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI) and pneumonia and described no significant differences with vaccination (Analysis 3.5).

Secondary outcomes

Analysis 1.10: likelihood of at least one episode of COPD exacerbation: For this outcome, we found four relevant studies (n = 446), with varying durations of follow-up: six months for Steentoft 2006, 12 months for Kostinov 2014 and Yilmaz 2013 and 24 months for Furumoto 2008. Results showed a statistically signifi-

cant difference with lower likelihood for vaccine than for control (OR 0.60, 95% CI 0.39 to 0.93) (Figure 7 and Figure 1), with no heterogeneity. When we used the 24-month follow-up period for Yilmaz 2013, which was affected by a greater number of withdrawals, the result was similar (Analysis 3.6) but showed greater heterogeneity (OR 0.53, 95% CI0.34 to 0.81; Chi^2 = 5.66, df = 3 (P = 0.13), I^2 = 47%).

Figure 7. Forest plot of comparison: 1 Pneumococcal vaccine versus control, outcome: 1.1 At least 1 COPD exacerbation.



Analysis 1.11: COPD exacerbations: For this outcome, we found one relevant study with six months of follow-up (n = 373). Results showed a significant difference between vaccine and control groups (mean difference (MD) -0.59 episodes, 95% CI -0.80 to -0.38). Analysis 1.12: rate of COPD exacerbations per person-year: For this outcome, we found one relevant study with 12 months of follow-up (n = 36). Results showed no significant differences between vaccine and control groups (RR 0.87, 95% CI 0.44 to 1.72).

Lung function

Analysis 1.13: FEV_1: We found one relevant study with follow-up of 24 months (n = 144). Results showed no significant differences between vaccine and control groups for measurements taken at three, 12 and 24 months.

Health-related quality of life

Analysis 1.14: St George's Respiratory Questionnaire (SGRQ) overall score: We found one relevant study with follow-up of 24 months (n = 144). Results showed no significant differences between vaccine and control groups for measurements taken at three, 12 and 24 months.

Adverse effects

No data were available for meta-analysis. Adverse effects reported after vaccination in Ya Tseimakh 2006 included erythema and induration observed in 22% and fever and headache in 5%. Leech 1987 stated that "there were no adverse reactions to pneumococcal vaccine", and study authors for Alfageme 2006 indicated that "no patient reported any local or systemic reaction to the vaccine".

Sensitivity analysis

In sensitivity analysis of the likelihood of community-acquired pneumonia with removal of studies available only as conference abstracts, and with Teramoto 2007 and Ya Tseimakh 2006 excluded, effect size was lessened and became non-significant and

heterogeneity was eliminated, although the direction of effect remained the same (OR 0.80, 95% CI 0.51 to 1.25; four studies, n = 803).

Comparison 2: 23-valent pneumococcal polysaccharide vaccine (PPV-23) versus 7-valent diphtheria-conjugated pneumococcal polysaccharide vaccine (PCV-7); (one study; N = 181)

Only one study (n = 181) compared 23-valent pneumococcal polysaccharide vaccine (PPSV-23) with 7-valent diptheria-conjugated pneumococcal polysaccharide vaccine (PCV-7) (Dransfield 2009). The follow-up period was 48 months. This study found no statistically significant differences in likelihood between the two vaccines in terms of:

1. Analysis 2.1: incidence of community-acquired pneumonia (OR 1.01, 95% CI 0.40 to 2.56);
2. Analysis 2.2: all-cause mortality (OR 1.83, 95% CI 0.5 to 6.50);
3. Analysis 2.3: hospital admission (OR 0.91, 95% CI 0.47 to 1.74); and
4. Analysis 2.4: COPD exacerbation (OR 1.07, 95% CI 0.60 to 1.91).

We assessed short-term adverse effects of vaccines by using a seven-day diary (Analysis 2.5) and noted a statistically significant difference for PPSV-23 compared with PCV-7 in the likelihood of fatigue (OR 2.40, 95% CI 1.15 to 5.00) and redness or discolouration ≤ 15 cm (OR 3.52, 95% CI 1.51 to 8.21).

We found no statistically significant differences for PPSV-23 compared with PCV-7 in the likelihood of headache (OR 1.59, 95% CI 0.61 to 4.18), fever (OR 0.66, 95% CI 0.14 to 3.10), pain (OR 1.36, 95% CI 0.66 to 2.82), localised swelling (OR 1.61, 95% CI 0.74 to 3.52), limitation in arm movement (OR 1.85, 95% CI 0.88 to 3.90) or redness or discolouration > 15 cm (OR 4.67, 95% CI 0.22 to 99.46).

DISCUSSION

Summary of main results

For this systematic review update, a total of 12 randomised controlled trials (RCTs) (2171 participants) met our inclusion criteria. These investigators reported the effects of injectable pneumococcal polysaccharide vaccines (PPVs) in 2171 participants with chronic obstructive pulmonary disease (COPD). When compared with control for the primary outcome - protection against community-acquired pneumonia (CAP) - results showed a lower likelihood with vaccine (odds ratio (OR) 0.62, 95% confidence interval (CI) 0.43 to 0.89; GRADE: moderate). The number needed to treat for an additional beneficial outcome (NNTB) to prevent one episode of CAP was 21 (95% CI 15 to 74). However, for pneumococcal pneumonia, researchers reported no significant difference with vaccination (Peto OR 0.26, 95% CI 0.05 to 1.31; GRADE: low), with only three studies (Alfageme 2006; Leech 1987; Ya Tseimakh 2006) measuring events and observing very few events. The difference in results between CAP and pneumococcal pneumonia may be related to both the paucity of events and non-detection of pneumococcus.

We found no difference in mortality from cardiorespiratory causes between vaccine and control (OR 1.07, 95% CI 0.69 to 1.66; GRADE: moderate) in three studies (Alfageme 2006; Davis 1987; Leech 1987), nor in all-cause mortality in five studies (Alfageme 2006; Davis 1987; Leech 1987; Lin 2013; Yilmaz 2013) (OR 1.00, 95% CI 0.72 to 1.40; GRADE: moderate).

The likelihood of hospital admission for any cause or for cardiorespiratory causes did not differ between vaccine and control groups; three studies reported admission for all causes (Kostinov 2014; Steentoft 2006; Yilmaz 2013) (OR 0.74, 95% CI 0.32 to 1.74; GRADE: moderate), and one study for cardiorespiratory-related causes (Leech 1987) (risk ratio (RR) 0.89, 95% CI 0.51 to 1.58; GRADE: moderate). The likelihood of an emergency department visit for any cause was lower in one study (Yilmaz 2013) for vaccine than for control (OR 0.26, 95% CI 0.07 to 0.91; GRADE: moderate).

The likelihood of a COPD exacerbation (Figure 7) was significantly reduced (OR 0.60, 95% CI 0.39 to 0.93; GRADE: moderate) in four studies (Furumoto 2008; Kostinov 2014; Steentoft 2006; Yilmaz 2013). The NNTB to prevent one episode of acute exacerbation was 8 (95% CI 5 to 58), which represents a reduction in risk from 608/1000 for control to 482/1000 for vaccination (Figure 1). Three of these studies defined exacerbations of COPD as worsening respiratory symptoms beyond normal day-to-day variation, and the basis for exacerbations was not given in Kostinov 2014, as the definition was not based on any need for additional treatment, and we were not able to classify the severity of the exacerbations. Ya Tseimakh 2006 provided no definition of an exacerbation (published abstract only) and reported a lower exacerbation rate over six months (Analysis 1.11; mean difference (MD) -0.59, 95% CI -0.80 to -0.38). The rate of exacerbation in Lin 2013 was not lower with vaccination; this study assessed the effect of vaccination on moderate exacerbations of COPD (Burge 2003), defined as the requirement for treatment with parenteral corticosteroids with or without an antibiotic (Analysis 1.12; RR 0.87, 95% CI 0.44 to 1.72).

One study (Ya Tseimakh 2006) reported local adverse effects in the vaccination group only, with erythema occurring in 22% of vaccinated participants. Another study (Alfageme 2006) found no significant difference in lung function between vaccine and control groups.

No studies provided data on days of disability from respiratory illness or cost-effectiveness of pneumococcal vaccination for meta-analyses comparing vaccine and control.

A single study (Dransfield 2009) comparing 23-valent pneumo-

coccal polysaccharide vaccine and 7-valent pneumococcal conjugate vaccine reported no differences in vaccination outcomes for CAP (OR 1.01, 95% CI 0.40 to 2.56), for mortality from all causes (OR 1.83, 95% CI 0.5 to 6.50), for hospital admission for any cause (OR 0.91, 95% CI 0.47 to 1.74) or for likelihood of experiencing a COPD exacerbation (OR 1.05, 95% CI 0.58 to 1.88). The likelihood of some mild adverse effects was higher with vaccination, with increased likelihood for PPV-23 compared with PCV-7 for fatigue (OR 2.40, 95% CI 1.15 to 5.00), local redness or discolouration $\leq$ 15 cm (OR 3.52, 95% CI 1.51 to 8.21) and limitation of arm movement (OR 1.85, 95% CI 0.88 to 3.90).

Overall completeness and applicability of evidence

Some studies described gender imbalance among participants; three studies included more than 80% male participants (Alfageme 2006; Lin 2013; Yilmaz 2013). Cigarette smoking is recognised as the single biggest risk factor in the development of COPD, and in some studies, gender imbalance reflects the imbalance among smokers or among participants treated in veterans' healthcare facilities. We examined studies for differences in baseline characteristics that might potentially confound results. Baseline forced expiratory volume in one second (FEV_1) and FEV_1/forced vital capacity (FVC) did not significantly differ across groups in all fully published studies nor in studies for which study authors supplied data. Influenza vaccination was similar in Furumoto 2008 (100% vaccination and control) and Yilmaz 2013 (62% vaccination, 52% control) - two studies that contributed to analysis of COPD exacerbations, but Kostinov 2014 and Steentoft 2006 did not report influenza vaccine status.

Treatments given in control groups varied. In Furumoto 2008 and Leech 1987, intervention groups received both a pneumococcal polysaccharide vaccine and an influenza vaccine, and the control group received only the influenza vaccine. In Alfageme 2006, Kostinov 2014, Steentoft 2006,Teramoto 2007, Trofimov 2010 and Ya Tseimakh 2006, control groups did not receive a vaccine. Analysis by severity of COPD showed no significantly different effects for risk of pneumonia for severe compared with moderate airflow limitation.

Results may be compared with those reported by RCTs that did not provide separate data for participants with COPD. In several older studies, for example, Klastersky 1986, in which participants had bronchogenic carcinoma, investigators found a small advantage for vaccination regarding likelihood of pneumococcal infection, Gaillat 1985 found a lower likelihood of pneumonia but no effect on mortality among residents living in aged-care facilities and Koivula 1997 found no reduction in pneumonia events overall but a protective effect of pneumococcal vaccination in persons at increased risk of pneumonia (age $\geq$ 70 years, heart disease, lung disease, bronchial asthma, alcoholism, institutionalised or permanently bedridden). Simberkoff 1986 showed no difference in pneumonia among high-risk participants (age > 55, chronic renal, hepatic, cardiac or pulmonary disease; alcoholism; or diabetes mellitus). Ortqvist 1998, which included 21% of participants 50 to 85 years of age with COPD, found no reduction in risk of pneumonia, pneumococcal pneumonia or mortality with vaccination compared with placebo.

A recent large study (Bonten 2015) compared 13-valent pneumococcal conjugate vaccine versus placebo in 84,496 participants over 65 years of age at 101 community-based sites in the Netherlands, where pneumococcal vaccination in older adults was not routine. Risk of CAP in the PCV-13 group compared with the placebo group was reduced by 37.7% (95% CI 14.3 to 55.1), and risk of invasive pneumococcal disease was reduced by 75.8% (95% CI 46.5 to 90.3) in modified intention-to-treat (ITT) analyses. Results are not available for participants with COPD, but overall, 12.3% of participants were current smokers, 4.9% reported a diagnosis of asthma and 25.4% had been given a diagnosis of heart disease.

A systematic review (Kew 2014) showed that people with COPD treated with inhaled corticosteroids (budesonide and fluticasone, delivered alone or in combination with a long-acting beta agonist (LABA)) had increased risk of serious pneumonia resulting in hospitalisation. In this current review of effects of pneumococcal vaccines for preventing pneumonia, only three studies reported the proportion of participants using corticosteroids; Lin 2013 indicated that 100% of participants were taking inhaled corticosteroids, Steentoft 2006 revealed that 24% used oral corticosteroids in the comparison with control and Dransfield 2009 described use of inhaled corticosteroids by 65% of participants in comparisons of PPV-23 versus PCV-7. Subgroup analyses were not possible.

Clinical guidelines provided by internationally recognised respiratory societies have advocated use of pneumococcal vaccination in patients with COPD. Guidelines from the UK National Institute of Clinical Excellence (NICE) state that "pneumococcal vaccination and an annual influenza vaccination should be offered to all patients with COPD as recommended by the Chief Medical Officer" (NICE 2004). COPDX guidelines for Australia and New Zealand state that "pneumococcal immunisation (polyvalent covering 23 virulent serotypes) is recommended in people with COPD", and evidence for this recommendation is graded at level II (COPDX 2016). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines published jointly by the National Heart Lung and Blood Institute in the USA and the World Health Organization (WHO) advise that "pneumococcal vaccination should be offered to every COPD patient; vaccine appears to be more effective in older patients and those with more severe disease or cardiac comorbidity" (GOLD 2016).

The WHO (WHO 2012) has made recommendations for use of pneumococcal vaccines in children, which are influencing pneumococcal disease, carriage and herd protection. Pneumococcal conjugated vaccines PCV-10 and PCV-13 are licensed for prevention of invasive disease, pneumonia and acute otitis media caused

by respective vaccine serotypes in children from six weeks to five years of age, with high vaccine efficacy. The WHO recommends that inclusion of PCVs be given priority in childhood immunisation programmes worldwide, especially in countries with under-five-mortality of > 50/1000 live births. Although herd effects of immunisation in children have reduced invasive pneumococcal disease (IPD), it is recommended that adults over 65 should be immunised.

The studies included in this review reported a low frequency of proven pneumococcal pneumonia; thus we acknowledge the possibility of a type 2 error, given the rare events reported. Investigators have found that the overall contribution of pneumococcal pneumonia to overall CAP varies (Rodrigo 2015); between 2008 and 2013, rates of 17.1% to 37.3% were reported.

A recent systematic review aimed to determine the incidence and burden of vaccine-preventable pneumococcal disease in the adult population in the UK (Chalmers 2016). This study found a high burden of pneumococcal disease among adults, along with substantial ongoing changes in the epidemiology of pneumococcal disease. Among those > 65 years of age, the incidence of IPD in 2013-2014 was 20.58 per 100,000 population. However, the incidence of PCV13 serotype IPD among people > 65 years of age was 10.33 per 100,000 population from 2008 to 2010, and fell to 3.72 per 100,000 in 2013-2014. In this population, PCV-7 serotypes were reduced from 4.58 per 100,000 in 2008 to 2010 to 0.53 per 100,000 population in 2013-2014.

Quality of the evidence

We graded evidence showing beneficial effects on CAP (OR 0.62, 95% 0.43 to 0.89) and effects on mortality estimates (OR 1.07, 95% CI 0.69 to 1.66 for cardiorespiratory causes; OR 1.00, 95% CI 0.72 to 1.40 for all-cause mortality) as having moderate quality. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different. We graded evidence for the unchanged likelihood of hospital admission for any cause (OR 0.74, 95% CI 0.32 to 1.74) as having moderate quality. We graded the quality of evidence for the lower likelihood of an acute exacerbation of COPD (OR 0.25, 95% CI 0.16 to 0.38) as moderate; lack of participant and/or personnel blinding may have led to better general care and treatment for patients with COPD in the vaccinated group.

Potential biases in the review process

Methodological limitations

Twelve studies involving 2171 participants contributed data to this review. At the review level, we believe incomplete identification of studies was not an issue, and we found no evidence of publication bias. The average number of participants per study was 187, although individual studies reported from 36 to 600 participants; these relatively low numbers are probably too small, given the incidence of pneumococcal infection among study populations. It is likely that larger studies with participant numbers of around 1000 would be needed to demonstrate statistically significant effects.

Agreements and disagreements with other studies or reviews

A systematic review current to June 2012 (Moberley 2013) assessed the efficacy and effectiveness of PPVs in preventing pneumococcal disease or death among adults. In 18 RCTs involving 64,852 participants, investigators provided strong evidence of PPV efficacy against IPD (OR 0.26, 95% CI 0.14 to 0.45). They found efficacy against all-cause pneumonia in low-income (OR 0.54, 95% CI 0.43 to 0.67) but not in high-income countries among the general population (OR 0.71, 95% CI 0.45 to 1.12) and among adults with chronic illness (OR 0.93, 95% CI 0.73 to 1.19). Study authors noted that vaccine efficacy against primary outcomes appeared poorer among adults with chronic illness, but small number of identified studies limited power to detect significant effects. This review also found no significant change in all-cause mortality (OR 0.90, 95% CI 0.74 to 1.09).

Review authors have assessed evidence for effectiveness of pneumococcal vaccine in other chronic respiratory conditions; a systematic review of children and adults with bronchiectasis, current to November 2008, identified no eligible RCTs (Chang 2009). A systematic review, current to May 2014, conducted to assess the efficacy of pneumococcal vaccines in reducing morbidity among people with cystic fibrosis, also identified no relevant trials (Burgess 2014). A systematic review of the efficacy of pneumococcal vaccine in reducing mortality or morbidity from pneumococcal disease among patients with asthma (Sheikh 2002) found no evidence of effects on acute asthma exacerbations.

Studies using a retrospective, case-control design that often included people with chronic lung conditions showed the efficacy of pneumococcal vaccination to be approximately 50% to 80% against invasive pneumococcal disease in high-risk populations (Fedson 1994; Leophonte 2001). Prospective cohort studies have generally failed to show reductions in the risk of non-bacteraemic infection, although Alfageme 2006 and Jackson 2003 demonstrated protection against bacteraemia. Regardless of design, most studies have found that the protective efficacy of vaccination is uniformly diminished in elderly and immunocompromised individuals. Although cohort studies are potentially easier to conduct logistically (Hak 2006), evidence from these studies is subject to limitations in generalisability (Hak 2006) and in interpretation (Jackson 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-quality evidence derived from RCTs included in this review suggests that injectable polyvalent pneumococcal vaccines provide protection against community-acquired pneumonia and reduce the likelihood of exacerbations of chronic obstructive pulmonary disease (COPD). Evidence was insufficient for comparisons of different pneumococcal vaccine types. Evidence in this review supports pneumococcal vaccination for people with COPD, as recommended by respiratory guidelines.

Implications for research

Pneumococcal immunisation among children and older adults in many countries has reduced the incidence and changed the epidemiology of pneumococcal disease. Future randomised controlled trials restricted to people with COPD will be difficult to conduct with adequate power to detect significant effects, especially for rare events such as confirmed pneumococcal pneumonia.

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Robert Granger, an author of the original review published in 2004, contributed to study selection; data extraction/entry, analysis and interpretation; and writing of the final review. Sabin Smith, an author on the review in 2009, contributed to study selection; data extraction/entry, analysis and interpretation; and drafting of the final review.

Chris J Cates was the Contact Editor for this review and commented critically on it.

The Background and Methods sections of this review are based on a standard template used by the Cochrane Airways Review Group.

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REFERENCES

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alfageme 2006

Methods	Setting of study: population-based intervention Study design: RCT parallel Type of analysis: case available
Participants	Total number of participants: 600 (4 lost to follow-up; 2 from each group) Gender distribution: vaccine group M = 96.6%; control group M = 93.3% Mean age (years): vaccine group = 69; control group = 68 Age range: vaccine group = 62 to 73; control group = 61 to 73 Inclusion criterion: spirometric diagnosis of COPD Exclusion criteria: prior pneumococcal vaccination, pregnant, immunosuppressed, known neoplasia, renal insufficiency in dialysis, HIV infection, hypogammaglobulinaemia, anatomical and/or functional asplenia Diagnostic criteria (COPD): SEPAR criteria (Sociedad Espanola de Patologia Respiratoria, or Spanish Society of Respiratory Pathology), FEV_1 < 80% and FEV_1/FVC < 70%; severity of COPD: vaccine group FEV_1 < 40% = 132; ≥ 40% = 166; control group FEV_1 < 40% = 114; ≥ 40% = 184 Current smokers: vaccine group = 22%; control group = 26% Diagnostic criteria (pneumonia): clinical symptoms (lower respiratory tract infection with fever) and imaging findings (new infiltrate typical of pneumonia, which decreases during follow-up). Pneumococcal pneumonia diagnosed with isolated *S pneumoniae* in blood, pleural fluid or bronchial samples. Microbiological diagnosis (pneumococcus): presence of pneumonia and isolation of *S pneumoniae* from sputum, broncho-aspirate, blood, pleural fluid or CSF
Interventions	Vaccine type: 23-valent pneumococcal capsular polysaccharide Numbers in each group: intervention = 298; control (no intervention) = 298 Dose: 0.5 mL Pneumo-23, Sanofi-Pasteur MSD Delivery: subcutaneous injection in deltoid muscle Cointerventions: none Comparison: no vaccine Duration of study: vaccine group, median 980 days (range 20 to 1454); control group, median 978 days (range 21 to 1183)
Outcomes	Types of outcomes measured: - Acute exacerbations: definition: (1) increased dyspnoea, (2) increased sputum volume and (3) increased sputum purulence and (4) absence of newly appeared infiltration on a chest radiograph; 2 of the 3 respiratory symptoms present, or 1 of these and 1 additional symptom, such as fever with no other causes or increased cough; I = 30, C = 9 - Pneumonia: definition: clinical symptoms (cough, sputum or fever) plus increased white blood cell count or serum C-reactive protein and appearance of a new infiltration on chest radiograph; pneumonia-free survival plot, log rank = 1.15, P = 0.28 (NS)) - Number of hospital admissions (yes, all causes): I = 18, C = 6 - Change in lung function: reported, but data cannot be used

Alfageme 2006 (*Continued*)

	- All-cause mortality in year post vaccination: no	
Notes	C = control, I = intervention	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation code developed with a computer random number generator in block lengths of 20 (10 in each group)
Allocation concealment (selection bias)	Unclear risk	"They were then randomly assigned to the intervention group" Not stated if allocation was performed centrally or with the use of sealed opaque envelopes
Blinding (performance bias and detection bias) Assessors	Low risk	"The vaccination status of the patient was kept in a specific encrypted database and was not stated in the patients' clinical records. The main investigator of this study (IA) was the only person with access to this database, but this investigator did not participate in the follow-up or in adjudicating the outcome events. This task was performed by the physicians conducting the follow-up, who were unaware of the treatment group allocation of their patients. These investigators were committed not to ask patients about their vaccination status. "
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding measures used in the study "A considerable limitation of this study is the lack of a blind placebo comparison group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four patients (2 from each arm of the study) were lost to follow-up and were excluded from final analyses A minimum follow-up period of 3 years was given for each participant, except 115, who died before the end of follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it appears that published reports include the prespecified outcomes

Alfageme 2006 (*Continued*)

Other bias	Low risk	No other issues were noted.

Davis 1987

Methods	Study design: randomised, double-blind, placebo-controlled trial Method of randomisation: random number table. Participants studied for 1 to 48 months of treatment Study outcomes assessed by person blinded to Tx allocation? yes
Participants	Total number of participants: 103 Gender distribution: not stated Mean age (years): intervention group = 64 ± 10, control group = 61 ± 10 Age range: not stated Inclusion criterion: COPD (assessed by clinical and pulmonary function criteria) Exclusion criteria: - Reversible airflow obstruction in the absence of chronic bronchitis (cough 3 of 12 months for 3 consecutive years) or emphysema as judged clinically, radiologically and by lung function testing - Malignant neoplasms - Sickle cell disease - Severe renal impairment - Severe hepatic impairment Diagnostic criteria (COPD): ATS standards Severity of COPD: active: FEV_1 (L) = 1.33 ± 0.61; FEV_1/FVC = 52 ± 13; placebo: FEV_1 (L) = 1.47 ± 0.75; FEV_1/FVC = 55 ± 14 Smoking status: active: current = 53%, never n = 5; placebo: current = 33%, never n = 5 Diagnostic criteria (pneumonia): clinical and imaging findings in the presence of pneumococcus in sputum Etiological diagnosis (pneumococcus): diagnosis only if pathogens isolated from blood or body fluids. Processed < 6 hours after collection Microbiological methods described Baseline characteristics (smoking status): - Current smokers: PLA: 27/53; VAX: 17/50 (P = 0.036 for difference); non-smokers: PLA: 5; VAX: 5
Interventions	Vaccine type: 14 pneumococcal capsular polysaccharide antigens Number in each group: intervention = 50; placebo = 53 Dose: 0.5 mL (50 mcg of each of the 14 capsular antigens) Delivery: subcutaneous injection Cointerventions: none Comparison: saline Duration of study: 24 to 32 months Participants followed up for 48 months (mean follow-up in each arm: PLA: 32.2 months; VAX: 31.7 months)
Outcomes	Incidence of pneumonia: community-acquired pneumonia and putative pneumococcal pneumonia: clinical and imaging findings in the presence of pneumococcus in sputum Pneumonia-free survival plots: no hazard ratio, P = 0.249

Davis 1987 (*Continued*)

	All-cause mortality survival plots: no hazard ratio, P = 0.718 Antibody titers: not analysed Sputum flora: not analysed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study participants arranged in a double-blind manner on the basis of a table of random numbers to a group receiving placebo or to a group receiving vaccine
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Assessors	Low risk	Double-blind study; study outcomes assessed by person blinded to Tx allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study; placebo injection given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of withdrawals/losses to follow-up similar in both groups
Selective reporting (reporting bias)	Low risk	Protocol not available but all outcomes specified in methods are reported
Other bias	Low risk	None noted

Dransfield 2009

Methods	Design: randomised controlled trial, parallel group Setting: NHLBI COPD Clinical Research Network; 10 centres, USA Comments: study registered online (NCT00457977) and completed in May 2011 Author's name: Mark T. Dransfield Institution: National Heart, Lung and Blood Institute Email: mdransfield99@msn.com Address: University of Alabama at Birmingham and the Birmingham VA Medical Center, 422 THT, 1900 University Blvd, Birmingham, AL 35294, USA Follow-up: 48 months
Participants	Inclusion criteria: - > 40 yo male and female - ≥ 10 pack-year cigarette smoking history

	- Clinical diagnosis of moderate to very severe COPD (defined as FEV_1/FVC < 70% and FEV_1 < 70% predicted) - Never received PPSV-23 OR did not receive PPSV-23 during the 5 years before randomisation Exclusion criteria: - Diagnosis of asthma - Sensitivity to pneumococcal vaccination - Bleeding disorder, chronic anticoagulation or the presence of conditions known to impair pneumococcal vaccine response - Acute illness requiring antibiotics or steroids within the past month or not expected to survive 12 months N = 181; PPSV-23 n = 90, PCV-7 n = 91 No statistically significant differences between pretreatment groups was reported Age, years (%): 64 (10); 63 (9) FEV_1 (% predicted): 44.8 (15); 44.9 (15) ICS use %: 64; 66 Current smoker %: 36; 36 Pack-years of smoking: 55 (27); 52 (28) Male %: 37; 38 LTOT %: 32; 23 Previous pneumonia %: 45; 44 Hospitalisation or unscheduled emergency visit (≤ 1 year before enrolment) %: 11; 18 Received systemic steroids and/or antibiotics %: 34; 38 Vaccine naive %: 42; 45 Years since last vaccination %: 8.4 ± 3.5; 7.6 ± 2.7
Interventions	23-Valent pneumococcal polysaccharide vaccine (PPV-23) 0.5 mL intramuscular 7-Valent diphtheria-conjugated pneumococcal polysaccharide vaccine (PCV-7) 1.0 mL intramuscular
Outcomes	Vaccine responsiveness: antibody levels (IgG) not included in meta-analysis Acute exacerbation COPD - Pneumonia: self-reported by participants; no diagnostic criteria described - Hospitalisation - Fatigue - Headache - Limitation of arm movement - Redness or discolouration ≤ 15 cm - Redness or discolouration > 15 cm - Localised swelling
Notes	Sponsorship source: 639191; National Heart, Lung and Blood Institute of the National Institutes of Health (U10 HL074441, U10 HL074418, U10 HL074428, U10HL074409, U10 HL074407, U10 HL074422, U10 HL074416, U10 HL074408, U10 HL074439, U10 HL074431, U10 HL074424)

Risk of bias

Bias	Authors' judgement	Support for judgement

Dransfield 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation was performed after linking to the clinical trial co-ordinating centre website and stratified by study centre
Allocation concealment (selection bias)	Low risk	Independent third party allocation. Randomisation was performed after linking to the clinical trial co-ordinating centre website and stratified by study centre
Blinding (performance bias and detection bias) Assessors	Unclear risk	Open-label trial with no blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded, PPV group received influenza, control group received only influenza. Lack of blinding was not likely to affect measurement of dichotomous outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Approximately 15% of people in both groups were lost to follow up and exited the study early. Reasons for withdrawal were given
Selective reporting (reporting bias)	Low risk	All outcomes reported in methods and trial registration are available in publications
Other bias	Unclear risk	Trial relied in part on self-reported vaccination; some participants may have been misclassified as vaccine naive or previously vaccinated, or may have been enrolled < 5 years after previous PPSV-23

Furumoto 2008

Methods	Study design: parallel-group randomised controlled trial Location, number of centres: 13 hospitals in the district of Kyushu and Okinawa, Japan Duration of study: 2 years (November 2001 to April 2002)
Participants	Number screened: ≥ 383 potentially eligible patients with CLD contacted by researchers Number randomised: 191 (55 with COPD) Number completed: 167; intervention group n = 87, control group n = 80 Gender distribution: intervention = 69% male; control = 57.5% male Mean age (years): intervention = 67.8 (SD 9); control 70.1 (SD 9.5) Inclusion criteria: - Patients with chronic lung disease (CLD) who previously experienced acute exacerbations and were able to comply with a schedule of monthly clinical visits - Between 40 and 80 years of age

	- Investigators selected participants. No diagnostic criteria for COPD were given Exclusion criteria: - Patients who were pregnant or were immunocompromised, with conditions such as active malignant disease, renal insufficiency in dialysis or HIV infection, hypogammaglobulinaemia or anatomical or functional asplenia, who had previously received 23-valent PV (Pneumovax, Banyu, Japan) Baseline details: Participants with CLD included 55 with COPD (24 PV + IV, 31 IV), 50 with sequelae of pulmonary TB (33 PV + IV, 17 IV), 62 with other CLD (bronchiectasis 20, asthma 13, pneumoconiosis 14, interstitial pneumonia 9, diffuse panbronchiolitis 5, sarcoid 1) (30 PV + IV, 32 IV)
Interventions	Vaccine type: intervention pneumococcal polysaccharide vaccine (PV) and a trivalent, split virion, influenza vaccine (IV) containing A/NewCaledonia/20/99H1N1, A/Panama/2007/99H3N2 and B/Johannesburg/5/99 for the 2001/2002 season; for the 2002/2003 season, a vaccine containing A/NewCaledonia/20/99H1N1, A/Panama/2007/99H3N2 and B/Guangdong/7/97 Control: a trivalent, split virion, influenza vaccine containing A/NewCaledonia/20/99H1N1, A/Panama/2007/99H3N2 and B/Johannesburg/5/99 for the 2001/2002 season; for the 2002/2003 season, a vaccine containing A/NewCaledonia/20/99H1N1, A/Panama/2007/99H3N2 and B/Guangdong/7/97 but no PV
Outcomes	Primary outcomes: - Time to first episode of pneumonia or to acute exacerbation (AE) after enrolment in the study: data not available for participants with COPD only - Pneumonia: diagnostic criteria: clinical symptoms (cough, sputum or fever) plus increased WBC count or increased C-reactive protein or appearance of new infiltration on CXR; data available for participants with COPD - Exacerbations: definition: 2 or 3 of increased dyspnoea, increased sputum volume, increased sputum purulence plus absence of new infiltration on CXR, or 1 of these symptoms and 1 additional symptom plus absence of new infiltration on CXR; data available for participants with COPD. Kaplan-Meier survival curves for infectious acute exacerbation demonstrated a significant difference between the 2 groups (P = 0.041) - Infectious acute exacerbation: defined by increase in WBC count or increased C-reactive protein. Pneumoccal AE: defined as isolating sputum *S pneumoniae*. Participants examined monthly by study investigators. Asked to visit study hospital at any onset fever, cough or sputum, or if experiencing breathlessness during 2-year period; data available for participants with COPD Secondary outcomes: - Mortality data not available for participants with COPD alone
Notes	Data included only for participants with COPD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in equal proportions to either group

Furumoto 2008 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes were held by study administrators
Blinding (performance bias and detection bias) Assessors	High risk	No attempt was made to blind clinical assessors to vaccine allocation in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not blinded; PPV group received influenza, and control group only received influenza. Lack of blinding was not likely to affect measurement of dichotomous outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	During 2-year follow-up period, 2 and 11 participants were lost from the PV + IV and IV groups, respectively. In addition, early termination of follow-up occurred for 5 participants from the PV + IV group and for 6 participants from the IV group because they wanted to withdraw from the study. Subsequently, 87 participants in the PV + IV group and 80 in the IV group completed the analysis
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it appears that published reports included prespecified outcomes
Other bias	Low risk	None noted

Kostinov 2014

Methods	Sponsorship source: not stated Country: Russia Setting: 2 centres: Mechnikov Research Institute of Vaccines and Sera, Ministry of Health Omsk; Polyclinic Tyumen Authors' names: Kostinov MP, Ryzhov AA, Magarshak OO, Zhirova SN, Protasov AD, Erofeev YUV, Miunova OV, TOlokonnikova IN, Liverko EV Institution: Mechnikov Research Institute of Vaccines and Sera, Moscow
Participants	Design: randomised controlled trial, parallel group Follow-up: 12 months Inclusion criteria: - Participants 30 to 55 years of age - Diagnosis of COPD according to GOLD 2011 - on the basis of patient history, complaints: cough, sputum production, shortness of breath worsening on exercising - All patients had undergone spirometry and bronchodilator reversibility testing (400 mcg of salbutamol).

Kostinov 2014 (*Continued*)

	- FEV_1 reversibility < 12% (or < 200 mL), ratio FEV_1/FVC < 70% Exclusion criteria: - Age < 30, > 50 - Pneumococcal vaccination over past 3 years - Acute infection (TB, active phase of chronic viral hepatitis), mental disorders, renal or hepatic insufficiency, neoplastic disease, chronic disease in exacerbations, hypersensitivity to vaccine components, severe complications of prior vaccinations, pregnancy, autoimmune disease Groups: PPSV-23 n = 100; no vaccine n = 100 Age (years): 30 to 50 FEV_1 % predicted: not known ICS use %: not known Current smoker %: not known Pack-years of smoking: not known Male: 41 (41%); 31 (31%) LTOT: not known Previous pneumonia: not known Hospitalisation or unscheduled emergency visit (≤ 1 year before enrolment): 16; 6
Interventions	Vaccine Pneumo-23 (Sanofi, France), intramuscular 0.5 mL, once after signing of informed consent
Outcomes	Acute exacerbation COPD Hospitalisation
Notes	Publication in Russian. Liliya Eugenevna Ziganshina

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were randomised into groups with the use of the method of serial (sequential) numbers" in translated text
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Assessors	Unclear risk	No information provided, no reference to blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No reference to blinding but no placebo given in control group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants randomised to treatment and number of participants analysed the same; no withdrawals reported

Kostinov 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	Results for all outcome measures were reported.
Other bias	Low risk	No issues of concern in translation of paper

Leech 1987

Methods	Setting: Montreal Chest Hospital (stable ambulatory population) Study design: randomised, double-blind, placebo-controlled trial Type of analysis: case available Follow-up: 24 months
Participants	Total number of participants: 189 Gender distribution (male): vaccine = 66; placebo = 69 Mean age of participants (years): vaccine = 66 ± 9; placebo = 67 ± 9 Age range (years): 40 to 89 Inclusion criterion for active group: patients seen in outpatient clinic who had COPD (FEV_1 < 1.5 L) Exclusion criteria: previous pneumococcal vaccination, asthma, cystic fibrosis or bronchiectasis Diagnostic criteria (COPD): not stated, other than prior diagnosis of COPD by physician Severity of COPD: vaccine group (mean) FEV_1 = 0.94 L; FVC = 2.18 L/s; placebo group (mean) FEV_1 = 0.96 L; FVC = 2.13 L/s Microbiological diagnosis (pneumococcus): not stated, although sputum cultured in 10% of participants N = 189 (VAX: 92; PLA: 97) Gender distribution: PLA = 69 M; VAX = 66 M Mean age: PLA = 67 (SD 9); VAX = 66 (SD 9); FEV_1 (L): PLA = 0.96 (SD 0.30); VAX = 0.94 (SD 0.26); FVC: PLA = 2.13 (SD 0.64); VAX = 2.18 (SD 0.58)
Interventions	Vaccine types: 14-valent pneumococcal polysaccharide (in 1 arm) and influenza vaccination (in the other arm) Numbers in each group: intervention = 92; placebo = 97 Dose: not stated Delivery: injection Cointerventions: none Comparison: saline (in 1 arm) and influenza vaccination (in the other arm) Follow-up points: 6-month intervals Duration of study: 2 years Influenza vaccination (given at baseline, end of years 1 and 2, unless previous adverse reaction or declined)
Outcomes	Incidence of pneumonia: diagnostic criteria (pneumococcal pneumonia): pneumonia defined as symptoms of lower respiratory tract infection (fever, increased cough and change in colour or increase in quantity of sputum) and evidence of new infiltrate on chest x-ray Upper respiratory tract infection (URTI): definition: symptoms of sore throat, runny nose, fever and increased cough without increase in quantity or change in colour of

	sputum Mortality (all-cause) Hospital admission (all-cause); length of hospital stay; emergency visits (all causes); hospital admissions, emergency visits to clinic or emergency department assessed by participant/family interview and chart review Adverse events (pneumococcal sepsis)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Makes reference to study participants "randomly assigned" to control or intervention group; however, does not make reference to method of sequence generation Participants stratified by age and FEV_1
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Assessors	Unclear risk	Described as double-blind study but no information on blinding of assessors given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study with placebo injection given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"A total of 23 patients (12%) could not be traced for follow-up and were not included in the analysis of death rates. At each follow-up interview some patients refused to answer questions and were not included in the analysis of hospital admissions and emergency visits. 59% followed up at 24 months"
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it appears that published reports include prespecified outcomes
Other bias	Low risk	No other issues identified

Lin 2013

Methods	Sponsorship source: not declared in trial registration Country: Taiwan (from March 2009 to May 2010) Setting: outpatient department of tertiary medical centre, Chest Division, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan Authors' names: Ming-Tzer Lin[1,2,3], Shih-Lung Cheng[4] Institution: Far Eastern Memorial Hospital, Taipei City, Taiwan Email: lightpool2010@gmail.com Addresses: Department of Internal Medicine, Hsiao Chung-Cheng Hospital; Department of Internal Medicine, National Taiwan University Hospital; Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University Design: randomised controlled trial, parallel group
Participants	Inclusion criterion: - Diagnosis COPD (FEV_1/FVC < 70% with exposure to smoking) with high daily dose of ICS (beclometasone equivalent dose > 1000 mcg/d) Exclusion criterion: - Received PPSV-23 in recent 5 years or immunosuppressed status Group differences: Demographic data were compatible between groups, except PPSV-23 group had higher number of previous pneumonia episodes than control group (P = 0.038) PPSV-23 n = 19, placebo n = 17 Age (years): 68.9 (9.2); 72.8 (6.7) FEV_1 % predicted: 43.1 (12.3); 46.5 (11.1) ICS use %: 100% 2000 mcg BDP (1250 to 2000); 100% 1500 mcg BDP (1250 to 2000) Current smoker %: 10 (52%) ; 4 (24%) Pack-years smoking: 57.8 (32.1); 62.7 (32.8) Male: 18 (95%); 14 (82%) Long-term oxygen therapy: 3 (16%); 3 (18%) Previous pneumonia in past 1 year: 0; 0 Hospitalisation or unscheduled emergency visit (≤ 1 year before enrolment): 1 (0 to 3) ; 1 (0 to 2) Received systemic steroids and/or antibiotics: NA; NA Vaccine naïve: NA; NA Years since last vaccination: > 5: > 5
Interventions	PPSV-2323-Valent pneumococcal polysaccharide vaccine 0.5 mL subcutaneously Placebo normal saline 0.5 mL subcutaneously
Outcomes	Acute exacerbation COPD (person-years). Moderate exacerbation defined as an exacerbation treated with parenteral corticosteroids with or without an antibiotic Pneumonia in person-years. Pneumonia was diagnosed according to primary clinician's judgement Hospitalisation in person-years Death Change in lung function (postbronchodilator FEV_1, FVC) listed in trial registration but not reported in conference presentation

Lin 2013 (*Continued*)

Notes	Data supplied as conference presentation ClinicalTrials.gov Identifier: sponsor: NCT01381367 Far Eastern Memorial Hospital: first received: 16 February 2009 Information provided by Far Eastern Memorial Hospital Last updated: June 24, 2011; last verified: June 2011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as double-blinded, randomised controlled trial. Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Described as double-blinded, randomised controlled trial. Allocation after enrolment, method not reported
Blinding (performance bias and detection bias) Assessors	Unclear risk	Described as double-blinded. Placebo used in control group. No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded. Placebo used in control group. No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 patients recruited: 19 PPSV-23/17 placebo. Outcome data for all participants reported
Selective reporting (reporting bias)	Low risk	All primary and important secondary outcomes listed in trial registration were available in poster report. Lung function not reported
Other bias	Low risk	Study not fully published, but poster presentation includes study methods and results. No other issues noted

Steentoft 2006

Methods	Setting of study: hospital-based Study design: RCT parallel: 1 control group with 3 levels of steroid load, block-randomised to vaccine or to no vaccine Type of analysis: case available

Steentoft 2006 (*Continued*)

Participants	Total number of participants: 49 Gender distribution: M = 27; F = 22 Mean age: control: 67.5 years Intervention: 65, 72 and 71 years for the 3 groups Age range (years): 47 to 86 Inclusion criterion: COPD Diagnostic criteria (COPD): COPD defined by GOLD guidelines (FEV_1/FVC < 70%, FEV_1 reversibility-test < 200 mL) Exclusion criterion: prior pneumococcal vaccine Severity of COPD at baseline: - Control: FEV_1% = 50.2 - Intervention: FEV_1% = 48.2, 46.0 and 44.2 for the 3 groups Smoking status: - Active: current = 46%, past = 54% - Placebo: current = 58%, past = 42% Diagnostic criterion (pneumonia): radiologically verified, but no other criteria stated Etiological diagnosis (pneumococcus): not described
Interventions	Vaccine type: 23-polyvalent pneumococcal vaccine Numbers in each group: - Intervention = 37 - Placebo = 12 Dose: 0.5 mL Delivery: subcutaneous injection Cointerventions: - Three groups with various exposure patterns to oral prednisolone * No steroids 3 months before vaccination, then steroids for 4 weeks after vaccination * Long-term steroid treatment, before and after vaccination * Vaccination after 4 weeks with steroid treatment, then no steroids after vaccination Groups 1 and 3 above received 37.5 mg starting dose of prednisolone, tapered to 0 during respective time frames Comparison: no vaccine Duration of study: 6 months
Outcomes	Types of outcomes measured: - Acute exacerbations (definition: incidents with fever and expectoration) - Pneumonia (definition: radiologically verified pneumonia) - Number of hospital admissions (all-cause) - Improvement/worsening in lung function (reported, not analysed) - Extra prednisone use: not analysed - Extra beta agonist use: not analysed - Antibiotics: not analysed - Antibody titres post vaccination- not analysed
Notes	

Risk of bias

Steentoft 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were block-randomised to vaccine or no vaccine.
Allocation concealment (selection bias)	Low risk	Third party held randomisation schedule.
Blinding (performance bias and detection bias) Assessors	Unclear risk	Not stated for clinical diagnoses if outcomes assessed by person blinded to Tx allocation. Laboratory staff assessing antibody levels were blinded to allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo injection given in control group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data on withdrawals given
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it appears that published reports include prespecified outcomes
Other bias	Low risk	None noted

Teramoto 2007

Methods	Study design: parallel-group randomised controlled trial Setting: Toyko, Japan Duration of study: 2 years No funding declared
Participants	Number screened: not available Number randomised: 196 Number completed: unclear Gender distribution: not reported Mean age and range (years): 77.8 (75.1 to 80.5) Inclusion criteria: elderly patients with COPD, diagnostic criteria not stated Exclusion criteria: not reported
Interventions	Intervention: 23-valent pneumococcal polysaccharide vaccine Control: no vaccination Cointerventions: none Treatment period: single PPV vaccination administered to intervention group Follow-up period: 2 years

Teramoto 2007 (*Continued*)

Outcomes	Pneumonia: definition: radiographically proven community-acquired pneumonia of pneumococcal or unknown aetiology. Survival plot for community acquired pneumonia: no significant difference reported
Notes	Study available only as abstract publication. Study author contacted for details of study and outcome data 25/09/09, but no response received by 01/03/10

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of allocation sequence generation method, although study described as randomised
Allocation concealment (selection bias)	Unclear risk	No description of method used
Blinding (performance bias and detection bias) Assessors	Unclear risk	No mention regarding blinding of assessors
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo injection given in control group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on withdrawals after randomisation
Selective reporting (reporting bias)	Unclear risk	One outcome reported in abstract. Other data not published yet
Other bias	Low risk	None noted

Trofimov 2010

Methods	Sponsorship source: not known Country: Russia Setting: St Petersburg State Medical University Author's name: Tromifov VI Institution: ZH, Mikrobiol, Moscow Design: randomised controlled trial, parallel group
Participants	Inclusion criteria for types of participants recruited into the study were not reported Exclusion criteria for types of participants recruited into the study were not reported Group differences: groups comparable by age, sex, history and lung function PPSV-23 n = 20: control n = 25 Male: 14/20 (70%); 16/25 (64%) Age (years): 56.38 (2.78); 52.75 (2.48)

Trofimov 2010 (*Continued*)

	FEV_1 % predicted: 55.8 (2.8); 67.7 (3.1) ICS use %: not known Current smoker %: not known LTOT: not known Previous pneumonia: not known Hospitalisation or unscheduled emergency visit (≤ 1 year before enrolment): not known Received systemic steroids and/or antibiotics: not known Vaccine naive: not known Years since last vaccination: not known Pack-years of smoking: not known
Interventions	PPSV-23: Vaccine Pneumo-23 Injectable, route of delivery not reported, dosage not reported Control: standard treatment
Outcomes	Stable remission of disease during follow-up of 6 months
Notes	Paper in Russian. Translator: Liliya Eugenevna Ziganshina 24/03/15

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described in translated text as open randomised study, but no method specified
Allocation concealment (selection bias)	Unclear risk	No information on allocation
Blinding (performance bias and detection bias) Assessors	High risk	Open randomised study; no placebo
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open randomised study; placebo not given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	45 participants randomised; no information on withdrawals
Selective reporting (reporting bias)	Unclear risk	Lung function, blood count, sputum cytology, immunological parameters and stability of disease were listed as outcomes. Results for lung function were not presented. All intervention groups were described as having 'stable remission of disease' and 20% in standard treatment group
Other bias	Low risk	None noted

Ya Tseimakh 2006

Methods	Setting of study: Barnaul, Russia Study design: parallel-group randomised controlled trial Duration of study: 6 months
Participants	Number screened: not available Number randomised: 373 Number completed: 373 Gender distribution: not available Mean age (years): intervention 57.9 ± 0.51; control 57.8 ± 0.95 Inclusion criteria: - Patients with COPD (diagnostic criteria not stated) - Age 18 to 70 years - Frequency of exacerbations of COPD before beginning of studies ≥ 2 times per year Exclusion criterion: - Patients with immunodeficiency, long-term systemic glucocorticoids
Interventions	Intervention: pneumococcal polysaccharide vaccine 'Pneumo 23' Control: no vaccine. Cointerventions: none Treatment period: single vaccination given to control group Follow-up period: 6 months
Outcomes	COPD exacerbations - no definition given: reported mean rate with SD Acute respiratory infection (ARI): no definition given Adverse events (erythema, induration, fever, headache): % reported for vaccine group
Notes	Only interim results available, as abstract publication. Study authors contacted for 12-month data without response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised controlled trial; no description of method used for randomisation
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment method used; control group did not receive treatment
Blinding (performance bias and detection bias) Assessors	High risk	No blinding of participants or study personnel
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo injection given in control group

Ya Tseimakh 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information supplied regarding withdrawals
Selective reporting (reporting bias)	Unclear risk	Publication as abstract only; no response to request data
Other bias	Low risk	No other issues identified

Yilmaz 2013

Methods	Sponsorship source: no information available Country: Turkey/UK Setting: tertiary hospital, conducted between July 2006 and October 2008 Comments: "Publication details abstract 2013; 187 (meeting abstracts): A2182. Unpublished data requested and supplied by author" Authors' names: Yilmaz D, Uzaslan E, Ege E Institution: Uludad University Medical Faculty, Bursa/St George's, London Email, Dilber Yı lmaz Durmaz: drdilberyilmaz@gmail.com Address: St George's Hospital, University of London, Uludag University Medical Faculty, Bursa, Turkey Design: randomised controlled trial, parallel group Follow-up: 24 months
Participants	Inclusion criteria: - Clinical diagnosis of COPD ≥ 12 months before baseline visit - Age ≥ 40 - Written informed consent - Former or current smoker with a smoking history ≥ 10 pack-years Exclusion criteria: - Vaccination with PPV within previous 5 years - Immune suppression - Chronic renal failure - Bronchiectasis - Previous lung surgery - Malignancy - COPD exacerbation or pneumonia within previous 30 days - Unstable cardiac disease - Pregnancy or suspected pregnancy Group differences: PV and placebo group had no significant difference in terms of age, sex, GOLD stages, annual influenza vaccination, pneumonia history, number of exacerbations and pneumonia in the past 1 and 2 years (P > 0.05) PPSV-23 n = 116; placebo n = 28 Group differences: no significant differences in baseline characteristics between the 2 groups. All differences between baseline characteristics were non-significant Age (years): 65.3 ± 9.3; 64.9 ± 8.8 FEV_1 (L): 1.48 (± 0.617); 1.408 (± 0.54) ICS use %: NA; NA Current smoker %: NA; NA

Yilmaz 2013 (*Continued*)

	Pack-years of smoking: 48.6 ± 27.9; 40.6 ± 23.6 Male: 108/116 (93%); 26/28 (93%) LTOT: NA; NA Previous pneumonia: 74 (63%); 16 (57%) Hospitalisation or unscheduled emergency visit (≤ 1 year before enrolment): NA; NA Received systemic steroids and/or antibiotics: NA; NA Vaccine naive: 0; 0 Years since last vaccination: NA Mean FEV_1 (mL): 1438 ± 617; 1408 ± 540
Interventions	PPSV-23: 23-valent PPV (Pneumo 23, Lyon, France), dose NA, route not stated Placebo: not described
Outcomes	Acute exacerbation COPD (defined as an acute event characterised by worsening of respiratory symptoms beyond normal day-to-day variations) Courses of antibiotics Hospitalisation Death Emergency department visits FEV_1 (L) SGRQ (St George's Respiratory Questionnaire)
Notes	Published as abstract; full unpublished manuscript supplied by study authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, prospective, single-blind, 24-month trial; no details on randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Randomised, prospective, single-blind, 24-month trial; no details on allocation method. Unequal group numbers 3:1 (active:placebo)
Blinding (performance bias and detection bias) Assessors	Unclear risk	Described as prospective, single-blind, 24-month trial; no details on which group was blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as prospective, single-blind trial. No indication that placebo injection was used in control group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study authors report that all participants were followed to the end of 2 years

Selective reporting (reporting bias)	Low risk	All results were reported. Results for all outcomes listed in methods were reported
Other bias	Low risk	No other issues identified

AE: acute exacerbation; ARI; acute respiratory infection; ATS: American Thoracic Society; C; control; CLD: chronic lung disease; COPD: chronic obstructive pulmonary disease; CSF: cerebrospinal fluid; CXR: chest x-ray; F: female; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HIV: human immunodeficiency virus; I: intervention; ICS: inhaled corticosteroids; IgG: immunoglobulin G; IV: influenza vaccine; LTOT: long-term oxygen therapy; M: male; MSD: Merck Sharpe and Dohme; NHLBI: National Heart, Lung and Blood Institute; PCV: pneumococcal conjugated vaccine; PLA: placebo; PPSV: pneumococcal polysaccharide vaccine; PV: polysaccharide vaccine; RCT: randomised controlled trial; *S pneumoniae: Streptococcus pneumoniae*; SD: standard deviation; TB: tuberculosis; Tx: treatment; VA: Veterans Administration; VAX: vaccination; WBC: white blood cell

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

Study	Reason for exclusion
Aboussouan 1996	Review article
Austrian 1976	Participants are unlikely to have had COPD, and certainly no results are available for persons with COPD
Austrian 1981	Review article
Austrian 1984	Editorial
Bacle 1997	Review article
Bentley 1981	Review article
Bolan 1986	Not an RCT
Broome 1981	Review article
Butler 1992	Retrospective analysis of vaccine efficacy
Butler 1993	Retrospective analysis of vaccine efficacy
Chang 2012	Cohort study
Chodosh 1991	Review article
Christenson 2001	Prospective study (not an RCT)

(*Continued*)

Dilokthornsakul 2014	Study observed the association between pneumococcal vaccine and thrombocytopaenia in participants with COPD. Not an efficacy study of pneumococcal vaccinations in participants with COPD
Douglas 1979	Review article
Douglas 1984	Study carried out in children 6 to 54 months
Ekwurzel 1938	Excluded, as participants unlikely to have had COPD ("youthful group, 80% being under 25 years of age")
Ewig 1999	Review article
Farr 1995	Matched case-controlled study
Fedson 1989	Review article
Fedson 1994	Review article
Fedson 1999	Review article
Felton 1938	Cohort observation study
Ferguson 1993	Review article
Filice 1990	Review article
Fine 1994	Meta-analysis
Forrester 1987	Case-controlled study
Foschino 1995	Oral immunomodulator (not injectable vaccine)
Gable 1990	Retrospective cohort study
Gaillat 1985	No data available for participants with COPD
Gaillat 2009	Narrative review
Gardner 1993	Review article
Greenberg 2014	Wrong patient population. Participants were not patients with COPD
Gross 2010	Narrative review
Hak 1998	Prospective cohort study
Halasa 2001	Injectable vaccine includes antigen from pneumococcus and other bacteria (written in Polish language)
Han 2011	Narrative review

(*Continued*)

Hilleman 1981	Review article
Hirschmann 1981	Review article
Hirschmann 1994	Commentary
Horwood 2002	Review article
Hughes 2011	Cross-sectional study of predictors of colonisation of *Pneumococcus* bacterium in participants with COPD
Hung 2010	Prospective cohort study
Jackson 2003	Retrospective cohort study
Jimenez-Garcia 2007	Descriptive study of influenza and pneumococcal vaccination coverage among participants suffering from COPD
Jonsson 2002	Study compares 23 valent pneumococcal vaccine or type 6B polysaccharide conjugated to tetanus toxoid in participants with COPD vs healthy adult controls
Kaiser 1974	Retrospective analysis of isolates
Kaufman 1941	Participants not adequately randomised. Participants allocated to active treatment by volunteering 1 year followed by by alternate allocation in the subsequent year
Kaufman 1947	Likely to have included participants with COPD, given the age range of those involved in the study (80% > 60 years), although inclusion of persons with COPD was not explicitly stated. Request was made to originating institutions to provide relevant analyses of COPD subgroup, but no response was obtained
Klastersky 1986	No data available for participants with COPD
Klein 1983	Trial of immunisation rates
Koivula 1997	No data available for participants with COPD
Kraus 1985	Study of antibody responses
LaForce 1989	Review article
Lai 2007	Experimental study of antibody responses to a 23-valent pneumococcal polysaccharide vaccine and clinical outcome in Taiwanese participants with COPD
Landesman 1983	Study of antibody responses
Larsson 1998	Review article
Lee 2007	Retrospective cohort study

(*Continued*)

Leophonte 2001	Review article
MacIntyre 2010	Study assessed safety of concomitant zoster vaccination with pneumococcal vaccination in healthy participants without COPD
MacLeod 1945	CCT in young adults; COPD unlikely
Madison 1998	Review article
Meyer 2006	Comparison of Pneumovax given by inhalation, alveolar vaccination or bronchial vaccination vs standard intramuscular vaccination. No placebo control
Monso 2003	Commentary
Nichol 1999	Retrospective cohort control study
Ochoa-Gondar 2008	Prospective cohort study
Orcel 1994	Oral immunomodulator (not injectable vaccine)
Ortqvist 1998	No data available for participants with COPD
Patrick 1981	Cost/benefit analysis
Preheim 1978	Case report
Ricci 2014	Wong intervention. Study assessed efficacy of a sublingual pneumococcal vaccination
Riley 1977	No data available for participants with COPD
Rochemaure 1988	Antigens for this oral immunomodulator are taken from *Klebsiella pneumoniae* and *Escherichia coli* (not *Streptococcus pneumoniae*).
Saag 1998	Survey
Schenkein 2008	Narrative review of pneumococcal vaccination in COPD. Not an RCT
Schnelle 2010	Not an RCT
Schwartz 1982	Review article
Sehatzadeh 2012	Meta-analysis
Shapiro 1984	Case-controlled study
Shapiro 1987	Correspondence

(*Continued*)

Shapiro 1991	Case-controlled study
Sheikh 1999	Asthma study
Simberkoff 1986	No data available for participants with COPD
Simberkoff 1993	Review article
Sims 1988	Case-controlled study
Sisk 1986	Cost/benefit analysis; no data on efficacy
Smit 1977	Participants were young adult novice miners, with no indication of chronic lung disease. Wrote to study authors for further information, but received no response (Oct 2004)
Sumitani 2008	Not an RCT. Observational study; participants immunised with influenza vaccine (I-V) and 23-valent pneumococcal vaccine (P-V)
Van Amptin 1998	Retrospective study of patients hospitalised with infection
Vila-Corcoles 2012	Case-controlled study
Watanuki 2007	Cohort follow-up study. Study author request for study details 12/05/09, but no response received
Wencker 1999	Alpha 1 antitrypsin deficiency
Wenzel 1976	Inappropriate intervention including mycoplasma rather than *Streptococcus pneumoniae*
WHO 1999	Position paper
WHO 1999b	Review article
Wiebel 1977	Antibody response study
Willems 1980	Non-randomised cost-effectiveness study
Williams 1986	Review article
Wright 1914	Participants were young (otherwise healthy) mining labourers with no indication of having COPD

CCT: case-controlled trial; COPD: Chronic obstructive pulmonary disease; RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Pneumococcal vaccine versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Community-acquired pneumonia: at least 1 episode	6	1372	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.43, 0.89]
1.1 PPV-23 serotypes	5	1269	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.42, 0.89]
1.2 PPV-14 serotypes	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.17, 3.68]
2 Community-acquired pneumonia: rate per person-year	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
2.1 PPV-23 serotypes	1	36	Rate Ratio (Fixed, 95% CI)	0.37 [0.12, 1.14]
3 Pneumococcal pneumonia: at least 1 episode	3	1158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.05, 1.31]
3.1 PPV-23 serotypes	2	969	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.78]
3.2 PPV-14 serotypes	1	189	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.80 [0.15, 393.72]
4 Death from cardiorespiratory causes	3	888	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.69, 1.66]
4.1 PPV-23 serotypes	1	596	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.88]
4.2 PPV-14 serotypes	2	292	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.44, 2.18]
5 Death from all causes	5	1053	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.72, 1.40]
5.1 PPV-23 serotypes	3	761	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.69, 1.51]
5.2 PPV-14 serotypes	2	292	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.48, 1.86]
6 Hospital admission, any cause: at least 1 episode	3	391	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.32, 1.74]
6.1 PPV-23 serotypes	3	391	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.32, 1.74]
7 Hospital admission: cardiorespiratory-related	1		Rate Ratio (Random, 95% CI)	Totals not selected
7.1 PPV-14 serotypes	1		Rate Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
8 Hospital admission: all-cause	1		Rate Ratio (Random, 95% CI)	Totals not selected
8.1 PPV-23 serotypes	1		Rate Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
9 ED visit, any cause: at least 1 episode	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 At least 1 COPD exacerbation	4	446	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.93]
10.1 PPV-23 serotypes	4	446	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.93]
11 COPD exacerbation rate	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 PPV-23 serotypes	1	373	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-0.80, -0.38]
12 COPD exacerbations: rate/person-year	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
12.1 PPV-23 serotypes	1	36	Rate Ratio (Fixed, 95% CI)	0.87 [0.44, 1.72]
13 Lung function: FEV_1 (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 24 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Quality of life: SGRQ overall	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

14.3 24 months	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Comparison PPV-23 versus PCV-7

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Community-acquired pneumonia: at least 1 episode	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Death from all causes	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Hospital admission, any cause: at least 1 episode	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Acute exacerbation COPD	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Fatigue	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Headache	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Fever	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Pain	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 Redness or discolouration ≤ 15 cm	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 Redness or discolouration > 15 cm	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.7 Localised swelling	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.8 Limitation of arm movement	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Analysis by follow-up period/subgroup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pneumonia by lung function at baseline	1	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.41, 1.22]
1.1 FEV_1 < 40% expected	1	246	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.23, 1.00]
1.2 FEV_1 ≥ 40% expected	1	350	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.50, 2.48]
2 Hospital admission, any cause: by follow-up periods	3	377	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.22]
2.1 6-12 months	2	249	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.12]
2.2 12-24 months	1	128	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.11, 1.19]
3 Hospital admission, cardiorespiratory-related: by follow-up periods	1		Rate Ratio (Random, 95% CI)	Subtotals only
3.1 7-12 months	1	160	Rate Ratio (Random, 95% CI)	0.89 [0.59, 1.36]
3.2 13-18 months	1	150	Rate Ratio (Random, 95% CI)	1.22 [0.69, 2.16]
3.3 19-24 months	1	112	Rate Ratio (Random, 95% CI)	0.70 [0.24, 1.99]
4 Emergency department visit, any cause: by follow-up period	1		Odds Ratio (IV, Fixed, 95% CI)	Totals not selected

4.1 3-12 months	1		Odds Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 12-24 months	1		Odds Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Emergency visits (by cause)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 Due to URTI	1		Rate Ratio (Fixed, 95% CI)	1.29 [0.68, 2.47]
5.2 Due to LRTI	1		Rate Ratio (Fixed, 95% CI)	1.00 [0.75, 1.33]
5.3 Due to pneumonia	1		Rate Ratio (Fixed, 95% CI)	0.99 [0.52, 1.88]
6 At least 1 COPD exacerbation: varying follow-up	4	432	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.34, 0.81]
6.1 12 months	2	249	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.19]
6.2 > 12-24 months	2	183	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.15, 0.63]

Analysis 1.1. Comparison 1 Pneumococcal vaccine versus control, Outcome 1 Community-acquired pneumonia: at least 1 episode.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 1 Community-acquired pneumonia: at least 1 episode

Study or subgroup	Pneumococcal Vaccine n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 PPV-23 serotypes					
Alfageme 2006 (1)	25/298	33/298		41.4 %	0.74 [0.43, 1.27]
Furumoto 2008 (2)	6/24	5/31		4.5 %	1.73 [0.46, 6.56]
Steentoft 2006 (3)	11/37	5/12		7.3 %	0.59 [0.15, 2.28]
Teramoto 2007 (4)	16/100	32/96		37.5 %	0.38 [0.19, 0.75]
Ya Tseimakh 2006 (5)	2/297	2/76		4.3 %	0.25 [0.03, 1.81]
Subtotal (95% CI)	**756**	**513**		**95.0 %**	**0.61 [0.42, 0.89]**
Total events: 60 (Pneumococcal Vaccine), 77 (Control)					
Heterogeneity: Chi^2 = 5.42, df = 4 (P = 0.25); I^2 =26%					
Test for overall effect: Z = 2.57 (P = 0.010)					
2 PPV-14 serotypes					
Davis 1987 (6)	3/50	4/53		5.0 %	0.78 [0.17, 3.68]
Subtotal (95% CI)	**50**	**53**		**5.0 %**	**0.78 [0.17, 3.68]**
Total events: 3 (Pneumococcal Vaccine), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
Total (95% CI)	**806**	**566**		**100.0 %**	**0.62 [0.43, 0.89]**
Total events: 63 (Pneumococcal Vaccine), 81 (Control)					
Heterogeneity: Chi^2 = 5.52, df = 5 (P = 0.36); I^2 =9%					
Test for overall effect: Z = 2.57 (P = 0.010)					
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 =0.0%					

(1) 32 months median

(2) 24 months

(3) 6 months

(4) 24 months

(5) 6 months

(6) 24 months

Analysis 1.2. Comparison 1 Pneumococcal vaccine versus control, Outcome 2 Community-acquired pneumonia: rate per person-year.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 2 Community-acquired pneumonia: rate per person-year

Study or subgroup	Experimental N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 PPV-23 serotypes						
Lin 2013 (1)	19	17	-0.9943 (0.5745)		100.0 %	0.37 [0.12, 1.14]
Subtotal (95% CI)	**19**	**17**			**100.0 %**	**0.37 [0.12, 1.14]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.73 (P = 0.084)						

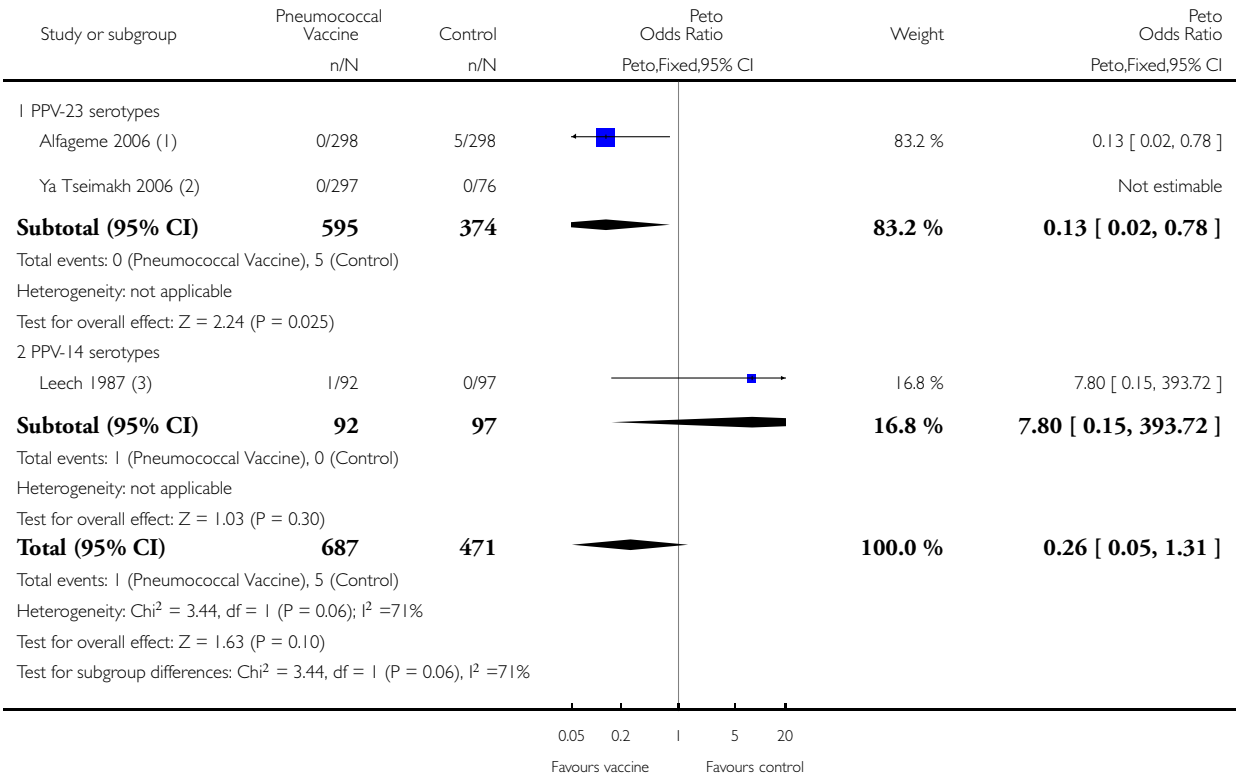
(1) 12 months

Analysis 1.3. Comparison 1 Pneumococcal vaccine versus control, Outcome 3 Pneumococcal pneumonia: at least 1 episode.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 3 Pneumococcal pneumonia: at least 1 episode



(1) 32 months median

(2) 6 months

(3) 24 months

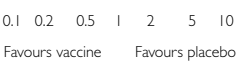
Analysis 1.4. Comparison 1 Pneumococcal vaccine versus control, Outcome 4 Death from cardiorespiratory causes.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 4 Death from cardiorespiratory causes

Study or subgroup	Pneumococcal Vaccine n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 PPV-23 serotypes					
Alfageme 2006 (1)	33/298	30/298		68.7 %	1.11 [0.66, 1.88]
Subtotal (95% CI)	**298**	**298**		**68.7 %**	**1.11 [0.66, 1.88]**
Total events: 33 (Pneumococcal Vaccine), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					
2 PPV-14 serotypes					
Davis 1987 (2)	8/50	7/53		14.7 %	1.25 [0.42, 3.75]
Leech 1987 (3)	5/92	7/97		16.6 %	0.74 [0.23, 2.42]
Subtotal (95% CI)	**142**	**150**		**31.3 %**	**0.98 [0.44, 2.18]**
Total events: 13 (Pneumococcal Vaccine), 14 (Control)					
Heterogeneity: Chi^2 = 0.41, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
Total (95% CI)	**440**	**448**		**100.0 %**	**1.07 [0.69, 1.66]**
Total events: 46 (Pneumococcal Vaccine), 44 (Control)					
Heterogeneity: Chi^2 = 0.47, df = 2 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.31 (P = 0.76)					
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 =0.0%					



(1) 36 months

(2) 48 months

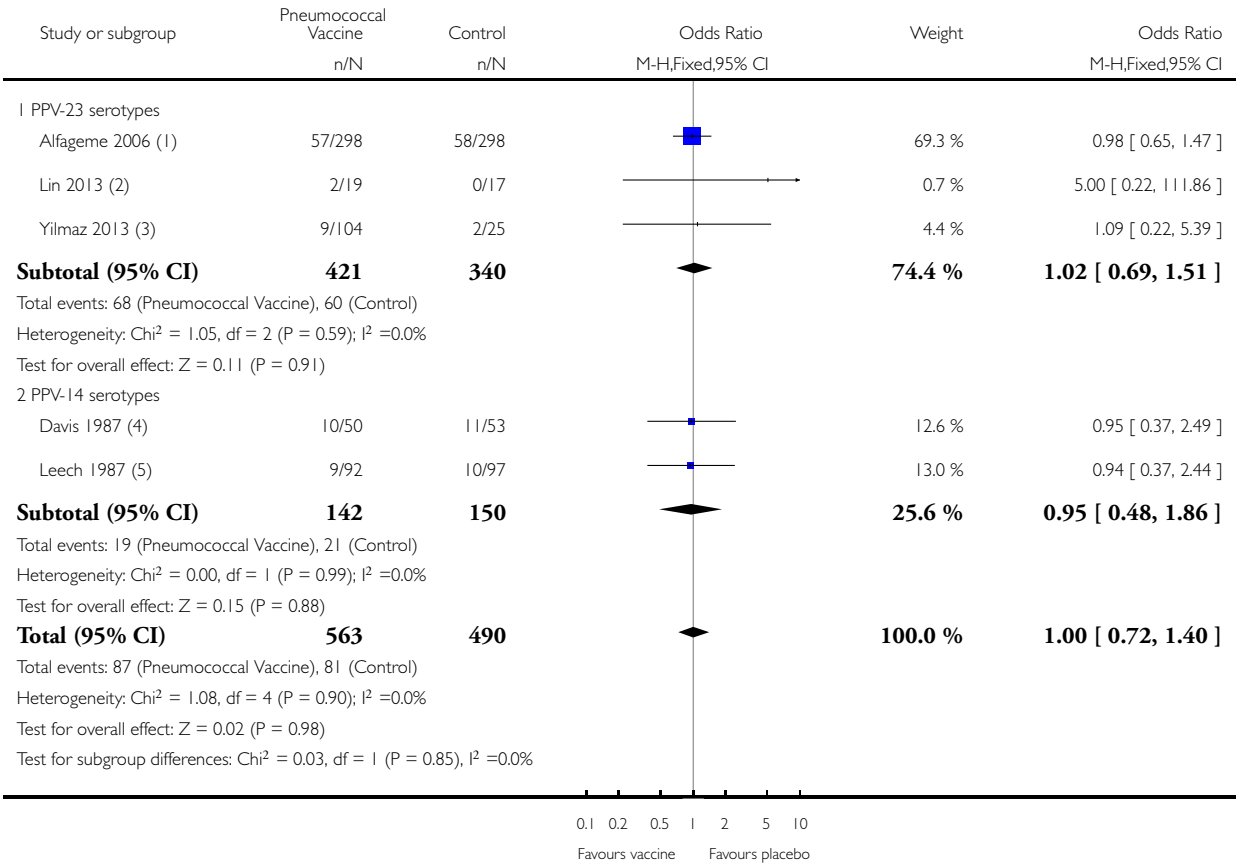
(3) 24 months

Analysis 1.5. Comparison 1 Pneumococcal vaccine versus control, Outcome 5 Death from all causes.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 5 Death from all causes



(1) 36 months

(2) 12 months

(3) 24 months

(4) 48 months

(5) 24 months

Analysis 1.6. Comparison 1 Pneumococcal vaccine versus control, Outcome 6 Hospital admission, any cause: at least 1 episode.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 6 Hospital admission, any cause: at least 1 episode

Study or subgroup	Pneumococcal Vaccine n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 PPV-23 serotypes					
Kostinov 2014 (1)	1/100	3/100		24.7 %	0.33 [0.03, 3.19]
Steentoft 2006 (2)	18/37	6/12		38.7 %	0.95 [0.26, 3.48]
Yilmaz 2013 (3)	10/114	3/28		36.6 %	0.80 [0.21, 3.13]
Total (95% CI)	**251**	**140**		**100.0 %**	**0.74 [0.32, 1.74]**
Total events: 29 (Pneumococcal Vaccine), 12 (Control)					
Heterogeneity: Chi^2 = 0.65, df = 2 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

(1) 12 months

(2) 6 months

(3) 3-12 months

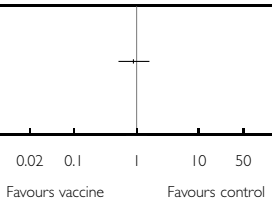
Analysis 1.7. Comparison 1 Pneumococcal vaccine versus control, Outcome 7 Hospital admission: cardiorespiratory-related.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 7 Hospital admission: cardiorespiratory-related

Study or subgroup	Vaccine N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Rate Ratio IV,Random,95% CI
1 PPV-14 serotypes					
Leech 1987 (1)	76	84	-0.1112 (0.2887)		0.89 [0.51, 1.58]



(1) 7-12 months

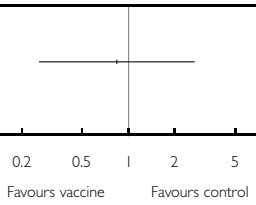
Analysis 1.8. Comparison 1 Pneumococcal vaccine versus control, Outcome 8 Hospital admission: all-cause.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 8 Hospital admission: all-cause

Study or subgroup	Vaccine N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Rate Ratio IV,Random,95% CI
1 PPV-23 serotypes					
Lin 2013 (1)	19	17	-0.1744 (0.5983)		0.84 [0.26, 2.71]



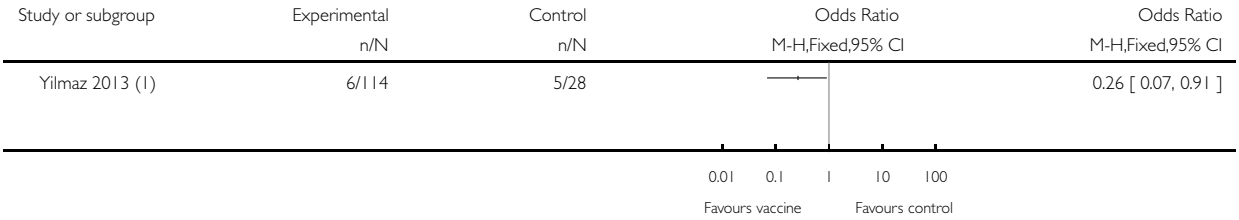
(1) 12 months

Analysis 1.9. Comparison 1 Pneumococcal vaccine versus control, Outcome 9 ED visit, any cause: at least 1 episode.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 9 ED visit, any cause: at least 1 episode



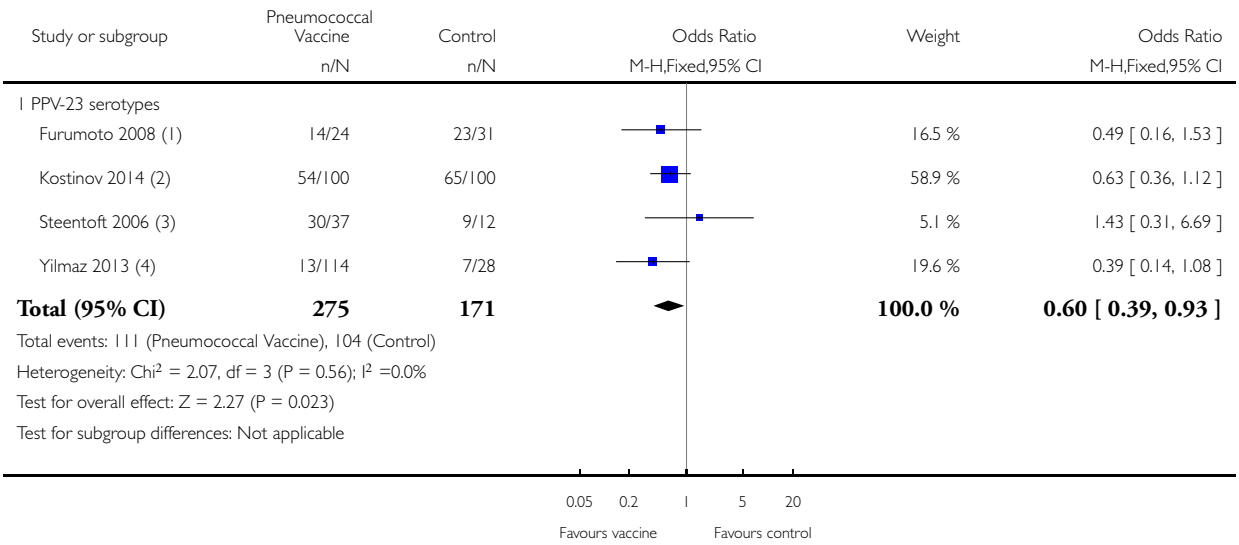
(1) 3-12 months

Analysis 1.10. Comparison 1 Pneumococcal vaccine versus control, Outcome 10 At least 1 COPD exacerbation.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 10 At least 1 COPD exacerbation



(1) 24 months

(2) 12 months

(3) 6 months

(4) 12 months

Analysis 1.11. Comparison 1 Pneumococcal vaccine versus control, Outcome 11 COPD exacerbation rate.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 11 COPD exacerbation rate

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 PPV-23 serotypes							
Ya Tseimakh 2006 (1)	297	0.78 (0.8445)	76	1.37 (0.8282)	←	100.0 %	-0.59 [-0.80, -0.38]
Subtotal (95% CI)	**297**		**76**		◆	**100.0 %**	**-0.59 [-0.80, -0.38]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.52 (P < 0.00001)							

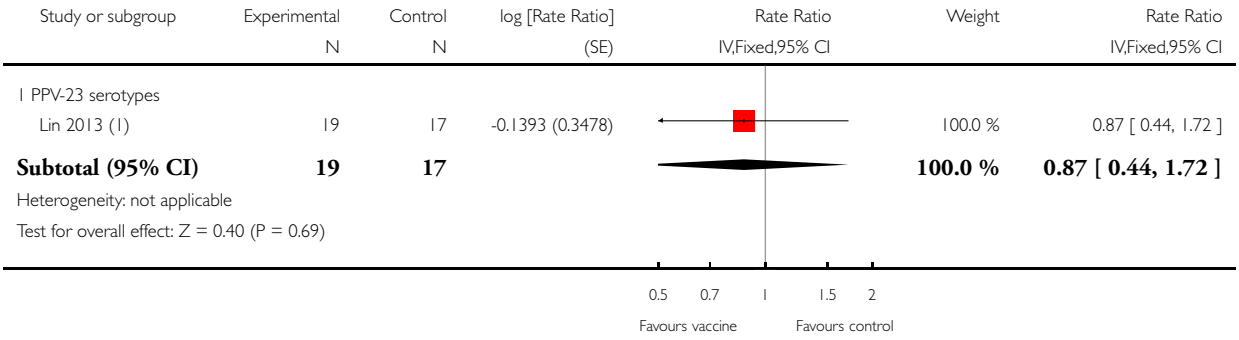
(1) 6 months

Analysis 1.12. Comparison 1 Pneumococcal vaccine versus control, Outcome 12 COPD exacerbations: rate/person-year.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 12 COPD exacerbations: rate/person-year



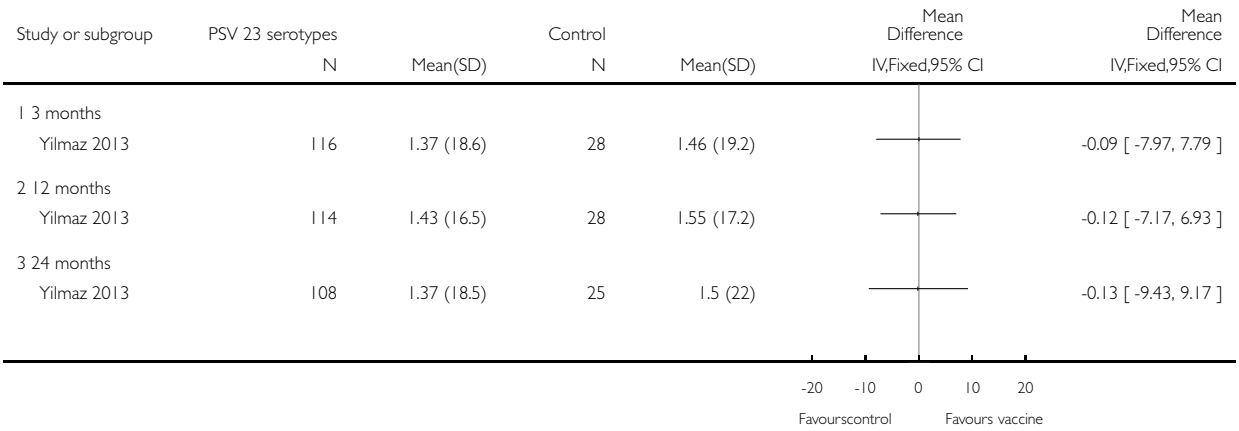
(1) 12 months

Analysis 1.13. Comparison 1 Pneumococcal vaccine versus control, Outcome 13 Lung function: FEV1 (L).

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 13 Lung function: FEV_1 (L)



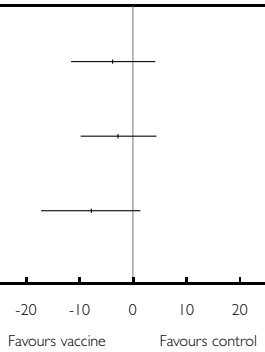
Analysis 1.14. Comparison 1 Pneumococcal vaccine versus control, Outcome 14 Quality of life: SGRQ overall.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 14 Quality of life: SGRQ overall

Study or subgroup	PSV 23 serotypes N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 3 months						
Yilmaz 2013	116	31.23 (18.6)	28	34.99 (19.2)		-3.76 [-11.64, 4.12]
2 12 months						
Yilmaz 2013	114	26.65 (16.5)	28	29.37 (17.2)		-2.72 [-9.77, 4.33]
3 24 months						
Yilmaz 2013	108	28.3 (18.5)	25	36.19 (22)		-7.89 [-17.19, 1.41]



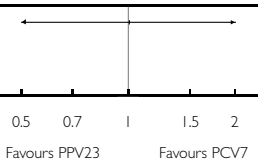
Analysis 2.1. Comparison 2 Comparison PPV-23 versus PCV-7, Outcome 1 Community-acquired pneumonia: at least 1 episode.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 2 Comparison PPV-23 versus PCV-7

Outcome: 1 Community-acquired pneumonia: at least 1 episode

Study or subgroup	PPV23 n/N	PCV7 n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Dransfield 2009 (1)	10/90	10/91		1.01 [0.40, 2.56]



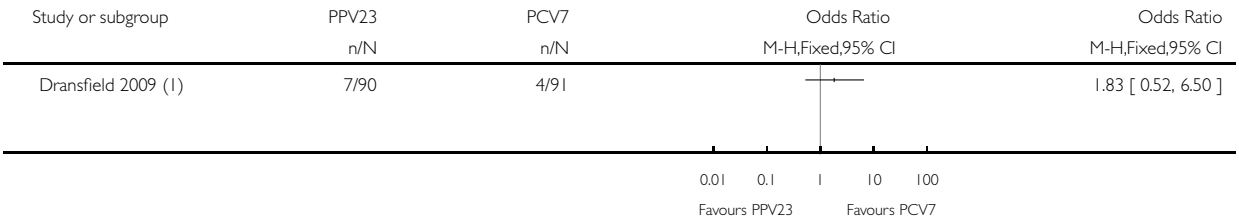
(1) 48 months

Analysis 2.2. Comparison 2 Comparison PPV-23 versus PCV-7, Outcome 2 Death from all causes.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 2 Comparison PPV-23 versus PCV-7

Outcome: 2 Death from all causes



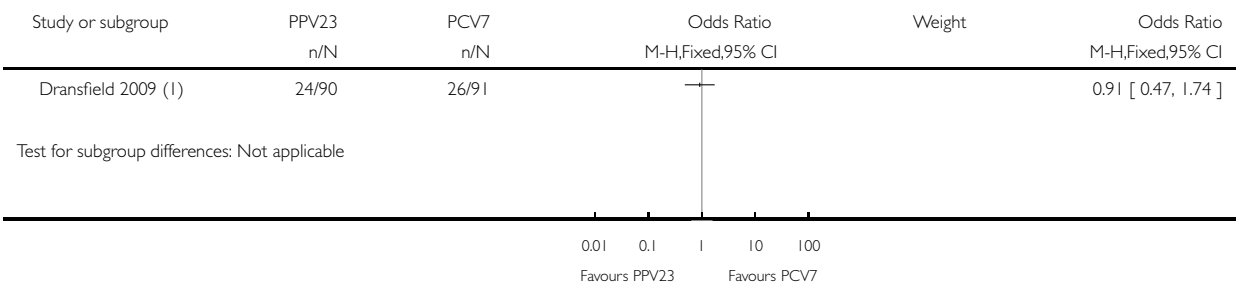
(1) 48 months

Analysis 2.3. Comparison 2 Comparison PPV-23 versus PCV-7, Outcome 3 Hospital admission, any cause: at least 1 episode.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 2 Comparison PPV-23 versus PCV-7

Outcome: 3 Hospital admission, any cause: at least 1 episode



(1) 48 months

Analysis 2.4. Comparison 2 Comparison PPV-23 versus PCV-7, Outcome 4 Acute exacerbation COPD.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 2 Comparison PPV-23 versus PCV-7

Outcome: 4 Acute exacerbation COPD

Study or subgroup	PPV23 n/N	PCV7 n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Dransfield 2009 (1)	43/90	42/91		1.07 [0.60, 1.91]

(1) 48 months

Analysis 2.5. Comparison 2 Comparison PPV-23 versus PCV-7, Outcome 5 Adverse effects.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 2 Comparison PPV-23 versus PCV-7

Outcome: 5 Adverse effects

Study or subgroup	PPV23 n/N	PCV7 n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Fatigue				
Dransfield 2009	39/63	23/57		2.40 [1.15, 5.00]
2 Headache				
Dransfield 2009	13/63	8/57		1.59 [0.61, 4.18]
3 Fever				
Dransfield 2009	3/63	4/57		0.66 [0.14, 3.10]
4 Pain				
Dransfield 2009	39/63	31/57		1.36 [0.66, 2.82]
5 Redness or discolouration ≤ 15 cm				
Dransfield 2009	27/63	10/57		3.53 [1.51, 8.21]
6 Redness or discolouration > 15 cm				
Dransfield 2009	2/63	0/57		4.67 [0.22, 99.46]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	PPV23 n/N	PCV7 n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
7 Localised swelling				
Dransfield 2009	23/63	15/57		1.61 [0.74, 3.52]
8 Limitation of arm movement				
Dransfield 2009	29/63	18/57		1.85 [0.88, 3.90]

Analysis 3.1. Comparison 3 Analysis by follow-up period/subgroup, Outcome 1 Pneumonia by lung function at baseline.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 3 Analysis by follow-up period/subgroup

Outcome: 1 Pneumonia by lung function at baseline

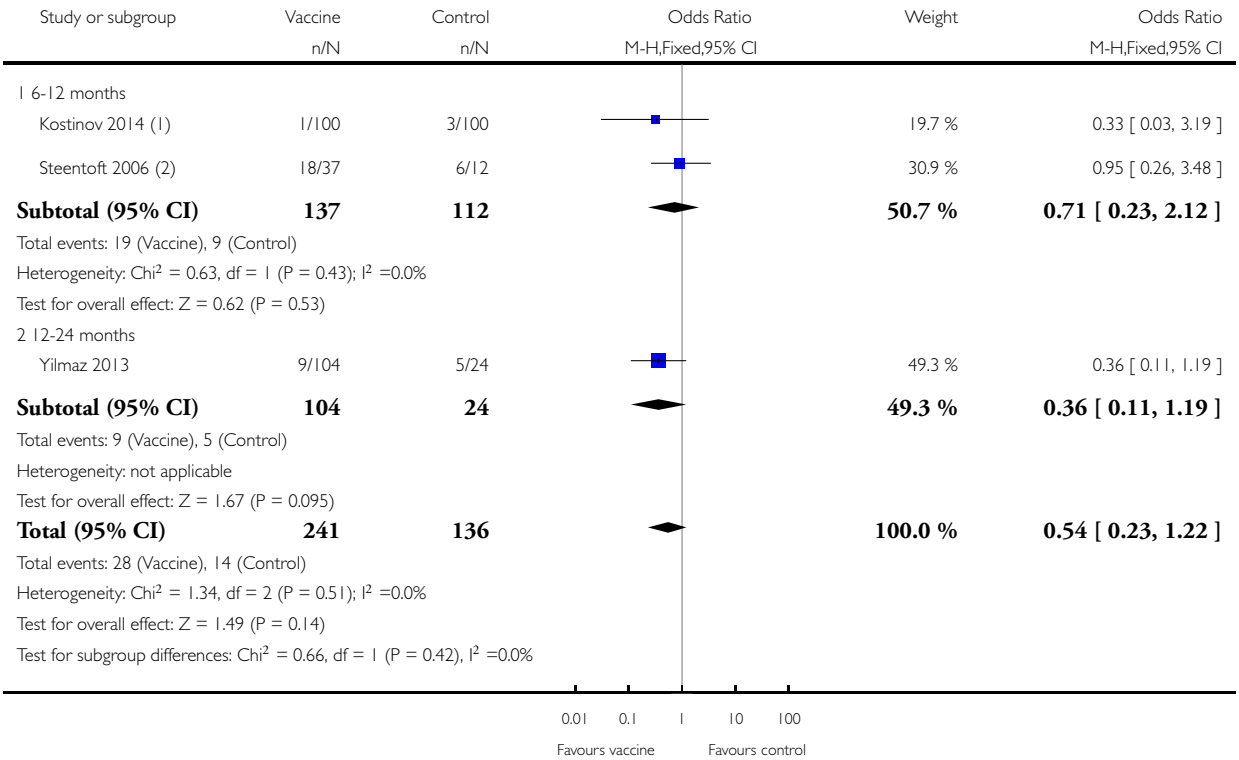
Study or subgroup	Vaccine n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 FEV_1 < 40% expected					
Alfageme 2006	12/132	20/114		53.6 %	0.48 [0.23, 1.00]
Subtotal (95% CI)	**132**	**114**		**53.6 %**	**0.48 [0.23, 1.00]**
Total events: 12 (Vaccine), 20 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.96 (P = 0.050)					
2 $FEV_1 \geq$ 40% expected					
Alfageme 2006	13/166	13/184		46.4 %	1.12 [0.50, 2.48]
Subtotal (95% CI)	**166**	**184**		**46.4 %**	**1.12 [0.50, 2.48]**
Total events: 13 (Vaccine), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)	**298**	**298**		**100.0 %**	**0.71 [0.41, 1.22]**
Total events: 25 (Vaccine), 33 (Control)					
Heterogeneity: Chi^2 = 2.36, df = 1 (P = 0.12); I^2 =58%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Chi^2 = 2.36, df = 1 (P = 0.12), I^2 =58%					

Analysis 3.2. Comparison 3 Analysis by follow-up period/subgroup, Outcome 2 Hospital admission, any cause: by follow-up periods.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 3 Analysis by follow-up period/subgroup

Outcome: 2 Hospital admission, any cause: by follow-up periods



(1) 12 months

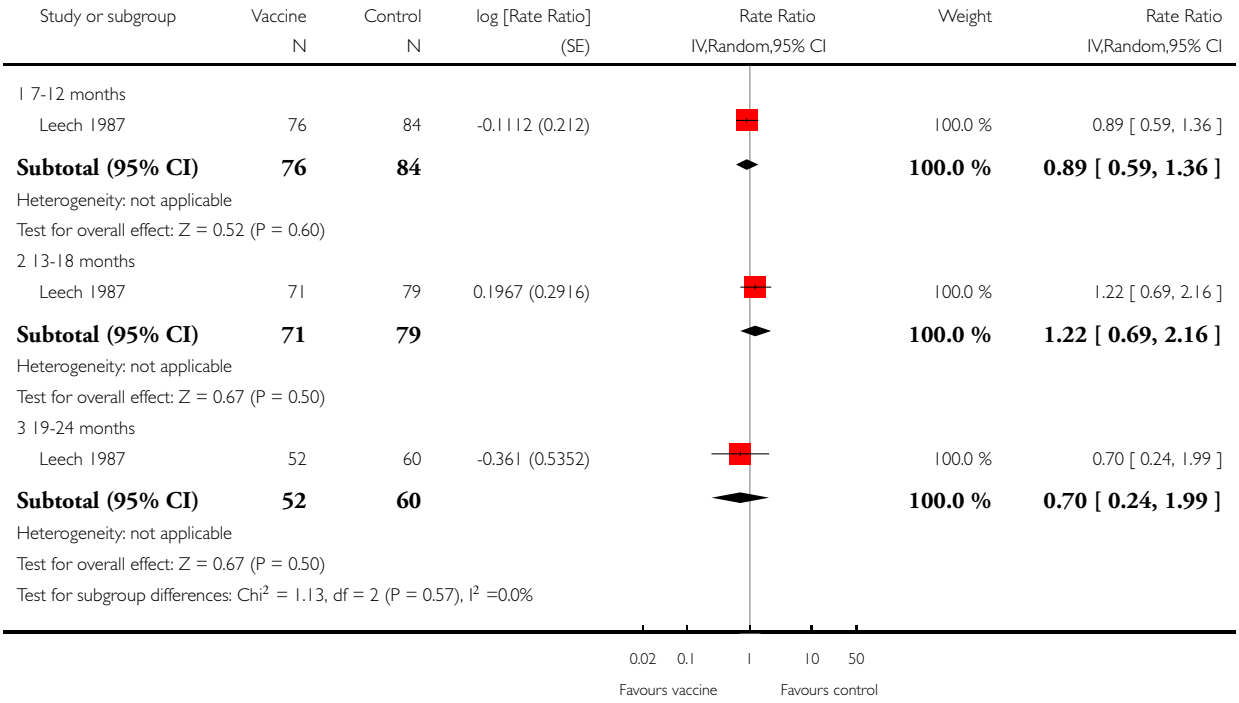
(2) 6 months

Analysis 3.3. Comparison 3 Analysis by follow-up period/subgroup, Outcome 3 Hospital admission, cardiorespiratory-related: by follow-up periods.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 3 Analysis by follow-up period/subgroup

Outcome: 3 Hospital admission, cardiorespiratory-related: by follow-up periods

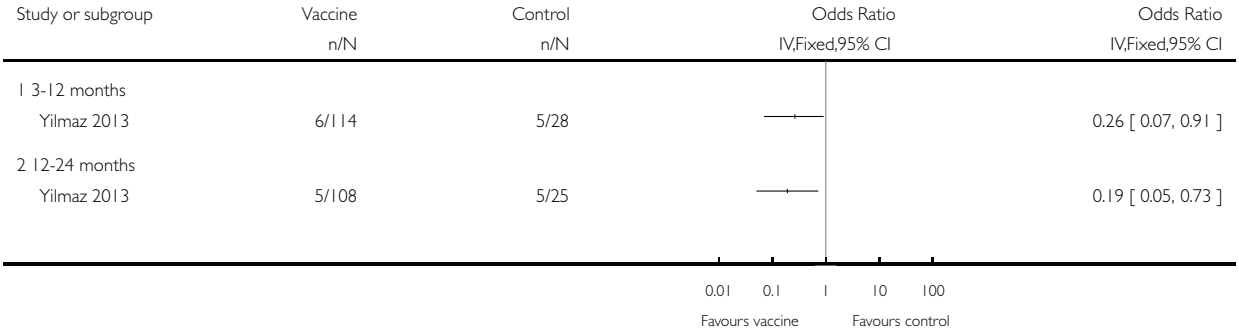


Analysis 3.4. Comparison 3 Analysis by follow-up period/subgroup, Outcome 4 Emergency department visit, any cause: by follow-up period.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 3 Analysis by follow-up period/subgroup

Outcome: 4 Emergency department visit, any cause: by follow-up period

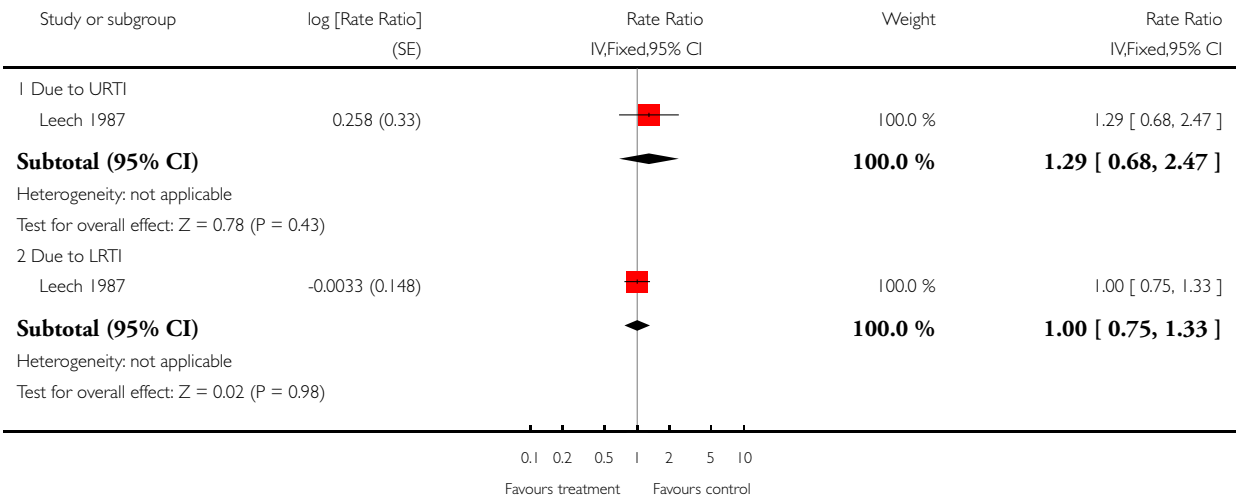


Analysis 3.5. Comparison 3 Analysis by follow-up period/subgroup, Outcome 5 Emergency visits (by cause).

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

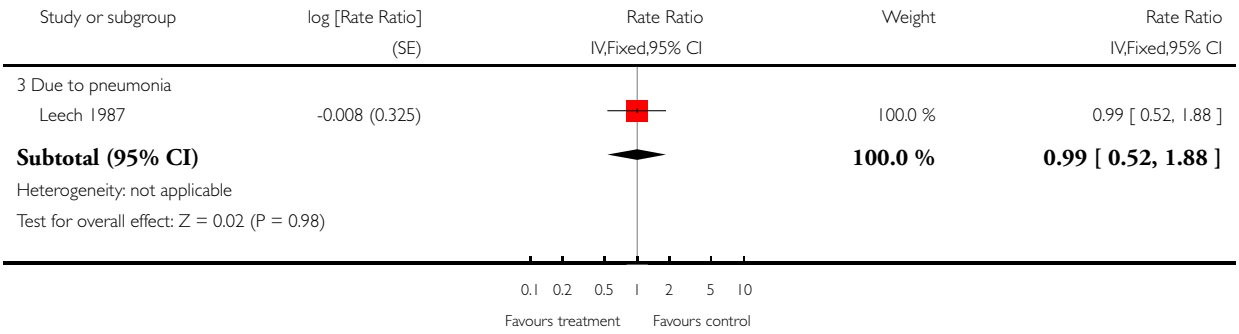
Comparison: 3 Analysis by follow-up period/subgroup

Outcome: 5 Emergency visits (by cause)



(*Continued* . . .)

(. . . *Continued*)

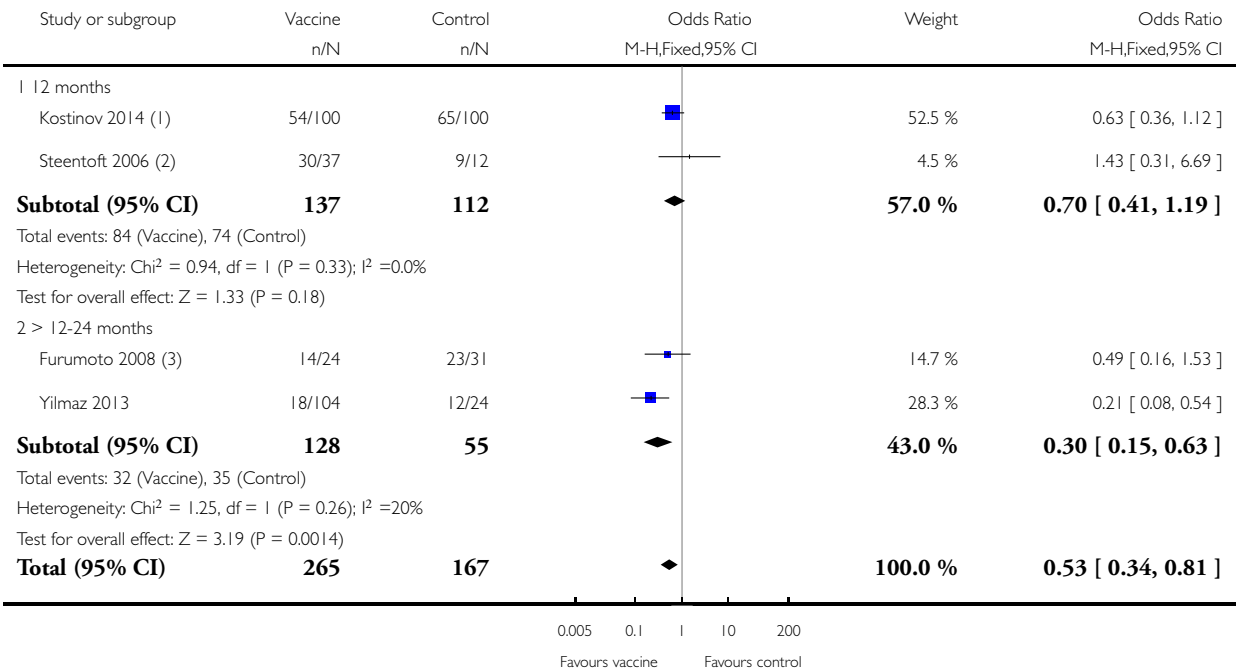


Analysis 3.6. Comparison 3 Analysis by follow-up period/subgroup, Outcome 6 At least 1 COPD exacerbation: varying follow-up.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

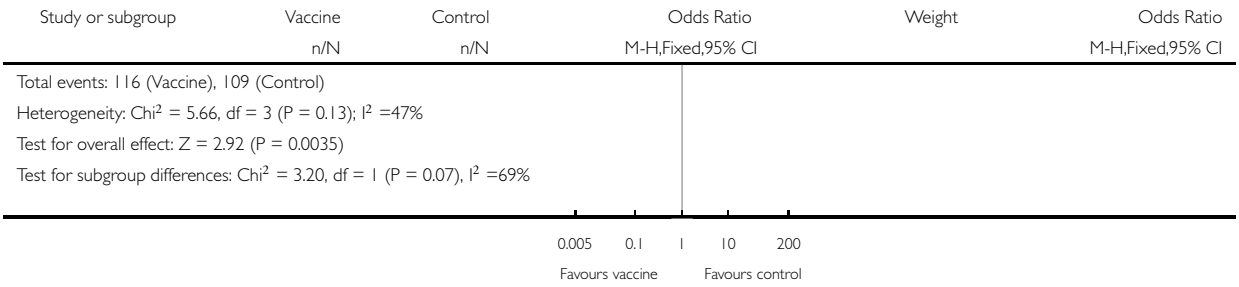
Comparison: 3 Analysis by follow-up period/subgroup

Outcome: 6 At least 1 COPD exacerbation: varying follow-up



(*Continued* . . .)

(. . . *Continued*)



(1) 12 months

(2) 6 months

(3) 24 months

ADDITIONAL TABLES

Table 1. Comparison of studies

Study ID (n)	Vaccine 1	Comparison	Setting/ Follow-up, months	Mean age/ % male	Mean FEV_1 (L) or % predicted	% AE 12 months	% ICS	% prior pneumonia	% current smokers
Alfageme 2006 (n = 600)	23-valent PPV	No vaccine	Seville, Spain/32 median	69/98	1.2 ± 0.8	NA	NA	18	24
Davis 1987 (n = 103)	14-valent PPV 0.5 mL SC	Saline 0.5 mL SC	New York, USA/24 to 32	63/NA	1.4 ± 0.7	NA	NA	26	43
Dransfield 2009 (n = 181)	23-valent PPV	7-valent PCV	USA 21 centres/48	64/37	45%	15	65	45	36
Furumoto 2008 (n = 55 with COPD)	14-valent PPV + influenza	Influenza	Kyushu & Okinawa, Japan/24	69/64	NA	NA	NA	NA	NA
Kostinov 2014 (Russian paper) (n = 200)	23-valent PPV	No vaccine	Russia/12	30-70/36	NA	NA	NA	NA	NA

Table 1. Comparison of studies (*Continued*)

Leech 1987 (n = 189)	14-valent PPV + influenza	Saline + influenza	Montreal Canada/24	68/71	0.95 ± 0.3	NA	NA	NA	NA
Lin 2013 (abstract & poster) (n = 36)	23-valent PPV	Saline	Taipei, Taiwan/12	71/89	1% to 45%	> 50	100 (> 1500 mcg/d)	> 50	37
Steentoft 2006 (n = 49)	23-valent PPV 0.5 mL SC	No vaccine	Denmark/6	65-72/55	0.8 to 1.2	NA	OCS 24%	NA	46
Teramoto 2007 (Abstract) (n = 196)	23-valent PPV	No vaccine	Japan/24	78/NA	NA	NA	NA	NA	NA
Trofimov 2010 (Russian paper) (n = 45)	23-valent PPV	No vaccine	Russia/6	55/67	62%	NA	NA	NA	NA
Ya Tseimakh 2006 (abstract) (n = 373)	23-valent PPV	No vaccine	Russia/6	69/57	62%	100	OCS not allowed	NA	60
Yilmaz 2013 (abstract & unpublished paper) (n = 144)	23-valent PPV	Placebo	Turkey & UK/24	65/93	1.4 L ± 0.6	NA	NA	NA	NA

AE = acute exacerbation of COPD.
ICS = inhaled corticosteroids.
OCS = oral corticosteroids.
PCV = diphtheria-conjugated pneumococcal polysaccharide vaccine.
PPV = pneumococcal polysaccharide vaccine.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

COPD search

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

Filter to identify RCTs

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

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

Appendix 2. Search strategy to retrieve relevant trials from the CAGR

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Pneumococcal Vaccines
#8 ((vaccin* or immuni*) and pneum*)
#9 Pneumovax
#10 Pnu-Imune
#11 Pnu-Immune
#12 Prevnar
#13 "Pneumo 23"
#14 #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 #6 and #14
[In search line #4, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, COPD]

Appendix 3. Search strategies

CENTRAL search

#1 MeSH descriptor Lung Diseases, Obstructive, this term only
#2 MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees
#3 emphysema*
#4 chronic* near/3 bronchiti*
#5 (obstruct*) near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#6 COPD
#7 COAD
#8 COBD
#9 AECB
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Pneumococcal Vaccines explode all trees
#12 pneum* near/3 (vaccin* or immuni*)
#13 Pneumovax or Pnu-Imune or Pnu-Immune or Prevnar or Prevenar or "Pneumo 23"
#14 (#11 OR #12 OR #13)
#15 (#10 AND #14)

MEDLINE search

1 exp Pulmonary Disease, Chronic Obstructive/
2 (obstruct$ adj3 (lung$ or respirat$ or pulmonar$) adj3 disease$).mp.
3 Bronchiti$.mp.
4 emphysema$.mp.
5 ((lung$ or thorax) adj3 hyperlucen$).mp.
6 (chronic adj5 obstruct$).mp.
7 (pulmonar$ or lung$ or airway$ or airflow$ or bronch$ or respirat$).mp.
8 6 and 7
9 (COPD or COAD).mp.
10 AECB.mp.
11 1 or 2 or 3 or 4 or 5 or 8 or 9 or 10
12 Pneumococcal Vaccines/
13 (pneum$ adj3 (vaccin$ or immuni$)).mp.
14 (Pneumovax or Pnu-Imune or Pnu-Immune or Prevnar or Prevenar or "Pneumo 23")
15 12 or 13 or 14
16 11 and 15
17 (clinical trial or controlled clinical trial or randomized controlled trial).pt.
18 (randomized or randomised).ab,ti.
19 placebo.ab,ti.
20 dt.fs.
21 randomly.ab,ti.
22 trial.ab,ti.
23 groups.ab,ti.
24 or/16-22
25 Animals/
26 Humans/
27 24 not (24 and 25)
28 23 not 26
29 16 and 27

Embase search

1 Chronic Obstructive Lung Disease/
2 Emphysema/
3 exp Lung Emphysema/
4 Chronic Bronchitis/
5 (obstruct$ adj3 (lung$ or respirat$ or pulmonar$) adj3 disease$).mp.
6 Bronchiti$.mp.
7 emphysema$.mp.
8 ((lung$ or thorax) adj3 hyperlucen$).mp.
9 (chronic adj5 obstruct$).mp.
10 (pulmonar$ or lung$ or airway$ or airflow$ or bronch$ or respirat$).mp.
11 9 and 10
12 (COPD or COAD).mp.
13 AECB.mp.
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11 or 12 or 13
15 Pneumococcus Vaccine/
16 (pneum$ adj3 (vaccin$ or immuni$)).mp.
17 (Pneumovax or Pnu-Imune or Pnu-Immune or Prevnar or Prevenar or "Pneumo 23")
18 15 or 16 or 17
19 14 and 18
20 Randomized Controlled Trial/
21 Controlled Study/
22 randomization/
23 Double Blind Procedure/
24 Single Blind Procedure/
25 Clinical Trial/
26 Crossover Procedure/
27 follow up/
28 exp prospective study/
29 or/19-27
30 (clinica$ adj3 trial$).mp.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (mask$ or blind$ or method$)).mp.
32 exp Placebo/
33 placebo$.mp.
34 random$.mp.
35 (latin adj3 square$).mp.
36 exp Comparative Study/
37 ((control$ or prospectiv$ or volunteer$) adj3 (trial$ or method$ or stud$)).mp.
38 (crossover$ or cross-over$).mp.
39 or/30-38
40 29 or 39
41 exp ANIMAL/
42 Nonhuman/
43 Human/
44 41 or 42
45 44 not 43
46 40 not 45
47 19 and 46

WHAT'S NEW

Last assessed as up-to-date: 25 November 2016.

Date	Event	Description
23 November 2016	New search has been performed	Searches updated for this review identified 5 additional studies (Dransfield 2009; Kostinov 2014; Lin 2013; Teramoto 2007; Yilmaz 2013) that compared vaccine versus control and involved 606 participants. This review was last updated in 2010. The review now includes a total of 12 studies involving 2171 participants
23 November 2016	New citation required and conclusions have changed	This update, which includes additional studies, now shows statistical significance in reducing the likelihood of community-acquired pneumonia (odds ratio (OR) 0.62, 95% confidence interval (CI) 0.43 to 0.89), as well as statistical significance in reducing the likelihood of an acute exacerbation of chronic obstructive pulmonary disease (COPD) (OR 0.60, 95% CI 0.39 to 0.9) One included study (Dransfield 2009) compared 2 different vaccine types and found no significant differences for the primary outcomes

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 4, 2006

Date	Event	Description
4 June 2014	Amended	We included comparison of vaccine types.
13 May 2010	New citation required and conclusions have changed	We promoted pneumonia to a primary outcome for the 2010 update and added 'Risk of bias' tables. We included 3 new studiesidentified by searches run up to March 2010 Data for community-acquired pneumonia changed the size of the effect estimate, although it remained not statistically significant. In the previous version of the review, the OR was 0.89 (95% CI 0.58 to 1.37). With the addition of new data, the pooled effect estimate was OR 0.72, 95% CI 0.51 to 1.01
31 July 2008	Amended	We converted this review to new review format.

(*Continued*)

21 July 2006	New citation required and conclusions have changed	We made substantive amendments.

CONTRIBUTIONS OF AUTHORS

Julia AE Walters: author of the review in 2009 and 2016: contributed to selection of studies; data extraction, analysis and interpretation; and writing of final review versions.

Joanne Ngie Qing Tang: author of the review in 2016: contributed to selection of studies; data extraction, analysis and interpretation; and writing of final review versions.

Phillippa Poole: developed the original protocol; edited and reviewed update drafts in 2004, 2009 and 2016.

Richard Wood-Baker: developed original protocol; contributed to review versions in 2004 and 2009 through study selection; data extraction/entry, analysis and interpretation; and writing of the review; reviewed Results and Conclusions in update drafts in 2016.

DECLARATIONS OF INTEREST

Richard Wood-Baker has received financial support for his research activities and expenses for presentation; full details are available at http://airways.cochrane.org/more-about-us

Julia Walters has received financial support for research and expenses for presentation; full details are available at http://airways.cochrane.org/more-about-us.

Joanne Tang has no known conflicts of interest.

Phillippa Poole has no known conflicts of interest.

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- JT, Australia.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review authors promoted pneumonia from a secondary to a primary outcome in the 2010 update. For the 2016 version of the review, review authors have changed the title to highlight the focus on the clinically relevant outcome of pneumonia. We have updated the Background by including information on new vaccines and guidelines. Studies comparing different types of vaccines have been conducted since the 2010 update, and we have included one of them (Dransfield 2009). Since the last update (in 2010), we have added new standard Cochrane headings and tables assessing risk of bias and providing a summary of findings.

INDEX TERMS

Medical Subject Headings (MeSH)

Pneumococcal Infections [mortality; *prevention & control]; Pneumococcal Vaccines [*administration & dosage]; Pulmonary Disease, Chronic Obstructive [*complications; mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Middle Aged