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Vaccines for preventing pneumococcal infection in adults

[Review]

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Outline

Graphics

Abstract

Background: Diseases caused by *Streptococcus pneumoniae (S. pneumoniae)* continue to cause substantial morbidity and mortality throughout the world. Polysaccharide pneumococcal vaccines have been developed for over 50 years and may have the potential to prevent disease and death.

Objectives: To assess the effectiveness of polysaccharide pneumococcal vaccination in preventing disease or death in adults.

Search strategy: Trials were identified by electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) issue 2, 2003 (which includes the Cochrane ARI Group's specialised register); MEDLINE (January 1966 to June 2003); and EMBASE (1974 to June 2003). We searched existing literature. The bibliographies of all newly revealed studies were read in order to identify further studies. The vaccine manufacturers, the lead authors of newly identified studies not included in existing meta-analyses were contacted.

Selection criteria:

A) Prospective, randomised or quasi-randomised studies comparing pneumococcal vaccines with placebo, control vaccines or no intervention.
B) Case-control studies (including indirect cohort studies) assessing pneumococcal vaccine effectiveness against invasive pneumococcal disease. Cohort studies are excluded.

Data collection and analysis:

A) Randomised studies
Trial quality assessment was conducted by two reviewers (JH and DT). Data extraction was

done by three reviewers (JH, DT, KD). There were many instances of unclear or incomplete data in the trial reports, and the final dataset was arrived at after much deliberation and discussion, including comparison with the data used in two previous reviews of this question. Due to the age of the trials (dating back to 1954 in one case) it was not generally possible to obtain clarification from the authors, though a partial clarification was achieved in one case.
B) Non-randomised studies
Study quality was assessed by two reviewers (RA and KD).

Main results: The combined results from the randomised studies fail to show that the polysaccharide pneumococcal vaccine is effective in preventing either pneumonia (outcome 6: odds ratio = 0.77, confidence interval 0.58, 1.02, number = 14) or death (outcome 8: odds ratio 0.90, confidence interval 0.76, 1.07, number = 11). Despite encouraging data from some very early trials, pooling trials published from 1977 on suggests there is no effect (outcome 6; odds ratio = 0.96, confidence interval 0.80, 1.15, number = 12; outcome 9: odds ratio = 0.98, confidence interval 0.88, 1.09, number = 10). The available data cannot distinguish whether this heterogeneity in results is due to improvements in trial methodology and reporting, to differences in trial setting or to real loss of efficacy over time. This is because the early, poorly reported trials were conducted in high-risk healthy populations where the expected benefit is greatest.

The case-control studies show significant efficacy in preventing invasive pneumococcal disease: OR 0.47 (CI 0.37, 0.59) corresponding to an efficacy of 53%.

Conclusions: While polysaccharide pneumococcal vaccines do not appear to reduce the incidence of pneumonia or death in adults with or without chronic illness, or in the elderly (55 years and above), the evidence from non-randomised studies suggests that the vaccines are effective in the reducing the incidence of the more specific outcome, invasive pneumococcal disease, among adults and the immunocompetent elderly (55 years and above). Surveillance data suggest that infection rates vary widely between and also within countries, but a typical figure in developed countries is 0.01%, or 10 per 100,000 per year. Efficacy of 50% then corresponds to a number-needed-to-treat (NNT) of 20,000 vaccinations per infection avoided, and perhaps 50,000 per death avoided.

Issue protocol first published

1996 Issue 4

Date of last minor update

11 October, 2000

Date new studies found but not yet included or excluded

24 June, 2003

Issue next stage

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Background

Pneumococcal pneumonia, and other diseases caused by pneumococci, still cause substantial morbidity and mortality throughout the world. A leading cause of pneumonia at all ages and otitis media in early childhood, pneumococci also cause a number of other serious systemic infections including meningitis and bacteraemia. Mortality associated with pneumococcal pneumonia has remained unchanged at 25% over the past 40 years (Kramer 1987; Pallares 1995). Pneumococcal infections are responsible for 30-50% of community acquired pneumonia in the United Kingdom (Meyer 1992). The burden of pneumococcal disease particularly occurs among children in developing countries and the elderly (55 years and above) in developed countries (WHO 1999). The continuing burden of pneumococcal disease is made worse by increasing numbers of people with chronic disease or HIV infection, and an aging population in many countries. Antibiotic resistance is now a major threat to the successful treatment of infections (Tomasz 1995; Reacher 2000). Large numbers of people in economically developing countries lack access to even basic curative health care but might be reached by vaccination programmes.

For these reasons, vaccines against *S. pneumoniae* have been developed over many decades. The first pneumococcal polysaccharide vaccines for general use to appear in the United States were two hexavalent preparations which were licensed in the late 1940's. A 14-valent vaccine was licensed in the US in 1977 and a 23-valent vaccine licensed in 1983 (Fedson 1999). The capsular polysaccharide on the surface of the *S. pneumoniae* bacterium is the primary factor responsible for virulence and is the principle behind the development of the polysaccharide vaccines (Fedson 1999). There are about 90 different serotypes of *S. pneumoniae*, some are highly invasive whereas others rarely cause disease. Some of these serotypes are serologically related to each other so there is the possibility of protection being conferred to types related to those which are included in the vaccine. Over the past 60 years the vaccine has been progressively developed to attempt protection against increasing numbers of serotypes.

There is now an urgent need to know whether pneumococcal vaccines are effective in all populations, or whether only some groups will benefit. A review by the United States Centers for Disease Control (Butler 1993) showed that during the years 1978 to 1992, unvaccinated patients with systemic pneumococcal infections were infected with serotypes included in the 14-valent vaccine in 67% of cases, and with serotypes in the 23-valent vaccine in 88% of cases.

There are many differences in recommendations for the use of polysaccharide pneumococcal vaccine between countries. For example, in the United States it is recommended that the vaccine be administered to immunocompromised patients (those with anatomical or functional asplenia, leukaemia, lymphoma, myeloma, Hodgkin's disease or HIV infection), those suffering from cardiopulmonary and renal diseases, diabetes mellitus or for "other conditions" which could include alcoholism, cirrhosis, solid organ or bone marrow transplantation, cerebrospinal fluid leaks, smoking or previous hospital care. The vaccine is also recommended for nursing home residents and those aged over 65 years in the United States. In contrast, in the United Kingdom, pneumococcal vaccine is not recommended for nursing home residents (Fedson 1998).

Nevertheless, controversy about the effectiveness and value of the vaccine persists (Hirschmann 1994; Ruben 1995). There have been at least six previous meta-analyses of pneumococcal vaccine in adults. Cornu (2000), Moore (2000) and Fine (1994) concluded that the vaccine is effective against bacteraemic pneumococcal pneumonia in 'low risk', healthy

adults, but that the randomised controlled trials failed to demonstrate vaccine efficacy in those at 'high risk' (a heterogeneous group which included the elderly (55 years and above), those with chronic disease or the immunosuppressed). Hutchison (1999) reached a different conclusion, that there was no evidence that the vaccine was less efficacious for the elderly (55 years and above), institutionalised people or those with chronic disease. Watson (2002) found the vaccine was effective against mortality and all-cause pneumonia in non-industrialised countries but not in industrialised countries, and noted that the small numbers of cases of pneumococcal bacteraemia made it difficult to draw any firm conclusions for this outcome. Since the vaccine was re licensed in 1977, there have been a number of observational studies in which bacteraemia, an unequivocal endpoint and marker of severity for pneumococcal disease, has been used as the basis to assess the vaccine's effectiveness. It remains controversial whether these observational studies provide adequate evidence to justify use of the vaccine in the groups for whom it is being widely advocated, particularly the healthy elderly (55 years and above) (Bruyn 1992). Finally, Puig-Barbera et al (Puig-Barbera 2002) found no evidence supporting pneumococcal vaccine effectiveness to reduce or avoid *S. pneumoniae* disease in the elderly (55 years and above).

Objectives

To assess the effectiveness of pneumococcal polysaccharide vaccination in preventing disease or death in adults.
To assess effectiveness in the immunocompetent.
To assess effectiveness in the immunocompetent elderly (55 years and above).

Criteria for considering studies for this review

Types of participants

Adults of either sex aged 16 years and above. Studies on HIV-positive subjects were excluded (they are the subject of another Cochrane Review).

Types of intervention

Vaccination with any pneumococcal polysaccharide vaccine. Studies making the following comparisons were included: vaccine compared with placebo; vaccine compared with no intervention; a combination of pneumococcal vaccine with a non-pneumococcal vaccine (such as influenza vaccine) compared with the other vaccine given alone.

Types of outcome measures

Different outcomes were analysed for randomised and non-randomised studies, according to what is reported from each type of study. Typically a prospective study will report many outcomes on the vaccinated and control patients, whereas in case-control studies the clinical outcome measures are limited to the conditions that define the cases.

A. Randomised studies
Definitions are the same as those used by Fine (Fine 1994):
1. definitive pneumococcal pneumonia: clinically and radiographically confirmed pneumonia with *S. pneumoniae* isolated from a culture of blood, a transthoracic lung puncture specimen, or a sample from a usually sterile body fluid (e.g. peritoneal, pleural, cerebrospinal or joint);
2. definitive pneumococcal pneumonia for pneumococcal antigen types included in the vaccine;
3. presumptive pneumococcal pneumonia: clinically and radiographically confirmed pneumonia with *S. pneumoniae* isolated from a culture of sputum or nasal swab;
4. presumptive pneumococcal pneumonia for pneumococcal antigen types included in the vaccine;

5. pneumococcal disease: a non-pneumonic pneumococcal infection with *S. pneumoniae* isolated from blood or a usually sterile body fluid;
6. pneumonia (all causes): defined independent of the cause of pneumonia as a clinical history of lower respiratory tract infection confirmed by the presence of a radiographic infiltrate;
7. bronchitis: a non-pneumonic lower respiratory tract infection of any cause;
8. mortality (all causes);
9. mortality due to pneumonia;
10. mortality due to pneumococcal infection.
B. Non-randomised studies
1. invasive pneumococcal disease: a pneumococcal infection with *S. pneumoniae* isolated from a culture of blood, a transthoracic lung puncture specimen, or a sample from a usually sterile body fluid (e.g. peritoneal, pleural, cerebrospinal or joint);
2. invasive pneumococcal disease for pneumococcal antigen types included in the vaccine. Indirect cohort studies, in which patients with non-vaccine-type disease serve as controls, contribute to this outcome only.

Types of studies

A) Prospective, randomised or quasi-randomised trials in adults comparing polysaccharide pneumococcal vaccines with placebo, control vaccines or no intervention.

B) Non-randomised studies assessing pneumococcal vaccine effectiveness specifically against invasive pneumococcal disease:
*case-control studies comparing vaccination status between adult patients with invasive pneumococcal infections and controls with no pneumococcal infection;
*indirect cohort studies in patients with pneumococcal infections, comparing the vaccination rate between vaccine-type and non-vaccine type patients. The rationale for indirect cohort studies is that if the vaccine is effective, vaccinated patients are protected primarily against infection caused by serotypes contained in the vaccine. Cases with vaccine-type infections will therefore tend to have a lower vaccination rate than those with non-vaccine type infections. An indirect cohort study is in effect a case-control study where the 'cases' are patients with vaccine-type disease, and the 'controls' are otherwise similar patients but with non-vaccine-type disease.

The review was originally planned to include only randomised trials, addressing the outcomes listed for them below. It was subsequently widened to include observational studies, specifically of invasive pneumococcal disease, because the very low numbers of such cases found in the prospective studies provided no opportunity to demonstrate the effectiveness of the vaccine.

Search strategy for identification of studies

Randomised trials were identified by electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) issue 2, 2003 (which includes the Cochrane ARI Group's specialised register); MEDLINE and EMBASE.

The following terms were used to search MEDLINE (January 1966 to June 2003):
pneumococcal vaccine'or'pneumococcal immunisation'and 'trials'or'controlled trials'.
The following terms were used to search EMBASE (1974 to June 2003):
pneumococcal vaccine'or'pneumococcal immunisation'and 'trials'or'controlled trials'.

The bibliographies of previous meta-analyses of pneumococcal vaccine (Fine 1994; Hutchison 1999); trials revealed by hand-searching 'Vaccine' from its first issue to the end of 1995; the bibliographies of newly retrieved trials in order to identify further trials; contacting vaccine

manufacturers to identify any remaining published or unpublished randomised controlled trials; contacting lead authors of any new trials not included in the existing reviews (Fine 1994; Hutchison 1999) to identify any remaining published or unpublished randomised controlled trials; and contacting authors of any other trials published within the last ten years.

Non-randomised trials were identified through electronic searches of MEDLINE (1966 to June 2003); EMBASE (1974 to June 2003); and the bibliographies of existing literature reviews (Fedson 1999; Leophonte 2001).

There was no language restriction to the literature search.

Methods of the review

This Cochrane Systematic Review includes data from randomised controlled trials (RCTs) and from non-randomised case-control studies. The two types of study address distinct endpoints, and are analysed and reported separately, with different results. The Review Protocol specifies review only of RCTs, and this was done. Non-randomised studies were then included when it became apparent (a) that analysing the RCTs had yielded a generally negative result for the outcomes specified in the protocol; (b) that the RCTs lacked statistical power to assess effectiveness against invasive pneumococcal disease (IPD), a serious but relatively rare event; and (c) that reviewing the non-randomised studies on this additional outcome might permit the vaccines' value to be demonstrated.

TRIAL QUALITY ASSESSMENT
The randomised trials were assessed for their quality, non-blinded, by John Holden and David Tatham. The non-randomised studies were assessed for their quality, non-blinded, by Ross Andrews and Keith Dear. No use has been made of the quality scores.
Assessment of the quality of the randomised trials was made according to quality of randomisation expressed by concealment of participants' allocation. The quality of the trials was assessed after Jadad (1996). The trials were assessed independently by John Holden and David Tatham and any inconsistency in the scores was discussed so as to agree on a final score.
Each trial was scored on these criteria:
* Was the trial described as randomised?
* Was the randomisation sequence described and appropriate?
* Was the trial described as double blind?
* Was the double blinding method described and appropriate?
* Was there a description of withdrawals and drop-outs?

Thus each trial could score from zero to five points.

The point for randomisation was not given if a randomisation method was described but was inappropriate. The point for double blinding was not given if a blinding method was described but was inappropriate.
All non-randomised studies identified were assessed independently by Ross Andrews and Keith Dear. Brief descriptions of the studies are provided below including reasons for exclusion of some studies that have been included by previous reviewers.
DATA COLLECTION
Data from the RCTs were extracted from the published reports independently by John Holden, David Tatham and Keith Dear. Items recorded, in addition to the outcome data, were:
* The country where the study was carried out.
* A brief description of the subjects (e.g. Gold miners; ambulatory patients).
* Age range, or some indication thereof as provided in the published report, e.g. "82% aged

over 55".
* The sample size.
* Pneumonia incidence %: studies were considered to be in high-risk populations where the incidence in the study group exceeded 10%.
* Whether the study was blinded.
* Whether the study was on subjects with chronic disease.
* Whether the study was on elderly (55 years and above) subjects.
* Whether the study was carried out in an institutional setting.
* Whether a randomised trial or pseudo-randomised.
* The valence of the vaccine used (2, 6, 12, 14, 17 or 23).

The Jadad quality score (0-5, see above) was then calculated and added to the table of study descriptions.

Data from the non-randomised studies were extracted from the published reports independently by Ross Andrews and Keith Dear. Items recorded were:

* The study period (e.g. 1978 to 1980).
* The valence of the vaccine that had most commonly been given to vaccinated subjects (14, 23 or both).
* A description of the study design (e.g. indirect cohort, hospital-based).
* A description of each available subgroup, e.g. "aged over 55, immunocompetent".
* Outcome: numbers of cases and controls who had received the vaccine.

Based on its description, each subgroup was then classified for analysis, e.g. "healthy elderly" (55 years and above).
A justification of the decision to include or exclude the data was also added: e.g. data were excluded if the same study appeared again in a subsequent report. These details appear under "Description of Studies" below.

STATISTICAL METHODS

Randomised studies: analysis was carried out in Metaview, combining tables of discrete data to estimate odds ratios (OR) and confidence intervals (95% CI). Random effects models were used when indicated by the presence of significant heterogeneity. The possibility of publication bias in the RCTs was examined using funnel plots and other statistical methods: details of these methods are shown together with their results, below.

Non-randomised studies: results are expressed in terms of vaccine efficacy, calculated as 100 (1- odds ratio). Because all but one of these studies were matched case-control studies (Butler 1993 was unmatched), simple analysis of the 2 x 2 table of vaccination status against case-control status is invalid. Instead, each contributing report provides an estimate of the OR based on conditional logistic regression, which allows for the matching. We combined these values using the meta command of Stata, version seven, which calculates a weighted average log-OR. Because of the small numbers of studies, the fixed effect result is reported. In most cases, the studies reported efficacy, but this was converted back to OR for meta-analysis then reconverted for presentation here.

SUB GROUP ANALYSIS

Subgroups of randomised studies could not be clearly identified possessing single defining characteristics, so no subgroup analyses were attempted among the randomised studies. However, all randomised trials included were on immunocompetent subjects. Analyses addressing objectives two and three were therefore carried out only using non-randomised studies.

Analyses were performed on two subgroups of subjects from non-randomised studies:

* Studies on immunocompetent subjects. Study subjects were considered immunocompetent if they were not severely immunocompromised. Unless they could be identified within the study, non-randomised studies that included immunocompromised subjects (those with HIV/AIDS, haematologic cancers or receiving prednisolone) were excluded. Trials on chronically ill but not otherwise immunocompromised patients were included. Patients with chronic pulmonary disease, chronic alcoholism, diabetes mellitus, chronic renal failure requiring dialysis and congestive heart failure were considered immunocompetent.
* Studies on the immunocompetent elderly. The definition of "elderly" in this context has variously been taken to refer to trials in which the majority of subjects were over 55, 65 or 70. In our data, study subjects aged 55 years or more were considered 'elderly'.

Description of the studies

This long section has four parts:

* A) Randomised trials
* B) Non-randomised studies
* C) Randomised trials excluded
* D) Non-randomised studies excluded.

A) RANDOMISED TRIALS

Austrian 1976, 13v

Two later groups of South African gold miners were recruited to a trial in which 1493 received 13 valent pneumococcal vaccine and 3002 acted as controls. Numbers of exclusions are not clear. Follow up was for two years. Published information is largely in pooled format and therefore is difficult to interpret reliably, with the exception of all-cause pneumonia. This pair of studies, reported together with others in a paper in the Transactions of the Association of American Physicians, was labelled 'Austrian et al, 1976' by Fine (1994) and "Austrian (b)" by Hutchison (1999). The only data we use are drawn from Fig.7, on "Radiologically confirmed pneumonia irrespective of cause", with an odds ratio of 0.44.

Austrian 1980, Grp1(Dorothea Dix Hospital)

Two studies were reported in Austrian (1980). The first started in January 1973 (Group 1) and involved residents of the Dorothea Dix Hospital for the mentally ill in North Carolina, USA, who were randomly assigned to receive (effectively) 12 valent pneumococcal vaccine (607 subjects) or placebo (697 controls). Follow up continued for three years (average 2.2 years). The number of exclusions was uncertain.

Austrian 1980, Grp2 (Kaiser Permanente Medical Center)

A second study was performed at the Kaiser Permanente Medical Center in San Francisco, USA. Of adults invited to participate, 36% accepted and were randomly assigned to 12 valent vaccine (6782 subjects) or placebo (6818 subjects). Recruitment occurred for 12 months from January 1974 and follow up, of mean duration 2.5 years, ceased in October 1976.

Davis 1987

Patients with chronic obstructive pulmonary disease attending two New York hospital chest clinics were randomly assigned to receive either 14 valent pneumococcal vaccine (50 patients) or placebo (53 patients). 53% of those vaccinated were still smoking compared to 33% of the controls ($p = 0.036$). Vaccination was performed in 1978 to 80. The number of potential participants excluded is unknown. The maximum period of follow-up was approximately four years.

Gaillat 1985

This study was performed on elderly people (mean age 74 years) living in 50 hospices or retirement homes in south-east France. From 2540 potential subjects, 1686 (66%) were randomly allocated to receive 14 valent pneumococcal vaccine (937), or not be vaccinated (749). The main exclusion was a short life expectancy. Vaccination was performed in 1980 and there was a two-year follow-up period, with reporting by reply cards and follow-up visits by investigators. Active participation was considered to be 71 to 77%. The unbalanced randomisation outcome (55.6% vaccinated, $p < 0.0001$) casts serious doubt on the adequacy of concealment of allocation.

Honkanen 1999

This trial compared the effectiveness of simultaneously administered influenza vaccine and 23-valent pneumococcal vaccine (13,980 subjects, the IP group) to that of influenza vaccine alone (12,945 controls, the I group). Men and women aged 65 or over in districts in northern Finland were recruited in two cohorts, in late 1992 and in 1993, with a maximum three year (average 1.4 year) follow-up until 1995. This very large trial was aimed at entire elderly populations: 48% of the elderly population of the target districts were recruited in 1992 (n = 9,875) and 75% in 1993 (n = 16,050).

Allocation was entirely non-random, being determined by year of birth, with subjects born in even-numbered years receiving both vaccines (IP) and subjects born in odd-numbered years receiving only influenza vaccine (I). Subjects were permitted to swap groups on request: about 2% of the IP group and about 3% of the I group as treated were such transfers, having initially been allocated to the other group.

Kaufman 1947

In each of six years, residents of New York City Home were randomly selected to receive either 2-valent (1937 to 38) or 3-valent (1939 to 42) pneumococcal vaccine, or to be left unvaccinated. The scheme for randomisation cannot be determined now, although the numbers vaccinated each year were always divisible by 50. The trial was not placebo-controlled: unvaccinated subjects received no injection. It is uncertain whether individuals were vaccinated twice. Follow-up, which was for 18 months only after each year's vaccination campaign, is of unknown completeness. Although this study was conducted in hospitals there is no information on patients' pre-existing medical conditions, and mortality was low suggesting a relatively healthy population. 79% of subjects were 60 years of age or above.

Vaccination reduced the incidence of pneumonia by 62% (confidence interval 52%, 70%) and reduced deaths by 64% (confidence interval 48%, 75%).

Klastersky 1986

50 patients with bronchogenic carcinoma in Brussels, Belgium were randomly allocated to receive 17 valent pneumococcal vaccine. 26 patients received vaccine; 21 placebo; three were lost to follow up and not further considered. The number of exclusions, the time of vaccination and duration of follow up are not stated.

Koivula 1997

Pneumococcal capsular polysaccharide vaccine was offered to elderly men and women (aged 60 years or above) in a town in Eastern Finland in late 1982 of whom 67% responded. They were followed up for three years to detect radiologically confirmed pneumonia. A total of 2837 subjects took part in the trial; 1364 vaccinees receiving 14 valent pneumococcal vaccine and influenza vaccine and 1473 controls receiving influenza vaccine alone.

Leech 1987

Patients with chronic obstructive pulmonary disease attending a hospital out patient clinic in Canada were randomly assigned to receive influenza vaccine with either 14 valent pneumococcal vaccine (92 patients) or placebo (97 patients). Vaccination was performed in October and November 1981 and follow up was for a maximum of 2.2 years. Apart from those previously vaccinated, other exclusions were not stated. 23 patients could not be traced and were excluded from analysis of death rates. Since these losses to follow-up were not reported by randomisation group, the denominators are unknown and the death data cannot be used. There were six deaths among the vaccinees and 11 among the controls, yet the survival curves shown are very close. This suggests that most of the losses must have been from the vaccination group, casting further doubt on the reliability of these data.

Ortqvist 1998

Patients aged 50 to 85 years who had been treated as in-patients for community acquired pneumonia in one of six tertiary care hospitals in Sweden, but who were not immunocompromised, were included in this study which ran from 1991 to 1995. From a potential study population of 1549 patients, 894 (58%) were excluded, mainly for 'presumed poor compliance' e.g. severe chronic alcoholism, or refused consent. Of the rest, 339 were randomly assigned to receive 23 valent pneumococcal vaccine and 352 received placebo. There was a high incidence of (recurrent) pneumonia of 17% during a mean follow-up period

of 2.5 years. The majority of patients in this study were diagnosed with pneumococcal pneumonia from the presence of pneumococcal antibody. Fedson (1999) has queried the use of antibody tests to pneumolysin on the basis that their predictive value appears to be poor. This outcome is therefore classed here as "presumptive" not "definitive" pneumococcal pneumonia.

Riley 1977

Subsistence farmers and their families from Papua New Guinea were randomly allocated to receive either 14 valent pneumococcal vaccine (5946) or placebo (6012). An unknown number of people were excluded from the study, which involved about half the local population. Numbers of deaths and their cause were determined for three years for the whole sample. Morbidity was determined for a subset of 5373 people, 2713 from the vaccinated group and 2660 from the control group, who were visited and questioned fortnightly for 16 months.

Simberkoff 1986

Patients over 55 years of age with chronic disease at one of five medical centres in the United States were randomly allocated to receive 14 valent pneumococcal vaccine (1150 patients) or placebo (1145 controls). Vaccination was performed from 1981 and the mean duration of follow up was 2.9 years. The two groups were well balanced for risk factors. The number of exclusions is not clear.

Smit 1977, Grp 1

Novice miners at a South African gold mine were randomly allocated to receive 6-valent pneumococcal vaccine or meningococcal vaccine or placebo. Although all participants gave informed consent, the number excluded is unknown. The maximum duration of follow-up was 2.3 years.

Smit 1977, Grp 2

Novice miners at a South African gold mine were randomly allocated to receive 12-valent pneumococcal vaccine or meningococcal vaccine or placebo. Although all participants gave informed consent, the number excluded is unknown. The maximum duration of follow-up was 1.6 years.

B) NON-RANDOMISED STUDIES

Butler 1993

Subgroups: immunocompetent, immunocompetent elderly.

An indirect cohort study based on pneumococcal isolates referred for serotyping to the Centers for Disease Control and Prevention (CDC) from 54 participating hospital laboratories in 26 American states over a 14 year period (1978 to 1992). Isolates from vaccinated persons who subsequently developed invasive pneumococcal disease were also solicited. The "cohort" consisted of 2837 persons aged five years or more who had invasive pneumococcal disease of a known serotype, were of known vaccination status and had onset of illness within the study period. Median age was over 50 years. Ascertainment of comorbid diseases and vaccination status were based on information recorded on a standardised form by the person submitting the isolate for serotyping. Subjects may have received either the 14 valent or 23 valent vaccine. The vaccination type was classified based on the date of vaccination, those vaccinated before 1 January 1984 were allocated to the 14 valent vaccine while those vaccinated on or after that date were allocated to the 23 valent vaccine. Vaccine effectiveness against invasive pneumococcal disease caused by serotypes contained within the relevant vaccine was measured using the indirect cohort method (Broome 1980). The method compares the proportion of pneumococcal isolates caused by vaccine serotypes in vaccinated and unvaccinated persons and assumes the risk of infection due to a serotype contained within the vaccine is similar among the populations from which the isolates were obtained.

Farr 1995

Subgroups: none.

A hospital based matched case-control study with subjects recruited over seven years (1981 to 1987). Subjects were recruited from hospital records at the University of Virginia Health Services Center, Charlottesville, USA. The case group consisted of 85 patients aged two years or more (mean age 58) who had been diagnosed with invasive pneumococcal disease and had at least one chronic illness recognised as an indication for pneumococcal vaccine.

Age 65 years was considered a recognised indication for pneumococcal vaccine. There was one matched control per case for 20 cases, two matched controls per case for 63 cases and three matched controls per case for two cases. Cases and controls were matched on age, gender, date of hospitalisation, condition that constituted the major indication for vaccination, the recognised duration of that condition, the number of previous hospitalisations and the type of primary medical care. Indications for vaccination were based on medical record review. Ascertainment of vaccination status was based written documentation from hospital records and the patients primary physician. Serotype data were not presented. The available vaccine changed during the course of this study (late 1983) but no data were provided on which vaccine had been received by the vaccinated subjects. Vaccine effectiveness was assessed for either the 14 valent or 23 valent vaccine against any invasive pneumococcal disease rather than the more specific outcome of invasive pneumococcal disease caused by serotypes contained within the relevant vaccine. Risk strata are reported in the results as 'high', 'moderate', 'low' but are undefined so it was not possible to include these subjects in the sub-group analyses.

Forrester 1987

Subgroups: none.

A hospital based case-control study matched 1:1 with subjects restricted to males aged 30 years or more, recruited over 5.5 years (1979 to 1985). The case group consisted of 89 patients who had been diagnosed with invasive pneumococcal disease of a known serotype at the Denver Veterans Administration Center, Colorado, USA. 30% of cases were nosocomially acquired, previous history of invasive pneumococcal disease was not reported. Cases and controls were matched on age, date of hospitalisation and comorbid diseases. Indications for vaccination and ascertainment of vaccination status were obtained from hospital records. All vaccinated subjects had received a 14 valent polysaccharide pneumococcal vaccine. Possible vaccination by physicians outside the hospital system were not evaluated. Although designed as a matched case control study, a matched analysis was not conducted to measure vaccine effectiveness against invasive pneumococcal disease caused by serotypes contained within the vaccine. Instead the indirect cohort method was used which effectively limited the analysis to the "case" arm of the study comparing the vaccination status among those cases due to a serotype contained the 14 valent vaccine to the vaccination status of those cases that were due to a serotype not contained in the vaccine. The study was seriously underpowered for this type of analysis. Of the 89 cases, 20 were immunosuppressed but data were not presented on the serotype and vaccination status of the subgroup.

MMWR 2001

Subgroups: none.

A nested case-control study with two controls per case (unmatched) conducted to investigate an outbreak of pneumococcal pneumonia in 2001 among residents of a nursing home in New Jersey, USA. The case group consisted of nine patients hospitalised with pneumonia between 31 March and 27 April 2001, median age 86 years (range 78 to 100 years). Seven of the nine cases had blood cultures positive for the same pneumococcal serotype. The isolates also belonged to the same clonal group and had similar antibiotic sensitivities. The serotype was a type contained within the 23 valent polysaccharide vaccine. Two controls per case were randomly selected from nursing home residents without symptoms of pneumonia who resided in the wing where most of the cases (seven) had resided. Information on exposures of interest were obtained from nursing home records using a standardised form, these included: vaccination status, recent antibiotic therapy, history of pneumonia, hospitalisations during the preceding year, recognised indications for pneumococcal vaccine and physical functioning. All vaccinated subjects had received the 23 valent vaccine. Although all subjects were elderly, no indication was given of the immunocompetence of the subjects so this study was not included in any subgroup analyses.

Shapiro 1984

Subgroups: immunocompetent, immunocompetent elderly.

A hospital based case-control study matched 1:1 with subjects recruited over 4.5 years (1978

to 1982). The case group consisted of 90 patients aged 18 years or more who presented at the Yale-New Haven Hospital, Connecticut, USA with a first episode of invasive pneumococcal disease and at least one indication for pneumococcal vaccine that had been recognised prior to the selected hospitalisation. Cases and controls were matched on age, date of hospitalisation, condition that constituted the indication for vaccination and the recognised duration of the condition within the study period. Age 55 years was considered a recognised indication for pneumococcal vaccine. Indications for vaccination were based on medical record review. Ascertainment of vaccination status was based written documentation from hospital records, personal physicians and clinics, and nursing home records where appropriate. All vaccinated subjects had received a 14 valent polysaccharide pneumococcal vaccine. For most cases the serotype of the isolates were not determined, no serotype data were presented. Therefore vaccine effectiveness was measured against any invasive pneumococcal disease rather than the more specific outcome of invasive pneumococcal disease caused by serotypes contained within the 14 valent vaccine.

Shapiro 1991

Subgroups: immunocompetent, immunocompetent elderly.

A hospital based case-control study matched 1:1 with subjects recruited over 5.75 years (1984 to 1990) from 11 major hospitals in Connecticut, USA. The case group consisted of 1054 patients with invasive pneumococcal disease of a known serotype who were selected by prospective active surveillance through the microbiology laboratories of participating hospitals. Serotyping was performed without knowledge of the case's vaccination status or eligibility for the study. Cases were aged 18 years or more with at least one indication for pneumococcal vaccine that had been recognised prior to the selected hospitalisation. Age older than 55 years was considered a recognised indication for pneumococcal vaccine. Cases and controls were matched on age, site of hospitalisation, date of hospitalisation, condition that constituted the indication for vaccination and the recognised duration of the condition within the study period. Indications for vaccination were based on medical record review by research assistants blinded to the research hypotheses. Ascertainment of vaccination status was based on written documentation from hospital records, personal physicians and clinics, and nursing home records were appropriate. Subjects may have received either the 14 valent or 23 valent vaccine. Those who had received the 14 valent vaccine and were subsequently infected by a serotype that was in the 23 valent vaccine but not the 14 valent vaccine were classified as unvaccinated. Vaccine effectiveness was measured against invasive pneumococcal disease caused by serotypes contained within the relevant vaccine and against serotypes not contained within the relevant vaccine. Vaccine effectiveness was also determined using the indirect cohort method.

Sims 1988

Subgroups: immunocompetent elderly.

A hospital based case-control study based on the methods of Shapiro and Clemens, 1984 but restricted to subjects aged 55 years or more who were not immunosuppressed. Subjects were recruited from hospital admission records at one of five participating hospitals in eastern Pennsylvania, USA over 6.5 years (1980 to 1986). The case group consisted of 122 patients who had been diagnosed with invasive pneumococcal disease. 17% of cases were nosocomially acquired, previous history of invasive pneumococcal disease was not reported. Two controls were matched per case on site of hospitalisation, date of hospitalisation and comorbid disease/s. Although restricted by age (55 years or more), cases and controls were not matched on age within that group. Exclusion for immunosuppression was based on review of medical records. Indications for vaccination were based on medical record review. Ascertainment of vaccination status was based written documentation from all health care providers listed in the hospital records or nominated by the subject or their next of kin. The available vaccine changed during the course of this study, the 23 valent vaccine replaced the 14 valent in late 1983, but no data were provided on which vaccine had been received by the vaccinated subjects. Serotype of the isolates was only available for 25 cases (21%). Therefore vaccine effectiveness in this study was assessed for either the 14 valent or 23 valent vaccine against any invasive pneumococcal disease rather than the more specific outcome of invasive

disease caused by serotypes contained within the relevant vaccine.

C) RANDOMISED TRIALS EXCLUDED

Austrian 1976, 6v

Novice miners mostly from Malawi and Mozambique starting work at a South African gold mine were randomly assigned to receive pneumococcal vaccine or meningococcal vaccine or placebo. In the initial study 4497 men were recruited in late 1972. A 6-valent vaccine was used. Although there are published results from this trial, they were obtained in March 1974, part way through the trial and 10 months before its anticipated end in January 1975. No explanation was given and no earlier or later results are provided. Because of the possibility of selective reporting of these interim results, for whatever reason, we consider them unsafe and have excluded this trial. Some data from it were pooled with later trials and reported in Austrian 1976b, and these data are included in this review under that heading. This programme of research was discussed in several other papers (Austrian 1975; Austrian 1976b; Austrian 1977; Austrian 1981).

MacLeod 1945

This study is excluded because the cases of pneumonia were not radiologically confirmed and because of inadequate concealment of randomisation practice. Young men at a United States Air Force technical school were vaccinated with one of three lots of 4 valent pneumococcal vaccine (8586 subjects), the lots changing in their preparation and composition, or placebo (8449 subjects). The programme was started in September 1944 and seems to have run until April 1945. It may be assumed that there were very few exclusions in a military population in wartime. Average duration of follow up was 89 days. Allocation was quasi-random: initially haphazard and potentially not concealed, and then alternate. A definition of 'pneumonia' was not given, nor was the basis for allocation to pneumococcal type. The serotype appears to have been determined from sputum samples.

D) NON-RANDOMISED STUDIES EXCLUDED

Bentley 1981

This is a preliminary report from a prospective cohort study, which has been excluded because of significant problems with the study design as outlined below.

The cohort involved patients institutionalised at two chronic care institutions in the Rochester, New York area. Subjects were followed for the first 12 months or until discharged. There were 998 patients institutionalised when the trial began and an additional 546 who were admitted in the first 12 months. Although described as elderly, no data are provided on the age of the subjects. The exposure of interest was pneumococcal vaccination status and the outcome of interest included institutionally acquired pneumonia with *S. pneumoniae* isolated from a normally sterile site.

The primary physician selected patients to be offered pneumococcal vaccine with no guidance from the study group. This may have resulted in different risk profiles among the vaccinated and unvaccinated cohort. No data are provided on differences between the vaccinated and unvaccinated group in terms of age, chronic disease or immunosuppression. Assessment of person-time at risk was poorly defined. The number of vaccines and non-vaccinees were approximated based on assessments of vaccination status assessed at four points in time during the year. It is not clear whether persons vaccinated during the observation period were included as having contributed person-time first to the unvaccinated cohort and then to the vaccinated cohorts. Losses to follow-up were not specified. The person-time required in the cohort prior to an outcome being 'institutionally acquired' was not defined. Only four patients, all with radiologically confirmed pneumonia and blood cultures positive for *S. pneumoniae*, met our definition of invasive pneumococcal disease. Two vaccinated patients both had non-vaccine serotypes detected from blood cultures, while one unvaccinated patient had a vaccine serotype and another unvaccinated patient a non-vaccine serotype.

Bolan 1986

These data are included in the subsequent report by Butler et al (Butler 1993).

Brieman 2000

Subgroups: none.

A hospital based matched case-control study with subjects recruited over 3.25 years (1992 to

1995) from four hospitals in Atlanta, USA. The case group consisted of 176 patients aged 18 to 55 years who were known to be HIV seropositive before admission to one of the participating hospitals with invasive pneumococcal disease. Serotyping was performed without knowledge of the case's vaccination status. Cases and controls were matched by date of hospitalisation, hospital of admission and HIV stage based on either CD4 lymphocyte count or clinical stage. Potential controls were excluded if they had any evidence of pneumococcal disease or pneumonia of unknown aetiology. There was one matched control for 25 cases and two matched controls for 151 cases. Ascertainment of vaccination status was obtained by contacting all physicians who had cared for each subject since 1988. No information is provided on how physicians were identified or how many physicians were contacted per subject. Based on the study period, vaccinated subjects would have received the 23 valent vaccine. Vaccine effectiveness was measured against any invasive pneumococcal disease and against the more specific outcome of invasive pneumococcal disease caused by serotypes contained within the 23 valent vaccine.
This study is excluded because the subjects were HIV positive.

Broome 1980

These data are included in the subsequent report by Butler et al (Butler 1993).

Christensen 2001

This is an interim report of the first six months of a three year prospective study involving all individuals aged 65 years or more in Stockholm County, Sweden (259,627 persons). Subjects were offered influenza and/or pneumococcal vaccination over an eight week period (22 September 1998 to 13 November 1998) and the details were recorded including an identification code unique to each Swedish citizen. The vaccination data were matched against hospital discharge data using the unique identification number. The outcome of interest was the discharge diagnoses based on ICD-10-CM coding from all hospitals in Sweden and included invasive pneumococcal disease (ICD-10: A40.3, G00.1). There are no data provided in the interim report to validate the discharge coding but it has been assumed that the coding is valid and as such meets our definition of invasive pneumococcal disease. This study is excluded due to the lack of any controlling for potential confounders inherent in the unadjusted data from a cohort study.

Dworkin 2001

This is a retrospective cohort study conducted in the USA of 39,086 HIV-infected persons identified from January 1990 to December 1998. Pneumococcal disease was defined as physician-diagnosed pneumonia, meningitis, bacteraemia, sepsis, endocarditis, pleural effusion, or joint infection for which *S. pneumoniae* was identified as the etiologic agent. The method used to identify *S. pneumoniae* was not recorded and there were no data provided on vaccine effectiveness against invasive pneumococcal disease. As such the study does not provide data of the types included in this review.

Methodological qualities of included studies

Table 01 shows quality assessment scores of the randomized controlled trials using the system of Jadad 1996. On the 0 to 5 scale, seven of the 15 studies scored three or better, with a median publication date of 1987, and eight scored two or worse, with a median publication date of 1977.

Results

Results (A) - randomised controlled trials
ALL TRIALS
Outcome 1 - Definitive pneumococcal pneumonia: eight trials
Including Kaufman: odds ratio = 0.28 (confidence intervals 0.15, 0.52) $p < 0.0001$, heterogeneity $p = 0.41$(random effects model);
Omitting Kaufman: odds ratio = 0.40 (confidence intervals 0.16, 1.02) $p = 0.05$: heterogeneity $p = 0.39$ (random effects model);
Omitting Kaufman: odds ratio = 0.35 (confidence intervals 0.16, 0.77) $p = 0.009$ (fixed effects model).

Combining all eight studies returns a highly significant result favouring vaccination, with no significant heterogeneity. This analysis is dominated by one study, Kaufman (Kaufman 1947), which reported an odds ratio of 0.21 (confidence intervals 0.10, 0.45) and which receives 54% of the weight. Omitting this study, which is the oldest of the eight and which received a quality score of zero gives a less strong result which is statistically significant only if the fixed effects model is used.
The forest plot sorted by year shows that the evidence for efficacy is coming chiefly from the older studies. The three studies conducted up to 1985 all had odds ratios less than 0.3, while four of the five more recent studies had odds ratios of 0.8 or more (the exception is Ortqvist (Ortqvist 1998) who saw one case among the vaccinees and five among the controls, giving odds ratio = 0.21). The correlation between odds ratio and year of study is however not statistically significant (p = 0.13, Kendall's tau).
Given limited number subjects with definitive pneumococcal pneumonia (there were only seven cases of definitive pneumococcal pneumonia in the control group of the five most recent studies), there was insufficient power to test whether or not definitive pneumococcal pneumonia was being prevented.
Outcome 2 - Definitive pneumococcal pneumonia (vaccine types only): four trials
Including Kaufman: odds ratio = 0.18 (confidence intervals = 0.05, 0.58) p = 0.004, heterogeneity p = 0.5 (random effects model)
Omitting Kaufman: odds ratio = 0.27 (confidence intervals 0.06, 1.19) p = 0.08, heterogeneity p = 0.052 (random effects model);
Omitting Kaufman: odds ratio = 0.24 (heterogeneity 0.06, 0.96) p = 0.04 (fixed effects model).
As with outcome 1, the result is significant but this is largely due to the influence of Kaufman (Kaufman 1947). Omitting Kaufman returns a borderline result whose statistical significance depends on the model used. The problem of insufficient power noted for outcome 1 is further compounded for this more specific outcome.
Outcome 3 - Presumptive pneumococcal pneumonia: seven trials
Including Kaufman: odds ratio = 0.52 (confidence intervals 0.31, 0.87) p = 0.01, heterogeneity p = 0.0039 (random effects model);
Omitting Kaufman: odds ratio =0.60 (confidence intervals 0.34, 1.06) p = 0.08, heterogeneity p = 0.022 (random effects model).
The same pattern is seen: a significant result which is highly dependent on the oldest study, Kaufman (Kaufman 1947).
The statistically significant heterogeneity among the remaining six studies can be explained by contrasting the two oldest studies, each of which individually showed a significant benefit from vaccination, and the four more recent studies which all showed no significant effect. Smit (Smit 1977, Grp 1), Grp 1 odds ratio = 0.37, Smit (Smit 1977, Grp 2), Grp 2 odds ratio = 0.31. Klastersky (Klastersky 1986), odds ratio = 0.24, Simberkoff (Simberkoff 1986), odds ratio = 1.07; Davis (Davis 1987), odds ratio = 0.57, Ortqvist (Ortqvist 1998) odds ratio = 1.04.
Although Klastersky showed a very small odds ratio, it was a small trial with only four cases of pneumonia, and this result is not inconsistent with the other recent trials.
Outcome 4 - Presumptive pneumococcal pneumonia (vaccine types only): five trials
Including Kaufman: odds ratio = 0.29 (confidence intervals 0.10, 0.84) p = 0.02, heterogeneity p = 0.005 (random effects model);
Excluding Kaufmann: odds ratio = 0.41 (confidence intervals 0.13, 1.30) p = 0.13, heterogeneity p = 0.021 (random effects model).
Once again, the trend in favour of vaccination depends critically on the Kaufman study to achieve statistical significance. The statistically significant heterogeneity among the remaining four studies is due to a discrepancy between the two oldest studies, which each individually showed a significant benefit from vaccination, and the two more recent studies which each showed no effect: Smit (Smit 1977, Grp 1), Grp 1 odds ratio = 0.08; Smit (Smit 1977, Grp 2), Grp 2 odds ratio = 0.23, Simberkoff (Simberkoff 1986), odds ratio =1.07; Ortqvist (Ortqvist 1998), OR = 1.04.
Outcome 5 - Pneumococcal disease: three trials

The only useful data are from Austrian (1976): odds ratio = 0.18 (confidence intervals 0.09, 0.34) p < 0.0001. These are "lumped" data, reflecting the combined results of several trials with total denominators of 3953 vaccinees and 8024 controls, although the 13-valent trial itself included only 1493 vaccinees and 3002 controls. The total frequencies of pneumococcal disease were published in 1976 in graphical form only, without denominators: the values just quoted were provided by Prof. Austrian (personal communication). The other two trials reporting this outcome were Klastersky 1986 (no cases) and Leech 1987 (1 case, a vaccinee).
Outcome 6 - Pneumonia (all causes): 14 trials
odds ratio = 0.77 (confidence intervals 0.58, 1.02) p = 0.06, heterogeneity p < 0.0001 (random effects model);
odds ratio = 0.84 (confidence intervals 0.65, 1.08) p = 0.17, heterogeneity p < 0.0001 (random effects model, omitting Kaufman (Kaufman 1947);
odds ratio = 0.81 (confidence intervals 0.61, 1.08) p = 0.16, heterogeneity p < 0.0001 (random effects model, omitting Gaillat (Gaillat 1985) and Klastersky (1986)).
This outcome synthesises data from 14 of the 15 studies we have included. There is substantial and highly significant heterogeneity in the outcome (chi-squared = 108, 13df, p < 0.0001) so that a random effects model is necessary.
The result suggests a possibly substantial but not quite statistically significant reduction in the incidence of pneumonia. However this result relies heavily on several very old, poorly reported studies of dubious methodological quality. Eliminating just one such, (Kaufman 1947) removes the statistical significance of the result. Adjusting for publication bias by deleting the two least precise studies which had results favourable to vaccination (see below) similarly removes the significance.

HETEROGENEITY: sorting the forest plot by year shows a clear trend of reducing efficacy in the series of trials conducted from 1947 to 1980. Five of the seven trials from 1980 onwards show a slight disadvantage from vaccination. We have therefore explored the heterogeneity in this outcome by progressively eliminating the oldest studies. Table 02 shows the combined odds ratio, its p-value, and the heterogeneity p-value from analyses that progressively eliminate the oldest remaining studies, first eliminating Kaufman (Kaufman 1947) and finally leaving only the three studies performed in 1997 or later. When the analysis is restricted to the most recent nine or fewer studies, there is a non-significant trend towards vaccination being harmful, and there is no significant heterogeneity among these studies.

Several conclusions can be drawn from this exercise:
1. The collection of all 14 studies return highly heterogeneous results, but together are (borderline) significant in favour of vaccination;
2. This result is NOT robust to the likely impact of slight publication bias.
3. The heterogeneity between studies is due to a difference between the early studies and the more recent studies, from whatever cause;
4. The more recent studies are consistent, and together provide no evidence of vaccine efficacy in reducing the incidence of pneumonia.
The trend towards lack of effect and greater consistency between studies as the oldest studies are eliminated argues against this set of studies as a whole providing any evidence that vaccination with pneumococcal polysaccharide vaccines reduces the incidence of pneumonia. The final, most recent three studies are remarkably consistent as is indicated by the p-value for heterogeneity: Koivula (Koivula 1997) odds ratio = 1.15; Ortqvist (Ortqvist 1998) odds ratio = 1.18; Honkanen (Honkanen 1999) odds ratio = 1.16. These odds ratios greater than 1 reflect a slightly higher incidence of pneumonia among the vaccinated group, though the combined value of 1.16 is not significantly different from 1. As indicated in the study descriptions, Koivula (Koivula 1997) and Honkanen (Honkanen 1999) are similar designs and both measure the incremental benefit of both influenza and pneumococcal vaccine above that influenza vaccine alone in the prevention of pneumonia.
PUBLICATION BIAS: A funnel plot for all-cause pneumonia suggests that there may be

selection bias (publication bias). Two low-precision studies, Gaillat (Gaillat 1985) and Klastersky (Klastersky 1986), are well to the left of the plot, indicating an odds ratio less than one in favour of vaccination. There are no corresponding small trials to the right, as would be expected in the absence of selection bias. Gaillat (Gaillat 1985) has the smallest odds ratio of all 14 studies in this analysis at 0.20 (confidence intervals 0.06, 0.70). The low precision of this study outcome is not due to a small sample size, but to a low incidence of pneumonia: only three among 937 vaccinees versus 12 of 749 control subjects, an overall incidence of 0.9%. Omitting these two studies from the analysis eliminates the statistical significance of the result.
We have also examined the likely impact of publication bias using the 'Trim and Fill' method of Duval and Tweedie (Duval 2000). This method considers the degree of imbalance in a funnel plot, i.e. the excess of small studies on one side of the plot, and estimates how many studies may be missing from the other side that if replaced would re-balance the plot. At the first iteration, their L0 method suggested that there might be just one study missing, although this was not statistically significant (L0 = 1.3, p = 0.28). After trimming the single most extreme study, Gaillat (Gaillat 1985), there was no suggestion of any further excess of extreme studies (L0 = 0.4). We therefore completed the procedure by imputing a study similar to Gaillat (Gaillat 1985) but with the opposite result, i.e. with an log odds ratio of +1.33 instead of -1.33. Analysis of the augmented set of 15 studies yielded a combined random effects odds ratio of 0.81 (confidence intervals 0.61, 1.07) not very different from the original result of 0.77 (confidence intervals 0.58, 1.02).
Outcome 7 - Bronchitis: six trials
There was no apparent overall effect of vaccination on the incidence of bronchitis: random effects model, odds ratio = 1.02, confidence intervals 0.84, 1.23, p = 0.90, heterogeneity p = 0.041. The modest heterogeneity is ascribable to the by now expected trend towards greater benefit from vaccination in the older trials. The oldest trial, Smit (1977), showed the smallest odds ratio of 0.57, while the three trials conducted in 1980 or later all showed trends against vaccination. However no individual trial was significant in either direction.
Outcome 8 - Mortality (all causes): 11 trials
Again there is significant heterogeneity (chi-squared = 39, 10df, p < 0.0001). A random effects analysis of the odds ratio returns odds ratio = 0.90 (confidence intervals 0.76, 1.07), p = 0.20, suggesting a modest and not statistically significant benefit from vaccination.
The heterogeneity is chiefly attributable to Kaufman 1947 which gave a very low odds ratio of 0.36. Eliminating this study leaves no remaining statistically significant heterogeneity (heterogeneity p = 0.14). A fixed-effects analysis of the odds ratio now returns odds ratio = 0.95 (confidence intervals 0.90,1.01) p = 0.12: thus although the precision is improved by removing the anomalous study, the combined estimate is moved substantially towards the null hypothesis (odds ratio = 1) so that there is still no evidence of any effect of vaccination on mortality.

PUBLICATION BIAS: A funnel plot for the outcome 'Mortality (all causes)' shows no asymmetry, because the two small studies had mortality odds ratios close to the overall summary odds ratio. The most extreme study was Kaufman (Kaufman 1947) with an odds ratio of 0.36, but this study had the median precision among the 11 studies in this analysis and so makes no suggestion of selection bias detectable in the funnel plot.

Outcome 9 - Mortality due to pneumonia: eight trials
Odds ratio = 0.72 (confidence intervals 0.44, 1.19) p = 0.2, heterogeneity p = 0.0003 (random effects model).
There is no significant reduction in mortality from pneumonia. The heterogeneity is attributable to a steady reduction in apparent efficacy in the series of large trials conducted from 1947 to 1980: Kaufman (Kaufman 1947) odds ratio = 0.28; Riley (Riley 1977), odds ratio = 0.57; Austrian (Austrian 1980, Grp1), Grp1 odds ratio = 0.87; Austrian (Austrian 1980, Grp2), Grp2 odds ratio = 0.95; Simberkoff (Simberkoff 1986), odds ratio = 2.02. The subsequent three trials were all relatively small.

A logistic regression model including study effects and a treatment by year interaction shows the vaccination odds ratio increasing significantly over time, by a factor of 1.38 per decade (confidence intervals 1.20, 1.58, $p < 0.001$). The value of 1 (no difference) occurred according to this model in about 1986, and for 1947 the model predicts an odds ratio of about 0.28, fitting the 0.28 reported by Kaufman. We do not of course propose using the model to estimate present efficacy, since that would suggest that use of these vaccines has by now become distinctly dangerous, but these results do serve to emphasize the strong trend in the data and to caution against reliance on the early studies.
Outcome 10 - Mortality due to pneumococcal infection: two trials
odds ratio = 1.55 (confidence intervals 0.20, 11.9) $p = 0.7$, heterogeneity $p = 0.52$ (fixed effects model).
There is little data, and essentially no evidence either way regarding an effect of vaccination on this outcome.

RESULTS (B) - NON-RANDOMISED STUDIES

The data contributing to these analyses are shown in Additional Tables 3 and 4.

There is statistically significant evidence that vaccination is effective in reducing the risk of invasive pneumococcal disease (IPD). The odds ratio for all subjects is estimated as 0.47 (confidence intervals 0.37, 0.59) corresponding to an efficacy of 53%.

Outcome 1 - invasive pneumococcal disease (IPD)

* All data (4 studies) Efficacy 53% (confidence intervals 41, 63)
* Immunocompetent (two studies) Efficacy 56% (42, 66)
* Immunocompetent elderly (1 study) Efficacy 70% (confidence intervals 37, 86)

Outcome 2 - IPD (vaccine types)

* All data (three studies) Efficacy 56% (47, 63)
* Immunocompetent (three studies) Efficacy 57% (46, 66)
* Immunocompetent elderly (one study) Efficacy 75% (confidence intervals 57, 85)

Discussion

Pneumonia (all causes) and mortality (all causes) are probably the most readily understood outcomes, and most randomised studies reported one or both. They offer the opportunity to estimate the benefit a vaccination programme might bring to a population where the incidence of pneumonia and/or the mortality rates are known. The most fully reported outcome in the review is pneumonia (all causes), with data from 14 randomised studies. Examination of these data, and in particular the trend over the decades towards increasing trial quality, increasing vaccine valency, and yet decreasing apparent effect, suggests that a large, high quality study undertaken now might well fail to show any effect of polysaccharide pneumococcal vaccine on the incidence of pneumonia.

Possible reasons for this trend include that the early trials were in the pre-antibiotic era. Confirming pneumococcal disease is much harder now. Moreover, while pneumonia and death are easy to record, it is difficult to measure how much of this is due to *S. pneumoniae*. It was therefore decided, in the light of negative results from a review of randomised data only, that consideration of non-randomised studies would be added to this systematic review, thus providing an alternative means by which the vaccine might prove its worth. These studies indeed show that the vaccine is effective against invasive pneumococcal disease in immunocompetent persons, including the elderly.

We have reported sensitivity analyses exploring the influence of the study by Kaufman (Kaufman 1947). Examination of tables five to nine in the review by Hutchison (Hutchison 1999) suggests that this very old, incompletely reported study might by itself account for all their significant meta-analysis results.

The vaccine trials have studied its use in a wide variety of groups, with differing incidence of disease. The proportion of subjects developing pneumonia of any cause varied between 0.7% and 22.9% in included studies. There was no relationship between incidence of pneumonia and whether the trial gave positive results. Watson (Watson 2002) has suggested that the proportion of pneumonia due to *S. pneumoniae* in the population under study may be the critical factor in demonstrating an effect against all-cause pneumonia. Those populations where a high proportion of pneumonia is due to *S. pneumoniae* would be more likely to show a reduction in all-cause pneumonia due to vaccination. However, ascertaining the proportion of pneumonia which is due to *S. pneumoniae* is problematic (Fedson 1999).

While the proportion of pneumonia due to *S. pneumoniae* in the population under study may be one explanation for the failure to demonstrate efficacy against all-cause pneumonia, it is plausible that vaccination may protect against severe disease (blood stream infection, serious complications and death from blood stream invasions) but fail to prevent even pneumococcal pneumonia. Invasive pneumococcal disease is a rare disease, at the severe end of the spectrum of disease caused by *S. pneumoniae*. There were not sufficient cases of invasive pneumococcal disease among the randomised trails to enable assessment of this outcome. The case-control studies demonstrate that the polysaccharide pneumococcal vaccines were effective in preventing invasive pneumococcal disease among immunocompetent adults and the immunocompetent elderly.

The evidence of the case control studies seems to point to the vaccine protecting against severe infection, e.g. that accompanied by pneumococcal bacteraemia. It is difficult to estimate how great a problem that may be in any population. In contrast the most robust evidence, the meta-analyses of all-cause pneumonia and death, were the outcomes determined in nearly every trial. The combined randomised trials failed to show protection against these two major outcomes, which the vaccine might have been expected to prevent.

Although the reported incidence of invasive pneumococcal disease (0.008% to 0.030%) is much lower than all-cause pneumonia found in the randomised trials, mortality is reported to be 16 to 36% among all adults and 28 to 51% among those aged 65 years or more (Fedson 1999). Given the effectiveness of the polysaccharide vaccine against IPD demonstrated by the non-randomised studies, and the increasing antibiotic resistance of the organism (Klugman 1999), vaccination of persons at high risk of the disease but not severely immunocompromised may be indicated. The cost effectiveness of such a policy will of course depend on local conditions (Sisk 1997).

We did not find evidence to demonstrate that the polysaccharide vaccine is effective against invasive pneumococcal disease in severely immunocompromised adults.

Conclusions

Implications for practice

We believe the case for more widespread use of the vaccine is not unequivocally proven. The decision to offer vaccination must rest upon a difficult estimate of its local value in preventing invasive pneumococcal pneumonia, combined with a hope that it may afford some protection against pneumonia and death.

Implications for research

Given the seeming effectiveness of the vaccine in protecting individuals against IPD, commencing new randomised trials in populations at risk (principally, the elderly) would face ethical difficulties. The question of whether this class of vaccines prevents pneumonia and death to a measurable degree may be accessible only through ecological studies, comparing entire populations under different vaccination policies. Polysaccharide vaccines may however have a place as control treatments in randomised trials of the newer conjugate vaccines, which this review does not consider.

Internal sources of support to the review

* St. Helens Multidisciplinary Audit Advisory Group UK

External sources of support to the review

*

Potential conflict of interest

None on the part of the authors.

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Professor Tom Jefferson and Professor Bob Douglas for encouragement and direction. Ron D'Souza, Acute Respiratory Infections Review Group Coordinator, for practical assistance in conducting this review.

Contribution of Reviewer(s)

Holden and Tatham were involved throughout, including in the preparation of the protocol and the initial searches for contributing studies.

Dear joined in November 1999 to assist with data extraction and meta-analysis of the RCTs.

Andrews joined in May 2001 to assist with incorporating non-randomised studies in the review.

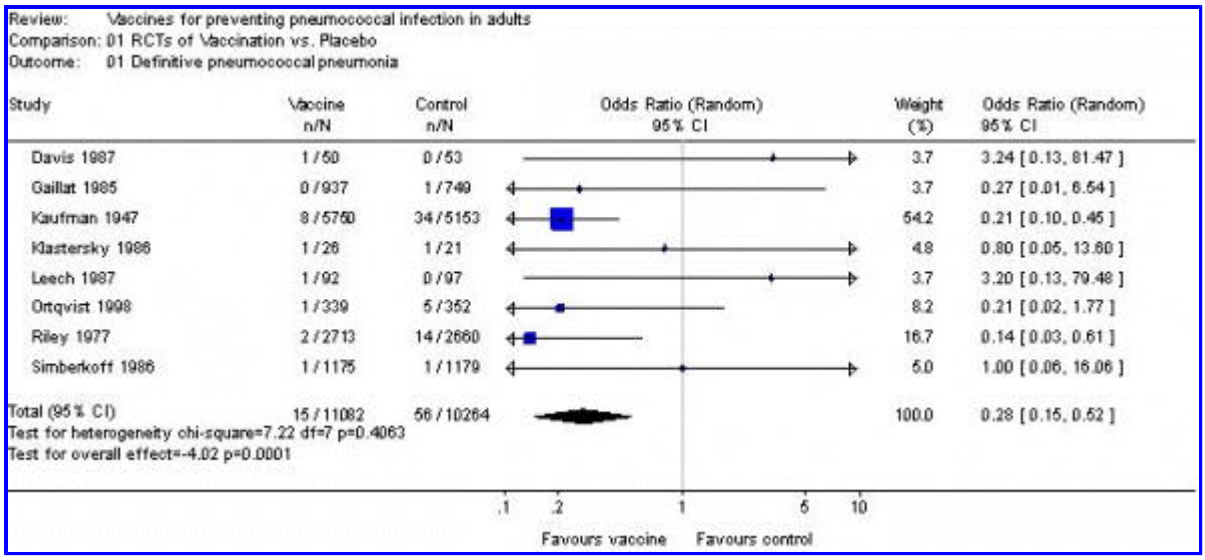
Synopsis

Polysaccharide pneumococcal vaccines do not appear to reduce pneumonia or pneumonia-related deaths in adults, but may be able to reduce invasive pneumococcal disease

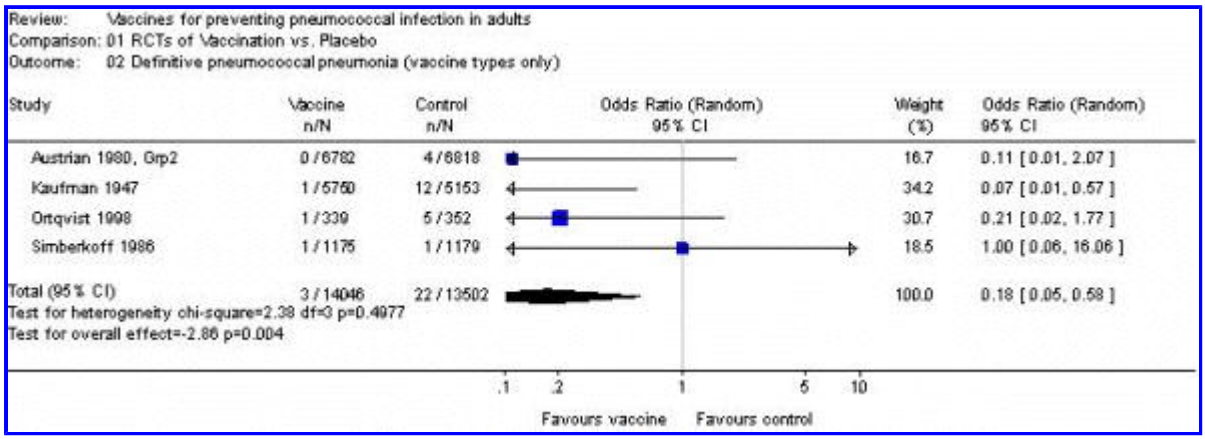
Pneumococcal bacteria are one of the main causes of pneumonia, a lung infection with a high mortality rate (about 25%). It is especially
life-threatening in older people and people with immune system problems (including HIV/AIDS). The review of trials of polysaccharide pneumococcal vaccines found that they do not reduce the incidence of pneumonia or deaths from pneumonia. However, research from other types of studies suggest that the vaccine may be able to reduce the incidence of another serious disease caused by these bacteria, invasive pneumococcal disease.

Table of comparisons

Fig 01 RCTs of Vaccination vs. Placebo



Definitive pneumococcal pneumonia



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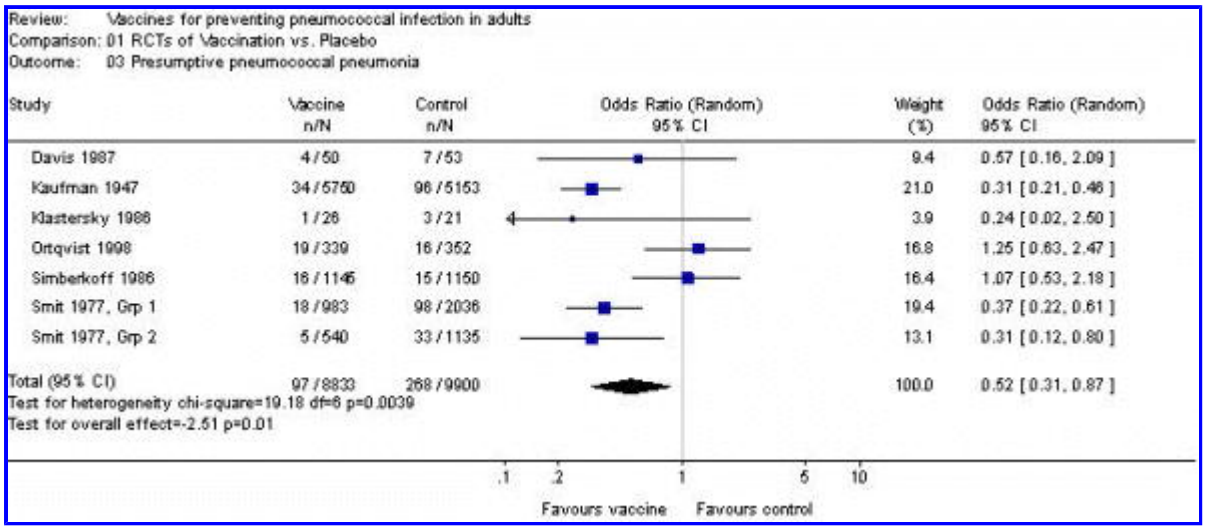
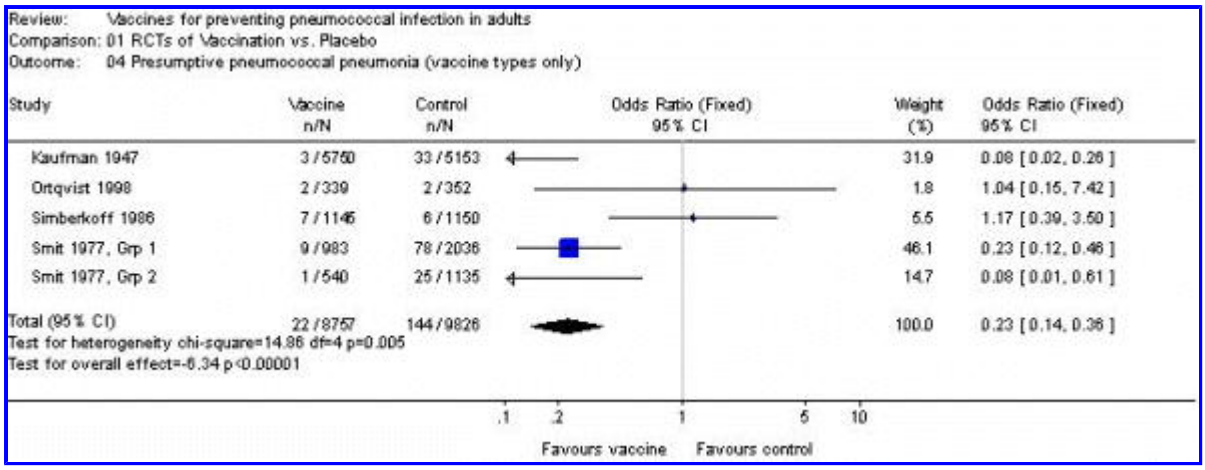
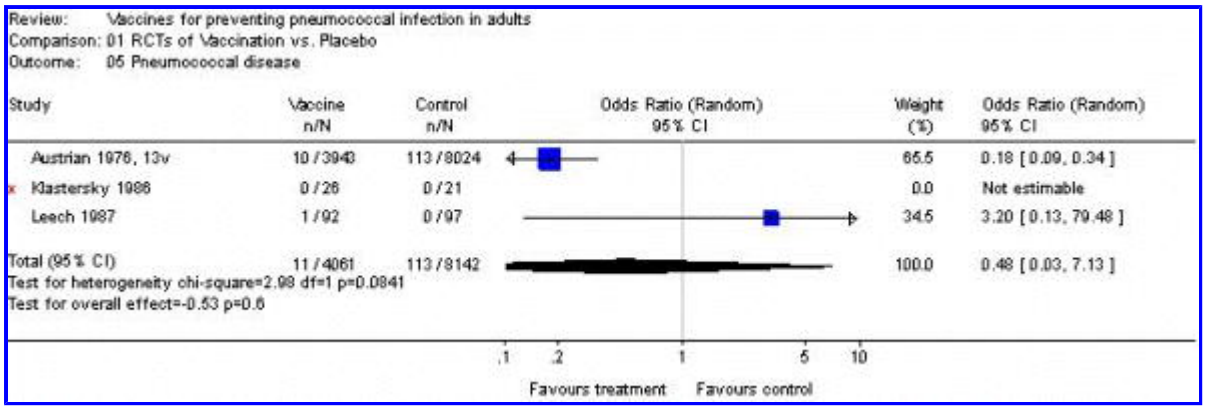


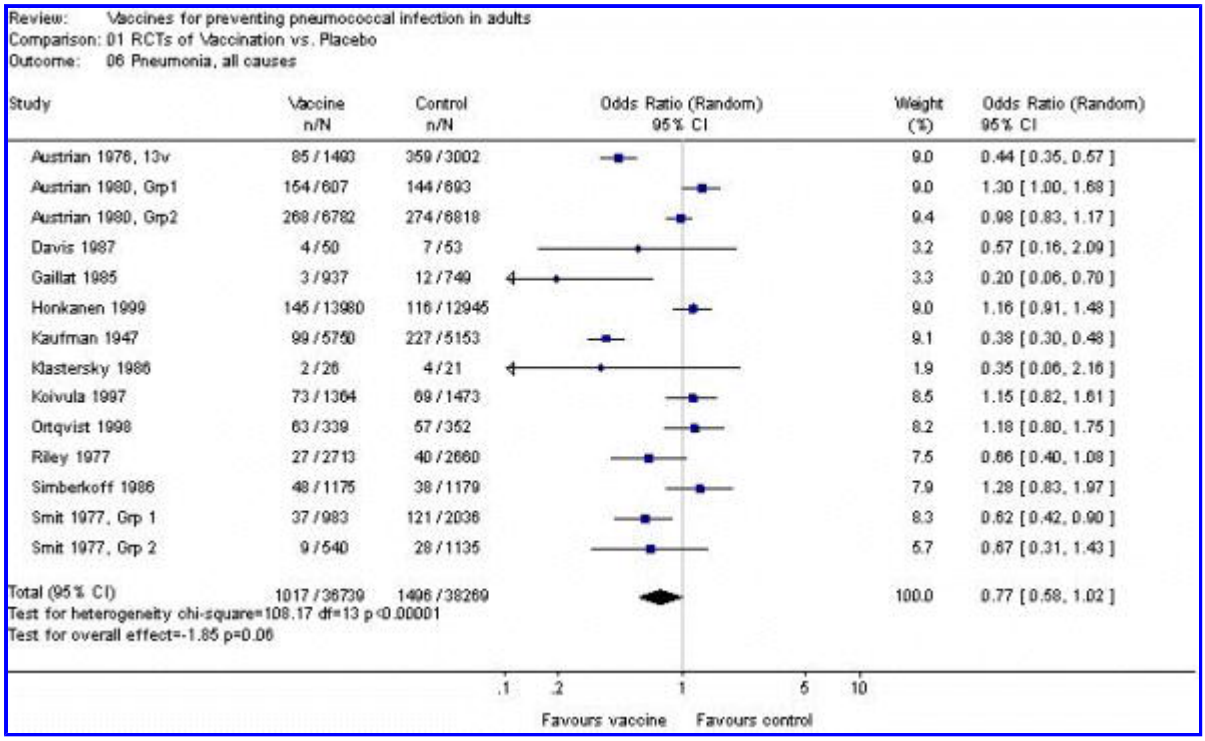
Presumptive pneumococcal pneumonia



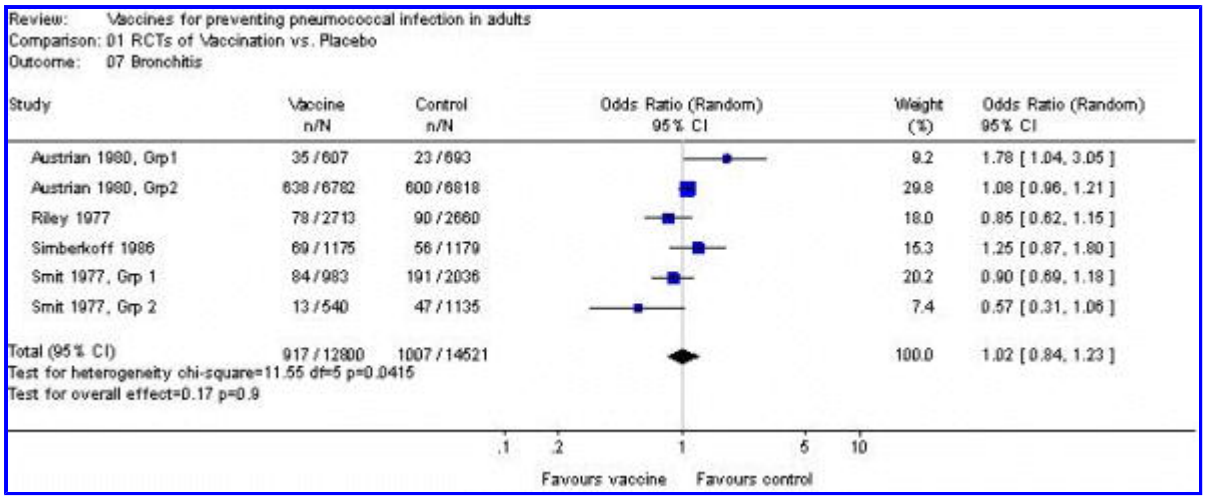
Presumptive pneumococcal pneumonia (vaccine types only)



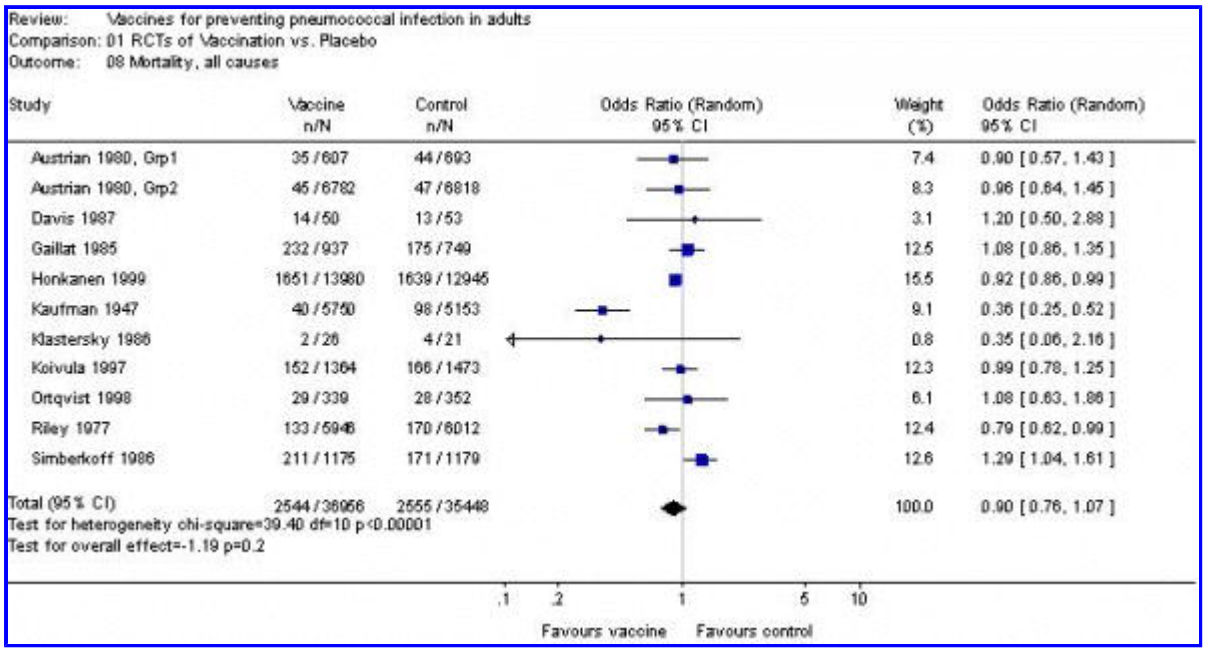
Pneumococcal disease



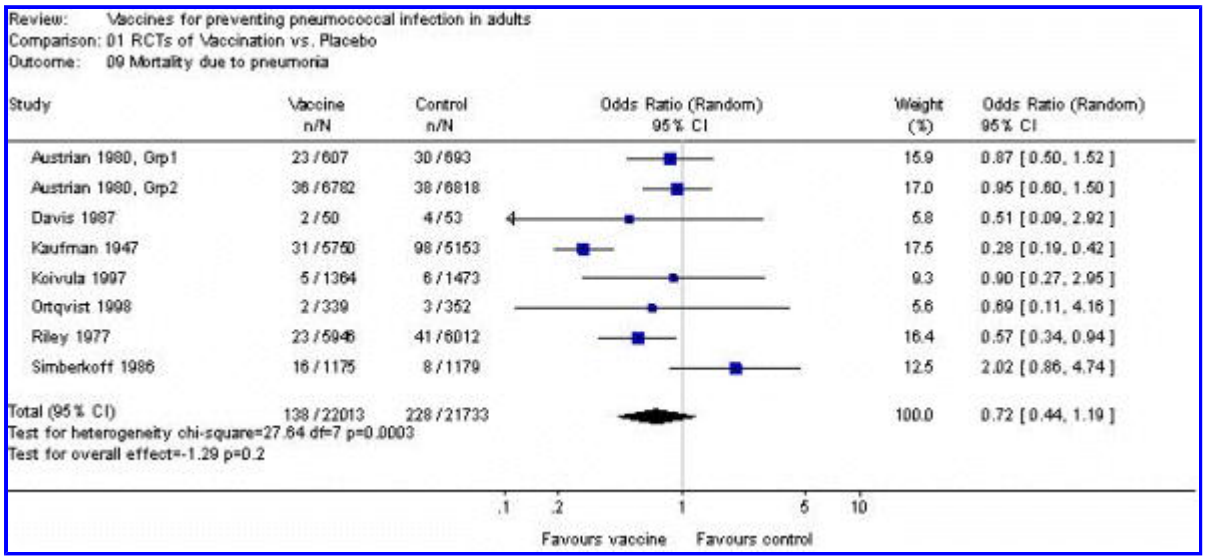
Pneumonia, all causes



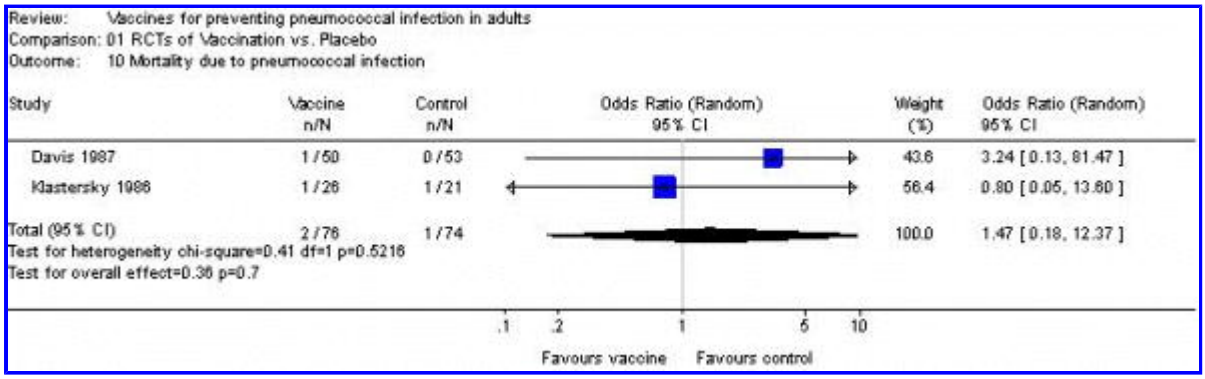
Bronchitis



Mortality, all causes



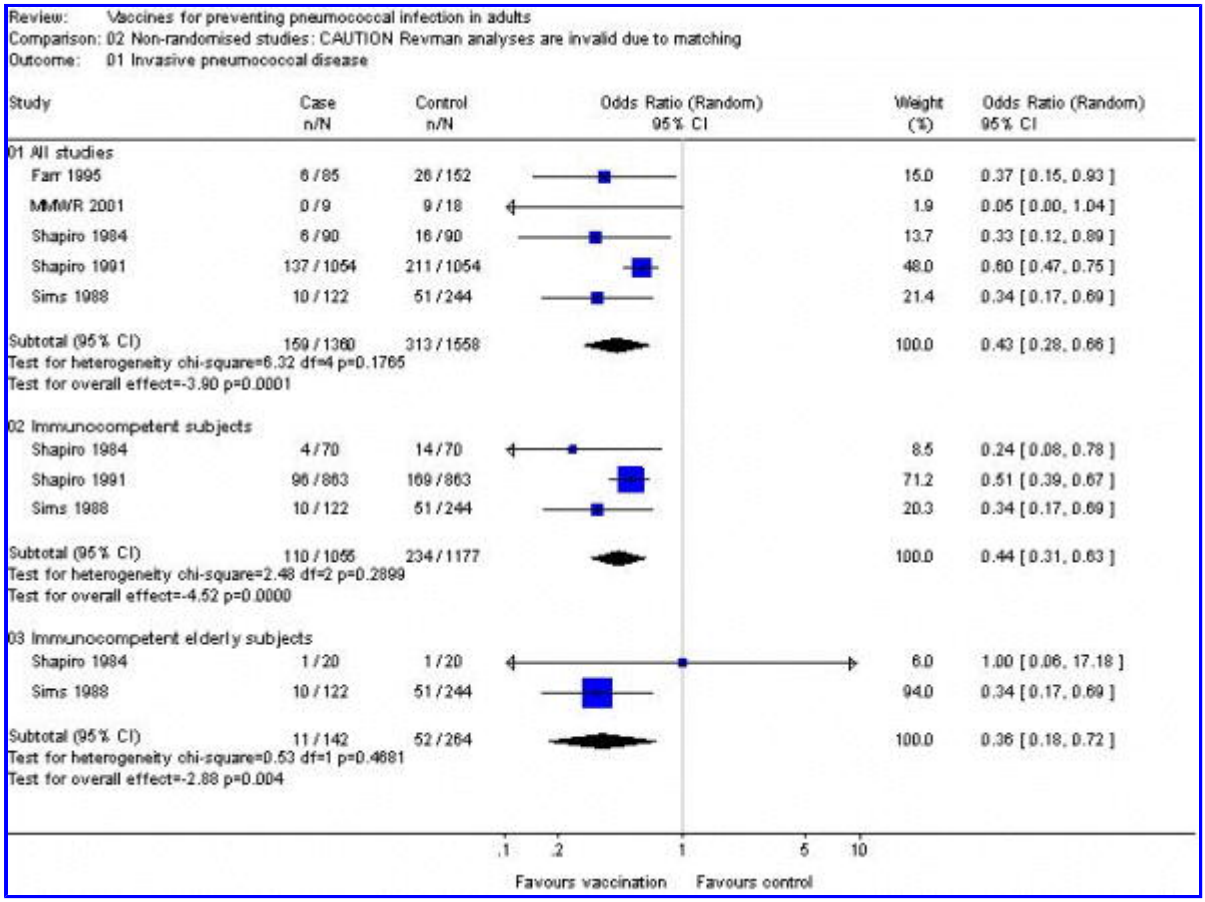
Mortality due to pneumonia



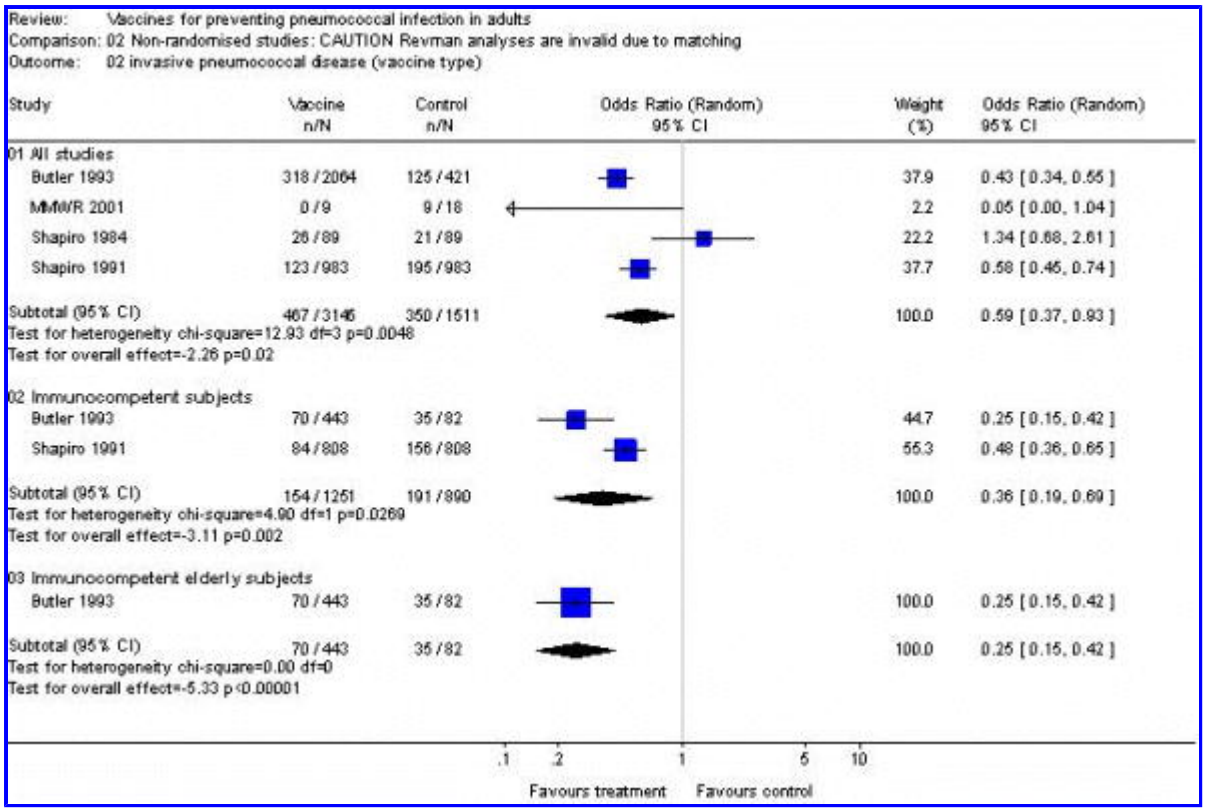
Mortality due to pneumococcal infection

Table of comparisons

Fig 02 Non-randomised studies: CAUTION Revman analyses are invalid due to matching



Invasive pneumococcal disease



invasive pneumococcal disease (vaccine type)

Characteristics of included studies

Study: Austrian 1976, 13v

Methods: Patients assigned vaccine/control from table of random numbers.

3 trials conducted.

Participants: 12000 young adult males mostly from Malawi and Mozambique working at the East Rand Proprietary Mine, Johannesburg, South Africa.

Interventions: 6-valent pneumococcal vaccine, Group A meningococcal vaccine or saline placebo.

13 valent vaccine later used.

Outcomes: Putative pneumococcal pneumonia, pneumococcal bacteremia.

Notes:

Allocation concealment: D

Study: Austrian 1980, Grp1

Methods: Patients randomly assigned to receive two 6-valent vaccinations or saline 'in double-blind fashion'

Participants: 1300 adult inpatients (older than three months), Dorothea Dix Mental Hospital, USA.

Interventions: 607 vaccinees; 693 controls.

6-valent vaccine or saline placebo.

Outcomes: Pneumonia, death, antibody levels

Notes:

Allocation concealment: D

Study: Austrian 1980, Grp2

Methods: Patients randomly assigned by colour codes.

Participants: 13,600 adults, Kaiser Permanente Health Plan, USA

Interventions: 6782 vaccinees; 6818 controls.

12-valent vaccine or saline placebo.

Outcomes: Pneumonia, death, antibody levels

Notes:

Allocation concealment: D

Study: Butler 1993

Methods: Unmatched case-control: CASES: patients with vaccine-type disease, CONTROLS: similar patients with serotypes not in the vaccine.

Participants: 2837 patients with pneumococcal bacteremia or meningitis. Median age 57 (515 vaccinated patients), 50 (2322 unvaccinated patients).

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Davis 1987

Methods: Double blind randomized controlled trial.

Patients arranged into 2 groups by table of random numbers.

Participants: 103 adults, New York, USA

Patients had COPD.

Interventions: 50 vaccinees, 53 controls.14-valent vaccine or saline placebo.

Outcomes: Antibody titres, bacteriology of sputum, respiratory infections or pneumonias and deaths.

Notes:

Allocation concealment: D

Study: Farr 1995

Methods: Matched case control: CASES: invasive pneumococcal disease plus a chronic illness listed as indicating vaccination CONTROLS: selected from all hospitalized patients, matched by age, gender, date of hospitalization, type and duration of chronic illness and more.

Participants: 85 cases, 152 controls. Up to three matched controls per case.

Ages at least two, mean 58 years.

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Forrester 1987

Methods: Hospital-based case-control study: matching by age, date of hospitalization and comorbid disease.

Participants: 89 males with invasive pneumococcal disease over 30 years old, and 1:1 matched controls.

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Gaillat 1985

Methods: Randomisation according at residential home level according to proportion of 'high-risk patients in each.

Participants: 1686 people in France aged between 55 & 85 yrs.

Interventions: 937 vaccinees; 749 controls.

14 valent vaccine.

Outcomes: Pneumonia or death

Notes:

Allocation concealment: D

Study: Honkanen 1999

Methods: Participants assigned according to year of birth, but some cross-over according to patient preference

Participants: 26295 people living in 35 districts in Northern Finland

Interventions: Over two years 13980 people received 23-valent pneumococcal vaccine and 12945 acted as controls. Both group received influenza vaccination

Outcomes: Pneumonia or death

Notes:

Allocation concealment: D

Study: Kaufman 1947

Methods: Controlled trial.

Patients selected at random during the pneumonia season.

Participants: Patients of New York City Home, USA.

Interventions: 5750 vaccinees; 5153 controls.

Type I & II polysaccharides administered. Later types I, II, III pneumococci polysaccharides administered.

Outcomes: Blood serum; incidence of pneumonia; death.

Notes: A continuation of Kaufman (1941)

Allocation concealment: D

Study: Klastersky 1986

Methods: Randomised controlled trial.

Participants: 47 patients in Brussels, Belgium with bronchogenic carcinoma prior to receiving radiotherapy/chemotherapy.

Interventions: 26 vaccinees; 21 controls.

17 valent vaccine or saline placebo.

Outcomes: Pneumonia or death

Notes:

Allocation concealment: D

Study: Koivula 1997

Methods: Randomised controlled trial.

Participants: 2837 elderly inhabitants of the study catchment area (Varkus, Finland).

Interventions: 1364 vaccinees; 1473 controls.

14 valent vaccine & influenza vaccine or influenza vaccine alone.

Outcomes: Pneumonia; death.

Notes:

Allocation concealment: D

Study: Leech 1987

Methods: Double blind randomized controlled trial. Follow-up for two years at six monthly intervals.

Participants: Charts of all patients in OPD at Montreal chest hospital, Canada between Jananuary and June. 1981

Interventions: 92 vaccinees; 97 controls.

14 valent vaccine or saline placebo given alongside influenza vaccine.

Outcomes: Death; interviews to discover: hospital admissions; length of hosptial stay; visits to emergency depts; FEV1; FVC & diagnosis at each event.

Notes:

Allocation concealment: D

Study: MMWR 2001

Methods: Matched case control

Participants:

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Ortqvist 1998

Methods: Double blind randomized controlled trial.

Participants: 691 non-immunocompromised adults aged 50 to 85 years who had been inpatients for pneumonia in Sweden.

Interventions: 339 vaccinees; 352 controls.

23 valent vaccine or saline placebo.

Outcomes: pneumonia (acute clinical symptoms or signs compatible with a LRTI and new infiltrate on CXR); pneumococcal pneumonia (pneumonia & +ve blood, pleural fluid or sputum culture); bacteraemic pneumococcal pneumonia; death from all causes.

Notes:

Allocation concealment: D

Study: Riley 1977

Methods: Double blind randomized controlled trial.

Mortality group.

Participants: Adults at Tari in Papua New Guinea Highlands.

Interventions: 5946 vaccinees; 6012 controls.

14 valent vaccine or saline placebo. Surveillance subset of 2713 vaccinees, 2660 controls for disease outcomes.

Outcomes: Pneumococcal infection confirmed by blood-culture and lung aspirate.

Notes:

Allocation concealment: D

Study: Shapiro 1984

Methods: Matched case control

Participants:

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Shapiro 1991

Methods: Matched case control

Participants:

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Simberkoff 1986

Methods: Double blind randomized controlled trial.

Participants: 2295 high risk patients, in the USA.

Interventions: 1175 vaccinees; 1179 controls.

14 valent vaccine or saline placebo.

Outcomes: Proved infections (eg. S.pneumoniae from CSF/joints); probable pneumococcal pneumonia (CXR evidence + S.Pneumoniae from sputum); probable pneumococcal bronchitis (eg. cough & more sputum without infiltrate on CXR & S.pneumoniae in sputum)

Notes: "High risk" = over 55 and presence of chronic renal, hepatic, cardiac, or pulmonary diseases, alcoholism or diabetes mellitus.

Allocation concealment: D

Study: Sims 1988

Methods: Matched case control

Participants:

Interventions: N/A

Outcomes: N/A

Notes:

Allocation concealment: D

Study: Smit 1977, Grp 1

Methods: Randomised controlled trial.

Participants: S.African gold miners.

Interventions: 983 vaccinees; 2036 controls.

6 valent vaccine.

Control = meningoccoal group A vaccine (1051 people); saline (985 people).

Outcomes: Antibody response and records of all LRTI's of any cause.

Notes:

Allocation concealment: D

Study: Smit 1977, Grp 2

Methods: Randomized controlled trial.

Participants: S.African gold miners.

Interventions: 540 vaccinees; 1135 controls.

12 valent vaccine.

Control = meningococcal types A&C vaccine (585 people); saline (550 people).

Outcomes: Antibody response and records of all LRTI's of any cause.

Notes:

Allocation concealment: D

RTI = respiratory tract infection.

LRTI = lower respiratory tract infections

Characteristics of excluded studies

Study: Ammann 1977

Reason for exclusion: Outcome was changes in antibody titres.

Study: Austrian 1976, 6v

Reason for exclusion: No useable data due to inadequate reporting.

Study: Bentley 1981

Reason for exclusion: Cohort study with non-random allocation of vaccine.

Study: Bolan 1986

Reason for exclusion: Data are included in a subsequent report: Butler 1993.

Study: Brieman 2000

Reason for exclusion: HIV positive

Study: Broome 1980

Reason for exclusion: Data are included in a subsequent report: Butler 1993.

Study: Christensen 2001

Reason for exclusion: Cohort study, not case-control. Also only early interim results are available.

Study: Douglas 1984

Reason for exclusion: Trial measures efficacy of vaccine in children.

Study: Douglas 1986

Reason for exclusion: Trial measures efficacy of vaccine in children.

Study: Dworkin 2001

Reason for exclusion: Cohort study, and not of invasive pneumococcal disease.

Study: Fletcher 1997

Reason for exclusion: Outcome was changes in antibody titres.

Study: Karma 1985

Reason for exclusion: Trial measures efficacy of vaccine in children.

Study: Kaufman 1941

Reason for exclusion: All results included in second report (Kaufman, 1947).

Study: MacLeod 1945

Reason for exclusion: No usable data due to inadequate reporting

Study: Nichol 1999

Reason for exclusion: Cohort study

Study: Rosen 1983

Reason for exclusion: Trial measures efficacy of vaccine in children.

Table 01 Quality assessment of pneumococcal trials (after Jadad et al.)

Study id: Austrian, 1976

Randomised: 1

Sequence ok:

Double blind:

Withdrawals:

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 1

Study id: Austrian, 1980 (1)

Randomised: 1

Sequence ok: 1

Double blind: 1

Withdrawals: 1

Blinding method: 1

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 5

Study id: Austrian, 1980 (2)

Randomised: 1

Sequence ok: 1

Double blind: 1

Withdrawals: 1

Blinding method: 1

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 5

Study id: Davis, 1987

Randomised: 1

Sequence ok: 1

Double blind: 1

Withdrawals:

Blinding method: 1

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 4

Study id: Gaillat, 1985

Randomised: 1

Sequence ok:

Double blind:

Withdrawals: 1

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 2

Study id: Honkanen, 1999

Randomised:

Sequence ok: 1

Double blind:

Withdrawals:

Blinding method:

Random. inapprop.:-1

Dbl-blind inapprop.:

Total score 0-5: 0

Study id: Kauffman, 1947

Randomised:

Sequence ok:

Double blind:

Withdrawals:

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 0

Study id: Klastersky, 1986

Randomised: 1

Sequence ok:

Double blind: 1

Withdrawals: 1

Blinding method: 1

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 4

Study id: Koivula, 1997

Randomised: 1

Sequence ok: 1

Double blind:

Withdrawals:

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 2

Study id: Leech, 1987

Randomised: 1

Sequence ok:

Double blind: 1

Withdrawals: 1

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 3

Study id: Ortqvist, 1998

Randomised: 1

Sequence ok: 1

Double blind: 1

Withdrawals: 1

Blinding method:

Random. inapprop.: 1

Dbl-blind inapprop.:

Total score 0-5: 5

Study id: Riley, 1977

Randomised: 1

Sequence ok:

Double blind: 1

Withdrawals:

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 2

Study id: Simberkoff, 1986

Randomised: 1

Sequence ok: 1

Double blind: 1

Withdrawals:

Blinding method: 1

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 4

Study id: Smit, 1977 (1)

Randomised: 1

Sequence ok:

Double blind: 1

Withdrawals:

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 2

Study id: Smit, 1977 (2)

Randomised: 1

Sequence ok:

Double blind: 1

Withdrawals:

Blinding method:

Random. inapprop.:

Dbl-blind inapprop.:

Total score 0-5: 2

Table 02 Sequential meta-analysis by year of study publication

Year of oldest study

1947

1976

1977

1980

1985

1986

1987

1997

Number of studies

14

13

12

9

7

6

4

3

Combined odds ratio

0.77

0.84

0.96

1.09

1.06

1.15

1.15

1.16

p-value, 2-sided

0.06

0.17

0.6

(0.3)

(0.7)

(0.09)

(.13)

(.10)

Heterogeneity p-value

< 0.01

< 0.01

< 0.01

0.09

0.11

0.68

.77

.99

Table 03 Vaccine efficacy (CI) against IPD

Subgroup: All studies

Study:

% Efficacy (CI):

Subgroup:

Study: Shapiro 84

% Efficacy (CI): 67 (13, 87)

Subgroup:

Study: Sims 88

% Efficacy (CI): 70 (37, 86)

Subgroup:

Study: Shapiro 91

% Efficacy (CI): 47 (30, 59)

Subgroup:

Study: Farr 95

% Efficacy (CI): 81 (34, 94)

Subgroup: Immunocompetent

Study:

% Efficacy (CI):

Subgroup:

Study: Sims 88

% Efficacy (CI): 70 (37, 86)

Subgroup:

Study: Shapiro 91

% Efficacy (CI): 53 (37, 65)

Subgroup: Immunocompetent elderly

Study:

% Efficacy (CI):

Subgroup:

Study: Sims 88

% Efficacy (CI): 70 (37, 86)

Table 04 Vaccine efficacy (CI) against IPD (vaccine type)

Subgroup: All

Study:

% Efficacy (CI):

Subgroup:

Study: Shapiro 91

% Efficacy (CI): 56% (42, 67)

Subgroup:

Study: Shapiro 91 indirect cohort

% Efficacy (CI): 48% (3, 72)

Subgroup:

Study: Butler 93 indirect cohort

% Efficacy (CI): 57% (45, 66)

Subgroup: Immunocompetent

Study:

% Efficacy (CI):

Subgroup:

Study: Shapiro 91

% Efficacy (CI): 61% (47,72)

Subgroup:

Study: Shapiro 91

% Efficacy (CI): 62% (24, 81)

Subgroup:

Study: Butler 93

% Efficacy (CI): 49% (23, 65)

Subgroup: Immunocompetent elderly

Study:

% Efficacy (CI):

Subgroup:

Study: Butler 93

% Efficacy (CI): 75% (57, 85)

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