

Vaccines for preventing pneumococcal infection in adults (Review)

Dear KB G, Andrews RR, Holden J, Tatham DP



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[Intervention Review]

Vaccines for preventing pneumococcal infection in adults

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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).

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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%.

Authors' 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.

PLAIN LANGUAGE SUMMARY

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.

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).

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 stud-

ies), 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, Ortvqvist (Ortvqvist 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; Ortvqvist (Ortvqvist 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 Klaster-sky 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 Klustersky (Klustersky 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 trials 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.

AUTHORS' 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.

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* Indicates the major publication for the study

FEEDBACK**Best systematic of 23-valent pneumococcal vaccine****Summary**

Dear Authors,

The inclusion of non-controlled studies in the current systematic review is clearly a step forward. The case-control studies enables an analysis of invasive pneumococcal disease that is not possible to do with the prospective studies that have been performed, due to lack of power. However, there is also a well performed cohort study, adjusted for background factors, that showed the same preventive efficacy against IPD (Jackson NEJM May 2003). Why was that not included? The search strategy stated that you included papers up to June 2003.

For your information, there are some new data from the study that was published as an early report in Lancet 2001 by Christenson et al. This, however, was published during the fall of 2003. (Hedlund J, Christenson B, Lundbergh P, Örtqvist Å. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a one-year follow-up. *Vaccine* 2003; **21**: 3906-11). Although we are still working with a “complete” background adjustment of the groups to minimise biases, the results of this paper was sex and age adjusted. In addition, a comparison was made between influenza season and non-influenza. In that comparison it can be seen that there was a significant prevention against both influenza, pneumonia and IPD during the influenza season in patients who had received influenza and/or pneumococcal vaccine. During the non-influenza season, however, there was no difference concerning

influenza, whereas there was still a significant protection against pneumonia. For IPD the RR was the same as during the influenza season (0.47), but there was too few cases to make it significant.

Finally, in your conclusions you make a mistake by stating that typical figures of IPD in developed countries is about 10 per 100.000 per year. That may be so for the whole population, but in the elderly where this calculation is of interest, the correct figure is about 50 per 100.000 per year, thereby reducing the NNT to about 4000 vaccinations per infection avoided.

With the best wishes,

Ake

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

Author's reply

See reply to comment # 2

Contributors

Ake Ortvist

Biased assessment of pneumococcal vaccine effect

Summary

The assessment of pneumococcal vaccine in preventing invasive pneumococcal disease (IPD) of this review is biased in favour of the vaccine and some graphs are misleading.

Take notice that:

No quality assessment has been made of the observational studies included.

Results of heterogeneous studies are displayed in forest plots (see autocorrelation 06 for instance) where results obtained in young adults are displayed with results obtained in the elderly. This is not appropriate and is misleading for the non-expert.

Assessment of effectiveness of IPV rests on results of Kaufman 1947, no random assignment, no blind researchers, no placebo group, only three serotypes vaccine (?); Shapiro 1984, results go in favour of the vaccine when data is unmatched(!). Simm 1988, excluded 46% of subjects because of lack of information and did not provide information on pneumococcus serotypes; Shapiro 1991, excluded 121 cases because they were originated by one of the 23 serotypes included in the 23 valent vaccine, but nevertheless reports a non-biased effectiveness in the elderly of 0.6 (IC95% 0.29 to 1.23); and Butler 1993, no exposure information on 36% of subjects included, a rate that would invalidate any observational study.

This could go on, but you can go to Puig-Barbera et al to get a much more "Cochrane" description and analysis of the data available.

In our current state of knowledge it cannot be assured that the polysaccharide non-conjugated vaccine is free of deleterious effects in the elderly. Applying the precautionary principle this possibility should be clearly discarded. Meanwhile influenza vaccine does a tremendous good job preventing pneumonia in the elderly.

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

Author's reply

We entirely agree that any positive assessment of the vaccine rests on the very old pseudo-randomised trial of Kaufman (1947), and on the observational studies. However, we do point out the crucial importance of the Kaufman study in the RCT part of our review. Our analyses are presented both with and without this study for this reason. Indeed our conclusions from this part of the review are decidedly negative: for example we suggest that a large RCT carried out now would fail to show any benefit. We include a table showing how the apparent efficacy of the vaccine increases monotonically as one progressively includes the poorer quality, older studies, and point out that several recent high quality randomised studies consistently showed no effect against all-cause pneumonia. Fedson and Liss have argued that the failure of other meta-analyses to demonstrate a benefit against this outcome should be seen as an inconclusive rather than negative result on the grounds that, if 30 to 50% of all pneumonias are pneumococcal, a VE of 50% against pneumococcal pneumonia equates to a VE of 15 to 25% against all-cause pneumonia. (Fedson, 2004) Our results cannot discount this possibility.

We note your concern about the inclusion criteria for observational studies but believe a more fundamental issue was the decision to incorporate observational studies within the review. Our initial review was conducted in accordance with the protocol. That version of the review reached a largely negative assessment of the efficacy of polysaccharide pneumococcal vaccines in preventing pneumonia and death. It was felt by the Editors that this would deliver an unbalanced message, since it made no mention of other important medical endpoints that the RCTs do not address, in particular invasive pneumococcal disease. The review was therefore expanded specifically in order to include the observational studies and it could be argued that the impact of this decision was to bias the review in favour of the vaccine. Whether such a process is proper for a Cochrane Systematic Review is perhaps doubtful but we have still attempted to assess the evidence fairly. We note that Ave Orqvist has indicated support for this approach in other comments posted on this review. Dr Puig-Barbera suggests we should read the paper by Puig-Barbera et al to “get a much more ”Cochrane“ description and analysis of the data available”. The clear implication here is that our results are biased by the manner in which we included and analysed the non-randomised studies. It is true that we have not included a formal, numerical assessment of quality of the observational studies. Probably there is no scale for such studies that would serve as well as the Jadad scale does for RCTs. We have noted the criteria used for assessment of observational studies by Puig-Barbera et al but do not agree that these criteria are any more valid than the approach used by us. We note with interest that according to the criteria of Puig-Barbera et al, the study by Forrester et al was rated ahead of a number of other observational studies and was included when others were excluded. In our review, we have described a number of serious flaws in Forrester et al, not least of which was the failure to conduct a matched analysis on a matched case control study. From the paper by Puig-Barbera et al, it appears that the observational studies have been analysed in an unmatched fashion. We believe this is invalid since, as we have explained in our review, all but one of the observational studies included were matched case-control studies. For our analysis we combined the estimates of OR based on conditional logistic regression in each study (which accounts for the matching) and calculated a weighted average log-OR using Stata. Furthermore, it is simplistic to assume that an unmatched analysis of such studies will always approach the null and that failure to do so represents bias in the study.

We do acknowledge that it might be of value to report the high exclusion rates in the observational studies and are grateful for the (implied) suggestion. As for the forest plots, they can be stratified in many ways. We suggest that the date of publication is more important in this regard than the age range of subjects.

We agree with Dr Orqvist’s suggestion that the NNT should be calculated for the older age group rather than for all adults.

We thank Dr Puig-Barbera and Dr Orqvist for their comments, and thank the Comments Editor for permitting this response.

Ross Andrews

John Holden

David Tatham

Keith Dear

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

Contributors

Joan Puig-Barbera

Reply to comment by Dr Puig-Barbera

Summary

Dear Dr Puig-Barbera,

There are small or big flaws in all studies. The results of the case-control studies included in the Cochrane analysis are corroborated by the results of the two most recent prospective studies (Honkanen and our own) where there was a clear trend for a 70-80% protection of the 23-valent vaccine against bacteremic pneumococcal pneumonia. A similar finding was published in a cohort study, adjusted for background factors, by Lisa Jackson in NEJM 2003.

Although I agree with you concerning the good effect of influenza vaccine, you’re of course aware of that there is no prospective controlled study in the elderly showing that influenza vaccine prevents against severe influenza or pneumonia? The only controlled study showing a protection of the vaccine against clinical (irrespective of severity) and serological influenza.

With the best wishes,

Ake

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

Author's reply

See reply to comment #2

Contributors

Ake Ortvist

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INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Pneumococcal Vaccines [*therapeutic use]; Pneumonia, Pneumococcal [*prevention & control]; Prospective Studies; Randomized Controlled Trials

MeSH check words

Adult; Aged; Humans; Middle Aged