Pneumococcal polysaccharide vaccine: a systematic review of clinical effectiveness in adults

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Authors' objectives
To assess the effect of pneumococcal polysaccharide vaccine on clinical outcomes.

Searching
MEDLINE (from 1966 to March 1999; updated in May 2000), EMBASE (from 1980 to March 1999), the Cochrane Controlled Trials Register, CINAHL, the InterDEC database, ASSIA, grey literature databases, SIGLE and Internet sources (e.g. Medscape, the Centers for Disease Control, dotPharmacy, WebDoctor and InPharma) were searched. The search terms used to search MEDLINE were stated. Reference lists in relevant reports, publications (including HMSO Immunisation against Infectious Disease 1996) and textbooks were checked. Articles quoting previous meta-analyses were traced using the Science Citation Index. Manufacturers of vaccines, authors of recently published trials and experts were contacted for additional or unpublished trials and data. Studies in any language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared pneumococcal polysaccharide vaccine with no vaccine were eligible for inclusion. Studies of newer conjugate vaccines and studies of prototype vaccines used in the 1940s were excluded. In some of the included studies, other vaccines (influenza or meningococcal) were also given to both treatment arms. The studies were conducted in industrialised and less industrialised countries.

Participants included in the review
Studies of adults were eligible for inclusion. The included studies were of high-risk patients (bronchial carcinoma, chronic renal, hepatic, cardiac pulmonary disease, alcoholism, diabetes), elderly people living in the community, members of health plans aged older than 45 years, psychiatric in-patients, retirement home residents, geriatric in-patients, patients older than 50 years with previous pneumonia, novice gold miners and subsistence farmers.

Outcomes assessed in the review
Studies that reported the clinical outcomes in numerical format (including numerator and denominator) were eligible for inclusion. Studies that assessed all-cause pneumonia using a combination of clinical and radiographic evidence were included, whereas those that diagnosed pneumococcal pneumonia using potentially unreliable tests were excluded. The review assessed all-cause pneumonia, pneumococcal pneumonia, pneumococcal bacteraemia and overall mortality. The duration of follow-up, where stated, ranged from 2 to 4 years.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the 5-point Jadad scale which considers randomisation, blinding and withdrawals. Studies scoring less than 3 were classified as low quality. Two reviewers independently assessed validity using unmasked reports while a third reviewer checked these assessments using a sample of reports. Any disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted data from unmasked reports while a third reviewer checked the data using a...
sample of reports. Any disagreements were resolved through discussion. The tabulated information included details of the setting (industrialised or non industrialised country), characteristics of the participants, main exclusion criteria, the duration of follow-up and the number of patients per treatment arm.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to the setting, as either an industrialised or less industrialised country. Studies in industrialised countries were then grouped as high-risk (chronic organ dysfunction or immunosuppression) and older age (older than 65 years). Within these groups the studies were combined, where sufficient data were presented, by estimating the pooled relative risk (RR) and 95% confidence intervals (CIs) using random-effect and fixed-effect models. Three RCTs were excluded from the meta-analysis since they were not adequately reported and the reported outcome 'putative pneumococcal pneumonia' was not defined. For less industrialised countries, data were only available for a meta-analysis of all-cause pneumonia.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. A sensitivity analysis was performed by analysing the data from only high-quality studies (quality score of 3 or more).

**Results of the review**

Sixteen RCTs, published in 12 reports, were included (over 50,000 patients).

Few individual RCTs reported statistically significant results.

Studies in industrialised countries. Vaccination increased overall mortality, all-cause pneumonia and pneumococcal pneumonia but the increase was not statistically significant. For overall mortality (8 RCTs, 22,760 patients), the RR (fixed-effect) was 1.07 (95% CI: 0.97, 1.18) and no significant heterogeneity was found (P=0.62). For all-cause pneumonia (9 RCTs, 49,685 patients), the RR (random-effects) was 1.03 (95% CI: 0.86, 1.25) and significant heterogeneity was found (P=0.00). For pneumococcal pneumonia (5 RCTs, 32,854 patients), the RR (fixed-effect) was 1.06 (95% CI: 0.82, 1.38) and no significant heterogeneity was found (P=0.49).

Vaccination reduced bacteraemia but the reduction was not statistically significant (6 RCTs, 29,641 patients). The RR (fixed-effect) was 0.53 (95% CI: 0.22, 1.29) and no significant heterogeneity was found (P=0.61).

The results were only slightly altered after excluding the lower quality RCTs and the results for all-cause pneumonia were no longer statistically heterogeneous (P=0.52). For all-cause pneumonia (7 RCTs, 21,074 patients), the RR (random-effects) was 1.10 (95% CI: 0.99, 1.22). The results for all meta-analyses were presented.

High-risk patients.

Vaccination increased overall mortality, all-cause pneumonia and pneumococcal pneumonia but the increase was not statistically significant. Vaccination reduced bacteraemia but the reduction was not statistically significant. Data were presented. The results were similar after excluding the one low-quality RCT.

Unselected elderly patients. The results were similar for overall mortality and pneumococcal pneumonia for all studies and for high-quality studies. Data were presented.

Less industrialised countries.

Vaccination significantly reduced all-cause pneumonia (3 RCTs, 10,067 patients); the RR was 0.67 (95% CI: 0.52, 0.87) and no significant heterogeneity was found (P=0.87); the number-needed-to-treat (NNT) was 69. One RCT (11,958 patients) found that vaccination significantly reduced mortality; the RR was 0.79 (95% CI: 0.63, 0.99) and the NNT was 169. One RCT (5,383 patients) found that vaccination reduced bacteraemia but the reduction was not statistically significant; the RR was 0.14 (95% CI: 0.02, 1.14).
Authors' conclusions
The benefits of pneumococcal polysaccharide vaccine may depend upon the characteristics of the patients and the underlying epidemiology in the population targeted. The authors also concluded that there is no strong evidence to support the widespread vaccination of adults in the UK and USA.

CRD commentary
This was a well-conducted and clearly presented review. The review question was clear in terms of the study design, intervention, participants and outcomes. Many relevant sources were searched, attempts were made to locate unpublished studies, and no language restrictions were applied. The methods used to select studies were not described; hence, efforts made to reduce errors and bias cannot be judged. Two reviewers independently assessed validity and extracted the data, which reduces the potential for bias and errors. Validity was assessed, although there were some limitations of the criteria used. Relevant information on the included studies was tabulated.

The data were appropriately grouped and combined in meta-analyses and statistical heterogeneity was assessed. The influence of study quality on the results was explored by analysing data from high-quality studies separately. The evidence presented appears to support the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that there is no good evidence supporting the widespread vaccination of adults in the UK and USA.

Research: The authors did not state any implications for further research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.