The effectiveness of pneumococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomised controlled trials

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CRD summary
This review assessed the efficacy of pneumococcal polysaccharide vaccines in adults. The authors concluded that the vaccines showed approximately 50% protection against invasive disease but protection against all-cause pneumonia varied. Given the possibility that some studies might not have been found, and the differences between the studies included, the conclusions are appropriate.

Authors' objectives
To conduct a systematic review of observational studies of the effectiveness of pneumococcal polysaccharide vaccines.

Searching
MEDLINE was searched from 1966 to August 2003; the search terms were reported. The reference lists of retrieved studies were checked manually and the vaccine manufacturers were contacted.

Study selection
Study designs of evaluations included in the review
Any observational study that compared vaccinated individuals with a control group was eligible for inclusion. The included studies used a case-control, cohort or indirect cohort design.

Specific interventions included in the review
Any form of the pneumococcal polysaccharide vaccine (14 or 23 serotypes) was eligible for inclusion, and both types were used in the studies included.

Participants included in the review
Studies conducted in any adult population were eligible for inclusion. Most of the studies in the review were in elderly or chronic disease populations, mostly hospitalised. A few included studies were in patients positive for human immunodeficiency virus (HIV).

Outcomes assessed in the review
Studies that reported a clinically relevant outcome were eligible for inclusion. The two most commonly reported outcomes were invasive disease (defined as laboratory isolation of Streptococcus pneumoniae from a normally sterile site) and all-cause pneumonia (with code-based and clinical definitions accepted).

How were decisions on the relevance of primary studies made?
One reviewer selected papers for inclusion, and final decisions were made by consensus.

Assessment of study quality
The quality of the included studies was assessed using a system designed by the Ottawa-Newcastle group. This system scored studies across 3 areas: selection, comparability, and either outcome assessment (cohort studies) or exposure assessment (case-control studies). Possible confounding factors were considered and adjusted for. Two reviewers examined unmasked studies independently to assess quality.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
extraction. The numbers of vaccinated individuals among the cases and the controls were extracted from case-control and indirect cohort studies. The numbers of cases of pneumonia and invasive disease in the vaccinated and unvaccinated groups, as well as the person-years at risk, were extracted from cohort studies. It was unclear whether estimates of efficacy were extracted as reported, or were calculated from these data.

**Methods of synthesis**

**How were the studies combined?**

Estimates of efficacy were combined using a meta-analysis to obtain pooled estimates of the odds ratio (OR) or rate ratio (RR), together with 95% confidence intervals (CIs). The combined estimates were obtained by weighting the individual estimates from each study by the reciprocal of the standard error (which was calculated using the difference in the log of the upper and lower CIs reported).

**How were differences between studies investigated?**

The chi-squared test was used to investigate statistical heterogeneity between the studies. If this test showed that statistical heterogeneity was present, then a random-effects model was used to combine the results from the studies. Several meta-analyses were conducted according to characteristics of the study population (HIV positive, U.S. native, elderly and chronic disease), and for studies that estimated protection against invasive disease caused only by pneumococcal serotypes included in the vaccine. The authors compared these findings with the results from an existing meta-analysis of randomised controlled trials (RCTs) (see Other Publications of Related Interest).

**Results of the review**

Of the 19 included studies, 11 were case-control studies, 2 used an indirect cohort design, and 6 were cohort studies. Two of these studies were not included in the analysis.

The observational studies included in the review were assessed to be of moderate quality, with the length of follow-up restricted in all of the studies. Three studies could not be assessed for study quality because of the limited methodological information provided.

There were 13 observational studies that used invasive disease as an outcome, with a total of 4,984 events. The combined estimate showed that the vaccine had an efficacy of 53% (95% CI: 46, 59); the pooled OR was 0.47 (95% CI: 0.41, 0.54). This did not change significantly when combining only the case-control studies or cohort studies (both were conducted mainly in the elderly and chronic diseased). No statistically significant heterogeneity was found.

Five observational studies in the elderly used all-cause pneumonia as an outcome, with 263,300 person-years of observation; 5,513 events were observed. The combined estimate of vaccine efficacy was 32% (95% CI: 7, 50); the pooled RR was 0.68 (95% CI: 0.50, 0.93). There was statistically significant heterogeneity (chi-squared 72.3, d.f.=4, P<0.001). The exclusion of a large study of influenza and pneumococcal vaccine resulted in a non significant, heterogeneous pooled estimate of efficacy of 35% (95% CI: -7, 61).

The authors compared these results with a meta-analysis of RCTs that showed no statistically significant difference in invasive disease (homogeneous) or pneumonia (heterogeneous).

**Authors' conclusions**

Pneumococcal polysaccharide vaccines showed approximately 50% protection against invasive disease, but protection against all-cause pneumonia varied between the studies. The authors concluded that their findings were compatible with the results from a meta-analysis of RCTs.

**CRD commentary**

The review question was focused and clear in terms of the inclusion and exclusion criteria, and study designs that were suitable for evaluating the effects of health interventions when the outcome is rare were included. The authors acknowledged that it was possible that unpublished studies were not located, but no formal assessment of potential
publication bias was performed. In addition, only one reviewer selected the studies for inclusion, which meant that there was a possibility of selection bias. A validity assessment of the included studies was undertaken, using a schedule devised specifically for the study designs included in the review, and this was performed in duplicate.

Appropriate measures of effect were used, and statistical heterogeneity was assessed and investigated when it was found. The authors' cautious conclusions appear to follow from the evidence presented, given the possibility of publication bias and the presence of heterogeneity.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that the evidence base for plain polysaccharide vaccine must be supported by properly conducted randomised trials in elderly groups; this issue should possibly be considered in trials evaluating newer conjugate pneumococcal vaccines.

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Other publications of related interest

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