Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials

Authors' objectives
To assess the efficacy of the pneumococcal polysaccharide vaccine (PPV) in preventing Streptococcus pneumoniae (Sp)-related diseases in immunocompetent adults.

Searching
MEDLINE (from 1966 to 1999) and EMBASE were searched and the references of retrieved articles were examined. In addition, the pharmaceutical manufacturers of PPVs and authors of identified randomised trials of PPV were contacted for additional published or unpublished randomised trials. The searches were not restricted by language and the search terms were reported in the review.

Study selection
Study designs of evaluations included in the review
Randomised trials with a precisely described randomisation process, and comprising at least a PPV and control group (placebo, no vaccine or alternative vaccine), were eligible for inclusion. The duration of follow-up in the included studies ranged from 16 to 48 months.

Specific interventions included in the review
Studies examining the efficacy of the PPV were eligible for inclusion. The included studies compared vaccines of 6, 12, 13, 14, 17 or 23 valences with placebo, no vaccine, the influenza vaccine, or the meningococcal vaccine.

Participants included in the review
Studies targeting immunocompetent individuals aged over 18 years were eligible for inclusion. The study participants included patients with mental illness (hospitalised), chronic obstructive pulmonary disease, bronchogenic carcinoma or community-acquired pneumonia, those classified as high risk, and young male workers, ambulatory adults and elderly individuals.

Outcomes assessed in the review
Studies assessing definite pneumococcal pneumonia (Sp isolated from blood culture or other usually sterile fluid), all-cause pneumonia, presumptive pneumococcal pneumonia (Sp isolated from sputum or nasal swab culture), pneumonia-related mortality and/or all-cause mortality were eligible for inclusion. Infections diagnosed by electrophoresis of urine specimens were excluded from the review. All of the included studies assessed at least one of these end points, with the majority assessing two or more.

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
The validity of the included studies was evaluated according to the Cochrane Collaboration Method, using six quality criteria: selection of study participants, randomisation procedure, blinding procedure, description of the vaccine and control interventions, the proportion of patients lost to follow-up and intention-to-treat analysis. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Two investigators independently extracted the primary data. Any discrepancies were documented and resolved by
consensus. The number of outcome events was extracted for both the intervention and control groups, and odds ratios (ORs) were calculated together with 95% confidence intervals (CIs).

**Methods of synthesis**

How were the studies combined?
The studies were combined using the Mantel-Haenszel fixed-effect model and expressed as ORs. Where there was significant heterogeneity, a random-effects model was employed. Publication bias was assessed by determining the number of non significant trials needed to obtain a non significant result, together with funnel plots.

How were differences between studies investigated?
The Cochran Q statistical method was used to investigate heterogeneity. Sensitivity analyses were performed according to individual studies and statistical methods. Subgroup analyses were conducted to examine quality and population characteristics.

**Results of the review**

Eleven articles reporting 14 randomised controlled trials (n=48,837) were included in the review.

No publication bias was detected in any of the analyses.

The vaccine was associated with a significant decrease in the incidence of definite pneumococcal pneumonia, with an OR of 0.29 (95% CI: 0.2, 0.42). There was no significant heterogeneity between the studies (P=0.74). Similarly, a protective effect was found against presumptive pneumococcal pneumonia (OR 0.60, 95% CI: 0.37, 0.96). Significant heterogeneity was detected (P<0.001), which was not eliminated when lower quality studies were excluded.

No significant effect was found against all-cause pneumonia, with an OR of 0.78 (95% CI: 0.58, 1.07). Significant heterogeneity was detected (P<0.01); this remained significant even after the exclusion of lower quality studies. In a subgroup analysis of trials conducted in gold miners in South Africa, a significant reduction of all-cause pneumonia was found without significant heterogeneity (OR 0.52, 95% CI: 0.43, 0.63).

The PPV significantly decreased mortality due to pneumonia, with an odds ratio of 0.68 (95% CI: 0.51, 0.92). However, the authors found that this result was not robust: the addition of one single non significant trial led to a non significant result. No heterogeneity was detected. The vaccine did not significantly reduce all-cause mortality.

In a subgroup analysis of 7,909 high-risk patients over 55 years, no significant protective effect of the vaccine was found. This analysis had low statistical power due to the low number of events.

**Authors' conclusions**
The authors concluded that the PPV was highly effective in reducing definite (bacteremic) pneumococcal pneumonia by 71%, presumptive pneumococcal pneumonia by 40%, and mortality due to pneumonia by a possible 32%, but not all-cause pneumonia or death.

**CRD commentary**
The authors clearly reported the review question and the inclusion criteria. The search for primary studies was thorough. The results were examined in view of the quality assessment performed. It was unclear how many reviewers performed the quality assessment, or whether this was carried out independently. Details of the primary studies were extensive. The authors recognised and discussed the variability between the studies, particularly with regard to participant characteristics. It is noteworthy that, where reported, the populations of the included studies were largely male. In view of the data presented, the authors' conclusions appear to be both reasonable and reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.
Research: The authors recommended that a large-scale trial in elderly people be performed, given that the populations tested to date may not be representative of the target population.

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