Efficacy of pneumococcal vaccination in adults: a meta-analysis of randomized controlled trials

Authors' objectives
To quantify the efficacy of pneumococcal vaccination in preventing both pneumococcal infection-related and other clinically-relevant outcomes in adults.

Searching
MEDLINE was searched from 1966 to 1991 for publications in any languages, using the terms (explode)'pneumococcal infections' and (explode)'immunization' or (explode)'vaccines'. Additional published and unpublished studies were identified by examining references of obtained articles and by contacting lead authors and the vaccine's manufacturers.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with pneumococcal vaccine and control treatment groups.

Specific interventions included in the review
Pneumococcal vaccine.

Participants included in the review
Adults. The participants ranged from relatively healthy workers to older patients with bronchogenic carcinoma and obstructive pulmonary disease. Seven study groups were low risk and five were high risk. Studies were carried out in a broad range of countries.

Outcomes assessed in the review
Ten clinical outcomes were assessed: definitive pneumococcal pneumonia, definitive pneumococcal pneumonia for vaccine containing pneumococcal antigen types only (vaccine types only), presumptive pneumococcal pneumonia, presumptive pneumococcal pneumonia (vaccine types only), pneumococcal disease, pneumonia (all causes), bronchitis, mortality (all causes), mortality due to pneumonia and mortality due to pneumococcal infection.

How were decisions on the relevance of primary studies made?
Two investigators reached consensus on whether articles met the inclusion criteria.

Assessment of study quality
The trials' validity was assessed using a 23-item instrument evaluating: selection of patients, randomisation procedures, description of treatment regimens, blinding procedures, testing procedures, handling of withdrawals and use of appropriate statistical analyses. Two assessors blinded to the bibliographic details of the studies independently assessed them for quality. Any discrepancies in quality evaluations were resolved and total quality scores ranging from 0 (low) to 1 (high) were assigned to the trials.

Data extraction
Two investigators independently extracted predefined information. Any discrepancies were documented and resolved by consensus. The articles were also read by a third investigator to confirm study outcomes and number of outcome events. If either of these components were missing, the article's lead author was contacted to provide the information.
Methods of synthesis
How were the studies combined?
The studies were combined by two methods: Mantel-Haenszel ddds ratios and DerSimonian and Laird summary rate differences.

How were differences between studies investigated?
Separate Q-statistics were calculated to assess heterogeneity for the 9 outcomes where data were provided for 2 or more studies.

Stratified analyses were performed to assess the effect of 5 variables postulated to influence the efficacy of the pneumococcal vaccines: number of vaccine valences employed, location of the study, study quality, mean patient follow-up time, and risk of pneumococcal infection in the study population.

Results of the review
Nine RCTS are included (40,431 patients). Three reported data on two distinct vaccine and control study groups.

The summary rate differences and 95% confidence intervals (CIs) for the clinical outcomes (expressed as the number of cases per 1000) were: definitive pneumococcal pneumonia, 4 (95% CI: 0, 7, non significant); definitive pneumococcal pneumonia (vaccine types only), 8 (95% CI: 1, 16, p<0.05); presumptive pneumococcal pneumonia, 13 (95% CI: -21, 47, non significant); presumptive pneumococcal pneumonia (vaccine types only), 16 (95% CI: -3, 35, non significant); pneumonia (all causes), 6 (95% CI: -1, 13, non significant); bronchitis, 8 (95% CI: 0, 15, non significant); mortality (all causes), 1 (95% CI: -6, 8, non significant); mortality due to pneumonia, 2 (95% CI: -2, 5, non significant); and mortality due to pneumococcal infection, -3 (95% CI: -6, 0, non significant). Of the stratified analyses, only the comparisons of high- and low-risk populations showed a consistent relationship between these factors and vaccine efficacy. Summary rate differences (expressed as the number per 1000) demonstrated a protective effect in low-risk groups for: definitive pneumococcal pneumonia, 11 (95% CI: 2, 19, p<0.05); presumptive pneumococcal pneumonia, 41 (95% CI: 29, 54, p<0.05); and presumptive pneumococcal pneumonia (vaccine types only), 25 (95% CI: 15, 35, p<0.05). No protective effect was found for any of the study outcomes for high-risk patients.

Side-effects were reported in 3 studies. These were erythema and fever; no life threatening or fatal side-effects were reported in any of these studies.

Authors' conclusions
Pneumococcal vaccination appear efficacious in reducing bacteraemic pneumococcal pneumonia in low-risk adults. However, evidence from RCTs fails to demonstrate vaccine efficacy for pneumococcal infection-related or other medical outcomes in the heterogeneous group of patients currently labelled as high risk.

CRD commentary
A thorough and comprehensive systematic review. Sensitivity analyses and assessment of publication bias were carried out.

Both odds ratios and rate differences are reported. The highly significant degree of heterogeneity among the studies reporting pneumococcal infection-related outcomes, and the choice of a p<0.001 value (despite the low power of tests of heterogeneity), suggest the odds ratios should be treated with caution.

Implications of the review for practice and research
Pneumococcal vaccination is inappropriate for high-risk patients and does not appear to reduce mortality in any patient group.
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