The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses

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CRD summary
This review, which investigated the efficacy of pneumococcal polysaccharide vaccine (PPV) in the elderly, concluded that PPV provides some protection against invasive pneumococcal disease in the general elderly population and has a moderate effect in the high-risk elderly. The vaccine has little effect on pneumonia. The authors’ conclusions are based partly on previous meta-analyses and, as such, their validity cannot be assessed.

Authors' objectives
To investigate the efficacy of pneumococcal polysaccharide vaccine (PPV) against pneumococcal pneumonia and invasive pneumococcal disease (IPD) in the elderly, and to estimate its level of protection in high- and low-risk individuals.

Searching
MEDLINE was searched for published studies, with no year or language restrictions; the search terms were provided. In addition, previous reviews and meta-analyses were checked to ensure a complete list of studies, and the references of retrieved papers were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTS with a well-defined randomisation or quasi-randomisation process were included in the review.

Specific interventions included in the review
Studies with a PPV group and a control group (placebo or a control vaccine) were included in the review. Five of the included studies used a 14-valent vaccine, two used 23-valent, one used 17-valent, and one used 2- and 3-valent vaccines.

Participants included in the review
Studies that targeted immunocompetent and immunocompromised elderly individuals who were at least 50 years of age were included in the review. The mean age of the participants ranged from 61 to 74 years, and the proportion of chronically ill elderly ranged from 27 to 100%.

Outcomes assessed in the review
The studies had to assess pneumococcal pneumonia and/or IPD to be included in the review. The definition of pneumococcal pneumonia was a clinically and radiographically confirmed case of pneumonia, with Streptococcus pneumoniae cultured from sputum or a nasal swab. Diagnoses made on the basis of a two-fold rise in pneumolysin antibody level in paired serum samples, or a pneumococcal antigen detection by electrophoresis of a urine specimen, were also included. IPD patients had to be defined as bacteraemic cases with Streptococcus pneumoniae isolated from blood or any other usually sterile body fluid.

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
Study quality was assessed using the Jadad criteria, which considers randomisation, blinding and description of
withdrawals. Two reviewers assessed the validity of the included studies. Any disagreements were resolved through discussion.

**Data extraction**
Two authors independently extracted the data. Data were extracted on the type of interventions, number of serotypes included in the vaccine (valency), follow-up time and participants. The numbers of pneumococcal pneumonia and bacteraemic cases were extracted from each study and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. In addition, vaccine efficacy (VE) was calculated for each study (defined as one minus the OR, multiplied by 100). The number of high-risk individuals in each study was also extracted ('high-risk' was defined as those categories for which the vaccine is currently recommended in the UK). For the main analysis, study populations where at least 50% of the individuals had some chronic condition or immunodeficiency were considered at high risk; this was reduced to 20% of individuals for the sensitivity analysis. Any studies that did not provide adequate information on the participants' ages, the randomisation process or diagnostic procedures used were excluded from the analysis.

**Methods of synthesis**

**How were the studies combined?**
The ORs were pooled using the DerSimonian Laird random-effects model and corresponding 95% CIs were calculated.

**How were differences between studies investigated?**
Sensitivity analyses were carried out using RCTs only, using a fixed-effect model rather than a random-effects model, and after including case-control and indirect cohort studies. The results of the meta-analysis were compared with those of previous meta-analyses. Three of the studies were rated as methodologically weak. The majority of studies were assigned a quality score of 3 out of a maximum 5.

**Results of the review**
Nine studies (n=45,676) were included in the review: 6 RCTs (n=6,162) and 3 quasi-RCTs (n=39,514).

**Vaccine efficacy against pneumococcal pneumonia (7 studies).**
All 7 studies showed a negative or non significant effect against pneumococcal pneumonia in the elderly, with VE ranging from -28 to +76%. Three trials studied the effects of PPV on pneumococcal pneumonia in the general elderly population and found no significant protective effect of the vaccine (OR 0.84, 95% CI: 0.47, 1.50). Four trials studied a high-risk population and found a negative, non significant effect of vaccination (OR 1.20, 95% CI: 0.75, 1.92).

**Vaccine efficacy against IPD (6 studies).**
Two trials studied the effects of the vaccine on IPD in the general elderly population and found no statistically significant protective effect of the intervention (OR 0.35, 95% CI: 0.08, 1.49). Four studies carried out in the high-risk elderly found no statistically significant protective effect of the vaccine (OR 0.80, 95% CI: 0.22, 2.88).

There were few differences in the results when a fixed-effect model was used. Only including RCTs in the analyses did not change the results. The inclusion of one methodologically weak study in the analysis did not affect the results for VE against pneumococcal pneumonia, but the protective effect of the vaccine against IPD became statistically significant (OR 0.23, 95% CI: 0.12, 0.46). When the single, bacteraemic, terminally ill patient from another study was included in the analysis, VE against IPD in the high-risk group dropped considerably and the effect remained statistically non significant. When the results for pneumococcal pneumonia and IPD were analysed together, the protective effect of the vaccine was reduced and was non significant.

Estimates of VE from case-control and indirect cohort studies ranged from around 50 to 80% for IPD. The inclusion of all non-randomised studies in the analysis showed a reduced, but statistically significant, protective effect of PPV against IPD in the low-risk elderly (OR 0.53, 95% CI: 0.40, 0.70), and a greater and statistically significant efficacy in the high-risk group (OR 0.48, 95% CI: 0.29, 0.80).
Authors' conclusions
When taken with the results of other meta-analyses and observational studies, the results showed that PPV provides a reasonable degree of protection in the general elderly population against invasive disease and a moderate effect in the high-risk population. The vaccine appears to have little or no effect on pneumonia.

CRD commentary
The authors set out a clear objective at the beginning of the review. The inclusion criteria were defined in terms of the participants, interventions, outcomes and study design. Only one database was searched, which increases the possibility that relevant studies might have been missed. However, no language restrictions were applied and this reduces the risk of language bias. Only published studies were included in the review and publication bias was not assessed. It was unclear how many reviewers selected studies, but both the data extraction and quality assessment were carried out in duplicate, which helps to reduce the risk of bias. Study quality was assessed using appropriate criteria.

Details of the individual studies were presented, and the statistical methods used seem appropriate. Statistical heterogeneity did not appear to have been formally assessed; however, some study differences were identified and examined in sensitivity analyses. It was difficult to assess the validity of the authors' conclusions given that they were based on a combination of their own results, other meta-analyses, and observational studies. It was also unclear how the observational studies were identified or selected for inclusion in the analysis, and the quality of neither the observational studies nor the meta-analyses is known. Based on the results of this review's meta-analysis alone, the authors' conclusions about the protective effects of PPV against invasive disease seem somewhat overstated, given that a statistically significant protective effect of PPV was only seen when methodologically weak RCTs or observational studies, which are generally also of poorer quality, were included in the analysis.

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

Research: The authors stated that further studies would help clarify whether the vaccine has any effect in high-risk groups, and/or noninvasive pneumonia. However, they pointed out that the additional expense of performing these studies may not be worth it, given that the conjugate vaccine may be effective even in immunocompromised patients. The authors also stated that Bayesian value-of-information analysis is the most logical framework to determine whether more information is needed and, if so, how large any trial should be. They further stated that trials of the conjugate vaccine should be carried out in the elderly.

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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.