Efficacy of pneumococcal vaccination in children younger than 24 months: a meta-analysis

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CRD summary
The review concluded that pneumococcal conjugate vaccine produced a significant effect regarding prevention of invasive pneumococcal disease. The effects on prevention of otitis media and pneumonia were less striking. The review had some methodological problems (notably potential for heterogeneity and uncertain quality of individual trials) which mean that caution is warranted when interpreting the authors' conclusions.

Authors' objectives
To determine the protective clinical efficacy of pneumococcal conjugate vaccine (PCV) in reducing the incidence of invasive pneumococcal disease, pneumonia and acute otitis media in healthy infants younger than 24 months.

Searching
MEDLINE and EMBASE were searched from January 2000 to June 2008 for articles published in English. Search terms were reported. Reference lists of retrieved trials and review articles were searched.

Study selection
Randomised controlled trials (RCTs) that compared placebo or control vaccines with the protective efficacy of a series of PCV immunisations (three to four doses of any valency) in healthy infants younger than 24 months were eligible for inclusion. PCV had to be given before 12 months of age. Trials needed to provide intention-to-treat or per protocol data on the incidence of invasive pneumococcal disease, acute otitis media or pneumonia. Definitions were reported in the review.

The included trials studied PCV given three or four times between the ages of two months and 15 months. Vaccine valency was PCV-7 in most trials; PCV-9 and PCV-11 were also studied. Age at enrollment ranged from two to 24 months.

Two reviewers independently performed study selection. Disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed trial quality according to Jadad and Chalmers' scales. The number of trials that met each quality item was calculated. Discrepancies were resolved by consensus.

Data extraction
Two reviewers independently extracted data on incidence of invasive pneumococcal disease, acute otitis media and pneumonia. Data were used to calculate relative risks (RR) and 95% confidence intervals (CI). Discrepancies between reviewers were resolved by consensus.

Methods of synthesis
A DerSimonian and Laird random-effects meta-analysis was used to calculate pooled relative risks and 95% CIs. Risk reduction was calculated (1-RR). Sensitivity analysis was undertaken for PCV-7 and use of fixed-effect modelling. Publication bias was estimated by funnel plot assessment.

Results of the review
Nine trials were included in the review: six trials of PCV-7, two trials of PCV-9 and one trial of PCV-11. Sample sizes ranged from 856 to 39,836 infants. Most trials were double-blinded and provided study dates and a regimen definition. Few trials adequately assessed withdrawals/dropouts or tested randomisation and blinding.

Compared with control, there was a statistically significant reduced risk of invasive pneumococcal disease with all serotypes of PCV (RR 0.38, 95% CI 0.22 to 0.67; six trials). These results were still statistically significant across subgroups based on valency and serotypes, with an invasive pneumococcal disease risk reduction range from 62% to
89%.

Compared with control, there was a statistically significantly reduced risk of all episodes of radiograph confirmed pneumonia with PCV (RR 0.71, 95% CI 0.65 to 0.78; three trials), and a statistically significant reduced risk of all episodes of clinical pneumonia with PCV (RR 0.94, 95% CI 0.90 to 0.98; two trials), which equated to a risk reduction of between 6% and 29%.

Compared with control, there was a statistically significant reduced risk of all episodes of otitis media with PCV-7 (RR 0.94, 95% CI 0.91 to 0.96; two trials) alone, but this was not statistically significant for PCV-7 and PCV-11 when pooled. Various subgroup analyses were presented for otitis media, some of which were no longer statistically significant; the risk reduction for otitis media ranged from 6% to 55%.

There was no evidence of publication bias. The per protocol analysis was presented in the review.

Authors' conclusions
PCV produced a significant effect for prevention of invasive pneumococcal disease. Results on prevention of otitis media and pneumonia were less striking, but even small benefits had potential for a tremendous impact on the health of infants in developing and industrialised countries.

CRD commentary
Inclusion criteria for the review were clearly defined. Two relevant databases were searched. Only English-language articles were included, so there was potential for language bias. Publication bias was assessed and was not detected. Attempts were made to reduce reviewer error and bias throughout the review process. Quality assessment was conducted using a standard checklist, but results were not presented for each trial and so it was difficult to determine trial quality. Trials were pooled using meta-analysis. It was not always clear whether random-effects or fixed-effect models were used. The authors did not report on statistical heterogeneity and no forest plots were presented, which made it difficult to interpret the results.

Overall, potential for heterogeneity and uncertain quality of individual trials mean that the authors’ conclusions should be interpreted with caution.

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

Research: The authors stated that trials should better describe their methodology, patient sample, patient numbers throughout the trial and data collection dates. Journals could help promote good practice by refusing to publish articles that did not provide collection dates and patient numbers.

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