Comparing pneumococcal conjugate vaccine schedules based on 3 and 2 primary doses: systematic review and meta-analysis

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CRD summary
Three- and two-dose schedules of pneumococcal conjugate vaccine resulted in high levels of seropositivity. Three-dose schedules had a higher antibody level, especially for serotypes 6B and 23F. The clinical relevance of these differences was unknown. The authors' conclusions reflect the available evidence but the reliability of these conclusions is limited by statistical and clinical differences between the included studies.

Authors' objectives
To compare the effectiveness of pneumococcal conjugate vaccine (PCV) schedules containing three primary doses (with or without a booster) to those with two primary doses (with or without a booster).

Searching
Twelve databases (including MEDLINE and EMBASE) and trial registries were searched from inception to March 2010 without language restrictions. Search terms were reported in an appendix (supplementary data). References of review articles were checked. Experts in the field and vaccine manufacturers were contacted.

Study selection
Randomised controlled trials (RCTs), quasi-RCTs, cohort and case-control studies that enrolled children under 18 years old were eligible for inclusion. Studies had to make direct comparisons between PCV schedules with two primary doses or three primary doses with or without a booster dose and/or with and without a 23-valent pneumococcal polysaccharide vaccine (PPV) booster dose (full details of combination were given in the paper). PPV was not licensed for children under two years old.

The primary outcomes of interest were clinical, nasopharyngeal carriage and immunological outcomes.

Studies were conducted in 11 countries (in Europe, Africa, Asia, the Middle East and North America). Three RCTs used 7-valent PCV, four used 9-valent PCV and one used 10-valent PCV. One RCT studied children with sickle-cell disease. Intended and actually given doses varied. Age at the time of intended doses ranged from 1.5 months to 12 months. Ages at the time of actual given doses ranged from two months to 11.2 months. Studies in which all vaccinated children were HIV-positive and the control group of unvaccinated children were HIV-negative were excluded.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
The quality of the included studies was assessed using criteria that included comparability of groups, randomisation sequence generation, allocation concealment, blinding of outcome assessors and use of intention-to-treat or per protocol analysis.

It appeared that one reviewer assessed the studies and a second reviewer checked the quality assessment.

Data extraction
Data were extracted for invasive pneumococcal diseases, bacteraemia, pneumonia, otitis media, nasopharyngeal Streptococcus pneumoniae carriage and immunological outcomes that included IgG (immunoglobulin G) and opsonophagocytic activity.

For nasopharyngeal carriage outcomes, odds ratios (OR) with 95% confidence intervals were extracted for children who received three doses compared with the two-dose schedule. For immunological outcomes, absolute risk differences with 95% confidence intervals were calculated for children who received the three-dose and two-dose schedules. IgG antibody levels above a threshold of 0.35μg/mL were considered seropositive for all serotypes measured by any enzyme-linked immunoassay (ELISA). Geometric mean concentration data were used where seropositive data were not
available. The authors were contacted in case of discrepancies between data.

It appeared that one reviewer extracted data using a structured pilot form and a second reviewer checked the data extraction.

**Methods of synthesis**
The data were combined statistically using DerSimonian and Laird random-effects meta-analysis. Statistical heterogeneity was assessed using the $I^2$ statistic ($I^2 \leq 25\%$ were low, $\leq 50\%$ moderate and $\leq 75\%$ high).

**Results of the review**
Eight RCTs (2,101 participants), one cohort study and one case-control study were included in the review. In most studies it was not clear how randomisation was conducted and whether there was adequate allocation concealment and blinding.

Immunological outcomes were investigated in six combinations of PCV vaccine primary doses and boosters and PPV vaccine.

**Three versus two PCV doses without boosters (five RCTs, one cohort study):** Seropositivity levels following three or two primary PCV schedules were high for most serotypes. Differences between schedules were generally small and tended to favour three primary dose schedules, especially for serotypes 6B and 23F (heterogeneity was high for both studies). The cohort study compared the schedules implemented in different areas and found results were similar between the groups.

**Three PCV doses versus two plus booster:** At 13 months geometric mean concentrations in the three-dose no booster group were around one tenth of those in the two-dose plus booster group for all serotypes. At 19 months of age geometric mean concentrations were more similar with values in the three-dose no booster group (13 months after the primary dose) around half of those in the two-dose plus booster group (seven months after the booster) for all serotypes except 4.

**Three PCV doses plus booster versus two doses plus booster (two studies):** Seropositivity levels were similar but small differences favoured three-dose plus booster schedules for serotypes 6B and 23F (no heterogeneity).

**Three PCV doses with and without booster (two studies):** At 19 months of age (seven months after the booster) geometric mean concentrations values in the booster group were around 1.5 to three times higher than those in the non-booster group.

**Two and three PCV doses with booster versus with PPV (one study):** The results were almost identical in the PCV booster and PPV booster groups with more than 85% seropositive in both groups for all serotypes.

**Opsonophagocytic antibody (three studies):** Proportions at the group level with opsonophagocytic antibody titre at least 1:8 were similar to the proportions with ELISA antibody level at least 0.35μg/mL.

**Clinical outcomes:** There were no clinical outcomes data from RCTs. For the case-control study of invasive pneumococcal disease the adjusted odds ratios for disease caused by serotypes included in the vaccine were reported as: three versus two doses and no boosters (OR 1.5, 95% CI 0.54 to 4.35); three doses versus two doses plus booster (OR 1.5, 95% CI 0.15 to 14.6); three doses plus booster versus three doses without booster (OR 0, 95% CI 0 to 0.87); and three doses with booster versus two doses with booster (OR 0, 95% CI 0 to 10.1).

**Nasopharyngeal pneumonia carriage:** For three versus two primary doses each without boosters (two studies) there was no difference between the two schedules in prevalence of carriage of any pneumococcal serotype at six months of age. Only one trial reported data up to 17 months of age.

**Authors’ conclusions**
Both three and two PCV dose schedules resulted in high levels of seropositivity but three-dose schedules had a higher antibody level, especially for serotypes 6B and 23F both before and after a booster dose. The clinical relevance of these differences was unknown.
CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. The authors searched several databases and trial registries without language restrictions and also contacted manufacturers so relevant studies were unlikely to be missed. Two reviewers were involved in study selection and it appeared that this was also the case for data extraction and quality assessment.

Included trials were moderate to poor quality. It may not have been appropriate to combine trials which used 7-, 9- and 10-valent vaccines. There was some statistical heterogeneity, which the authors attempted to explore narratively.

There was a slight deviation from the protocol in study population and exclusion criteria as according to the study protocol all age groups would be considered and exclusion criteria for HIV status were not reported. The authors did not explain these changes.

The authors’ conclusions reflect the available evidence. The reliability of the conclusions is limited by statistical and clinical heterogeneity between the included studies; this limitation was acknowledged by the authors.

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

Research: The authors stated that use of pragmatic RCTs to introduce different schedules in different areas when PCV vaccine was introduced in large countries or regions and enhanced surveillance for pneumococcal disease would provide valuable information.

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