Immunogenicity of pneumococcal conjugate vaccines in infants after two or three primary vaccinations: a systematic review and meta-analysis


CRD summary
Most children were protected by two primary immunisations with PCV vaccine, apart from serotypes 6B and 23F in which the potential benefit of three primary vaccinations was considerable. The authors’ conclusions reflect the evidence presented but the unknown quality of the included studies and differences between the included studies make the reliability of the conclusions unclear.

Authors’ objectives
To evaluate the evidence on immunogenicity of pneumococcal conjugate vaccines (PCV) in infants comparing two and three primary immunisations before a booster dose is given.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from January 1999 to 2011. Search terms were reported. Studies reported in English, French and German were considered. Drug manufacturers were contacted for any relevant additional study material.

Study selection
The included studies had to report the proportion of children with ELISA antibody levels of at least 35μg/mL after primary infant immunisation.

Eligible studies were RCTs that compared two with three primary immunisations (type B) and single-arm trials (three primary immunisations) and compared antibody levels after two and after three immunisations in the same patients (type A). Studies of children immunised after six months were excluded. Three pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13) licensed in Europe and USA were eligible for inclusion in this study. The difference between the proportion of participants with antibody levels of at least 0.35μg/mL after two and three doses of PCV was chosen as an endpoint.

Studies were conducted in Germany, Poland, Spain, Denmark, Norway, Slovakia, Sweden, Fiji, Korea, Israel and The Gambia. RCTs used a vaccination schedule of two, four and six months. Schedules in single-arm trials varied. Antibody levels were evaluated one month after each vaccination for all studies.

The authors did not state how many reviewers were involved in study selection.

Assessment of study quality
The authors did not report that they assessed validity.

Data extraction
Data were extracted on the proportions of children who achieved the specified antibody level for each serotype after two and three doses of the vaccine.

Two reviewers independently extracted the data. Any disagreements were resolved by discussion to reach consensus.

Methods of synthesis
Pooled differences in the proportion of children with antibody levels of at least 0.35 μg/ml were calculated, with 95% confidence intervals (CIs). DerSimonian and Laird random-effects model meta-analysis was used. Statistical heterogeneity was assessed using the I² statistic.

Results of the review
For most serotypes, well over 90% of children had protective antibody levels after three doses.
Type A (four studies): One study used PCV7, one study used PCV7 and PCV10 and two studies used PCV13. Substantial heterogeneity ($I^2=97.9\%$) between serotypes and studies was observed. The largest differences between two and three doses was observed for serotypes 6B ($-49.4\%, 95\%\ CI -66.0\% \text{ to} -32.9\%$), 23F ($-26.9\%, 95\%\ CI -37.2\% \text{ to} -16.6\%$) and 6A ($-15.4\%, 95\%\ CI -20.6\% \text{ to} -10.3\%$). For all other serotypes the difference was less than 10%.

Type B (four RCTs): Three studies used PCV7 and one study used PCV10. There was a substantial heterogeneity ($I^2=90.4\%$) between serotypes and studies. The largest difference between groups of children achieving protective antibody levels was observed for serotypes 6B ($-20.3\%, 95\%\ CI -36.1\% \text{ to} -4.6\%$) and 23F ($-19.7\%, 95\%\ CI -32.8\% \text{ to} -6.5\%$). For all other serotypes, the difference was less than 10%.

Antibody levels at 12 months were reported for two studies.

Authors’ conclusions
Most children were protected by two primary immunisations with PCV vaccine except for serotypes 6B and 23F in which the potential benefit of three primary vaccinations was considerable. For all other serotypes, the difference between two and three primary immunisations was less than 10%.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Several relevant data sources were searched. The restriction to studies in English, German and French meant that language bias was possible. Two reviewers extracted data. The authors did not report how many reviewers performed study selection so some studies may have been missed.

The authors did not report any assessment of study quality so it was difficult to assess the reliability of the evidence included in the review. Use of a random-effects model was appropriate considering the substantial statistical heterogeneity between both studies and serotypes. The authors attempted to explain possible sources of the heterogeneity.

The authors’ conclusions reflect the evidence presented but the unknown quality of the included studies, high heterogeneity and possible language bias make the reliability of the conclusions unclear.

Implications of the review for practice and research
Practice: The higher cost of three primary immunisations and one booster meant that a reduction to two primary immunisations and one booster dose might be considered in countries where serotypes 6B and 23F were relevant.

The authors did not state any implications for further research.

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