Efficacy of Haemophilus influenzae type b vaccination of children: a meta-analysis
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CRD summary
This review assessed the efficacy of the Haemophilus influenzae type b (Hib) vaccine in children under 5 years old. The authors stated that Hib conjugate vaccines are safe and effective in reducing the risk of all forms of invasive Hib disease. Despite some limitations in the trial data and uncertainties in the review methodology, the authors’ conclusions appear to be supported by the evidence presented.

Authors’ objectives
To provide quantitative estimates of the protective efficacy of the Haemophilus influenzae type b (Hib) vaccine against invasive Hib disease, bacterial pneumonia and meningitis in children under 5 years old.

Searching
MEDLINE (1966 to 2005), EMBASE (1990 to June 2005) and the Cochrane CENTRAL Register (Issue 3, 2000); the search terms were provided. The reference lists of retrieved articles and review articles were screened for additional studies, while two leading authors in the research area were contacted for further unpublished or ongoing studies. All of the studies included in the review were published.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-randomised (quasi-RCTs) were included. Prevalence studies of Hib oropharyngeal carriage, control programmes, reviews, immunogenicity studies and trials using historical comparisons were excluded. The duration of follow-up in the included studies varied between 5 and 36 months.

Specific interventions included in the review
Studies of Hib vaccination for the prevention of invasive Hib disease were eligible. All of the included studies assessed the conjugate Hib vaccine (PRP-T, PRP-D, PRP-OMP, HbOC) which was administered on the same day as the combined diphtheria, pertussis and tetanus (DPT) vaccine. Studies that compared the efficacy of two Hib vaccines were excluded. Three of the included studies compared the Hib vaccine with placebo, four with no vaccine, while one compared the Hib vaccine against a hepatitis B vaccine. Most of the included studies used three doses of intramuscular vaccine, but one used two doses and another used four doses.

Participants included in the review
Healthy children aged under 5 years old were eligible. The participants in the included studies were aged between 6 weeks and 24 months and received their first dose of the vaccine at age 2 or 3 months.

Outcomes assessed in the review
The primary outcome measure was the overall incidence of invasive Hib disease. Invasive Hib disease was defined as an illness during which Hib is isolated from a normally sterile body fluid such as blood or cerebrospinal fluid. Only bacteriologically confirmed invasive Hib disease was considered in the analysis of efficacy. The incidences of meningitis, bacterial pneumonia, all-cause mortality, Hib-specific mortality and adverse events were also included.

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
The authors assessed whether randomisation was well described (unit and method of allocation); whether blinding of the treatment administration and outcome assessment was adequate; whether follow-up was available; and which
criteria were used to diagnose Hib disease.

The authors did not state how many reviewers performed the validity assessment.

**Data extraction**

One reviewer extracted data from the studies using a pre-piloted data extraction form. This was checked by a second reviewer and any disagreements were resolved through discussion.

In addition to the standard categories of data the reviewers also recorded the human immunodeficiency virus (HIV) status of the participants, country of origin and any concurrent vaccines administered. For all studies it was noted whether vaccine efficacy could be calculated on an 'any dose' basis (i.e. data available for all participants receiving at least one vaccine dose) or on an 'all dose' basis (i.e. data available for participants receiving all assigned doses). The authors performed an intention-to-vaccinate analysis for 'any dose received', calculating odds ratios (ORs) and relative risk reduction or protective effect (1 minus the OR) as percentages, with 95% confidence intervals (CIs).

**Methods of synthesis**

**How were the studies combined?**

The studies were combined using a random-effects model and efficacy estimates reported as summary ORs with 95% CIs. The authors stated that they used a fixed-effect model when significant heterogeneity was detected.

**How were differences between studies investigated?**

Heterogeneity was assessed using the chi-squared (Q) statistic; a P value of less than 0.10 was considered statistically significant. Heterogeneity was also quantified using the I-squared statistic. A sensitivity analysis was performed using a fixed-effect model to evaluate the robustness of the authors' conclusion. In addition, pre-specified subgroup analyses were performed according to country of origin (developing versus developed), age of the children at first vaccination, number of doses received, baseline risk and HIV status.

**Results of the review**

Eight studies were included: 6 RCTs (n=190,288) and 2 quasi-RCTs (n=175,080). In total 185,138 children received the Hib vaccine and 180,230 remained unvaccinated. Two of the RCTs were cluster randomised by either district or health centre. The authors also found two unpublished abstracts, which were not included in the analysis but are mentioned in the discussion.

Four trials were carried out in the USA and one each in Finland, the UK, Chile and Gambia. The overall mean protective efficacy of the vaccine against invasive Hib (8 trials) was 84% (OR 0.16, 95% CI: 0.08, 0.31). However, there was significant heterogeneity (chi-squared 23.03, P=0.0008, I-squared 73.9%) due to one study carried out in Alaska. When this study was removed, the protective efficacy against invasive Hib was 86% (OR 0.14, 95% CI: 0.09, 0.20; chi-squared 7.31, P=0.20).

Against meningitis (4 trials) the protective efficacy was 75% (OR 0.25, 95% CI: 0.08, 0.84), and against bacterial pneumonia (4 trials) it was 69% (OR 0.31, 95% CI: 0.10, 0.97). Only 2 trials reported all-cause mortality, and the overall protective efficacy in these trials was 6% (OR 0.94, 95% CI: 0.74, 1.19). None of the trials reported data on Hib-specific mortality.

Adverse events were reported in 6 studies, but were mainly mild and transient with similar event rates being reported in both the vaccine and control groups. In general, serious adverse events were rare.

Subgroup analyses showed differences in the overall protective effect against invasive Hib which was dependent on: the number of doses used (one versus two doses); when the first dose was administered (2 months old versus 3 months old); baseline risk for Hib; and type of conjugate vaccine administered. With the exception of age at first dose, the differences were usually small. There were no differences in the overall efficacy between developing and developed countries, and none of the studies reported the HIV status of the children.
The only factor included in the sensitivity analysis that changed the overall protective efficacy against Hib was the presence or absence of double-blinding.

**Authors' conclusions**
The results provided firm evidence that Hib conjugate vaccines are safe and effective in reducing the risk of all forms of invasive Hib disease.

**CRD commentary**
This review was clearly presented and was based on well-defined inclusion criteria. However, without further details about how the studies were selected for inclusion and how their quality was assessed, it is difficult to assess whether bias might have been introduced during the review process. The authors made reasonable attempts to locate all the available data, although only published data were included in the analysis, which may suggest a risk of publication bias. It would also have been informative to have had more detail about the heterogeneity associated with the summary estimates of meningitis, bacterial pneumonia and all-cause mortality for which there were limited data. There was also relatively little data relating to adverse events and the effect of HIV status, which is an important consideration in developing countries. The authors also identified the use of cluster randomisation in some of the studies, but did not report whether the individual study authors accounted for this in their analyses and what effect this could have on the review data. The authors did, however, carry out an extensive examination of the possible effects of factors such as country of origin, vaccination regimen and baseline risk. Sensitivity analyses looking at the effect of study quality and methodology on the robustness of the findings were also conducted. Despite the limitations of the data and the uncertainties in the review methodology, the authors' conclusions would still appear to be reasonable, although it would also seem appropriate to further highlight the lack of data in populations where HIV is prevalent.

**Implications of the review for practice and research**
Practice: The authors supported the use of conjugate Hib vaccines for the vaccination of children in developing countries.

Research: The authors recommended an improvement in the reporting of safety and mortality data in future vaccine trials. They also expressed an urgent need for local or regional data on Hib disease burden, background epidemiology and the cost analysis of Hib disease. The effectiveness and safety of combination vaccines designed to minimise the number of injections given will need further evaluation. More research is also needed to evaluate the efficacy of Hib vaccines in immunocompromised patients or those with chronic illnesses.

**Bibliographic details**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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Record Status
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.