

Supplementary text 1

Systematic Review of RCTs of Haemophilus influenzae Type b Conjugate Vaccines: Efficacy and immunogenicity

Review protocol

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Definitions

Booster (or Booster dose)	A Hib-conjugate vaccination which is planned to be given some time (e.g. more than 2 months) after the primary series (see definition below). This definition is used in order to include both traditional and experimental Hib vaccination schedules.
Carriage Effectiveness	The colonization of the nasopharynx by Haemophilus influenzae type b The extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population [1]. In this review it refers to the impact of Hib vaccine on disease and carriage when it is implemented in a routine field setting. In the context of this review it refers to clinical outcomes assessed in settings other than randomized (or quasi-randomized) controlled trials, and refers to any result, not only those which are beneficial.
Efficacy	Efficacy has been defined as “the extent to which a specific intervention, procedure, regimen, or service provides a beneficial result under ideal conditions”[1], but in this review it will be used to mean the extent to which a Hib vaccine affects clinical outcomes assessed in randomized (or quasi-randomized) controlled trials only. This will be estimated through the equation: $VE = 1 - \left[\frac{\text{rate (or risk) in vaccinated}}{\text{rate (or risk) in unvaccinated}} \right] \times 100$
Primary series	Two, or three doses of Hib vaccine given relatively close together (e.g. one to two months apart); or one dose of vaccine where there is a prolonged interval (planned) before the next (booster) dose (e.g. more than 2 months). This definition is used so as to include both traditional and experimental Hib vaccination schedules.

Abbreviations

Hib	Haemophilus influenzae type b
PRP	Polyribosylribitol phosphate
PRP-D	PRP conjugated to diphtheria toxoid
PRP-HbOC	PRP conjugated to diphtheria toxin CRM 197
PRP-OMP	PRP conjugated to outer membrane protein of Neisseria meningitidis
PRP-T	PRP conjugated to tetanus toxoid
VE	Vaccine efficacy
WHO	World Health Organization

1 *Background*

Haemophilus influenzae type b (Hib) is an encapsulated, Gram-negative coccobacillus, and is an important cause of meningitis and pneumonia in children. Other important, but less frequent, manifestations of Hib infection include epiglottitis, septicaemia, cellulitis, arthritis, osteomyelitis and pericarditis. If the bacterial agent is detected in body fluids or tissues that normally are sterile, such as blood and cerebrospinal fluid, this is defined as invasive disease. Pneumonia by itself is not considered to be invasive disease for the purposes of this review, but pneumonia and invasive disease may occur concurrently. Invasive Hib disease typically occurs in early childhood (with the majority of disease occurring between 3 months and 3 years of age) and is relatively uncommon after five years of age.

Two types of Hib vaccines have been developed; polysaccharide vaccines and conjugate vaccines. The polysaccharide vaccines (PRP), contain pure capsular polysaccharide of Hib and were the first Hib vaccines licensed. Although polysaccharide vaccines produce an immune response in children above 2 years of age, they fail to adequately do so in younger infants. To overcome this problem, several conjugate vaccines, conjugating PRP to a protein carrier such as diphtheria toxoid (PRP-D), non-toxic mutant diphtheria toxin CRM 197 (oligosaccharide conjugate PRP-HbOC), or outer membrane protein of Neisseria meningitidis (PRP-OMP) were developed. The conjugate Hib vaccines, prepared either as single antigens or as part of combination vaccines, substantially improved the immunogenicity of Hib vaccines in young children. Another conjugate vaccine has since been licenced, conjugating PRP to tetanus toxoid (PRP-T). Trials demonstrate that these three Hib conjugate vaccine formulations have similar but not identical immunogenicity profiles. Regardless of these differences, PRP-T has shown high effectiveness and herd immunity in all populations evaluated and this formulation has become the most commonly used Hib conjugate vaccine worldwide. Studies showed that PRP-D was less immunogenic than other conjugates, and it has been withdrawn from the market [2].

A range of schedules have been used for conjugate Hib vaccines, usually consisting of 2 or 3 doses in the primary vaccination series, and sometimes followed by a booster which is usually given in the second year of life. The World Health Organization (WHO) position paper, published in 2006, recommends the use of a 3 dose primary series, with the first dose given to infants as young as 6 weeks of age, with a 4 to 8 week interval between doses [2]. For children aged older than 12 months who have not received their primary immunization series, WHO states that a single dose of the vaccine is sufficient. WHO further acknowledged that "the need for and timing of a booster dose of Hib vaccine in developing countries require further study". Two systematic reviews conducted in 2007 and 2008 considered randomized controlled trials (RCTs) and searched Medline, Embase, and the Cochrane Central Register of Controlled Trials [3, 4]. It appears that both reviews included only studies that compare conjugate Hib vaccine to no vaccination or placebo, although Obonyo et al. did not explicitly state the inclusion criteria. Both concluded that conjugate Hib vaccines are effective but neither contained comparisons of different schedules of Hib vaccine administration.

A systematic review of evidence from all available sources will summarize the evidence available to date and identify gaps in evidence. Through this it will provide parameters for infectious disease modelling, form a basis for a framework for guiding decisions on appropriate Hib vaccinations schedules and aid the targeting of primary research to fill the identified data gaps.

2 Objective

To systematically identify and synthesize data on immunogenicity, clinical efficacy, and effectiveness of Hib conjugate vaccine for a variety of schedules.

3 Study questions

Study questions are listed below. In this list, the term “relevant outcomes” refers to immunogenicity, clinical efficacy and Hib carriage. Each question is applicable to both general population and high-risk subgroups (e.g. HIV-infected children). These questions are further illustrated in Table 1.

The primary questions to be examined by this review are:

1. What is the effect on relevant outcomes (see above for definition) of using a 2-dose Hib-conjugate primary vaccine schedule rather than a 3-dose primary schedule?

The secondary questions to be examined by this review are:

1. What is the effect of any Hib conjugate vaccine schedule on relevant outcomes?
2. What is the effect of the number of Hib conjugate vaccine doses on relevant outcomes?
3. What is the effect of the age at initiation of Hib vaccination on relevant outcomes?
4. What is the effect of the length of dosing interval on relevant outcomes?
5. What is the effect of giving a booster on relevant outcomes?
6. Table 1: Study questions

	Clinical efficacy	Carriage	Immunogenicity
Any Hib conjugate vaccine schedule	✓	✓	✓
Number of Hib conjugate vaccine doses	✓	✓	✓
Age at initiation of Hib vaccination	✓	✓	✓
Length of dosing interval	✓	✓	✓
A booster dose	✓	✓	✓

All questions apply to both general population and high-risk subgroups

4 Methods

We will identify and critically appraise the best available evidence that addresses important outcomes and provide an evidence profile that summarises the findings for each outcome. In this section we set out the methods for preparing the systematic review.

4.1 Inclusion Criteria

We will search for reports of studies in which the population, comparison group, intervention, and outcomes fulfil the following criteria:

4.1.1 Study design inclusion criteria

We will consider the following study designs for inclusion: Randomized controlled trials; quasi-randomized controlled trials (e.g. those with allocation strategies based on alternation, date of birth or case record number).

4.1.2 Population inclusion criteria

Children up to the age of 5.99 years will be eligible to contribute outcome data to this review. There will be no restriction on location and high-risk groups will also be eligible

4.1.3 Intervention inclusion criteria

Hib conjugate vaccines of the following types will be considered:

- PRP-HbOC (diphtheria CRM₁₉₇ protein conjugate)
- PRP-OMP (outer membrane protein (*Neisseria meningitidis*) conjugate)
- PRP-T (tetanus toxoid conjugate)

4.1.4 Comparison inclusion criteria

One or more of the following comparisons:

1. A comparison between Hib conjugate vaccination (any schedule) and placebo, a non-Hib vaccine, or no comparison vaccine.
2. A comparison between different numbers of doses of Hib-conjugate vaccine in the primary vaccination series.
3. A comparison between different ages at first vaccination and/or different dosing intervals where the same numbers of doses of Hib conjugate vaccine are given in the primary vaccination series. Intended ages at vaccination for such comparisons should to differ by at least 1 month between groups, or, if intended age ranges for vaccination are given for each group, the age ranges should to overlap by less than 50%.
4. A comparison between a booster dose of Hib-conjugate vaccine and the same primary schedule without the booster dose, or between schedules which are the same except for the booster dose being given at a different age.
5. Any other comparison encountered in the course of the review which might be relevant for optimizing schedules for Hib-conjugate vaccines.

4.1.5 Outcomes to be reported for study to be eligible for inclusion

The populations in which these outcomes occur, the intervention examined and the comparisons of interest are listed above. To be eligible for inclusion, the study must

additionally report one or more of the following:

Immunogenicity (ELISA or other appropriate laboratory tests)

- a. seropositivity after vaccination (e.g. PRP antibody concentration of > 0.15 µg/ml, or > 1.0 µg/ml)
- b. seroconversion (changing from seronegative before vaccination to seropositive after vaccination)
- c. geometric mean concentration (or titer)

Clinical efficacy

WHO definitions will be used for these outcomes.

- a. All-cause pneumonia (radiologically confirmed pneumonia where possible, and stratified by severity if reported)
- b. Definitive Hib pneumonia (radiologically confirmed pneumonia and positive blood, lung tissue or empyema fluid culture for Hib)
- c. All cause mortality
- d. Mortality due to pneumonia (radiologically confirmed pneumonia)
- e. Hib-related mortality (death of a child with documented Hib infection)
- f. Invasive Hib disease (bacteremia/septicemia, meningitis etc)
- g. Epiglottitis

Each clinical outcome must be collected as a specific clinical outcome within the trial in order to be eligible for inclusion. Clinical outcomes other than mortality that are collected as adverse events and serious adverse events are not eligible for inclusion.

Nasopharyngeal carriage

- a. percentage carriage of *Haemophilus influenzae* type b (Hib) before and after vaccination

4.2 Exclusion criteria

- Uncontrolled studies, observational intervention studies, and animal and laboratory studies will be excluded.
- Studies on vaccines which have never been licensed and whose development has been permanently or indefinitely halted will be excluded.
- Clinical outcomes other than mortality that are collected as adverse events and serious adverse events are excluded.

4.3 Search strategy

4.3.1 Electronic databases

The following databases will be searched from beginning of records for each database through to 2009 without language restrictions:

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- MEDLINE (Ovid Silver Platter).
- The Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL));
- National and international registries on clinical trials as detailed by the Cochrane Handbook (Box 6.2.h)[5, 6]. These include databases covering Australia, China, India, Japan, the Netherlands, New Zealand, South Africa, the United Kingdom, the United States and well as the European Union, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and other international registers.
- Regulatory authority dossiers for licensure (e.g. FDA)
- African Index Medicus (AIM); Indian Medlars Centre (IndMed); Latin American and Caribbean Health Sciences Literature (LILACS), and other regional databases.

Search terms

Search terms will use Medical Subject Headings (MeSH) or terms specific to each database and will be based on search strategies defined in the Cochrane Handbook [5, 6] and will include:

- terms relating to Hib vaccine/s, and
- terms relating to the word conjugate
- terms combining vaccination and Hib disease

We will not specify search terms for population group, study design or outcome.

4.3.2 Additional searches

Due to much data on Hib-conjugate vaccine remaining unpublished we will perform additional searches.

- We will search for potentially eligible studies in the reference lists of relevant reviews and articles identified through the electronic literature search, based on the titles of cited papers.
- We will contact experts in the field of Hib-conjugate vaccine to determine if they are aware of unpublished or ongoing trials which may be eligible for inclusion.
- We will contact the manufacturers of Hib-conjugate vaccines to obtain unpublished data on trials of such vaccines.

4.4 Selection of eligible studies

The lists of articles identified by the search strategy will be independently reviewed by at least two suitably qualified reviewers using the inclusion and exclusion criteria listed in paragraphs 4.1 and 4.2. Any study selected as being potentially eligible by either reviewer or which contains insufficient information for a decision to be made, will be retained for review of the full text.

4.4.1 Potentially eligible studies

Decisions on inclusion or exclusion will be based on the criteria listed in sections 4.1 and 4.2. The reviewers will read the abstract of each identified article if fewer than 500 articles are returned in total. If the searches identify 500 or more articles, the reviewers will select potentially eligible titles first and will then read the abstracts of titles that potentially fit the inclusion criteria. If no abstract is available electronically, the full text of the article will be

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requested. The abstracts of articles identified through additional searches will be reviewed in the same manner as for studies identified through database searches. Reasons for exclusion will be recorded in detail.

4.4.2 Retrieval of full-text articles

We will obtain the full text of articles or other documents reporting studies identified as being potentially eligible for inclusion. We will make every effort to locate documents through internet downloads, inter-library loans and contacting authors of reviews citing potentially eligible documents. We will request translation if necessary to confirm or refute eligibility.

4.4.3 Selection of studies for inclusion

Each full text article will be examined by two reviewers and lists of studies considered eligible for inclusion will be compared. Studies identified by both reviewers as being eligible for inclusion and having adequate data for extraction will be included in the review. Where there are discrepancies, the reasons for these will be discussed and a decision about inclusion reached by consensus. If there is no agreement, a further independent reviewer will adjudicate to make a final decision about eligibility.

4.5 Data extraction forms

We will develop forms for extracting consistent data about:

- exposures and outcomes (including methods or criteria for diagnosis);
- tests used to assess outcomes, any cut-off points used in the assessment of immunogenicity and the time between last vaccination and outcome assessment
- occurrence of disease which may affect immunogenicity outcomes;
- co-administration of other vaccines or pharmaceuticals;
- potential confounders if relevant;
- background data (e.g. geographic and demographic information);
- methodological and reporting quality (specific for each type of study design and based on published checklists of items likely to cause bias); and
- other potentially relevant information such as funding source.

Study designs will also be assessed to determine whether results are a measure of direct effects, indirect effects, or a combination of both.

Data extraction forms will be designed to capture any information for the outcomes listed in paragraph 4.1.5. If an outcome can be assessed by more than one diagnostic method a hierarchy of these methods will be defined as the extraction form is being developed and finalized prior to data analysis. If an outcome was assessed by more than one diagnostic method within a study, results obtained by each method will be extracted. We will pilot test the forms to ensure ease of use and capture of all relevant data. The forms will be developed using Epidata (Epidata version 3.1, EpiData Association, Odense, Denmark).

4.6 Data extraction

Appropriately qualified people will extract and enter data independently and in duplicate from each included study. Articles in languages other than English will either be translated first and then duplicate data extraction conducted as above or, if there are two reviewers who understand the language of publication, they will extract the data directly.

Data entry will be into Epidata. The two files of independently extracted data will be

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compared using the validation function available in this program. Discrepancies in data extraction or data entry will be resolved by consensus. If there is no agreement a third independent reviewer will adjudicate to make a final decision.

Studies might be excluded at the data entry stage if it becomes apparent that inclusion criteria are not met or there is not enough information in the documents to extract the required data.

If authors are contacted for further information on their studies we will give all authors of eligible studies a similar chance to respond to queries in order to minimize bias which might be introduced through selective contact of authors.

4.7 Data analysis

We will produce descriptive tables summarising information about study design, study quality and results of all included studies.

We will analyse and report available data for each outcome as defined. The primary analysis will be intention to treat analysis of clinical outcomes. If there is more than one study reporting an exposure-outcome association, or the frequency of an outcome, we will present these in forest plots and consider combining the data statistically in a meta-analysis. We will examine heterogeneity of the results first using chi-square tests and I-square tests.[7] If meta-analysis is appropriate, we will calculate summary weighted effect measures and 95% confidence intervals, using random effects models [8]. If the results are too heterogeneous to combine statistically, we will explore this using stratification and/or meta-regression techniques as appropriate. Stratification will be on criteria such as quality of study, the conjugated molecule in the Hib vaccine, baseline intervention (e.g. placebo or non-Hib vaccine), time since last vaccination, the randomization scheme (individual vs. cluster) and other suitable criteria.

If sufficient data are available, results will also be examined for apparent bias in the reporting/publication of studies using funnel plots and the Egger test.[9]

Data analysis will be conducted with Stata (Intercooled Stata 9.2 , StataCorp, Texas, USA)

4.8 Assessment of study quality

Due to the influence study quality can have on meta-analyses [10] , we will assess study quality using checklists of items associated with methodological and reporting quality that are specific to each study design (e.g. for RCTs, those listed in Egger et al. 2001 [9]).

4.9 Report writing

Reports will be written following the appropriate guidelines (e.g. PRISMA Statement Guidelines for reporting of meta-analyses and systematic reviews of randomised controlled trials) and will clearly present the methods used as well as findings.

5 Protocol amendments (Finalised May, 2012)

1. Review of observational study designs removed from protocol because a review of observational data will be conducted by a separate research group.
2. Co-administration questions removed. These have been addressed in a published review.
3. Minor amendment made to comparison eligibility criteria: the first eligible comparison modified to include a comparison to no vaccination (original statement only stated a comparison to placebo or a non-Hib vaccine).
4. Eligible comparisons were modified to remove comparisons where vaccines with different conjugated molecules were used (either within or between compared schedules). This was because comparisons involving different conjugated molecules did not directly address key questions about the number and timing of doses.
5. Eligibility criteria were modified for comparisons where the groups compared received the same number of primary and booster dose but the timing of doses varied. Intended ages at vaccination for such comparisons needed to differ by at least 1 month between groups, or, if intended age ranges for vaccination were given for each group, these needed to overlap by less than 50%.
6. Eligibility criteria for clinical outcomes modified to specify that clinical outcomes must be collected as a specific clinical outcome within the trial. Clinical outcomes other than mortality that are collected as adverse events and serious adverse events are excluded because individual outcomes are not systematically assessed and assessed time periods are short.
7. Eligibility criteria relating to the intervention (specifically age at vaccination) simplified. Original criteria included specifications about eligible ages at primary and booster doses. However, this added complexity to assessment of eligibility and criteria were therefore modified to state that children up to the age of 5.99 years would be eligible to contribute outcome data to the review.
8. EMBASE removed from electronic databases searched. EMBASE returned an excessive number of hits (around 4000) which were poorly specific to Hib. All RCTs included in previous reviews were found by the MEDLINE search.
9. Analysis was modified to state that the molecule used for conjugation in the Hib vaccine would be used as a variable by which to stratify studies because it was considered that different classes of vaccines might differ in relative effects.

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