

**Systematic review of observational data on effectiveness of *Haemophilus influenzae* type b (Hib) vaccines to allow optimization of vaccination schedules**

**Charlotte Jackson, Andrea Mann, Punam Mangtani, Paul Fine  
London School of Hygiene and Tropical Medicine  
October 2012**

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## **ACKNOWLEDGEMENTS**

We thank Ana Maria Henao Restrepo and Ximena Laurie for support in conducting this review. We are also grateful to Pippa Scott and colleagues at the University of Bern for carrying out and sharing the results of the literature search and initial screening. Kenda Cunningham, Rein Houben and John Bradley assisted with translations.

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## **LIST OF ABBREVIATIONS**

CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
DTaP	Diphtheria – tetanus – acellular pertussis vaccine
DTwP	Diphtheria – tetanus – whole cell pertussis vaccine
EPI	Expanded Programme on Immunization
EU	European Union
GMC	Geometric mean concentration
GMT	Geometric mean titre
HbOC	Polyribosylribitol phosphate – mutant diphtheria toxin conjugate vaccine
Hib	<i>Haemophilus influenzae</i> type b
OR	Odds ratio
PRP	Polyribosylribitol phosphate
PRP-D	Polyribosylribitol phosphate – diphtheria toxoid conjugate vaccine
PRP-OMP	Polyribosylribitol phosphate – <i>Neisseria meningitidis</i> outer membrane protein conjugate vaccine
PRP-T	Polyribosylribitol phosphate – tetanus toxoid conjugate vaccine
RCT	Randomised controlled trial
SES	Socioeconomic status
VE	Vaccine effectiveness
WBC	White blood cell
WHO	World Health Organization

## ***EXECUTIVE SUMMARY***

### *Objective*

The objective of this report is to summarise available evidence from observational studies on the effectiveness of Hib vaccines against clinical outcomes, to support decisions regarding optimising vaccination schedules.

### *Review methods*

Electronic databases and trial registers were searched in June 2012. Studies were eligible for inclusion in the review if they used an observational design and reported the effectiveness of Hib vaccines as a function of number of doses, time between doses, age at initiation of vaccination, or co-administration with other vaccines or medical preparations. The results are summarised descriptively. Some relevant data on immunogenicity and carriage following different vaccination schedules are also presented.

### *Results*

The literature search identified 3718 articles, of which 31 (reporting on 30 studies) were included in the review: 18 case-control studies, 8 cohort studies and 4 studies which estimated vaccine effectiveness using the screening method. Eligible studies consistently reported that two or three doses of Hib vaccine are highly effective (>85%) against Hib meningitis and invasive Hib disease, whilst one dose usually has much lower effectiveness. Estimates of effectiveness against radiologically confirmed pneumonia were lower than those against Hib meningitis and invasive Hib disease ( $\leq 55\%$  after three doses). No studies directly compared different ages at vaccination or intervals between doses; comparisons were therefore made between studies in which different schedules were used. Studies generally reported the intended, rather than the actual, ages at vaccination; there was no clear difference in estimates of dose-specific effectiveness related to the intended age at initiation of vaccination. Limited evidence from cohort studies suggests older age at initiation leads to higher VE against invasive Hib. Most of the case-control studies used appropriate controls and adjusted for some important confounders. Three of the 8 cohort studies included in the review were at least moderately likely to be biased due to lack of control for confounding.

In one case-control study, there was some evidence that dosing intervals within a three-dose schedule had been longer in pneumonia cases than in controls. Data from a second case-control study suggested that older age at the third dose might be associated with an increased risk of Hib meningitis. Hib vaccine appears to be less effective when administered with acellular pertussis vaccine than when given with whole cell pertussis vaccine. The limited data available from two cohort studies suggest that a booster dose enhances protection when given in addition to a full primary series, and one of these studies suggests a booster compensates at least to some extent for incomplete primary vaccination. There is weak evidence that hexavalent vaccines are less effective than quadrivalent or pentavalent vaccines.

Although not reviewed systematically in this report, immunogenicity data support the conclusion from the clinical data that two or three doses of Hib conjugate vaccine are more effective than one dose. One immunogenicity study suggested that the antibody response to vaccination increased with age, but reported substantial rises in antibody titres following vaccination even for children vaccinated at the age of 2-3 months. The response to a booster dose also appeared to increase with age. Immunogenicity data are consistent with a lower effectiveness of Hib conjugate vaccine administered with acellular (as compared to whole cell) pertussis vaccine.

Hib conjugate vaccines may be effective against carriage as well as clinical disease, but the data identified in the course of this review do not suggest a dose-response relationship or allow comparisons of different vaccination schedules.

### *Conclusions*

At least two doses of Hib vaccine are required to achieve high effectiveness, typically reported as 85% or greater against invasive Hib disease and Hib meningitis. The available observational data allow only limited comparisons of different Hib vaccination schedules and do not strongly suggest an optimum schedule, although a booster dose appears to be beneficial. Hib vaccines are less effective and less immunogenic when administered in combination with acellular pertussis vaccines than when given separately or with whole cell pertussis vaccines. Further data are required relating vaccine effectiveness to age at initiation of vaccination and dosing intervals.

## **1. INTRODUCTION**

This project forms part of the WHO/IVR initiative to assist in the optimisation of vaccination schedules. Reviews have been commissioned by several groups to review data on effectiveness drawn from clinical trials (University of Bern) and from observational studies (this project, LSHTM), as well as data on Hib disease epidemiology, Hib vaccine impact and on herd immunity induced by Hib vaccines.

The aim of this review is to summarise the published evidence on effectiveness of Hib vaccines, drawn from observational studies, with reference to schedule-relevant factors and clinical outcomes. In particular:

- Number of doses
- Age at initiation of Hib vaccine series
- Interval between doses
- Implications of a booster
- Implications of co-administration of other vaccines

Previous reviews have summarised estimates of overall and dose-specific effectiveness of Hib vaccination from observational studies<sup>1,2</sup> and randomised controlled trials<sup>2,3</sup>. We add to these summaries by considering in more detail the implications of and for different vaccination schedules. We also briefly review data on the immunogenicity of Hib vaccines and their effectiveness against carriage, again with reference to schedule-relevant factors.

## **2. METHODS**

### **2.1. Data sources and search strategies**

The literature search was carried out by colleagues at the University of Bern. The following databases were searched in June 2012: Embase and Medline (simultaneously using Embase.com), the Cochrane Library (including the Cochrane Central Register of Controlled Trials), African Index Medicus (AIM), Indian Medlars Centre (IndMed), Latin American and Caribbean Health Sciences Literature (LILACS) and other regional databases.



The search strategy for each database included Medical Subject Headings or keywords relating to Hib vaccines, the word “conjugate”, and combinations of vaccination and Hib disease. No date or language restrictions were applied. Clinical trial registries and regulatory authority dossiers were also searched. Data published after the review was carried out, and publicly available surveillance reports, were identified through further literature and internet searches. Investigators who had conducted field studies on Hib incidence in countries which introduced Hib conjugate vaccine before 2007 were contacted to identify unpublished data. Finally, the reference lists of two systematic reviews <sup>1, 4</sup> were hand searched.

Colleagues at the University of Bern also performed some of the initial abstract screening. Further screening of abstracts and full text was carried out at LSHTM.

## **2.2. Inclusion criteria**

Study design: Case control and cohort studies were eligible for inclusion.

Population: We restricted this review to routine vaccination in general populations.

Intervention: Studies of currently licensed conjugate Hib vaccines were included <sup>a</sup>.

Comparison groups: We included studies which allowed assessment of vaccine effectiveness as a function of type of Hib vaccine, number of doses, age at first dose, interval between doses, receipt of a booster, or co-administration of other vaccines or medical preparations.

Outcomes: Studies which estimated the effectiveness of conjugate Hib vaccine against one or more of the following clinical outcomes were eligible: all cause pneumonia, Hib pneumonia, bacteraemia / septicaemia, meningitis, invasive Hib disease, all cause mortality, mortality due to Hib pneumonia, mortality due to invasive Hib disease, epiglottitis. Studies which did not include estimates of vaccine effectiveness, but presented sufficient data for it to be estimated, were also included.

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<sup>a</sup> One of the available hexavalent Hib-containing vaccines (Hexavac) has recently been withdrawn in the EU. One study in which this vaccine was used in some participants was included in the review.

(Vaccine effectiveness was defined as the reduction in incidence of the outcome as a function of vaccination or a particular vaccination schedule as compared to no vaccination or an alternative schedule.)

### **2.3. Exclusion criteria**

Study design: Ineligible study designs included both randomised and non-randomised trials, vaccine probe studies and studies which estimated the impact of vaccination at the population level ((trials and impact studies are subjects of separate independent reviews).

Population: Studies of special groups (e.g. children infected with HIV, re-vaccination of immunocompromised children or adults) were excluded.

Intervention: Studies were excluded if they reported on the effects of polysaccharide (non-conjugate) vaccine only, or if conjugate and non-conjugate vaccines were used but it was not possible to separate the effects of these different vaccines. Similarly, studies of only PRP-D vaccine (which is no longer used) were excluded, as were studies reporting on both PRP-D and other conjugate vaccines in which the different vaccines could not be separated.

### **2.4. Screening of abstracts and full text**

Initial screening of abstracts and full text classified the studies into *likely observational studies* of conjugate Hib vaccines which were likely to meet the inclusion criteria, *controlled trials* and *other* studies. The “other” group included reviews, letters, summaries, guidelines, animal and laboratory studies, studies of vaccination coverage or attitudes to vaccination, economic studies, studies in special groups, and studies of organisms other than Hib such as non-typeable *H. influenzae*. This screening was performed by one or two reviewers (for papers screened by the LSHTM and University of Bern teams, respectively).

The observational studies were screened further (by the LSHTM team) using a rapid electronic method: titles and abstracts were searched electronically for the following

terms (and variants) related to the target study designs: cohort, longitudinal, case-control, prospective, retrospective, matched pair, comparative, follow up, non randomised, observational.

Rapid electronic screening used terms only in the English language. All identified papers included a title in English; however some had abstracts in other languages without English translations. Therefore papers with titles which appeared potentially relevant to this review, and with abstracts in a language other than English, were marked for retrieval in full.

Papers identified through this process (initial screening classifying abstracts as observational, trials or other, followed by rapid electronic screening of observational studies) were further assessed based on titles and abstracts, and the full text retrieved if potentially eligible. Full text screening was performed by one reviewer, with guidance from others on particular papers as necessary.

Papers which were not identified by the electronic screening, but which were included in a previous review of observational studies of Hib vaccination <sup>1</sup>, were also included.

Forms for screening and data extraction were created in web-based systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada).

## **2.5. Data extraction**

Data from each eligible study were extracted by a single reviewer. Extracted data included information about the study population, vaccination schedules and occurrence of the outcome of interest, for each comparison presented.

The data extraction forms included questions, specific to case-control and cohort studies, intended to inform judgement about quality and risk of bias for each included study. Key methodological concerns for each study were noted and are summarised in the text. For case-control studies, much of the required information was similar to that included in a previous systematic review of observational studies of Hib

vaccination, and the data are presented in a similar format<sup>1</sup>; however, we also extracted data on additional factors relevant to vaccination schedules.

## **2.6. Analysis**

The results are presented numerically and descriptively, focussing on factors relevant to schedule decisions (number of doses, age at initiation of vaccination, dosing intervals and implications of both a booster and co-administration with other vaccines). Cohort and case-control studies are presented separately. The search identified insufficient data for meaningful meta-analysis.

## **2.7. Studies using the screening method**

Several studies included in the O’Loughlin review used the screening method<sup>b</sup> to estimate vaccine effectiveness. We considered screening method studies to be of a lower quality than case-control or cohort studies because the screening method does not allow for adjusting for confounding beyond age and sex and because it may produce biased estimates of VE (e.g. the population in which vaccine coverage is measured may not be representative of the population from which the cases arose). For completeness, we highlight the main points from each of the screening method studies included in the O’Loughlin review as well as screening method studies we identified by adding the terms “screening method” and “case population” to our rapid electronic screen of abstracts from observational studies.

## **2.8. Additional data on immunogenicity and carriage**

The systematic component of this review focuses on clinical outcomes. In addition, titles and abstracts of all papers identified in the initial search were further screened electronically for the words “antibody”, “antibodies”, “immunogenicity”, “immunogenic”, “carriage” and “colonisation”. Studies identified by these searches are not included in the systematic component of this report, but some results relevant to optimising schedules are presented in a non-systematic summary.

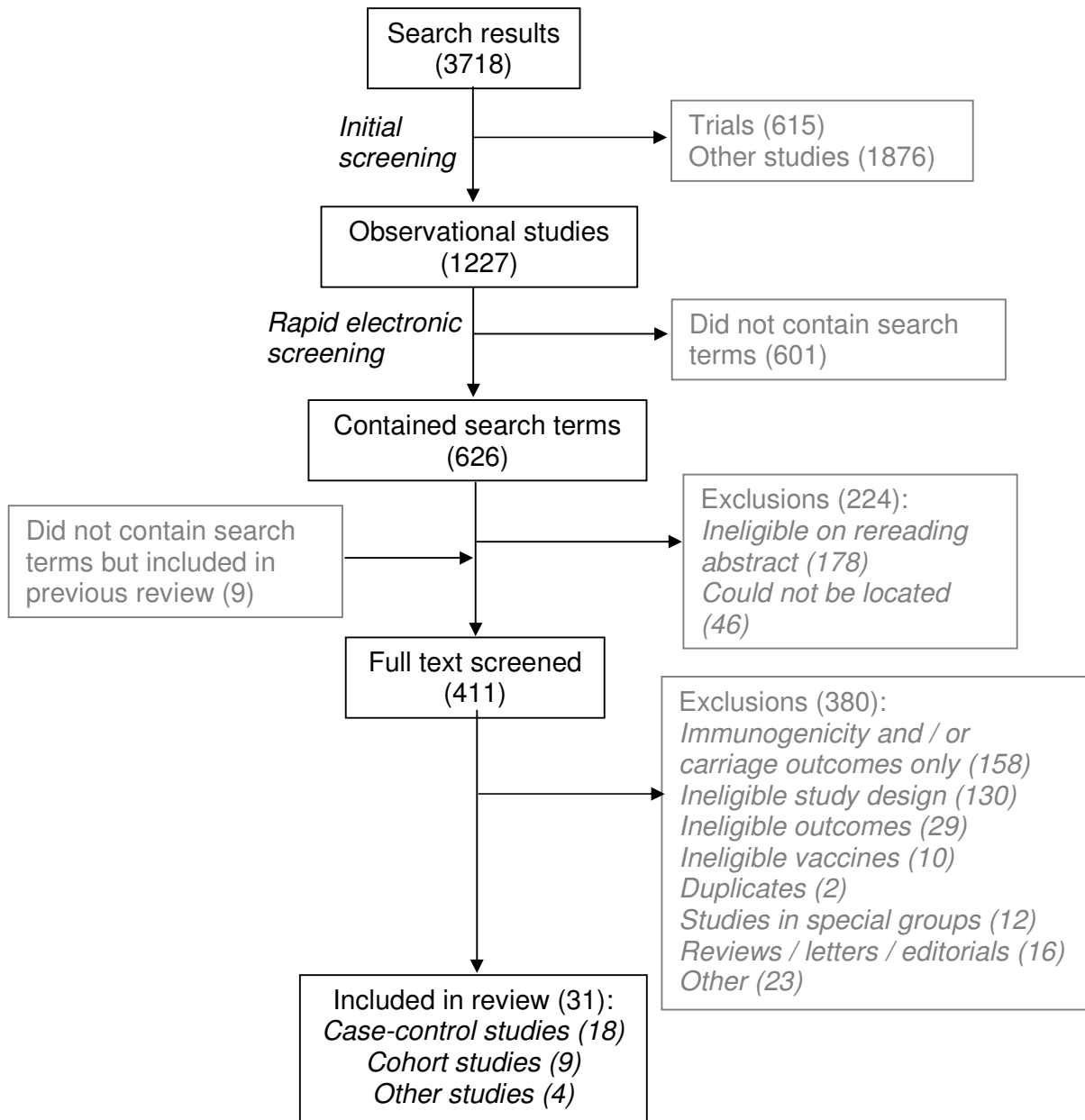
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<sup>b</sup> In screening method studies, vaccine effectiveness is calculated as  $1 - \frac{PCV(1PPV)}{[(1PCV)PPV]}$ , where PCV is the proportion of the cases who are vaccinated and PPV is the proportion of the population vaccinated (i.e., vaccine coverage) 5. Orenstein, W.A., et al., *Field evaluation of vaccine efficacy*. Bull World Health Organ, 1985. **63**(6): p. 1055-68.

### **3. RESULTS**

The literature search produced 3718 results, of which 31 papers reporting on 30 studies were included in the review: 18 case-control studies, 8 cohort studies and 4 others (Figure 1). Common reasons for exclusion were reporting of immunogenicity and / or carriage rather than clinical outcomes, ineligible study designs (e.g. trials or impact assessments), ineligible vaccines (PRP, PRP-D or studies in which individuals vaccinated with one of these could not be separated from those vaccinated with eligible vaccines) and ineligible outcomes (e.g. studies in which children received several vaccines including Hib but the outcomes of interest were not related to Hib).

Figure 1: Identification of eligible papers.



We did not identify any studies which directly compared schedules (e.g. directly compared cohorts of children whose vaccination was initiated at either 6 weeks or 2 months). Several studies presented stratum specific estimates of VE by number of doses received or by presence or absence of a booster dose but the reference group was always an unvaccinated group. Many of the comparisons we make in this report are between estimates of VE from different studies (separately for case-control and cohort studies).

### **3.1. Case-control studies**

Characteristics of the 18 identified case-control studies are summarised in Appendix Table 1. One of the case-control studies was nested within a quasi-randomised vaccine trial<sup>6</sup>; another was conducted during a non-randomised cluster trial of Hib-DTwP vaccine (cases and controls were drawn from communities in which health centres used the Hib-DTwP combination vaccine)<sup>7</sup>. The remaining studies were standard hospital- or population-based case-control studies. Four of the identified studies<sup>6, 8-10</sup> were not included in the previous review of observational studies<sup>1</sup>.

Amongst the 14 case-control studies which reported the intended vaccination schedule, 4 (conducted in Malawi<sup>11</sup>, Bangladesh<sup>7</sup>, Uganda<sup>12, 13</sup> and Rwanda<sup>14</sup>) used the recommended EPI schedule of 6, 10 and 14 weeks. Three studies from the Dominican Republic<sup>15</sup>, Brazil<sup>16</sup> and Colombia<sup>17</sup> reported an intended schedule of 2, 4 and 6 months, whilst two studies from the UK<sup>9, 10</sup> and one from The Gambia<sup>18</sup> used an intended schedule of 2, 3 and 4 months. In a study from the USA, the intended schedules were 2, 4 and 12 months for PRP-OMP and 2, 4, 6 and 15 months for HbOC<sup>19</sup>. The latter was the only schedule reported in a case control study to include a fourth (booster) dose of Hib vaccine. Two other studies from the USA reported intended schedules of 2, 4 and 6 months<sup>6, 20</sup>. None of the identified case-control studies directly compared the effectiveness of different vaccination schedules.

### 3.1.1. Number of doses

As previously reported from both observational studies<sup>1</sup> and controlled clinical trials<sup>21, 22</sup>, Hib conjugate vaccines are highly effective (typically >85% against Hib meningitis and invasive Hib disease) after two or three doses (Appendix Table 2, Figure 2). The most commonly reported outcomes in the identified case-control studies were confirmed Hib meningitis and invasive Hib disease; the estimated effectiveness after two or more doses ranged from 65% (95% CI -190 to 100%)<sup>7</sup> to 99% (95% CI 92-100%) against Hib meningitis. Excluding the estimate of 65% (see below), the lowest reported effectiveness against Hib meningitis after 2 or 3 doses was 87% (95% CI 14-100%)<sup>15</sup>. For invasive Hib disease, effectiveness after two or more doses ranged from 86% (95% CI 16-98%)<sup>20</sup> to 100% (95% CI 68-100%)<sup>19</sup>.

The estimate of 65% effectiveness against Hib meningitis after three doses was an outlier and had a very wide confidence interval (-190 to 100%)<sup>7</sup>. This is partly due to the small number of Hib meningitis cases: 15 in total, with no information on how many had received three doses of vaccine. The estimate of 65% was based on comparing cases to community controls; the study also estimated the three-dose VE against Hib meningitis based on hospital controls as 86% (95% CI -8 to 100%). The estimate of 65% may therefore be an underestimate of the effectiveness of three doses. However, the choice of controls is unlikely to account fully for the low estimate (65%), as the point estimates of one and two dose effectiveness were similar whether based on hospital or community controls (Appendix Table 2).

In general, the effectiveness of a single dose of Hib vaccine was reported to be lower (point estimates were ≤63% against any of the included outcomes) than that of two or three doses. Two studies carried out in the USA were exceptions to this, reporting 100% (95% CI 39 – 100%)<sup>19</sup> and 92% (95% CI 45 – 100%)<sup>23</sup> effectiveness of one dose of PRP-OMP against invasive Hib disease, although with wide CIs.

Two studies reported the effectiveness of three doses of Hib conjugate vaccine against radiologically confirmed pneumonia. In a study in Colombia in which PRP-T was intended to be given at 2, 4 and 6 months, effectiveness of three doses was reported to be 55% (95% CI 7-78%)<sup>17</sup>. In Bangladesh, three doses of combined Hib-DTwP vaccine were estimated to be 44% (95% CI 16-63%) or 32% (95% CI -2 to



54%) effective against radiologically confirmed pneumonia, based on hospital and community controls, respectively <sup>7</sup>. (These estimates are based on cases of pneumonia diagnosed both by study personnel and by an independent paediatrician who reviewed the radiograph. If the VE estimate is instead based on cases diagnosed by only study personnel or by only the independent paediatrician, then the estimate is lower than that stated above, potentially as low as 16% (95% CI -11 to 37%) based on community controls diagnosis by the independent paediatrician <sup>7</sup>.)

One further study, from Brazil, reported the effectiveness of two or more doses against radiologically confirmed pneumonia as 31% (95% CI -9 to 57%), based on an intended schedule of 2, 4, 6 months and using HbOC <sup>16</sup>. All of these estimates <sup>7, 16, 17</sup> of effectiveness against radiologically confirmed pneumonia are lower than those of the effectiveness of two or three doses against invasive Hib disease and Hib meningitis. This is of course expected, as the protection against all radiologically confirmed pneumonia reflects the proportion of all pneumonia specifically attributable to Hib, as well as the effectiveness of the vaccine.

Figure 2 summarises dose-specific vaccine effectiveness against Hib meningitis, invasive Hib disease and radiologically confirmed pneumonia, outcomes for which estimates were available based on more than one schedule (confidence intervals are omitted from the figure for clarity, but are given in Appendix Table 2).

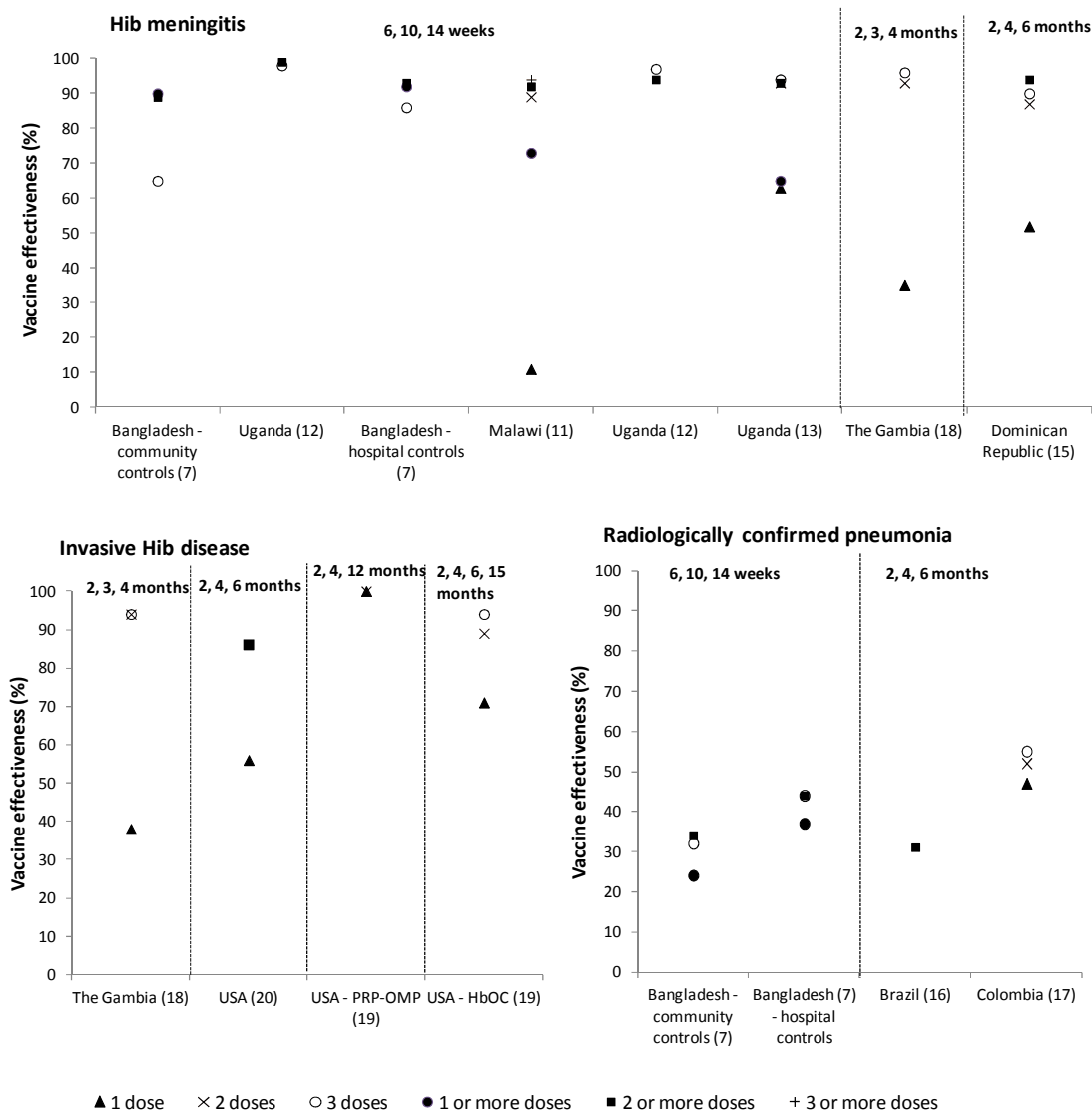
### *3.1.2. Age at initiation of Hib vaccination*

Only one study reported participants' actual age at vaccination (this study did not include estimates of dose-specific effectiveness or analyses of the effects of age at vaccination or dosing intervals) <sup>6</sup>. We therefore refer mainly to the intended vaccination schedule in each study.

The intended age at the first dose of Hib vaccine was either 6 weeks or 2 months in all of the case-control studies which reported this. For Hib meningitis, dose-specific vaccine effectiveness did not appear to vary between schedules beginning at 2 months and 6 weeks, although this is based on a small number of data points (Figure 2). Similarly, there was no clear difference in the dose-specific effectiveness against radiologically confirmed pneumonia in one study (using two different sets of

controls) using a 6, 10, 14 week schedule <sup>7</sup> and one using a 2, 4, 6 month schedule <sup>16</sup>, although a second study using a 2, 4, 6 month schedule reported slightly higher effectiveness estimates <sup>17</sup>. All studies which reported effectiveness against invasive Hib disease used an intended vaccination schedule beginning at 2 months of age.

*Figure 2: Dose-specific estimates of vaccine effectiveness against Hib meningitis, invasive Hib disease and radiologically confirmed pneumonia, from studies utilising different vaccination schedules. Confidence intervals are omitted for clarity, but see Appendix Table 2.*



One study in Uganda provided the median age at each dose for cases and controls <sup>12</sup> (Table 1). The median age at receipt of the third dose was greater for vaccinated

cases than for controls, but the difference was not assessed formally, the number of vaccinated cases was small, potential confounders of the relationship were not considered, and the estimate of vaccine effectiveness in this study (97-98% against confirmed Hib meningitis, depending on the source of controls) was not adjusted for age at vaccination.

*Table 1: Median age at receipt of first, second and third doses of Hib vaccine for Hib meningitis cases and controls, Uganda, 2002-2005. Intended vaccination schedule was 6, 10, 14 weeks. Source: Lee et al <sup>12</sup>.*

	<b>Median age [range] in weeks at vaccination (number vaccinated)</b>		
	<b>Dose 1</b>	<b>Dose 2</b>	<b>Dose 3</b>
<b>Cases</b>	7 [5-25] (5)	11 [10-25] (3)	32 [27-66] (3)
<b>Neighbourhood controls</b>	9 [3-64] (27)	13 [7-69] (35)	20 [12-52] (42)
<b>Hospital controls</b>	8 [2-133] (13)	13 [6-29] (21)	17 [11-80] (35)

### *3.1.3. Interval between doses*

In most reported schedules, doses were separated by either one month (6, 10, 14 weeks and 2, 3, 4 months) or two months (2, 4, 6 months and 2, 4, 12 months). There was no clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between studies using different intended dosing intervals (Figure 2).

There was little information about the actual (as opposed to intended) time intervals between doses. A study carried out in Colombia compared the time between doses of Hib vaccine in pneumonia cases and controls (Table 2) <sup>17</sup>. The median delay between both doses 1 and 2 and doses 2 and 3 was slightly greater for cases than for controls, but the study did not find evidence against these being chance findings ( $p = 0.08$  and  $p = 0.18$  for doses 1 and 2 and doses 2 and 3, respectively). An

interval of >90 days between doses 1 and 2 was associated with an increased risk of pneumonia (OR = 2.1, 95% CI 1.1 – 3.5, adjusted for “factors related to pneumonia” which may include previous hospitalisation due to respiratory infection, underlying illness, daycare attendance, household crowding, maternal education, prematurity, low birthweight, cooking in the sleeping room, health affiliation scheme; the crude OR for this relationship is not presented and no account is taken of age at first dose)<sup>17</sup>. It is not clear whether this period of 90 days was specified *a priori*.

*Table 2: Median time in days between doses of Hib vaccine in cases of radiologically confirmed pneumonia and controls, Colombia, 1998-2001. Intended vaccination schedule was 2, 4, 6 months. The number of individuals contributing data to each estimate is shown in parentheses. Source: de la Hoz et al<sup>17</sup>.*

	<b>Doses 1 and 2</b>	<b>Doses 2 and 3</b>
<b>Cases</b>	70 (77)	72 (124)
<b>Controls</b>	66 (147)	66.5 (309)

#### *3.1.4. Implications of a booster dose*

The case-control studies provide no information on the effects of a booster dose of Hib vaccine, as only one study reported including a booster dose in the vaccination schedule (this study did not compare VE in children who did and did not receive the booster)<sup>19</sup>.

#### *3.1.5. Implications of co-administration of Hib with other vaccines*

Two studies analysed the receipt of DTaP-Hib vaccine as a risk factor for vaccine failure, in children in the UK who had received three doses of Hib-containing vaccine<sup>9, 10</sup> (the cases in one of these studies appear to be a subset of the cases in the other, although the controls are different). In one study, after matching on date of birth and restricting analysis to case-control sets who were “the same age” (precise details are not given) at receipt of the third dose, the odds ratios for invasive Hib disease comparing children who had received 1, 2 or 3 doses of DTaP-Hib to children who had received 3 doses of DTwP were 1.13 (95% CI 0.54 – 2.39), 2.70 (95% CI 1.24 – 5.88) and 8.40 (95% CI 3.77 – 18.68), respectively<sup>10</sup>. The authors

linked these results to other evidence that DTaP-Hib is less immunogenic than Hib vaccine given with DTwP.

The results of the second study of DTaP-Hib are more difficult to interpret<sup>9</sup>. In this second study, attempts to match on age were only partially successful, leading the authors to conduct both an unmatched analysis on all participants and a matched analysis restricted to matched sets. The point estimates from the matched analysis suggested an increasing risk of invasive Hib disease with an increasing number of DTaP-Hib doses amongst children who had received three doses of Hib-containing vaccine, although the confidence intervals were wide and included 1. For example, the OR comparing children who had received three doses of DTaP-Hib compared to those who had received three doses of other Hib vaccines was 7.29 (95% CI 0.4 – 128). The authors note that the wide CIs are due partly to the reduction in sample size resulting from restricting the analysis to matched sets (the estimates are based on 45 observations; the breakdown into cases and controls is not given)<sup>9</sup>. In the unmatched analysis (based on 113 observations), there was no evidence of an increase in the risk of invasive Hib disease with the number of DTaP-Hib doses.

### *3.1.6. Quality of included case-control studies*

Most (15 of 18) of the included studies used community controls, e.g. by identifying potential controls from electronic registers or by door to door canvassing<sup>6-10, 12, 15-20, 23-25</sup>. In these studies, it seems likely that the controls came from the same population as the cases.

Five studies used hospital controls<sup>7, 11-14</sup> (two of these included both hospital and community controls<sup>7, 12</sup>). In three of these studies, in estimating vaccine effectiveness against Hib meningitis, controls were children who were hospitalised with pneumococcal meningitis<sup>11, 13, 14</sup> (all three studies were conducted before the introduction of pneumococcal vaccine in the respective countries). Two of these studies also estimated vaccine effectiveness against purulent meningitis and aetiology-negative meningitis (i.e. purulent meningitis with no cause identified)<sup>13, 14</sup>. For purulent meningitis, the controls in both studies were children with <20 white blood cells per µl of CSF (suggesting a viral CNS infection). For aetiology-negative

meningitis, the Uganda study again recruited controls with a possible viral CNS infection<sup>13</sup> whilst the Rwanda study used controls with pneumococcal meningitis<sup>14</sup>. It is not clear whether the hospital controls in these two studies came from the same population as the cases; however, the estimates of vaccine effectiveness against Hib meningitis from these studies were similar to those from other studies (Figure 2, Appendix Table 2).

The two other studies which used hospital controls recruited children who were hospitalised with conditions other than pneumonia and meningitis<sup>7</sup> or conditions other than meningitis, pneumonia, sepsis, bacteraemia, epiglottitis or otitis media (i.e. conditions potentially caused by Hib)<sup>12</sup>. If controls were admitted for vaccine-preventable diseases, then they would be likely to not be vaccinated against Hib, which would bias the estimate of vaccine effectiveness downwards. It is therefore reassuring that both of these studies reported similar estimates of vaccine effectiveness based on hospital and community controls<sup>7,12</sup>, and that in the only one of these two studies to report controls' reasons for admission, the most common were malaria, gastroenteritis and anaemia<sup>12</sup>.

All of the estimates from case-control studies were adjusted for one or more potential confounders at the design and / or analysis stage, except for one study of the effectiveness of vaccination against purulent meningitis in Rwanda<sup>14</sup>. All of the other studies either matched on or adjusted for age, and most took account of possible confounding by socioeconomic status (e.g. by using controls matched to cases on area of residence or by using hospital controls, see Appendix Table 1).

### *3.1.7. Conclusions from case-control studies*

The identified case-control studies confirm previous results<sup>1,3</sup> that 2 or 3 doses of Hib vaccine are effective against various forms of Hib disease (estimates of effectiveness against invasive Hib disease and Hib meningitis were typically >85%). Although most studies found a single dose of Hib vaccine to have relatively low effectiveness (≤63%), two studies reported high effectiveness against invasive Hib disease (92% and 100%) after one dose of PRP-OMP<sup>19,23</sup>. This is consistent with immunogenicity data showing higher anti-PRP antibody titres after a single dose of PRP-OMP vaccine compared to other conjugate Hib vaccines<sup>26</sup>.

None of the case-control studies directly compared vaccination schedules. Comparison between studies was restricted by the limited variation in both age at initiation and dosing intervals, but did not suggest that any one schedule was more effective than others. The effects of a booster dose could not be assessed as only one study included a booster dose in the intended vaccination schedule<sup>19</sup>. One study suggested that a lengthy delay between the first and second doses might be detrimental for protection against pneumonia<sup>17</sup>; however, that conclusion was based on a possibly post hoc division into delays of  $\leq 90$  and  $>90$  days. A second suggested that Hib meningitis cases may have been older than controls at receipt of the third dose<sup>12</sup>, but this comparison was based on only 3 fully vaccinated cases, was not assessed formally, and could be affected by confounders related to risk factors for Hib meningitis and late presentation for vaccination. Two case-control studies, both conducted in England and Wales and sharing some cases, concluded that vaccination with DTaP-Hib is less effective against invasive Hib disease than vaccination with DTwP-Hib<sup>9, 10</sup>.

### **3.2. Cohort studies**

Eight eligible cohort studies were identified (published in 9 papers), 6 of which estimated vaccine effectiveness against invasive Hib disease<sup>27-33</sup>, 1 which estimated VE against Hib meningitis only<sup>34</sup>, and the final study which estimated rate ratios for bacteraemia/septicaemia, meningitis, viral pneumonia and bacterial pneumonia associated with Hib vaccination.<sup>35</sup> Three of these 8 cohort studies<sup>30, 32, 34</sup> were included in the recent review of Hib vaccine effectiveness from case control and other study designs<sup>1</sup>. One study from Australia compared incidence of invasive Hib disease in the vaccination era to the pre-vaccination era, so that child years from the vaccination era were for vaccinees only and for the pre-vaccination era were historical, restricted to ages when children could have been vaccinated had the programme existed<sup>33</sup>. One study from Chile was a standard cohort design comparing contemporaneous cohorts of vaccinated and unvaccinated children made possible by phased introduction of Hib vaccination to health centres in the study area<sup>30</sup>. One study from England & Wales compared incidence among vaccinees (1992-99) to expected incidence informed by a survey in the pre-vaccination era (1985-90)<sup>27</sup>. Two studies from Germany employed a technique of ascertaining all invasive Hib

cases in the country during the study period, conducting a vaccine coverage telephone survey of a random sample of all children born in Germany during the study period and employing cohort logic in the analysis, assuming no cases in the random sample in which the vaccine coverage survey was carried out<sup>28, 29</sup>. One study from South Africa (reported in two papers) from 1997-2000 compared incidence of invasive Hib disease between vaccinated children who were part of a trial of pneumococcal vaccine which also had some children receiving DTwP-Hib (PRP-HbOC) and incidence in a historical cohort<sup>31, 32</sup>. Finally, there were 2 studies from Denmark in the 1990s to 2001 which made use of population, vaccination and hospitalisation registries linked by a common unique identifier to estimate VE against Hib meningitis and other outcomes<sup>34, 35</sup>. The 8 cohort studies reported on use of PRP-OMP (1 study), PRP-T (5 studies), or PRP-HbOC vaccine (3 studies); Hib was generally administered as quadrivalent vaccine with DTP but co-administered vaccines were not always reported (Table 3). In the 6 studies which reported co-administration of Hib vaccine with DTP, 3 used DTwP, 2 used DTaP and in one study both DTaP and DTwP were used at different times over the study period.

The 8 studies reported on a variety of different dosing schedules. The Australia study did not report the intended dosing schedule<sup>33</sup>. The study from Chile reported the intended schedule to be 2, 4, 6 months<sup>30</sup>. The South African study reported on an intended schedule of 6, 10 and 14 weeks<sup>31, 32</sup>. The study from England & Wales reported the intended schedule to be 2, 3, 4 months<sup>27</sup>. The two studies from Germany reported the intended schedule to be 2, 3, 4 months with a booster at 11 months or later<sup>28, 29</sup> while the two studies from Denmark reported that the schedules over the study periods were variously 5, 6, months with a booster at 15 or 16 months, changing later to a 3 dose schedule of 3, 5, and 12 months<sup>34, 35</sup>. The German and Danish studies were the only cohort studies of schedules which include a booster dose. However, the Danish studies cannot inform the usefulness of a booster dose because estimates of VE are not presented separately for schedules with and without a booster dose. None of the identified cohort studies directly compared the effect of different vaccination schedules on VE. Further study details of the studies are provided in Appendix Table 3. Estimates of vaccine effectiveness are given in Table 4.



Table 3: Summary of vaccines and schedules in cohort studies of Hib vaccine effectiveness

Country <sup>ref</sup>	Study period	Intended schedule	Hib vaccine	Other vaccines co-administered with Hib
<b>Invasive Hib disease</b>				
Australia <sup>33</sup>	1989-1996	Not stated.	PRP-OMPC, PRP-HbOC <sup>c</sup>	Not stated.
Chile <sup>30</sup>	1992-1995	2, 4, 6 mo	PRP-T	DTwP (quadrivalent), OPV
England & Wales <sup>27</sup>	1992-1999	2, 3, 4 mo	PRP-T, PRP-HbOC <sup>d</sup>	Monovalent or quadrivalent with DTwP
Germany <sup>29</sup>	1998-2002	2, 3, 4 +b11 (or later) mo	Conjugate molecule not stated.	DTaP (quadrivalent) or DTaP-IPV (pentavalent)
Germany <sup>28</sup>	2000-2005	2, 3, 4 +b11-14 mo	PRP-T	DTaP-HBV-IPV (hexavalent) <sup>e</sup>
South Africa <sup>31, 32</sup>	1997-2000 <sup>32</sup> , 1998-2004 <sup>31</sup>	6, 10, 14 w	PRP-HbOC	DTwP (quadrivalent) <sup>32</sup> ; DTwP, OPV and HepB on same schedule; unclear whether any administered in same syringe <sup>31</sup>
<b>Hib meningitis +/- other outcomes</b>				
Denmark <sup>34</sup>	1991-1999	May 1993 - 31 Dec 1995: 5, 6 mo + b16 mo <sup>f</sup> ; 1 Jan 1996-31 Dec 1996: 5, 6 mo + b15 mo; 1 Jan 1997 onwards: 3, 5, 12 mo	PRP-T	Not stated.
Denmark <sup>35</sup>	1990-2001	June 1993-1995: 5, 6, b16 mo; 1996: 5, 6, b15 mo; 1997-2001: 3, 5, 12 mo	PRP-T	wP (1990-1996: 0.5 dose with 5 w Hib); DT-IPV (1990-1996; 5, 6, 16 mo); DTaP-IPV (1997-2001; 3, 5, 12 mo)

<sup>c</sup> PRP-OMPC was used for the primary schedule in children born after 1 Dec 1992; in catch-up campaign (children born after July 1988), non-Aboriginal children were recommended PRP-HbOC while Aboriginal children were recommended PRP-OMP

<sup>d</sup> During 1992-96, PRP-T (monovalent) was the primary vaccine and PRP-HbOC was used for catch-up in children >1 of age at first vaccination; from 1996 onwards: primary vaccination was mostly with PRP-T (quadrivalent with DTwP) but PRP-HbOC was also available for primary vaccination

<sup>e</sup> One of the two hexavalent vaccines in use in Germany at the time of this study was withdrawn in the EU in 2012

<sup>f</sup> Routine Hib vaccination was introduced in May 1993 "with catch-up vaccination offered to all children less than 6 years of age"

### *3.2.1. Number of doses*

There are limited data from cohort studies to inform the optimal number of doses. The Danish study published in 2004 reports VE for 1, 2 or 3 doses<sup>34</sup> while the German studies present separate estimates of VE for <3 doses and 3 doses<sup>28, 29</sup>. The Danish study published in 2005 estimated per dose rate ratios for each of bacteraemia/septicaemia, meningitis, viral pneumonia and bacterial pneumonia among Hib vaccinees (using various schedules and valency of vaccines over the study period) which could inform this review but estimates are shown only in figures

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Table 4: Hib vaccine effectiveness from cohort studies

Country <sup>ref</sup>	Schedules, median age at dose in months		VE (95% CI)
	Intended	Actual (median)	
<b>Invasive Hib disease</b>			
Australia <sup>33</sup>	Not stated.	Not stated.	>=1 dose vs 0 doses: 91.7 % (79.6-96.6%); Adequate vaccination <sup>g</sup> vs 0 doses: 97.5% (82.0-99.7 %)
Chile <sup>30</sup>	2, 4, 6 mo	Not stated.	3 doses vs 0 doses: 91.7% (64.8 - 100%)
England & Wales <sup>27</sup>	2, 3, 4 mo.	Not stated.	3 doses vs 0 doses: 97.6% (96.9-98.1%) (higher for 5-11 and 12-23 month olds, slightly lower for older children) <sup>h</sup>
Germany <sup>29</sup>	2, 3, 4 +b11 (or later) mo	dose 1: 3.5 mo; dose 3: 6.2 mo; booster: 17.5 mo	a) 1-2 doses vs 0 doses: 89.6% (67.0-96.7%); b) 3 doses vs 0 doses: 96.7% (87.7-99.1%); c) Booster at 11 months or later after full priming (or any dose in the second year of life regardless of priming) vs 0 doses: 98.5% (94.5-99.6%)
Germany <sup>28</sup>	2, 3, 4 +b11-14 mo	dose 1: 3.3 mo (range 0.1-12.0 mo); dose 3: 6 mo (range 2.5-12.0 mo); booster: 15.3 mo (range 11.0-34.7 mo) <sup>i</sup>	a) 1-2 doses vs 0 doses: 68.4 % (19-87.6 %) (VE 57% in sensitivity analysis); b) 3 doses vs 0 doses: 90.4% (70.6-96.8%) (VE 85% in sensitivity analysis); c) Second year dose but incomplete primary series vs 0 doses: 100% (0-100%); d) Full primary series plus booster vs 0 doses: 100% (52.7-100%) <sup>j</sup>
South Africa <sup>31, 32</sup>	6, 10, 14 w	Not stated.	>=1 dose: 81.7% (59.4–91.8%); 3 doses: 83.2 % (60.3–92.9%) <sup>32</sup> ; <=3 doses vs 0 doses: 79.3 (65.7-87.5) <sup>31</sup>
<b>Hib meningitis +/- other outcomes</b>			
Denmark <sup>34</sup>	May 1993 - 31 Dec 1995: 5, 6 mo + b16 mo; 1 Jan 1996-31 Dec 1996: 5, 6 mo + b15 mo; 1 Jan 1997 onwards: 3, 5, 12 mo	Not stated.	1 dose: 97.74% (90.77–99.45%); 2 doses 98.94% (95.71–99.74%); 3 doses 99.29% (94.87–99.90%)
Denmark <sup>35</sup>	June 1993-1995: 5, 6, b16 mo; 1996: 5, 6, b15 mo; 1997-2001: 3, 5, 12 mo	Not stated.	Estimates of RRs for >=1 dose and per dose among vaccinees shown in figures only.

<sup>g</sup> To quote from the paper, "A child was considered adequately immunized 2 weeks after receiving a second dose of Hib vaccine before the age of 12 months or 2 weeks after receiving one dose of vaccine after the age of 12 months."

<sup>h</sup> Sensitivity analysis doubling number of cases minimally affects VE estimates (overall estimate 96.4% (95.7-97.0%))

<sup>i</sup> Ages at vaccination refer to coverage cohort only and are approx

<sup>j</sup> Authors calculated VE assuming a doubling of the proportion unvaccinated in sub-cohort (since sub-cohort possibly overestimated vaccine coverage due to wealthier than average population): VE estimates for a) 57.0% b) 85.8% c) 100% d) 100%

The available evidence regarding VE against invasive Hib disease, from the Chilean, English and German studies, suggests 3 doses provide higher protection than 1 or 2 doses, depending on the vaccine used (3-dose VE ranged from 90.4 to 97.6%; VE for 1-2 doses ranged 68.4 to 89.6%)<sup>28-30</sup>. The Australian study calculated VE against invasive Hib after adequate vaccination, which they defined as “2 weeks after receiving a second dose of Hib vaccine before the age of 12 months or 2 weeks after receiving one dose of vaccine after the age of 12 months” and reported it to be 97.5% (82.0-99.7 %)<sup>33</sup>. This estimate cannot be directly compared to the Chilean, English and German estimates of VE after 1-2 doses because the Australian estimate is likely to be based on a mix of children receiving primary schedule and catch-up vaccination (the schedule in use is not reported).

For Hib meningitis, the earlier of the two Danish studies (published in 2004 and using data from 1991-1999), which used various schedules over the study period and which did not specify what vaccines were used, presented dose specific VE which suggest high VE was achieved after a single dose: VE 1 dose: 97.74% (90.77–99.45%); 2 doses 98.94% (95.71–99.74%); 3 doses 99.29% (94.87–99.90%)<sup>34</sup>.

### *3.2.2. Age at initiation of Hib vaccination*

There are limited data from cohort studies to inform the optimal age at which to initiate Hib vaccination. In Denmark, the intended age at initiation of vaccination 3 or 5 months of age, as opposed to 2 months of age in the other cohort studies which reported the intended schedule<sup>34, 35</sup>. In the Danish study published in 2004, 3-dose vs 0 dose VE for PRP-T (it is unclear what vaccines were co-administered with this) against Hib meningitis was 99.3% (94.87–99.90%)<sup>34</sup>. In the South African study, in which age at initiation of vaccination was intended at 6 wks, 3- dose vs 0 dose VE against invasive Hib was estimated to be 83.2 % (60.3–92.9%); there was a high prevalence of HIV infection in the children in this study and effectiveness of 3 doses vs none was estimated as 96.5% (74.4–99.5%) in children who were not HIV-infected<sup>32</sup>. The 3-dose (vs 0 dose) VEs against invasive Hib from the Chilean, English and German studies, which all had intended age at initiation of 2 months, were slightly higher than the overall estimate from the South African study (ranging

from 90.4 to 97.6%)<sup>27-30</sup>. From these results one could tentatively suggest that older age at initiation leads to higher VE against invasive Hib.

### *3.2.3. Interval between doses*

There are limited data from cohort studies to inform the optimal interval between doses. The Chilean schedule has 2-month intervals: the VE for 3 doses vs 0 doses, quadrivalent vaccine, was 91.7% (64.8 - 100%)<sup>30</sup>. The German, English and South African schedules have 1-month intervals and report VE for 3 doses vs 0 doses which ranges from 83.2% and 97.6 %<sup>27-29, 31</sup>. Since the VE estimate for a 2-month interval is nested within the range of VE estimates for a 1-month schedule, there is no strong evidence from cohort studies for a difference in VE according to dosing interval.

### *3.2.4. Implications of a booster dose*

There are data from only 2 cohort studies to inform the implications of a booster dose on VE. Results from the German study of quadrivalent or pentavalent vaccines are consistent with some small additional benefit of a booster dose at 11 months (or later) to children who received all 3 doses in the primary schedule<sup>29</sup>. VE against invasive Hib disease comparing booster at 11 months or later after full priming (or any dose in the second year of life regardless of priming) vs 0 doses was 98.5% (94.5-99.6%) compared with a VE for 3 doses vs 0 doses of 96.7% (87.7-99.1%). Results from the German study of hexavalent vaccine effectiveness are consistent with an additional benefit of a booster dose to children who received all 3 doses in the primary schedule<sup>28</sup>. VE against invasive Hib disease for a second year dose but incomplete primary series vs 0 doses was reported as 100% (0-100%) compared with VE for 3 doses vs 0 doses of 90.4% (70.6-96.8%). The results of this study are also consistent with a booster compensating for an incomplete primary series. VE was 100% (based on 1536 vaccinees and 0 cases) for booster after incomplete primary series vs 0 doses compared with VE of 68.4 % for incomplete primary series vs 0 doses.

### *3.2.5. Implications of co-administration of Hib with other vaccines*

There are limited data from cohort studies to inform the implications with respect to VE of co-administering Hib with other vaccines. Based on the Chilean, German and

South African studies, 3 doses of quadrivalent (DTwP-Hib in South Africa and Chile, DTaP-Hib in Germany) or pentavalent (DTaP-IPV-Hib) vaccine (vs 0 doses) appear to result in VE estimates against invasive Hib of 83% to 97%<sup>29, 30, 32</sup> while the 3-dose VE against invasive Hib afforded by hexavalent vaccine (DTP-IPV-HepB-Hib) (vs 0 doses) in the later German study was 90%<sup>28</sup>. These are small differences based on small studies and therefore do not strongly indicate superiority of quadrivalent/pentavalent over hexavalent vaccine. Comparing the VE point estimates from the two German studies, 1-2 doses of quadrivalent/pentavalent vaccine appear more effective (VE 89.6%, 95% CI 67.0 – 96.7%)<sup>29</sup> than the same number of doses of hexavalent vaccine (VE 68.4%, 95% CI 19.0 – 87.6%)<sup>28</sup>, though there is some overlap in the confidence intervals for these two estimates<sup>28, 29</sup>. The Chilean and South African studies presented 3-dose VE against invasive Hib for Hib conjugate vaccine co-administered with DTwP in the range of 83 to 92%<sup>30, 32</sup>. The German studies, in which vaccines were co-administered with DTaP, reported 3-dose VEs against invasive Hib disease of between 90 (hexavalent) and 97% (quadrivalent/pentavalent). Since the range of VE estimates for vaccines co-administered with DTaP overlaps the range of VE estimates for vaccines co-administered with DTwP, there is no strong evidence from cohort studies for a difference in VE according to whether Hib is co-administered with whole cell or acellular pertussis.

### *3.2.6. Quality of included cohort studies*

The Australian study (which we draw on only in assessing optimal number of doses) did not report the vaccines used nor the intended schedule<sup>33</sup>. The authors did not carry out any control for confounding. It was not clear if assessment of invasive Hib disease was blind to exposure status. Nor was it clear if different exposure groups had the same schedule of follow-up for invasive Hib disease. In the Chilean study, the authors did not control for confounding<sup>30</sup>.

In the English study, the surveillance method used to ascertain invasive Hib disease changed in 1995: until 1995, paediatricians reported invasive Hib in vaccinees only; from Nov 1 1995, paediatricians were asked to report all cases of invasive Hib regardless of the vaccination status of the child<sup>27</sup>. Thus, incidence of invasive Hib was probably underestimated before Nov 1 1995. To determine how their results

could be affected by this, the authors reestimated 3 dose VE assuming a doubling of the number of invasive Hib cases among those receiving 3 doses of vaccine and found VE to be minimally affected (see footnote to Table 4).

In both German papers, it was unclear who was blinded to vaccination status of cases; it appears that laboratory staff were blind but that clinicians were not (case ascertainment was done using a combined system of hospital and laboratory surveillance)<sup>28, 29</sup>. An additional quality concern in the earlier of the two German papers is that it was unclear how the vaccination status of cases was ascertained<sup>29</sup>. Presumably an issue in both German studies, in the later paper the authors state it was possible the vaccine coverage of the non-cases from the telephone survey had been overestimated due to the survey population being overrepresentative of wealthier families<sup>28</sup>. The authors report the results of a sensitivity analysis assuming twice as many non-cases were unvaccinated as in the main analysis; this brought down estimates of VE for 1-2 doses vs 0 doses and 3 doses vs 0 doses (see footnote to Table 4). If these lower estimates of VE are closer to the truth, this adds weight to the tentative conclusions reached above that a) a booster dose of hexavalent vaccine compensates for an incomplete primary series of hexavalent vaccine and b) hexavalent vaccines provide lower VE than quadrivalent/pentavalent vaccines.

In the South African study, the provenance of the unvaccinated cohort is unclear<sup>31, 32</sup>. The authors do not state how vaccinated children were selected from the pneumococcal vaccine trial for inclusion in the Hib vaccine cohort study. The statistical methods used to estimate incidence were not described so that it is not clear if or how account was taken of losses to follow-up. In addition, there was no adjustment for confounding. The Danish studies did not report the rate of loss to follow-up separately for vaccinees and for children in the pre-vaccination period<sup>34, 35</sup>.

### *3.2.7. Conclusions from cohort studies*

There is limited evidence from cohort studies as to optimal Hib vaccination schedules. On number of doses, 3 doses appear to provide better protection against invasive Hib disease than 1 or 2 doses. For Hib meningitis, evidence from 1 study

suggests high VE is achieved after 1 dose, but the authors did not state what vaccine was used in this study. Limited data would suggest older age at initiation results in higher VE against invasive Hib. There is no strong evidence from cohort studies for a difference in VE according to dosing interval.

Evidence from only 2 cohort studies informs the usefulness of a booster. These studies suggest that among children receiving their full primary Hib course, there is higher VE against invasive Hib with a booster compared to without. One of these studies suggests in addition that a booster compensates at least to some extent for an incomplete primary course.

Finally, on the question of co-administering Hib with other vaccines, we do not find strong evidence to indicate superiority in general of quadrivalent or pentavalent over hexavalent vaccines. Comparing estimates from 2 studies provides weak evidence that DTaP-containing quadrivalent or pentavalent vaccines (Hib with DTaP +/- IPV) provide higher 1-2 dose (vs 0 dose) and 3-dose (vs 0 dose) VE against invasive Hib disease than hexavalent vaccine (which contains hepatitis B antigen in addition to DTaP-IPV). The cohort studies identified provide no strong evidence for a difference according to the pertussis antigen co-administered with Hib. Five of the included cohort studies were judged to have a low risk of bias because they adjusted for confounding<sup>27-29, 34, 35</sup> and conducted sensitivity analyses around key potential biases in their data sources<sup>27-29</sup>. The remaining 3 cohort studies are at least moderately likely to be biased due to lack of control for confounding<sup>30-33</sup>. The evidence base for informing optimal Hib vaccination schedules from cohort studies is limited.

### ***3.3. Other study designs included in O’Loughlin review***

Four studies included in the O’Loughlin review of Hib vaccine effectiveness under “other” study designs appeared to estimate vaccine impact, not effectiveness<sup>36-39</sup>. In these studies, incidence in the vaccine era was compared to incidence in the pre-vaccine era; incidence in the vaccine era did not take vaccine coverage into account (i.e. child years in the vaccine era would have been a mix of children who did and who did not receive Hib vaccination). We did not include these in our review because vaccine effectiveness compares risk of an outcome of interest between vaccinated



and (presumed) unvaccinated children and because studies of vaccine impact are being reviewed by others.

One study included in the O'Loughlin review of Hib vaccine effectiveness was described (by the authors of the original paper) as a hamlet-randomised, controlled, double-blind vaccine-probe study<sup>4</sup>. This study was excluded from our review because randomised controlled trials are the subject of another review.

### **3.4. Screening method studies**

Three studies included in the previous review of Hib vaccine effectiveness<sup>1</sup> used the screening method<sup>k</sup> to estimate vaccine effectiveness<sup>40-42</sup>. We also identified one further screening method study<sup>43</sup>.

Based on the screening method, in England & Wales during 1993-2003, when the intended schedule was 2, 3, 4 months, VE against invasive Hib disease for full primary vaccination or a single catch-up dose at age  $\geq 13$  months was estimated to be a low 57% (95% CI 42 to 67%), or 72% after adjusting for probable underestimation of vaccination coverage in the population<sup>41</sup>. VE against invasive Hib disease was only 49% (95% CI 32 to 64%) when vaccinees were defined only as children who received their 3 primary doses. This study used the same surveillance sources for invasive Hib disease, over a similar time period, as the cohort study by Heath *et al* which we reviewed above<sup>27</sup>. As an explanation for their low VE, Ramsay *et al* suggest that studies which compare incidence among vaccinees to incidence in a historical cohort, as the Heath paper did, will estimate the combined direct and indirect effects of vaccination (as children in the vaccine era are afforded both direct and indirect protection while children in the pre-vaccination era receive neither). In contrast, when VE is estimated based on incidence in contemporaneous vaccinated and unvaccinated children, only the direct effect is measured as all children benefit from indirect protection. The Ramsay study included data from the period Jan 2000-Aug 2002 during which approximately half of the Hib vaccinations given in England & Wales were co-administered with DTaP (whereas in the rest of the study period, and

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<sup>k</sup> In screening method studies, vaccine effectiveness is calculated as  $1 - \frac{PCV(1PPV)}{[(1PCV)PPV]}$ , where PCV is the proportion of the cases who are vaccinated and PPV is the proportion of the population vaccinated (i.e., vaccine coverage)

in the entire study period of the Heath paper, vaccines were either monovalent or co-administered with DTwP). So the lower VE in the Ramsay paper may also partly reflect specifically lower VE of Hib vaccines co-administered with acellular pertussis. In additional analyses, Ramsay *et al* estimated that VE overall (full primary vaccination plus catch up) and VE restricted to full primary vaccinees only were both higher within two years of vaccination than after two years, showing evidence for waning immunity. This Ramsay study also found that effectiveness was higher in children vaccinated at 13 months or older (as part of the UK's catch-up campaign) than in those vaccinated during infancy, though this has limited relevance to routine infant vaccination.

A German screening method study included in the previous review reported VE against invasive Hib disease during 1998 and 1999, when the intended schedule was DTaP-Hib or DTaP-IPV-Hib given at 2, 3 and 4 months followed by a booster at 11-15 months<sup>42</sup>. VE estimates presented in this paper agree with the general conclusion that 2 or 3 doses have similarly high effectiveness and that one dose has potentially lower VE (VE estimates were 67.9% (95% CI 32.8; 84.0) for one dose, 95.4% (92.7; 97.2) for two doses and 98.9% (98.3;99.3) for three doses, compared to 0 doses).

The third screening method study included in the previous review was from Australia in the period 1993-1996 and presents an overall VE against invasive Hib disease of 89% (no confidence interval is given)<sup>40</sup>. Vaccination was defined in any one of 10 ways based on vaccine used, number of doses and age at receipt and so it is not possible to integrate this result with the rest of our review of Hib vaccine schedules.

The additional screening method study, in Spanish, which was not included in the previous review, reported on invasive Hib disease in Valencia between Dec 1 1995 and Nov 30 1996<sup>43</sup>. VE for  $\geq 1$  dose vs 0 dose was reported to be 91% (95% CI 28-99%) based on two vaccinated cases (4.3% of all reported invasive Hib disease cases) and vaccine coverage of at least one dose of 32.5%. The type(s) of Hib vaccine in general use are not stated in the paper, but both of the vaccinated cases had received HbOC.

### **3.5. Immunogenicity data**

Although we have not systematically reviewed observational data on the immunogenicity of Hib vaccines, we present here some data relevant to schedule decisions, related mainly to issues raised by the clinical evidence summarised above. The studies included often summarised immunogenicity as the percentage of vaccinated individuals whose anti-PRP antibody titre exceeded 0.15µg/ml or 1.0µg/ml, as these are often taken to be correlates of short- and long-term protection, respectively <sup>44</sup>.

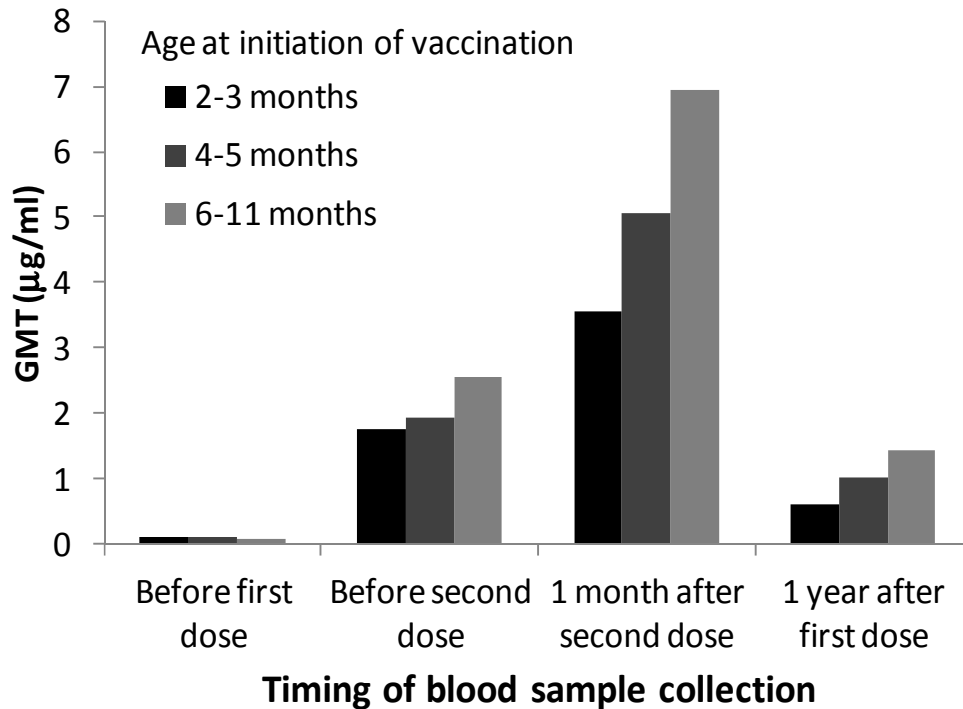
#### *3.5.1. Number of doses in the primary series*

In a study of the immunogenicity of HbOC and PRP-D vaccines carried out in Finland, 46 children received HbOC at ages 4 and 6 months, and 25 of these received a booster dose at 14 months <sup>45</sup> (PRP-D vaccines are not considered in this review). Blood samples were taken before each vaccination and one month after the second and third doses, and anti-PRP antibody titres measured. There was no increase in GMT after the first dose of HbOC (0.07µg/ml before, 0.09 µg/ml after); after the second dose, GMT increased to 4.32µg/ml and all children had a titre >0.15µg/ml <sup>45</sup>. (The effects of the booster dose are described in a subsequent section.)

In contrast, a study in the USA which used PRP-OMP vaccine did find an increase in GMT after a single dose <sup>46</sup>, including in those vaccinated at a similar age to, and according to the same schedule as, the children in the Finnish HbOC study described above <sup>45</sup> (Figure 3). In this study, 571 children were given two doses of PRP-OMP two months apart; 223 of the children were aged 3-11 months at the time of the first dose. For example, the GMT increased from 0.11 to 1.75µg/ml after a single dose administered at the age of 2-3 months. The GMT increased further in all age groups following the second dose, e.g. to 3.5µg/ml in those vaccinated at 2-3 months of age. The fold increases in GMT were 15-31, depending on age group after the first dose and 2-3 after the second <sup>46</sup>. There was little difference between age groups in the percentage of children whose antibody titres reached 1.0µg/ml after the first dose (76%, 75% and 72% of children aged 2-3 months, 4-5 months and 6-11

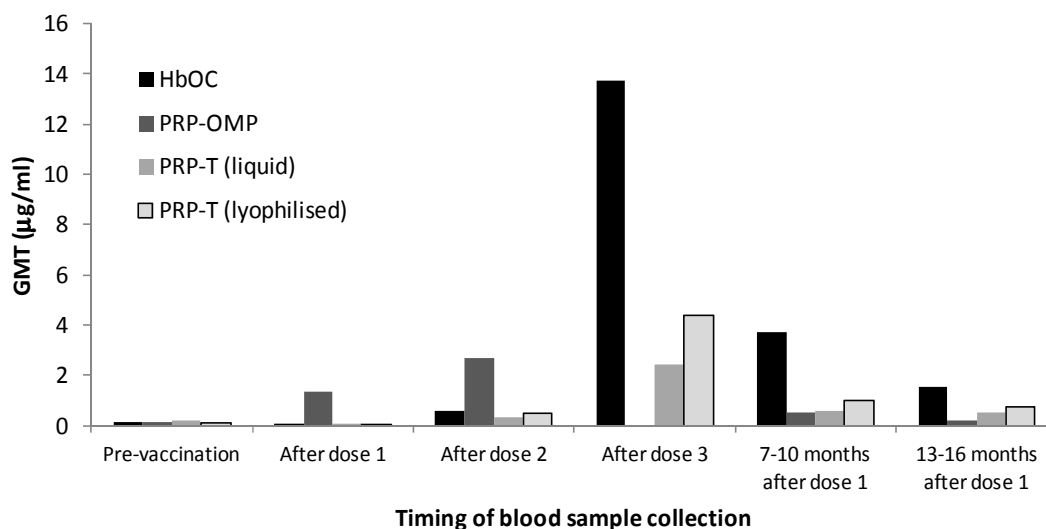
months at vaccination) or the second (91% of children aged <6 months and 92% of children aged 6-11 months) <sup>46</sup>.

*Figure 3: Geometric mean anti-PRP antibody titres in children vaccinated with two doses of PRP-OMP two months apart, beginning at different ages, in Arizona, California, Michigan and Florida (n ≈70, 45 and 95 for the three age groups, varying slightly between time points). Source: Shehab et al <sup>46</sup>.*



Another study, carried out in Alaska Native infants, compared three different Hib conjugate vaccines and also found that antibody titres were increased after one dose of PRP-OMP intended to be given at the age of 2 months, and increased further after a second dose intended to be given at 4 months (Figure 4) <sup>47</sup>. However, vaccination with HbOC or PRP-T required 3 doses (intended to be given at 2, 4 and 6 months) for a substantial rise in GMT. (Differences between the types of conjugate vaccines are discussed further below.)

Figure 4: Geometric mean anti-PRP antibody titre following vaccination of Alaska Native infants with different Hib conjugate vaccines. Source: Bulkow et al <sup>47</sup>.



### 3.5.2. Age at vaccination

In the US study of PRP-OMP given in two doses two months apart <sup>46</sup> the GMT following the first dose increased with age at first vaccination, being 1.75µg/ml, 1.93µg/ml and 2.56µg/ml for those aged 2-3, 4-5 and 6-11 months at vaccination, respectively (Figure 3). The fold increase in GMT following one dose also increased with age but was substantial in all groups, being approximately 15, 18 and 31 in the three age groups. However, the percentage with titres  $\geq 1.0\mu\text{g/ml}$  after the first dose was similar in the three age groups (76%, 75% and 71%, respectively). Following the second dose, the GMT increased 2-3 fold irrespective of age. GMTs were then 3.5µg/ml, 5.0µg/ml and 6.9µg/ml in the three age groups and the percentage with titres  $\geq 1.0\mu\text{g/ml}$  was 91% for those aged  $<6$  months and 92% for those aged 6-11 months at the start of vaccination. One year after the first dose, the GMTs were highest in those who had initiated vaccination later, but was reasonably high in all age groups (e.g. 0.62µg/ml in those first vaccinated at 2-3 months). The percentage of children with antibody titres  $\geq 0.15\mu\text{g/ml}$  or  $\geq 1.0\mu\text{g/ml}$  one year after the first dose is not stated, but  $>90\%$  of children in each age group had detectable antibody at this time point (the lower limit of detection was 0.125µg/ml) <sup>46</sup>.

### *3.5.3. Effect of a booster dose*

A UK study recruited, through immunisation clinics, 388 children aged 6 months to 4 years who had previously received their full primary Hib vaccine series and were given a booster dose in a catch-up campaign. Amongst these children, the GMC before the booster decreased with time since vaccination, and thus age<sup>48</sup>. Despite this, the post-booster GMC increased with age at boosting: 29.87µg/ml, 68.41µg/ml and 182.36µg/ml in each group one month after booster. All but one of the 344 participants who had a blood sample taken one month after the booster had a titre ≥0.15µg/ml one at that time, and all but three had a titre ≥1.0µg/ml.

In the Finnish study of 25 children given a primary series of HbOC at 4 and 6 months with a booster at 14 months, the GMT immediately prior to the booster dose was 1.12µg/ml. This increased to 58.3µg/ml following the booster<sup>45</sup>.

### *3.5.4. Type of conjugate vaccine*

The study of Alaska Native infants directly compared the immunogenicity of HbOC, PRP-OMP, PRP-T (stratified into liquid and lyophilised formulations) and PRP-D (not considered in this review), as children were given different vaccines depending on changes in clinic policy over time (Figure 4)<sup>47</sup>. PRP-OMP was intended to be given at 2 and 4 months, whilst the intended schedule for HbOC and PRP-T was 2, 4 and 6 months. The actual mean ages at receipt (considering all children, including those given PRP-D) were 6.4 weeks for the first dose, 15.5 weeks for the second and 25.2 weeks for the third (when the third dose was given).

After 1 or 2 doses, the antibody response to PRP-OMP was greater than that to the other vaccine types (Figure 4). However, after three doses, the GMT was highest with HbOC, and this difference persisted up to 16 months following the initiation of vaccination. 7-10 months after the first dose, >80% of the children in each group had antibody titres ≥0.15µg/ml. At age 15-18 months (13-16 months after the first dose), the percentage of children with titres ≥0.15µg/ml was substantial for all vaccines: 91% for HbOC, 71% for PRP-OMP, 86% for PRP-T (liquid) and 88% for PRP-T (lyophilised)<sup>47</sup>.

### 3.5.5. Co-administration with other vaccines

In a further US study, 228 children received 3 doses of combined DTaP-Hib, 42 received two doses of combined vaccine and one dose of DTaP and Hib separately (but simultaneously, at a separate site), and 50 received one dose of combined vaccine and two doses as separate vaccines (depending on the study protocol at the time of vaccination) <sup>49</sup>. The schedule was 2, 4, 6 months. The GMT of anti-PRP antibodies at age 7 months increased as the number of doses received as combination vaccines *decreased* (2.68µg/ml, 3.32µg/ml and 5.25µg/ml;  $p < 0.02$ ). The percentage of children with an antibody titre  $\geq 0.15\mu\text{g/ml}$  one month after the third dose was  $\geq 93\%$  in all three groups, but the percentage reaching  $\geq 1.0\mu\text{g/ml}$  increased as the number of doses received as combination vaccines decreased (75%, 86% and 92% in the three groups,  $p < 0.02$ ). This suggests that the immunogenicity of Hib vaccines is lower when administered in combination with DTaP than when DTaP and Hib vaccines are given separately (this study did not assess immunogenicity of Hib-DTwP combination vaccines). The comparisons were not adjusted for potential confounders, but the three groups were similar with respect to age, sex and ethnicity <sup>49</sup>.

A UK study also suggests relatively low immunogenicity of the DTaP-Hib combination <sup>48</sup>. In the UK, a catch-up campaign was initiated in 2003 to give a booster dose of PRP-T to children aged 6 months to 4 years <sup>48</sup>. A study of 388 children who had received their full primary series of three doses of Hib vaccine (of whom 267 were aged 2-4 years and so could have received DTaP-Hib, DTwP-Hib or a mixture of the two during their primary series) was conducted to assess the effects of DTaP-Hib versus DTwP-Hib on antibody levels several years after vaccination and on the response to a booster <sup>48</sup>. In this study, the pre-booster GMC in 2-4 year olds was lower ( $p < 0.001$ ) in those who had received 3 doses of DTaP-Hib for their primary series (0.21µg/ml, 95% CI 0.16 – 0.29µg/ml) than in those who had been vaccinated with 3 doses of DTwP-Hib (0.70µg/ml, 95% CI 0.49 – 1.00µg/ml). In those who had received a mixture of DTaP-Hib and DTwP-Hib, the GMC was intermediate between the two but very similar to the DTaP-Hib group (with overlapping CIs). However, there were no differences between the groups in GMC after the booster dose <sup>48</sup>.

A similar, but separate, UK study also reported an inverse association between the number of doses of DTaP-Hib received and anti-PRP GMC before administration of the booster dose: the GMCs were 0.61µg/ml, 0.42µg/ml, 0.39µg/ml and 0.30µg/ml in 2-4 year olds who had received 0, 1, 2 or 3 doses of DTaP-Hib, respectively ( $p = 0.02$ )<sup>50</sup>. In this second study, 86% of children who had received 0 or 1 doses of DTaP-Hib had antibody titres  $\geq 0.15\mu\text{g/ml}$ , compared to 64% of those who had received 2 or 3 doses ( $p = 0.002$ ).

### *3.5.6. Conclusions from immunogenicity data*

PRP-OMP appears to be more immunogenic after a single dose, than the other conjugate vaccines<sup>47</sup>, all of which require more than one dose to elicit a strong immune response. Antibody titres increase further after a second dose of PRP-OMP (none of the included studies used a three-dose primary series of PRP-OMP)<sup>46, 47</sup>. HbOC and PRP-T seem to require two or three doses (this has varied between studies) to stimulate a strong immune response. Three doses of HbOC appear to elicit higher antibody levels in the long term than two doses of PRP-OMP.

Based on the results of a single study<sup>46</sup>, GMTs (and increases following vaccination) appear to increase with increasing age at first vaccination, although this was not formally assessed. However, vaccinating children at 2-3 months of age resulted in a large (15-fold) increase in GMT compared to their pre-vaccination titres.

The antibody response to a booster dose appears to be highest if given relatively late (e.g. at the age of 2-4 years rather than 6-17 months)<sup>48</sup>, but even early boosting leads to antibody concentrations which are believed to be protective.

DTaP-Hib appears to be less immunogenic (with respect to the Hib component) than either DTwP-Hib or separately administered DTaP and Hib vaccines. This does not appear to affect the response to a single antigen Hib booster dose.



### **3.6. Effectiveness against carriage**

We did not systematically review studies reporting the effects of vaccination on carriage of Hib. Nevertheless, we summarise here the results of several observational studies of carriage, identified in the course of this review.

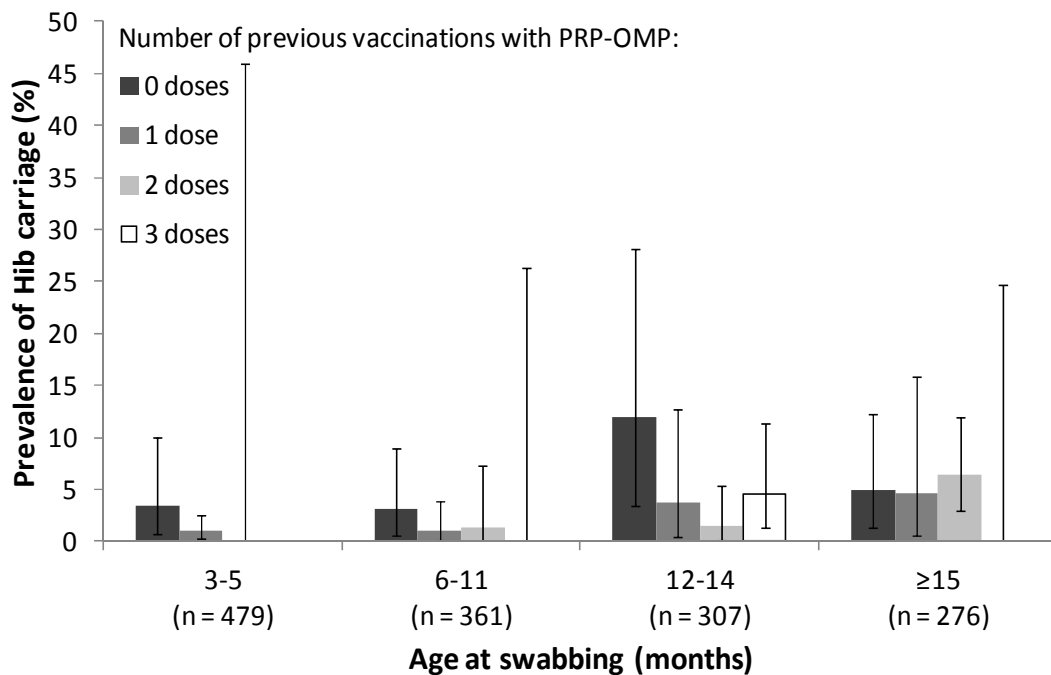
A case-control study conducted in three rural Alaskan villages found no evidence of an effect of vaccination on carriage of Hib<sup>51</sup>. Based on 16 carriers and 32 controls (matched on age and village), 62% of carriers and 62% of controls had received at least one dose of a Hib conjugate vaccine, implying 13% effectiveness of at least one dose against carriage but with an extremely wide confidence interval (95% CI -1000 to 93%). Restricting the analysis to children born after conjugate vaccine became available in this setting, there was no evidence of an effect on carriage of either PRP-OMP, HbOC or the time since last vaccination (<82 or ≥82 days, the median value). However, the number of carriers and controls was small and the confidence intervals wide.

A study in Turkey compared the prevalence of carriage in fully vaccinated, partially vaccinated and unvaccinated children (the intended vaccination schedule was 2, 4, 6 and 18 months, using PRP-T)<sup>52</sup>. 19/57 (33%) fully vaccinated children carried Hib in the oropharynx, compared to none of 17 partially vaccinated and 46/85 (54%) unvaccinated children. After adjusting for previous respiratory infection, having a sibling aged <5 years, breastfeeding and recent antibiotic use, the OR comparing unvaccinated to fully vaccinated children was 3.76 (95% CI 1.61 – 8.80). This implies a VE of 73% (95% CI 38-89%). This estimate is not adjusted for age, time since vaccination or socioeconomic status (although the authors state that there was no association between carriage and parental job)<sup>52</sup>.

A study in Native American children reported the prevalence of carriage in relation to age and the number of doses of PRP-OMP received (intended to be given in 3 doses at ages 2, 4 and 12-15 months)<sup>53</sup>. Overall, 65% of carriers and 80% of non-carriers had received at least one dose before the swab was taken; 13% of carriers and 36% of non-carriers had received the intended number of doses for their age. The point estimate of the prevalence of carriage was highest in unvaccinated children in all age

groups (Figure 5) but confidence intervals were wide (the number of carriers was <10 in each group) and there was no apparent dose-response relationship. After adjusting for age and the presence of a respiratory infection at the time of swabbing, the OR comparing children who were not age-appropriately vaccinated to those who were was 2.66 (95% CI 1.00 – 7.05,  $p = 0.05$ )<sup>53</sup>. This implies a VE against carriage of 62% (95% CI 0 – 86%).

*Figure 5: Prevalence of oropharyngeal carriage of Hib by Native American children, by age and number of previous doses of PRP-OMP. Error bars show 95% exact binomial CIs (or one-sided 97.5% CIs if the point estimate is zero). Source: Takala et al<sup>53</sup>.*



In the UK, carriage was assessed in 143 children (recruited via computerised immunisation records) who had received three doses of Hib-containing vaccine in relation to the number of doses given as DTaP-Hib<sup>50</sup>. Only three carriers were identified: one had received no doses of DTaP-Hib and two had received three doses. These small numbers do not allow a comparison of the effects of DTaP-Hib versus other vaccines on effectiveness against carriage.

The studies included here which report the prevalence of carriage according to the number of vaccine doses received did not suggest an obvious dose-response relationship, but the number of carriers was usually small. However, these studies of Hib vaccination indicate some reduction in carriage, perhaps with an effectiveness of 60-70%. They are thus consistent with population data showing dramatic impacts of Hib vaccines against invasive disease in several populations.

## **4. DISCUSSION**

### **4.1. Summary of key findings**

At least two doses of Hib vaccine are needed to confer high levels of protection (with the possible exception of the PRP-OMP vaccine, which may be effective after a single dose); effectiveness after two or three doses is typically >85% against Hib meningitis and invasive Hib disease. Whilst there may be no clear added benefit of three doses compared to two, in terms of protective effectiveness, other authors have summarised arguments against recommending a two dose schedule<sup>3</sup>: the effectiveness of two doses may vary with vaccine type, dose-specific effectiveness against carriage has not been assessed in detail, and a three dose schedule is practical if Hib vaccine is administered with DTP (under current recommendations for three doses of DTP)<sup>3</sup>.

We did not identify any observational studies which directly compared different vaccination schedules. Comparisons drawn between studies did not suggest an optimum vaccination schedule. From the limited evidence base, it appears that Hib vaccine administered with DTaP is less effective than Hib vaccine given with DTwP; that older age at initiation of vaccination increases vaccine effectiveness but that increasing age at third dose is a risk factor for disease; that long intervals between doses reduce their effectiveness; that a booster dose enhances the effectiveness of vaccination and that a booster compensates at least to some extent for an incomplete primary course. There is weak evidence that hexavalent vaccine is less effective than quadrivalent or pentavalent vaccine. Each of these findings is based on only one or two studies of either Hib meningitis or invasive Hib disease, with the exception of the conclusion concerning the dosing interval (for which the outcome of interest was radiologically confirmed pneumonia).

Immunogenicity data, although not reviewed systematically in this report, support an increasing benefit of vaccination with an increasing number of doses. This seems to be particularly important for vaccines other than PRP-OMP. Antibody titres following vaccination appear to increase as age at vaccination increases, but responses appear strong even at the age of 2-3 months; this is reassuring given the suggestion that delayed administration was a risk factor for vaccine failure in one of the case-control studies<sup>12</sup>. Serological data also show a lower immunogenicity of DTaP-Hib

combination vaccines compared to DTwP-Hib vaccines or separately administered DTaP and Hib vaccines.

From the evidence included in this report, the effects of vaccination on carriage of Hib are less clear (partly due to the small number of carriers identified in the studies). It appears that vaccination may have some effect in reducing carriage, but this cannot be reliably quantified from the evidence included in this review.

#### ***4.2. Strengths and limitations of identified data***

Although often considered inferior to data from randomised controlled trials, observational data can provide more realistic estimates of the effects of vaccination under field conditions. The case-control studies generally used appropriate controls and controlled for some confounding factors in the design and / or analysis of the study. Arguably the two most important confounders of the relationship between vaccination status and Hib disease are age and socioeconomic status. All but one of the case-control studies controlled for age, and most took some account of SES, either by matching or in the analysis. Of the cohort studies, five controlled for age at vaccination in the analysis but none controlled for SES (although one did control for receipt of other vaccines, which might reflect SES).

An important limitation of the identified data (for clinical, carriage and immunological outcomes) was the lack of information on the age at receipt of Hib vaccine and on dosing intervals. We were therefore only able to compare (descriptively) the dose-specific estimates of effectiveness under different intended schedules and could not investigate in detail the effects of age at vaccination, or time between doses, on effectiveness.

There are several caveats to the interpretation of the immunogenicity data. Levels of anti-PRP antibody of  $\geq 0.15\mu\text{g/ml}$  and  $\geq 1.0\mu\text{g/ml}$  are commonly taken to be correlates of short- and long-term protection, respectively<sup>44</sup> and were used in the studies included in this report. These values are based on studies of plain polysaccharide vaccines; lower antibody concentrations may be adequate for protection following

vaccination with a conjugate vaccine<sup>54</sup>. The antibody level required for protection may also vary between populations<sup>54</sup>. Therefore the percentage of individuals who reach these specified antibody titres may not be equivalent to the percentage of individuals who are protected from disease.

#### ***4.3. Strengths and limitations of review methods***

This review was based on a thorough search of available literature which identified a large number of potentially eligible studies. To manage this workload, we used a rapid electronic screening method to identify eligible studies. This will have missed any cohort or case-control studies which did not identify the study design in the title or abstract, or which did not include an abstract. However, we would expect higher quality studies to include this information in the abstract. Full text screening and much of the abstract screening were done by a single reviewer; a second reviewer was consulted when the eligibility of any study was unclear.

Many of the comparisons discussed are between studies. Possible differences in study design and conduct, in adherence to intended vaccination schedules, and in Hib epidemiology between settings mean that conclusions should be drawn cautiously. We did not combine study results in a meta-analysis to estimate vaccine effectiveness by schedule due to the small number of studies using any given schedule and reporting the same outcome. A previous meta-analysis of case-control studies estimated the effectiveness of two and three doses to be >90% against invasive Hib disease and confirmed Hib meningitis, but did not stratify by other schedule-relevant factors<sup>1</sup>.

Finally, we were unable to locate 46 of the papers which were identified as potentially eligible by the rapid screening. However, based on the titles and abstracts (which were checked by two reviewers), few of these appear likely to be eligible for the review.

#### **4.4. Conclusions**

The evidence summarised in this report shows that at least two doses of Hib vaccine are required to achieve high effectiveness (e.g. >85%), particularly for vaccines other than PRP-OMP, and that three doses may be more effective than two. It also supports, albeit less strongly, the following conclusions:

- A three dose primary series followed by a booster dose confers better protection than the same primary series without a booster
- A booster may also compensate for an incomplete primary series
- Vaccine effectiveness and immunogenicity may increase with age at initiation, but both are high even when the primary series is begun at a young age (e.g. 6 weeks as in the EPI schedule)
- Hib vaccines administered in combination with DTaP appear to be less immunogenic and less effective than Hib vaccines administered with DTwP or given separately from DTaP
- Hexavalent vaccines may be less effective than quadrivalent or pentavalent vaccines

The review also highlighted several important gaps in the observational evidence which limit the certainty with which we can draw conclusions:

- We identified no within-study comparisons of the effectiveness against clinical outcomes of different ages at initiation of vaccination, different dosing intervals or comparisons of schedules with and without a booster dose
- Most studies reported the intended vaccination schedule but not children's actual ages at vaccination

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## APPENDIX

Appendix Table 1: Summary of case control studies of Hib vaccine effectiveness against clinically important Hib disease (studies are grouped by outcome).

Country / reference	Year published	Schedule comparisons	Age group in months	Number of cases	Type of control *	Ratio of controls to cases	Length of study	Study timing †	Vaccination history	Type of Hib vaccine	Method of statistical analysis	Method of calculating VE	Factors adjusted for in estimating VE
<b>Invasive Hib disease</b>													
USA <sup>24</sup>	1992	1 or more HbOC vs no Hib vaccine	18-60	16	C	4 to 1	2 years, 2 months	P	Documented only	HbOC [PRP and PRP-D included in paper but not in this review]	Conditional logistic regression	1 - OR	Matching: age ( $\pm$ 1 day), area of residence
USA <sup>19</sup>	1994	1 dose HbOC vs no Hib vaccine 2 doses HbOC vs no Hib vaccine 3 doses HbOC vs no Hib vaccine 4 doses HbOC vs no Hib vaccine 1 dose PRP-OMP vs no Hib vaccine 2 doses PRP-OMP vs no Hib vaccine Intended schedule 2, 4, 6, 15 months (HbOC); 2, 4, 12 months (PRP-OMP)	1.5-35	105	C	7 to 1	2 years	P	Documented only	HbOC, PRP-OMP	Conditional logistic regression	1 - OR	Matching: age ( $\pm$ 2 months), area of residence Analysis: paternal ethnicity, gender, breastfeeding history, number sleeping in room with child, usual source of medical care
USA <sup>23</sup>	1994	1, 2 or 3 doses of Hib conjugate vaccine vs no Hib vaccine	2.5-59	45 in analysis of all conjugate vaccines combined; 39 in analysis of PRP-OMP	C	4 to 1	3 years	P	Documented only	PRP-OMP, HbOC, PRP-D	Conditional logistic regression	1 - OR	Matching: age (as close as possible), area of residence
USA <sup>8</sup>	1991	1 or more HbOC vs no Hib vaccine	18.5-59	59	C	2 to 1	1 year, 5 months	P	Documented only	HbOC [PRP and PRP-D included in paper but not in this review]	Conditional logistic regression	1 - OR	Matching: SES

Country / reference	Year published	Schedule comparisons	Age group in months	Number of cases	Type of control *	Ratio of controls to cases	Length of study	Study timing †	Vaccination history	Type of Hib vaccine	Method of statistical analysis	Method of calculating VE	Factors adjusted for in estimating VE
USA <sup>20</sup>	1999	1, 2, 2 or more, 3, and 3 or more doses of Hib conjugate vaccines vs no Hib vaccine Intended schedule 2, 4, 6 months	2-18	57	C	3 to 1	3 years 6 months	P	Documented only	HbOC (1 case received PRP-OMP and 1 control a vaccine other than HbOC but the type is not stated)	Conditional logistic regression	1 - OR	Matching: age (as close as possible), county of birth Analysis: single mother, household crowding
USA <sup>6</sup>	1991	3 doses of HbOC (intended schedule 2, 4, 6 months, mean ages at receipt 2.6, 4.9 and 7.2 months) vs no Hib vaccine	1.5 - 12	25 total; 13 included in matched analysis	C	≥7 to 1	2 years, 5 months	P	Documented only	HbOC	Conditional logistic regression	1 - OR	Matching: month of birth, sex, zip code Analysis: daycare attendance, ethnicity, family income
The Gambia <sup>18</sup>	2005	1, 2 or 3 doses vs no Hib vaccine Intended schedule 2, 3, 4 months but often given later	<72	46	C	10 to 1	4 years 8 months	P	Documented only	PRP-T	Conditional logistic regression	Not stated	Matching: age (± 2 weeks), area of residence
England & Wales <sup>9</sup>	2008	Any Hib vaccine vs no Hib vaccine; 3 doses of Hib-containing vaccine with 0, 1, 2 or 3 administered as DTaP-Hib. Intended schedule 2, 3, 4 months	<51	138 (any Hib vaccine vs none) 95 (doses of DTaP-Hib)	C	5 to 1	5 years	R	Parental report	Not stated	Conditional logistic regression	Not presented	Matching: age (same DOB), region
England & Wales <sup>10</sup>	2003	Any Hib vaccine vs no Hib vaccine; 3 doses of Hib-containing vaccine with 0, 1, 2 or 3 administered as DTaP-Hib. Intended schedule 2, 3, 4 months	Unclear	110	C	35 to 1		R	Documented only	Not stated	Conditional logistic regression	1 - OR	Matching: age (same DOB) Analysis: age at third dose

Country / reference	Year published	Schedule comparisons	Age group in months	Number of cases	Type of control *	Ratio of controls to cases	Length of study	Study timing †	Vaccination history	Type of Hib vaccine	Method of statistical analysis	Method of calculating VE	Factors adjusted for in estimating VE
<b>Hib meningitis</b>													
Australia <sup>25</sup>	1998	1 or more doses vs no Hib vaccine	2-60	8	C	4.8 to 1	2 years	P	Documented only	PRP-OMP	Conditional logistic regression	1 - OR	Matching: age (DOB in same calendar year and month), sex, area of residence Analysis: breastfeeding, exposure to cigarette / tobacco smoke, exposure to campfire smoke
Malawi <sup>11</sup>	2006	1, 2, at least 1, at least 2, or at least 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	2-59	43	H (children with <i>S. pneumoniae</i> meningitis)	5 to 1	3 years	Not stated	Not stated	Combined PRP-T, DTP, hep B	Logistic regression	1 - OR	Analysis: age, area of residence (within or outside Blantyre city), HIV status
Uganda <sup>12</sup>	2008	2 or more or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	3-59	41	C, H (children with conditions other than those potentially related to Hib)	3 to 1	3 years	P / R	Verbal and documented	Combined PRP-T, DTP, hep B	Conditional logistic regression	1 - OR	Matching: age (DOB ± 2, 3, 6 or 12 months for cases aged 3-6, 7-11, 12-23 and 24-59 months, respectively), neighbourhood Analysis: maternal education
Dominican Republic <sup>15</sup>	2008	1, 2, 3 or 2 or more doses vs no Hib vaccine Intended schedule 2, 4, 6 months	2-59	32	C	3 to 1	3 years 2 months	R	Verbal and documented	Combined PRP-T, DTP, hep B	Conditional logistic regression	1 - OR	Matching: age (DOB ± 60 or 180 days for cases aged <1 and 1-4 years, respectively), neighbourhood
Uganda <sup>13</sup>	2008	1, 2, 3 or 2 or more doses vs no Hib vaccine	0-59	Not stated	H (children with <i>S. pneumoniae</i> meningitis)	Not stated	6 years	Unclear	Verbal and documented	Combined PRP-T, DTP, hep B	Logistic regression	1 - OR	Analysis: age



Country / reference	Year published	Schedule comparisons	Age group in months	Number of cases	Type of control *	Ratio of controls to cases	Length of study	Study timing †	Vaccination history	Type of Hib vaccine	Method of statistical analysis	Method of calculating VE	Factors adjusted for in estimating VE
Bangladesh <sup>7</sup>	2007	1 or more, 2 or more or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	3-23	15	C, H (children with conditions other than pneumonia or meningitis)	Community: 4 to 1 Hospital: 2 to 1	3 years, 3 months	P	Documented only	Combined PRP-T DPT	Conditional logistic regression	Unclear	Matching (community controls only): age (DOB $\pm$ 1 month), sex, season, distance from hospital Analysis: age, number of doses; household income
The Gambia <sup>18</sup>	2005	1, 2 or 3 doses vs no Hib vaccine Intended schedule 2, 3, 4 months but often given later	<72	36	C	10 to 1	4 years 8 months	P	Documented only	PRP-T	Conditional logistic regression	Not stated (presumably 1 - OR)	Matching: age (DOB $\pm$ 2 weeks), area of residence Analysis: unspecified covariates (data were collected on distance from health centre, overcrowding, mother's education)
<b>Purulent meningitis</b>													
Rwanda <sup>14</sup>	2007	2 or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	0-59	45	H (children with <20 WBC per $\square$ CSF, non-turbid and negative for Hib)	1.5 to 1	4 years 6 months	R	Not stated	Combined PRP-T, DTP, hepatitis B	Not stated	1 - OR	None stated
Uganda <sup>13</sup>	2008	1, 2, 3 or 2 or more doses vs no Hib vaccine	0-59	Not stated	H (children with <20 WBC per microlitre CSF, of unknown cause)	Not stated	6 years	Unclear	Verbal and documented	Combined PRP-T, DTP, hep B	Logistic regression	1 - OR	Analysis: age
Bangladesh <sup>7</sup>	2007	1 or more, 2 or more or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	3-23	41	C, H (children with conditions other than pneumonia or meningitis)	Community: 4 to 1 Hospital: 2 to 1	3 years, 3 months	P	Documented only	Combined PRP-T DPT	Conditional logistic regression	Unclear	Matching (community controls only): age (DOB $\pm$ 1 month), sex, season, distance from hospital Analysis: age, number of doses; household income

Country / reference	Year published	Schedule comparisons	Age group in months	Number of cases	Type of control *	Ratio of controls to cases	Length of study	Study timing †	Vaccination history	Type of Hib vaccine	Method of statistical analysis	Method of calculating VE	Factors adjusted for in estimating VE
<b>Aetiology negative meningitis</b>													
Uganda <sup>13</sup>	2008	1, 2, 3 or 2 or more doses vs no Hib vaccine	0-59	Not stated	H (children with <20 WBC per microlitre CSF, of unknown cause)	Not stated	6 years	Unclear	Verbal and documented	Combined PRP-T, DTP, hep B	Logistic regression	1 - OR	Analysis: age
Rwanda <sup>14</sup>	2007	2 or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	0-59	13	H (children with <i>S. pneumoniae</i> meningitis)	1.5 to 1	4 years 6 months	R	Not stated	Combined PRP-T, DTP, hepatitis B	Not stated	1 - OR	None stated
<b>Radiologically confirmed pneumonia</b>													
Brazil <sup>16</sup>	2004	2 or 3 doses (or 1 at age >12 months) vs 0 or 1 (at age <12 months) doses Intended schedule 2, 4, 6 months	2-24	427	C	2 to 1	1 year, 4 months	P	Documented only	HbOC	Conditional logistic regression	1 - OR	Matching: age ( $\pm 4$ months), neighbourhood Analysis: age, sex, daycare attendance, previous flu-like illness, smokers at home, home ownership, mother's education
Colombia <sup>17</sup>	2004	1, 2 or 3 doses vs no Hib vaccine Intended schedule 2, 4, 6 months	2-24	389	C	2 to 1	2 years, 7 months	P	Documented only	PRP-T	Conditional logistic regression	1 - OR	Matching: age ( $\pm 1$ month), sex, area of residence, SES Analysis: maternal education, maternal smoking, number of smokers in household, daycare attendance, cooking in the sleeping room, underlying illness, previous hospitalisation, crowding

Country / reference	Year published	Schedule comparisons	Age group in months	Number of cases	Type of control *	Ratio of controls to cases	Length of study	Study timing †	Vaccination history	Type of Hib vaccine	Method of statistical analysis	Method of calculating VE	Factors adjusted for in estimating VE
Bangladesh 7	2007	1 or more, 2 or more or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	3-23	343	C, H (children with conditions other than pneumonia and meningitis)	Community: 4 to 1 Hospital: 2 to 1	3 years, 3 months	P	Documented only	Combined PRP-T DPT	Conditional logistic regression	Unclear	Matching (community controls only): age (DOB $\pm$ 1 month), sex, season, distance from hospital Analysis: age, number of doses; household income

Appendix Table 2: Hib vaccine effectiveness (VE) estimates from case control studies grouped by outcome measured, Hib vaccine doses received and control type.

Country / ref	Confirmed Hib meningitis					Probable bacterial meningitis				Aetiology negative meningitis				Invasive Hib disease				Radiologically confirmed pneumonia				
	2 doses	3 doses	≥1 dose	≥2 dose	≥3 doses	2 doses	3 doses	≥1 dose	≥2 dose	2 doses	3 doses	≥1 dose	≥2 doses	2 doses	3 doses	≥1 dose	≥2 doses	2 doses	3 doses	≥1 dose	≥2 doses	
<b>Vaccine effectiveness (95% CI) using community controls</b>																						
Uganda <sup>12</sup>		98 (89 to 100)		99 (92 to 100)																		
Dominican Republic <sup>15</sup>	87 (14 to 100)	90 (33 to 100)		94 (60 to 100)																		
Brazil <sup>16</sup>																					31 (-9 to 57)	
Colombia <sup>17</sup>																		52 (3 to 76)	55 (7 to 78)	47 (2 to 72)		
USA <sup>24</sup>																100 (-37 to 100)						
USA <sup>19</sup> - HbOC														89 (60 to 97)	94 (6 to 99)							
USA <sup>19</sup> - PRP-OMP														100 (68 to 100)								
USA <sup>23</sup> - all Hib conjugate vaccines combined														99 (69 to 100)	99 (-57 to 100)							
USA <sup>23</sup> - PRP-OMP																95 (66 to 99)						
USA <sup>20</sup>																	86 (16 to 98)					
USA <sup>6</sup>															100							
Bangladesh <sup>7</sup>		65 (-190 to 100)	90 (34 to 100)	89 (28 to 100)			40 (-138 to 85)	54 (-21 to 83)	71 (-1 to 92)											32 (-2 to 54)	24 (-6 to 43)	34 (6 to 53)
The Gambia <sup>18</sup>	93 (42 to 99)	96 (47 to 100)												94 (62 to 99)	94 (62 to 99)							
Australia <sup>25</sup>			75 (-266 to 98)																			

Country / ref	Confirmed Hib meningitis					Probable bacterial meningitis				Aetiology negative meningitis				Invasive Hib disease				Radiologically confirmed pneumonia			
	2 doses	3 doses	≥1 dose	≥2 dose	≥3 doses	2 doses	3 doses	≥1 dose	≥2 dose	2 doses	3 doses	≥1 dose	≥2 doses	2 doses	3 doses	≥1 dose	≥2 doses	2 doses	3 doses	≥1 dose	≥2 doses
USA <sup>8</sup>																100					
England <sup>9</sup>																96 (81 to 99)					
<b>Vaccine effectiveness (95% CI) using hospital controls</b>																					
Malawi <sup>11</sup>	89 (43 to 98)		73 (39 to 88)	92 (72 to 98)	94 (70 to 99)																
Uganda <sup>12</sup>		97 (75 to 100)		94 (74 to 99)																	
Uganda <sup>13</sup>	93 (42 to 99)	94 (48 to 99)	65 (41 to 79)	93 (69 to 99)		36 (-10 to 63)	68 (46 to 81)	38 (23 to 50)	53 (11 to 68)	66 (-10 to 90)	15 (-51 to 52)	31 (3 to 51)	35 (-11 to 62)								
Rwanda <sup>14</sup>									52 (5 to 75)				68 (-78 to 94)								

Appendix Table 3: Further details of cohort studies of Hib vaccine effectiveness against invasive Hib disease

Country <sup>ref</sup>	Number of participants	Method of ascertainment of exposure	Assessment of clinical outcomes	Method of statistical analysis	Factors adjusted for	Main quality concerns
<b>Invasive Hib disease</b>						
Australia <sup>33</sup>	Pre-vaccination era: 70254 to 72786 child-years under 5; Vaccination era, >=1 dose: 29546 to 41175 child-years under 5	Immunization register	1989 - Nov 1994: retrospective ascertainment from hospital laboratories and infection control records in five main towns in region; Dec 1994 - 1996: notifiable disease (via laboratories)	Rate ratio comparing incidence in those receiving vaccine (or in those adequately vaccinated) to pre-vaccination era incidence in children who would have received vaccine/been adequately vaccinated had the programme existed	None.	No control for confounding. Not clear if assessment of clinical outcome was blind to exposure status. Not clear if different exposure groups had the same schedule of follow-up for outcome.
Chile <sup>30</sup>	3 doses of DTP-Hib: 35 264; 3 doses of DTP only: 36 741	EPI clinic databases	Passive surveillance, of laboratory reports from 11 hospitals in study region which would admit pediatric patients, to identify Hib cases among study participants in 17 months following last vaccine administered as part of this study <sup>l</sup>	Rate ratio comparing incidence in vaccinated to unvaccinated cohort	None.	No control for confounding.
England & Wales <sup>27</sup>	Estimated 4,368,200 children received 3 doses during study period	From child's GP or district child health immunization computer	Active surveillance of pediatricians, ?passive surveillance of microbiologists and consultants in communicable disease control (Oct 1, 1992-Oct 31 1995 - Hib conjugate vaccinees only; from Nov 1 1995 - all cases regardless of vaccination status) for outcome in children under 5 years of age	Incidence among vaccinees <sup>m</sup> (1992-1999) compared with expected incidence informed by survey in pre-vaccination era (1985-1990)	Age (stratification)	Surveillance method for outcome changed in 1995 (to 1995, invasive Hib reported for vaccinees only; from Nov 1 1995, all cases of invasive Hib reported regardless of vaccination status) thus probably underestimated incidence before Nov 1 1995 (authors conducted sensitivity analysis).
Germany <sup>29</sup>	Cases: 36; Non-cases: 667 <sup>n</sup>	Cases: unclear.; Non-cases: Parents read from vaccination booklet during phone survey.	Nationwide passive hospital and laboratory surveillance for outcomes in children under 10 years of age	Multivariable Cox regression. Non-cases contribute follow-up time from birth or the start of surveillance period (whichever later). Cases contribute to the analysis cross-sectionally, on date of positive Hib culture, only. <sup>o</sup>	Age at vaccination; changing immunisation status of each non-case over-time	Blinding - lab staff apparently blind to vaccination status of cases, clinicians apparently not. Unclear how vaccination status of cases was ascertained

<sup>l</sup> The exposures assessed in this study (DTP-Hib vs DTP alone) were given between 1 Nov 1992 and 31 Oct 1993. Surveillance for invasive disease occurred between 1 Nov 1992 and 30 Apr 1995

<sup>m</sup> Follow-up time for non-cases in the vaccine era estimated using vaccine coverage figures and national birth and death rates

<sup>n</sup> Cases are all those in Germany between Jan 1998 and Jun 2002, identified through nationwide surveillance, and non-cases are a random sample ("sub-cohort") of all children born in Germany between 1 Jun, 1996 and 31 Dec, 1998 (the sub-cohort was assumed to contain no cases)

<sup>o</sup> Reference for method of statistical analysis: Moulton LH et al AJE 1995; 142 (9): 1000-1006.

Country <sup>ref</sup>	Number of participants	Method of ascertainment of exposure	Assessment of clinical outcomes	Method of statistical analysis	Factors adjusted for	Main quality concerns
<b>Invasive Hib disease</b>						
Germany <sup>28</sup>	Cases: 32; Non-cases: 2893 <sup>p</sup>	Cases: vaccination booklets or vaccinating paediatricians.; Non-cases: Parents read from vaccination booklet during phone survey.	Hospital / laboratory surveillance (presumably in children under 10 years of age, as for <sup>29</sup> , but not stated)	Multivariable Cox regression. Non-cases contribute follow-up time from birth or the start of surveillance period (whichever later). Cases contribute to the analysis cross-sectionally, on date of positive Hib culture, only.O	Age at vaccination; changing immunisation status of each non-case over-time	Blinding - lab staff apparently blind to vaccination status of cases, clinicians apparently not. Possible overestimate of vaccination coverage from telephone survey due to survey population being overrepresentative of wealthier.
South Africa <sup>31, 32</sup>	Vaccinated cohort: 19 267; Unvaccinated cohort: approx. 22000	Not stated, but presumably trial records (this study nested within Phase III trial of 9-valent pneumococcal vaccine)	"Daily laboratory surveillance of culture-confirmed invasive Hib disease was undertaken from January, 1997. There was active case detection during prospective studies evaluating invasive bacterial disease in children between March, 1997, and September,2000" in children under 1 year of age	Risk ratio comparing incidence in vaccinated to unvaccinated cohort <sup>q</sup>	None.	Provenance of unvaccinated cohort is unclear. Unclear how vaccinated children were selected from trial for inclusion in cohort study. Unclear what statistical methods used to estimate incidence; not clear how/if losses to follow-up were accounted for. No adjustment for confounding.
<b>Hib meningitis +/- other outcomes</b>						
Denmark <sup>34</sup>	All children in Denmark who were liveborn between 1 June 1987 and 31 December 1998 (542,100 children)	Immunization register	National Hospital Discharge Registry. All hospitalisations for children up to age 9 years between 1 Jan 1991 and 31 Dec 1999 were extracted	Log-linear multivariable Poisson regression to estimate rate ratio for association of outcome with 1, 2 or 3 doses of vaccine, relative to rate of outcome in pre-vaccination period	Age <sup>r</sup>	Rate of loss to follow-up not reported by exposure group.
Denmark <sup>35</sup>	Unvaccinated: 922480 child years under 5; At least one dose: 1977983 child years under 5	Immunization register	Linkage of information in hospitalization register to immunization register (exposure status) and population register for children under 5 years of age	Log-linear multivariable Poisson regression to estimate rate ratio for association of outcomes with >=1 Hib dose of Hib and per dose among vaccinees <sup>s</sup>	Age, calendar period, and receipt of other vaccines; age and calendar period interaction. <sup>t</sup>	Rate of loss to follow-up not reported by outcome. Estimates of vaccine effectiveness give in figures only.

<sup>p</sup> Cases are all those in Germany between Aug 2000 and Dec 2004, identified through nationwide surveillance, and non-cases are a random sample ("sub-cohort") of all children born in Germany between 1 Aug, 2000 and 31 Dec, 2004 (the sub-cohort was assumed to contain no cases)

<sup>q</sup> The calculation of the risk ratio for at least one dose was restricted to children <1; the unvaccinated cohort was restricted to children 6 weeks or older. The calculation of the risk ratio for fully vaccinated included children between 4.1 and 12.0 months of age in the unvaccinated cohort and all cases occurring at least 14 days after having received the third dose of Hib conjugate vaccine in the vaccinated cohort.

<sup>r</sup> The authors checked and there was no evidence for confounding by birth weight, birth method, gestational age, season, birth order or gender.

<sup>s</sup> This study was mainly about adverse effects of vaccines so the authors also presented associations with vaccination 14 d to 3 mo after receipt of any dose and greater than 3 mo after receipt of any dose.

<sup>t</sup> The authors report no confounding by sex, place of birth, birth weight, mother's country of birth, mother's age at birth, birth order, or season.