

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

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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, dosing interval, age at initiation of vaccination, or co-administration with other vaccines or medical preparations. Where appropriate, dose-specific estimates of vaccine effectiveness (VE) were summarised using random effects meta-analysis, for PRP-OMP and other vaccines separately. Some relevant data on immunogenicity and carriage following different vaccination schedules are also presented.

Results

The literature search identified 3892 articles, of which 33 (reporting on 32 studies) were included in the review: 20 case-control studies, 8 cohort studies and 4 studies which estimated vaccine effectiveness using the screening method. Meta-analysis of data from case-control studies using community controls produced effectiveness estimates of 55% (95% CI 2-80%), 94% (95% CI 65-99%) and 94% (95% CI 18-100%) after 1, 2 and 3 doses, respectively, against Hib meningitis. Based on hospital controls, effectiveness against Hib meningitis was 53% (-14-81%), 92% (75-97%) and 94% (65-99%) for 1, 2 and 3 doses. Based on case-control studies, VE against invasive Hib disease (for vaccines other than PRP-OMP) was estimated as 59% (30-76%) for 1 dose and 99% (77-100%) for 3 doses; insufficient data were identified to allow meta-analysis of estimates of two-dose VE against invasive Hib disease. Dose-specific data from cohort studies were more limited but the effectiveness of three doses was estimated as 96% (93-98%). 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 that older age at initiation may lead to higher VE against invasive Hib, although any effect was slight and VE was high even when vaccination was begun at 6 weeks of age. 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.

Data from two case-control studies in the UK suggested that Hib vaccine may be less effective when administered with acellular pertussis vaccine than when given with whole cell pertussis vaccine. Limited data from two cohort studies conducted in Germany were consistent with a slight additional benefit of a booster dose when given in addition to a full primary series, but the confidence intervals overlapped (VE estimates were 98.5% [95% CI 94.5-99.6%] and 100% [95% CI 52.7-100%] for three doses plus booster, compared to 96.7% [95% CI 87.7-99.1%] and 90.4% [95% CI 70.6-96.8%] for three doses without booster). One of these studies also suggested that a booster may compensate at least to some extent for incomplete primary vaccination.

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

Evidence from observational studies indicates that 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 favour any particular schedule. There is some evidence that DTaP-Hib vaccines are less effective and less immunogenic than DTwP-Hib 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
- Timing of vaccine failures and implications for the administration of a booster dose

Previous reviews have summarised estimates of overall and dose-specific effectiveness of Hib vaccination from observational studies ^{1,2} and randomised controlled trials ^{2,3}. 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 May 2010 and again in June 2012: Medline, the Cochrane Library, African Index Medicus, Indian Medlars Centre, Latin American and Caribbean Health Sciences Literature.

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 reviews ^{1, 4} 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 ^a.

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.

^a 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. A 10% random sample of the observational studies which did not pass electronic screening was manually screened to assess the sensitivity of the method.

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 ¹, were also included.

2.5. Data extraction

Data were extracted by one reviewer and checked by a second. Extracted data included information about the study population, vaccination schedules and occurrence of the outcome of interest, for each comparison presented. Some required information is presented in a similar format to the previous review ¹; we also extracted data on additional factors relevant to vaccination schedules.

The data extraction forms included questions, specific to case-control and cohort studies, intended to inform judgement about of the potential for bias for each included study. Due to the relatively small number of articles identified, we did not

exclude studies based on their potential for bias, but summarise key methodological concerns in the text.

For studies which reported individual-level data on vaccine failures, we extracted data on the age and the time since last dose at disease onset, in case such information gave some hint of the waning of vaccine-derived immunity. The validity of this approach is discussed in Section 4.3.

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

2.6. Analysis

For each outcome against which dose-specific VE was reported by three or more case-control studies, we performed random effects meta-analysis using the method of DerSimonian and Laird⁵ to calculate a pooled odds ratio (OR). The OR is related to VE by the equation $VE = 100 \times (1 - OR)$. Studies were eligible for meta-analysis if they reported VE for 1, 2 or 3 vaccine doses. Studies of PRP-OMP were analysed separately from other vaccines, as there is evidence that this vaccine is more immunogenic⁶⁻⁸ than other Hib vaccines, especially after a single dose.

Heterogeneity was assessed using the I^2 statistic, which measures the percentage of variation between studies which is attributable to heterogeneity⁹. Values of I^2 of 25%, 50% and 75% are considered to represent low, moderate and high heterogeneity, respectively⁹. We identified insufficient data to stratify by vaccination schedule.

The distributions of age at disease and time between last vaccine dose and disease were summarized graphically (stratified, where possible, by type of pertussis vaccine used in the vaccination schedule).

Statistical analysis was conducted using Stata 12.

2.7. Studies using the screening method

Several studies included in the O’Loughlin review ¹ used the screening method^b 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.

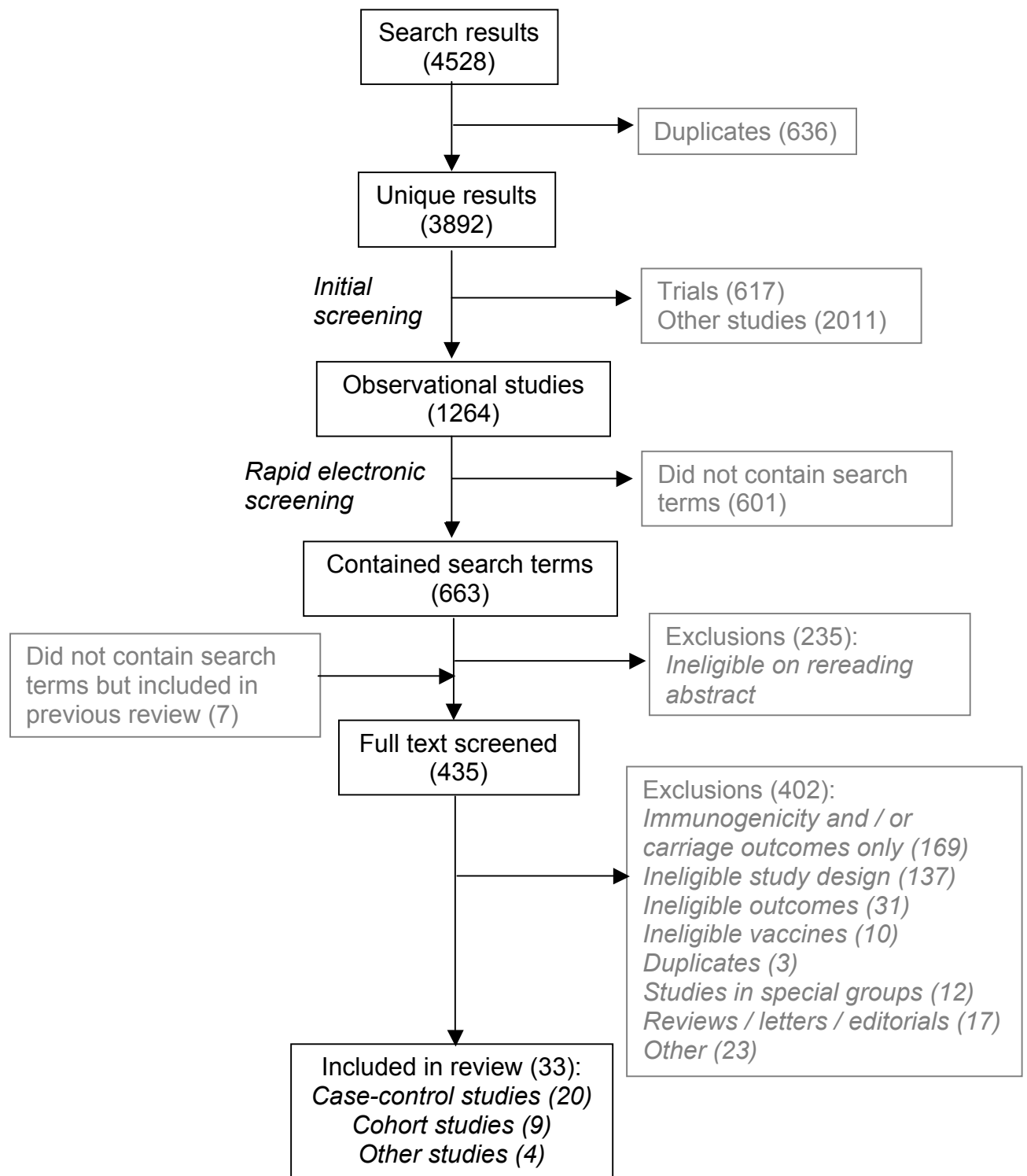
3. RESULTS

After de-duplication, the literature search produced 3892 results. Our screening process identified 26 eligible papers; 7 more were identified from the previous review ¹. Therefore 33 papers (reporting 32 studies) were included: 20 case-control studies, 8 cohort studies and 4 others (Figure 1). We note that the total number of search results reported in Figure 1 differs from that reported in the accompanying review of trial data. This is due to subsequent filtering of the results of the 2012 search update for RCTs: this review of observational studies includes only those studies not identified as RCTs by this automated filtering.

^b In screening method studies, vaccine effectiveness is calculated as $1 - [\text{PCV}(1 - \text{PPV})] / [(1 - \text{PCV})\text{PPV}]$, where PCV is the proportion of the cases who are vaccinated and PPV is the proportion of the population vaccinated (i.e., vaccine coverage) 10. Orenstein, W.A., et al., *Field evaluation of vaccine efficacy*. Bull World Health Organ, 1985. **63**(6): p. 1055-68.

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). We focus on Hib meningitis, invasive Hib disease and radiologically confirmed pneumonia, as these were the only outcomes for which VE estimates were available for more than one schedule. We present VE estimates for 1, 2 and 3 doses in the main text and include estimates for other numbers of doses (e.g. ≥ 1), and for other outcomes in the Appendix.

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 20 identified case-control studies are summarised in Appendix Table 1. Six of these studies ¹¹⁻¹⁶ were not included in the previous review ¹. One of the case-control studies was nested within an intervention study in which the primary analysis included children who were not offered the vaccine and those whose parents refused vaccination; we report only results from the nested case-control study ¹². 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) ¹⁷. The remaining studies were standard hospital- or population-based case-control studies.

Amongst the 15 case-control studies which reported the intended vaccination schedule, 6 (conducted in Malawi ¹⁸, Bangladesh ¹⁷, Uganda ^{19, 20}, Senegal ¹⁵ and Rwanda ²¹) used the basic EPI schedule of 6, 10 and 14 weeks. Three studies from the Dominican Republic ²², Brazil²³ and Colombia ²⁴ reported an intended schedule of 2, 4 and 6 months, whilst two studies from the UK ^{13, 14} and one from The Gambia ²⁵ 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 ²⁶. 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 ^{12, 27}. None of the identified case-control studies directly compared the effectiveness of different vaccination schedules.

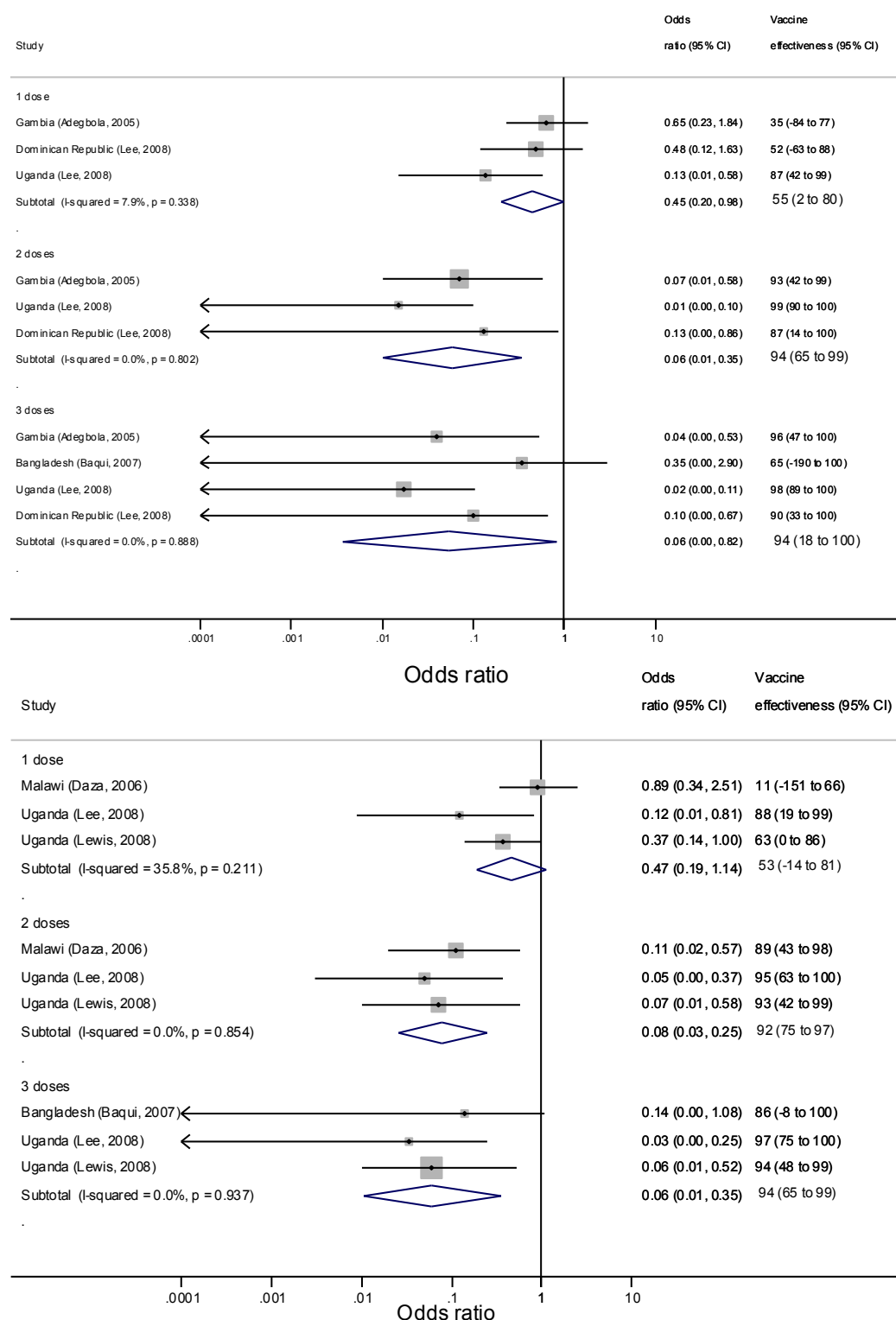
3.1.1. Number of doses

The effectiveness of one dose of Hib vaccine was often relatively low (point estimates were usually <65%, Figures 2-4). However, two studies carried out in the USA, using only or mainly PRP-OMP, reported VE >90% against invasive Hib disease after one dose^{26 28}. A study from Uganda reported VE as 87% (95% CI 42-99%) or 88% (95% CI 19-99%) against Hib meningitis following one dose (PRP-T in a pentavalent vaccine), based on community and hospital controls, respectively¹⁹.

VE against Hib meningitis after two or more doses ranged from 65% (95% CI 19 to 100%)¹⁷ to 99% (95% CI 92-100%)¹⁹ (Figure 2). 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%)²².

Meta-analysis of studies using community controls produced estimates of VE against Hib meningitis of 55% (95% CI 2-80%), 94% (95% CI 65-99%) and 94% (95% CI 18-100%) for 1, 2 and 3 doses, respectively (Figure 2). The corresponding estimates using hospital controls were similar (Figure 2): 53% (95% CI -14-81%), 92% (95% CI 75-97%) and 94% (95% CI 65-99%). There was no or very limited heterogeneity between studies using community controls; in studies using hospital controls, the one-dose estimates were moderately heterogeneous ($I^2 = 35.8\%$). All of these studies used PRP-T vaccine.

Figure 2: Dose-specific estimates, and results of meta-analysis, of vaccine effectiveness against Hib meningitis from case-control studies using community controls (top) and hospital controls (bottom). For each point estimate, the size of the box is proportional to its weight in the meta-analysis. Intended vaccination schedules were: 6, 10, 14 weeks (Uganda, Bangladesh, Malawi); 2, 3, 4 months (The Gambia), 2, 4, 6 months (Dominican Republic).

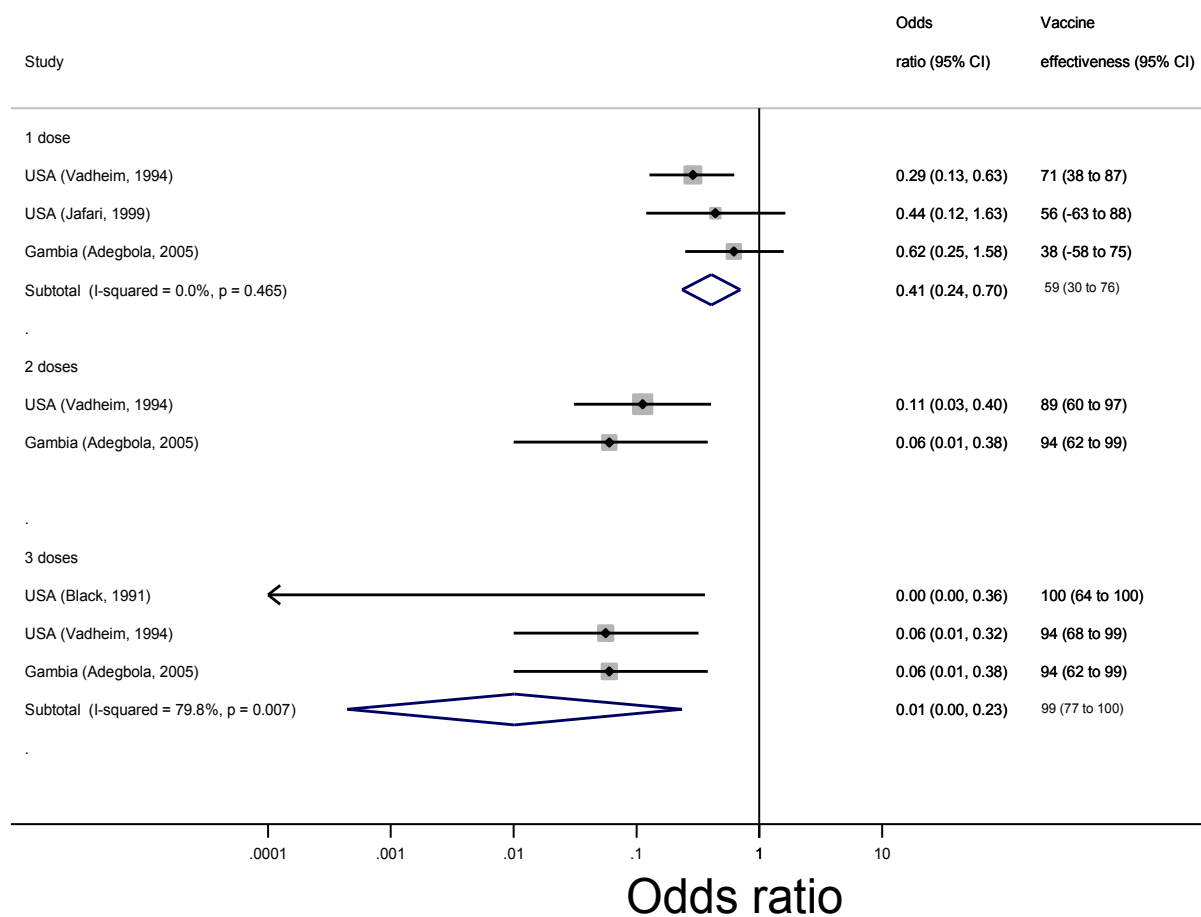


The estimate of 65% effectiveness against Hib meningitis after three doses was an outlier and had a very wide confidence interval (-190 to 100%)¹⁷. This is partly due to the small number of Hib meningitis cases: 15 in total, with no information on how many had received three doses of vaccine. The estimate 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.

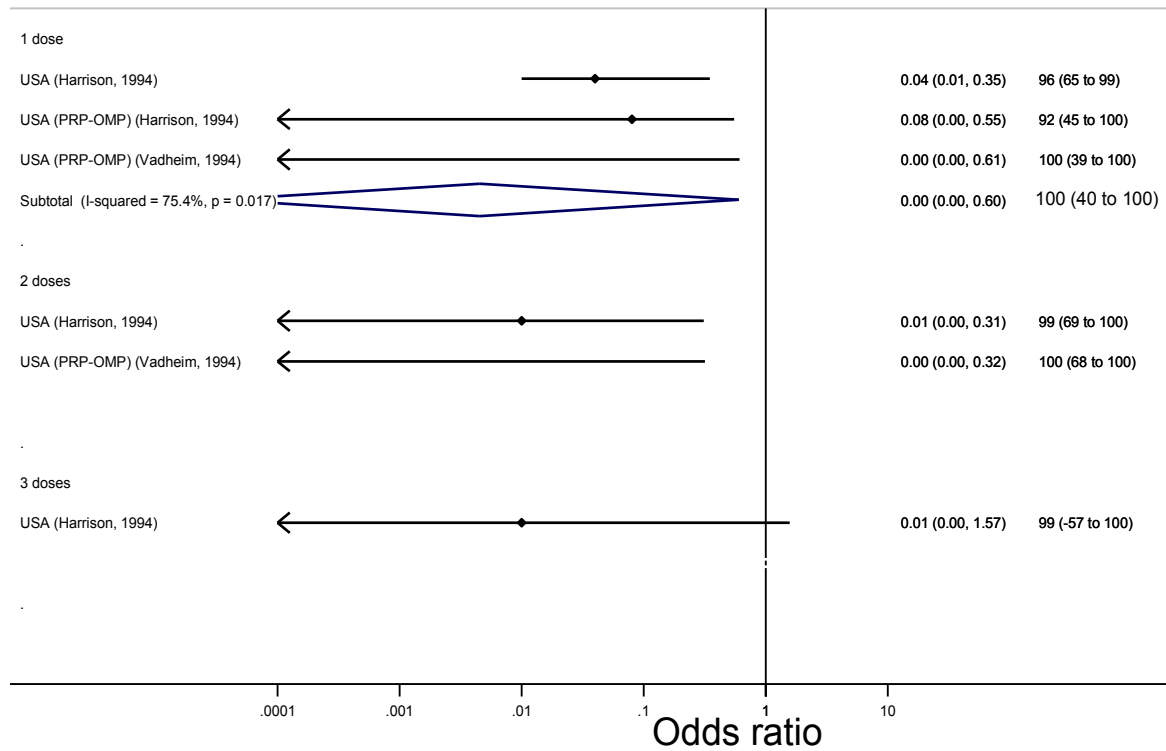
All of the case-control studies of invasive Hib disease used community controls. Estimates of VE after two or more doses ranged from 86% (95% CI 16-98%)²⁷ to 100% in two studies (95% CI 68-100% or 64-100%)^{12, 26}. The pooled estimates from meta-analysis for vaccines other than PRP-OMP were 59% (95% CI 30-76%) for one dose and 99% (95% CI 77-100%) for three doses (only two studies which used vaccines other than PRP-OMP reported two-dose VE against invasive Hib disease, so meta-analysis was not performed, Figure 3). There was high heterogeneity in the three-dose estimates ($I^2 = 79.8\%$) but not in the one-dose estimates ($I^2 = 0\%$).

For PRP-OMP, one-dose VE was estimated as 100% (95% CI 40-100%) but with high heterogeneity ($I^2 = 75.4\%$, Figure 3). The two estimates of two-dose VE for PRP-OMP were 99% (95% CI 69-100%) and 100% (95% CI 68-100%) (Figure 3). The one available estimate of VE following three doses of PRP-OMP was 99% (95% CI -57-100%, Figure 3).

Figure 3 (overleaf): Dose-specific estimates of vaccine effectiveness from case-control studies against invasive Hib disease from case-control studies using community controls, and the results of meta-analysis. Top: studies which used vaccines than PRP-OMP; bottom: studies which used mainly or exclusively PRP-OMP. For each point estimate, the size of the box is proportional to its weight in the meta-analysis. Intended vaccination schedules were 2, 4, 6, 15 months (Vadhiem HbOC); 2, 4, 12 months (Vadheim PRP-OMP); 2, 4, 6 months (USA Jafari, USA Black); 2, 3, 4 months (The Gambia); not stated (USA, Harrison). Hib vaccine was intended to be given with DTwP in The Gambia; of the US studies, one was conducted whilst only DTwP was available (Black) and the remainder were conducted whilst both DTaP and DTwP were in use ²⁹.



PRP-OMP

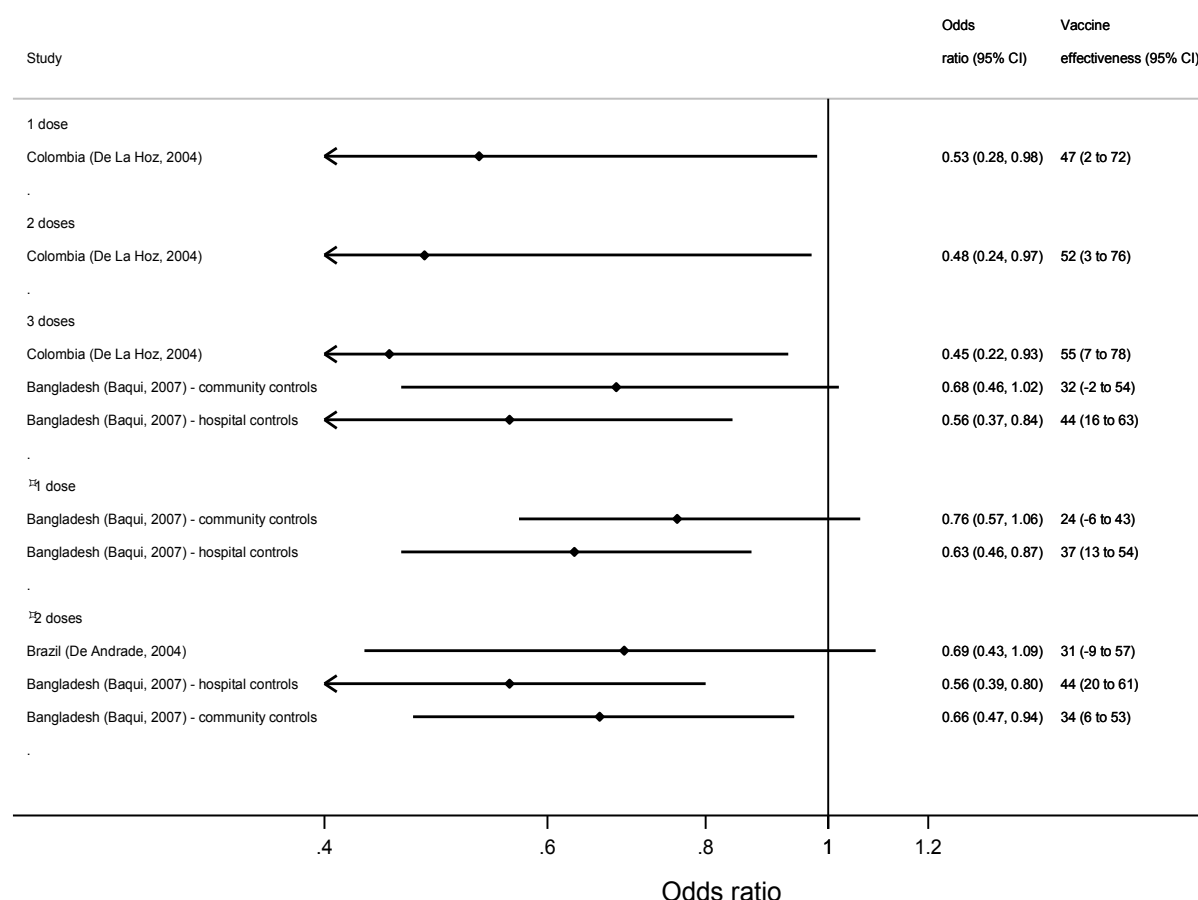


Three studies reported the effectiveness of three doses of Hib conjugate vaccine against radiologically confirmed pneumonia (Figure 4). In a study in Colombia in which PRP-T was intended to be given at 2, 4 and 6 months, effectiveness of three doses was reported to be 55% (95% CI 7-78%)²⁴. In Bangladesh, 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, respectively¹⁷. (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 paediatrician¹⁷.)

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 HbOC²³. All of these estimates^{17, 23, 24} 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.

Estimates of VE from case-control studies following imprecise numbers of doses are summarised in Appendix Table 2.

Figure 4: Dose-specific estimates of vaccine effectiveness against radiologically confirmed (all cause) pneumonia. Intended vaccination schedules were 6, 10, 14 weeks (Bangladesh); 2, 4, 6 months (Colombia, Brazil).



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)¹². 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 schedule¹⁷ and one using a 2, 4, 6 month schedule

²³, although a second study using a 2, 4, 6 month schedule reported slightly higher effectiveness estimates ²⁴. All studies which reported effectiveness against invasive Hib disease used an intended vaccination schedule beginning at 2 months of age.

One study in Uganda provided the median age at each dose for cases and controls ¹⁹ (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 ¹⁹.

	Median age [range] in weeks at vaccination (number vaccinated)		
	Dose 1	Dose 2	Dose 3
Cases	7 [5-25] (5)	11 [10-25] (3)	32 [27-66] (3)
Neighbourhood controls	9 [3-64] (27)	13 [7-69] (35)	20 [12-52] (42)
Hospital controls	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 (Figures 2-4).

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) ²⁴. 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) ²⁴. 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 ²⁴.

	Doses 1 and 2	Doses 2 and 3
Cases	70 (77)	72 (124)
Controls	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) ²⁶.

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 ^{13, 14} (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 (out of a total of three Hib-containing vaccines received) 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 ¹⁴. 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 ¹³. 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 relative risk of invasive Hib disease with an increasing number of DTaP-Hib doses amongst children who had received three doses of Hib-containing vaccine, with the baseline group being children who had received three doses of Hib vaccine which did not include DTaP (this appears to comprise children who had received three doses of DTwP-Hib). However, the confidence intervals were wide and included 1. For example, the OR comparing children who had received three doses of DTaP-Hib 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) ¹³. 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. Vaccine failures

Two case-control studies presented data on children who developed Hib disease despite having been vaccinated ^{19, 26}. In one of these studies, from Uganda ¹⁹, three children developed Hib meningitis after receiving two doses of Hib vaccine with DTwP, all within one year of the second dose (Appendix Figure 1). Three children who had received three doses developed Hib meningitis within three years of the third dose. These six vaccine failures ranged in age from 17 to 157 weeks ¹⁹.

The second case-control study to include data on vaccine failures was from the USA and reported 27 vaccine failures in total²⁶. Eighteen children were diagnosed with invasive Hib disease after a single vaccine dose, all within one year of vaccination (Appendix Figure 1). Six and three children developed disease after two and three doses, respectively, again within one year of the most recent dose.

3.1.7. Potential biases in included case-control studies

Most (17 of 20) of the included studies used community controls, e.g. by identifying potential controls from electronic registers or by door to door canvassing^{11-17, 19, 22-28, 30, 31}. In these studies, it seems likely that the controls came from the same population as the cases.

Five studies used hospital controls¹⁷⁻²¹ (two of these included both hospital and community controls^{17, 19}). In three of these studies, in estimating vaccine effectiveness against Hib meningitis, controls were children who were hospitalised with pneumococcal meningitis^{18, 20, 21} (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)^{20, 21}. 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 infection²⁰ whilst the Rwanda study used controls with pneumococcal meningitis²¹. 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 meningitis¹⁷ or conditions other than meningitis, pneumonia, sepsis, bacteraemia, epiglottitis or otitis media (i.e. conditions potentially caused by Hib)¹⁹. 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^{17, 19}, and that in the only one of these two studies to report controls' reasons for admission, the most common were malaria, gastroenteritis and anaemia¹⁹.

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 Rwanda²¹. 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).

3.1.8. Conclusions from case-control studies

The identified case-control studies confirm previous results^{1, 3} 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 ($\leq 63\%$), two studies reported high effectiveness against invasive Hib disease (92% and 100%) after one dose of PRP-OMP^{26, 28}. 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 vaccines³².

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 schedule²⁶. One study suggested that a lengthy delay between the first and second doses might be detrimental for protection against pneumonia²⁴; however, that conclusion was based on a possibly post hoc division into delays of ≤ 90 and >90 days. A second suggested that Hib meningitis cases may have been older than controls at receipt of the third dose¹⁹, 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^{13, 14}. The limited data on vaccine failures did not suggest an optimum time at which to administer a booster dose.

3.2. Cohort studies

Eight eligible cohort studies were identified (published in 9 papers), 6 of which estimated vaccine effectiveness against invasive Hib disease³³⁻³⁹, 1 which estimated VE against Hib meningitis only⁴⁰, and the final study which estimated rate ratios for bacteraemia/septicaemia, meningitis, viral pneumonia and bacterial pneumonia associated with Hib vaccination.⁴¹ Three of these 8 cohort studies^{36, 38, 40} were included in the recent review of Hib vaccine effectiveness from case control and other study designs¹. 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 existed³⁹. 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 area³⁶. 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)³³. 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^{34, 35}. 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^{37, 38}. 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^{40, 41}. 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 schedule³⁹. The study from Chile reported the intended schedule to be 2, 4, 6 months³⁶. The South African study reported on an intended schedule of 6, 10 and 14 weeks^{37, 38}. The study from England & Wales reported the intended schedule to be 2, 3, 4 months³³. The two studies from Germany reported the intended schedule to be 2, 3, 4 months with a booster at 11 months or later^{34, 35} 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^{40, 41}. 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 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 ^{ref}	Study period	Intended schedule	Hib vaccine	Other vaccines co-administered with Hib
Invasive Hib disease				
Australia ³⁹	1989-1996	Not stated.	PRP-OMPC, PRP-HbOC ^c	Not stated.
Chile ³⁶	1992-1995	2, 4, 6 mo	PRP-T	DTwP (quadrivalent), OPV
England & Wales ³³	1992-1999	2, 3, 4 mo	PRP-T, PRP-HbOC ^d	Monovalent or quadrivalent with DTwP
Germany ³⁵	1998-2002	2, 3, 4 +b11 (or later) mo	Conjugate molecule not stated.	DTaP (quadrivalent) or DTaP-IPV (pentavalent)
Germany ³⁴	2000-2005	2, 3, 4 +b11-14 mo	PRP-T	DTaP-HBV-IPV (hexavalent) ^e
South Africa ^{37, 38}	1997-2000 ³⁸ ; 1998-2004 ³⁷	6, 10, 14 w	PRP-HbOC	DTwP (quadrivalent) ³⁸ ; DTwP, OPV and HepB on same schedule; unclear whether any administered in same syringe ³⁷
Hib meningitis +/- other outcomes				
Denmark ⁴⁰	1991-1999	May 1993 - 31 Dec 1995: 5, 6 mo + b16 mo ^f ; 1 Jan 1996-31 Dec 1996: 5, 6 mo + b15 mo; 1 Jan 1997 onwards: 3, 5, 12 mo	PRP-T	Not stated.
Denmark ⁴¹	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)

^c 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

^d 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

^e One of the two hexavalent vaccines in use in Germany at the time of this study was withdrawn in the EU in 2012

^f 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 doses⁴⁰ while the German studies present separate estimates of VE for <3 doses and 3 doses^{34, 35}. 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

⁴¹.

Table 4: Hib vaccine effectiveness from cohort studies

Country ^{ref}	Schedules, median age at dose in months		VE (95% CI)
	Intended	Actual (median)	
Invasive Hib disease			
Australia ³⁹	Not stated.	Not stated.	>=1 dose vs 0 doses: 91.7 % (79.6-96.6%); Adequate vaccination ^g vs 0 doses: 97.5% (82.0-99.7 %)
Chile ³⁶	2, 4, 6 mo	Not stated.	3 doses vs 0 doses: 91.7% (64.8 - 100%)
England & Wales ³³	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) ^h
Germany ³⁵	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 ³⁴	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) ⁱ	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%) ^j
South Africa ^{37, 38}	6, 10, 14 w	Not stated.	>=1 dose: 81.7% (59.4–91.8%); 3 doses: 83.2 % (60.3–92.9%) ³⁸ ; <=3 doses vs 0 doses: 79.3 (65.7-87.5) ³⁷
Hib meningitis +/- other outcomes			
Denmark ⁴⁰	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 ⁴¹	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.

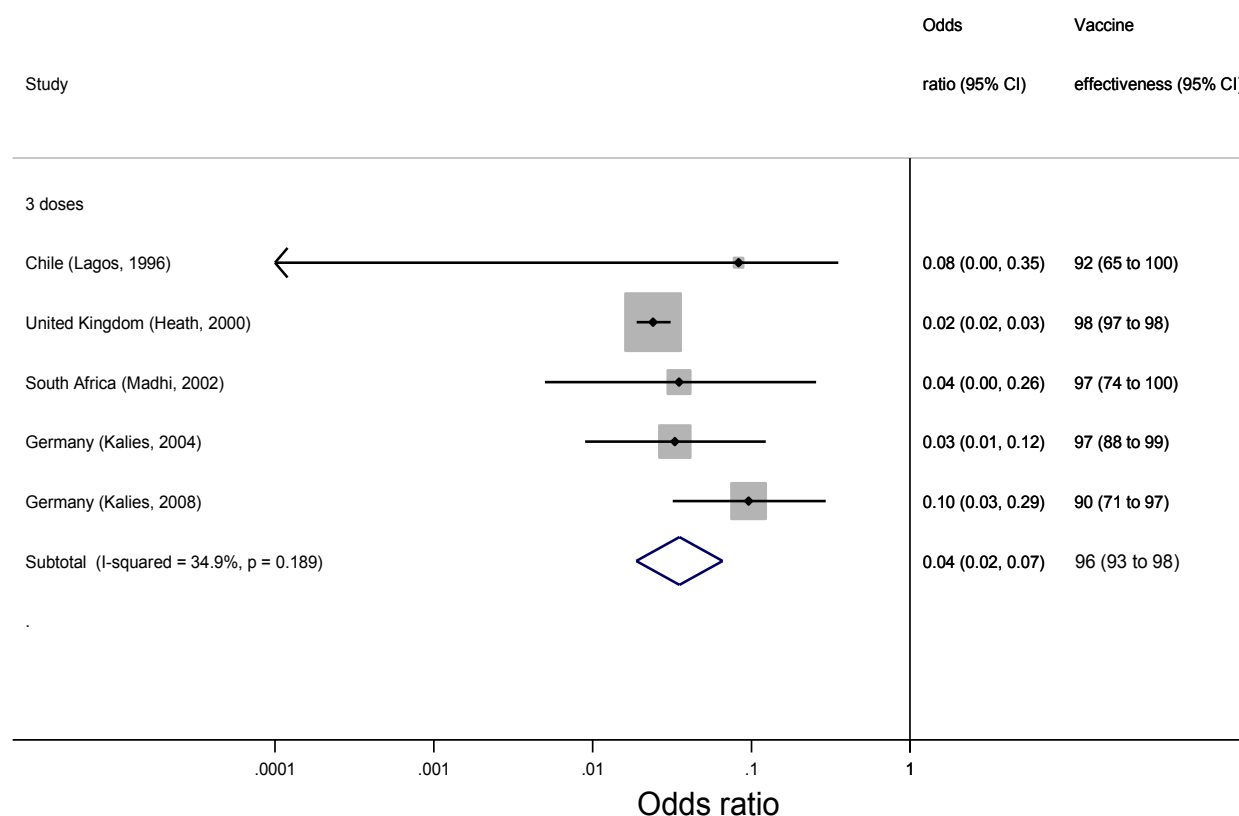
^g To quote from the paper: "A child was considered adequately immunized 2 weeks after receiving a second dose of Hib vaccine before the age of 12 months

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%)³⁴⁻³⁶. 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 %)³⁹. 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%)⁴⁰.

Sufficient data for meta-analysis of vaccine effectiveness were identified only for three doses against invasive Hib disease (Figure 5). The South African study stratified VE estimates by HIV status; only the estimate for HIV-uninfected children is included in the meta-analysis. The pooled VE estimate was 96% (95% CI 93-98%), with moderate heterogeneity ($I^2 = 34.9\%$)

Figure 5: Estimates of three-dose vaccine effectiveness against invasive Hib disease from cohort studies. Intended vaccination schedules were 6, 10, 14 weeks (South Africa); 2, 4, 6 months (Chile); 2, 3, 4 months (UK); 2, 3, 4, 11 months (Germany). Hib vaccine was given with DTwP in Chile, the UK and South Africa and with DTap in Germany



Appendix Table 4 summarises estimates of VE from cohort studies following imprecise numbers of doses.

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 was 3 or 5 months of age, as opposed to 2 months of age in the other cohort studies which reported the intended schedule^{40, 41}. In the 2004 Danish study, 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%)⁴⁰. 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-infected³⁸. 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 ranged from 90.4 to 97.6%³³⁻³⁶.

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%)³⁶. 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 %^{33-35, 37}. 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 schedule³⁵. 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: VE for the full primary series was 90.4% (70.6-96.8%), compared to 100% (52.7-100.0%) for the primary series plus booster³⁴. The point estimates from this study are also consistent with a booster compensating for an incomplete primary series, although the confidence intervals are wide due to the small number of cases. VE was 100% (95% CI 0 – 100%) for booster after

incomplete primary series vs 0 doses compared with VE of 68.4% (95% CI 19.0 – 87.6%) 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%^{35, 36, 38} 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%³⁴. 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%)³⁵ than the same number of doses of hexavalent vaccine (VE 68.4%, 95% CI 19.0 – 87.6%)³⁴, though there is some overlap in the confidence intervals for these two estimates^{34, 35}. 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%^{36, 38}. 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. Vaccine failures

Three cohort studies included data on the time since the last vaccine dose in vaccine failures^{34, 35, 37, 38}. In two of these studies (from South Africa and Germany), Hib vaccine was given with DTwP^{35, 37, 38}. All children in the German study, and all but one of the South African children not infected with HIV, developed disease within a year of receipt of their final dose of Hib vaccine (irrespective of the total number of doses, Appendix Figure 2). In the South African study, children infected with HIV appeared to develop disease later than vaccine failures who were not HIV-infected,

e.g. four HIV-infected children developed disease ≥ 2 years after receiving two or three doses^{37, 38}.

Amongst cohort studies in which Hib vaccine was given with DTaP^{34, 35}, almost all vaccine failures occurred within two years of receipt of the last dose of vaccine (Appendix Figure 3). Vaccine failures also occurred in two children who received two doses of monovalent Hib vaccine (12-23 months after the second dose) and one child who received two doses of DT-Hib (Appendix Figure 4).

The cohort study with the largest number of vaccine failures (96) did not report the time between vaccination and disease but did present the age distribution of children who developed invasive Hib disease after receiving three doses of Hib vaccine with DTwP (the third dose was intended to be given at 4 months)³³. All of these children were aged under 5 years; 37.5% were aged 12-23 months (Appendix Figure 2).

3.2.7. Potential biases in 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 schedule³⁹. 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 confounding³⁶.

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 child³³. 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)^{34, 35}. An additional quality concern in the earlier of the two German papers is that it was unclear how the vaccination status of cases was ascertained³⁵. 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 families³⁴. 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^{37, 38}. 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^{40, 41}.

3.2.8. Conclusions from cohort studies

Cohort studies provide limited data from which to compare 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. The optimum timing of a booster dose is not clear from either the VE estimates or the limited data on vaccine failures.

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^{33-35, 40, 41} and conducted sensitivity analyses around key potential biases in their data sources³³⁻³⁵. The remaining 3 cohort studies are at least moderately likely to be biased due to lack of control for confounding³⁶⁻³⁹. The evidence base for optimising 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 effectiveness⁴²⁻⁴⁵. 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 ⁴. 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 effectiveness¹ used the screening method^k to estimate vaccine effectiveness ⁴⁶⁻⁴⁸. We also identified one further screening method study ⁴⁹.

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 ≥ 13 months was estimated to be a low 57% (95% CI 42 to 67%), or 72% in a sensitivity analysis which assumed that vaccination coverage in the population was 2% than reported ⁴⁷. 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 (by Ramsay *et al*) ⁴⁷ used the same surveillance sources for invasive Hib disease, over a similar time period, as an earlier UK cohort study by Heath *et al* which we reviewed above ³³. 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 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

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

reflect 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 scheduled vaccination (66%, 95% CI 51-76%) than after two years (37% 95% CI 3-62%). This is consistent with waning immunity, although the CIs overlap. 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 ⁴⁸. 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) ⁴⁶. 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 ⁴⁹. VE for ≥ 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 ⁵⁰.

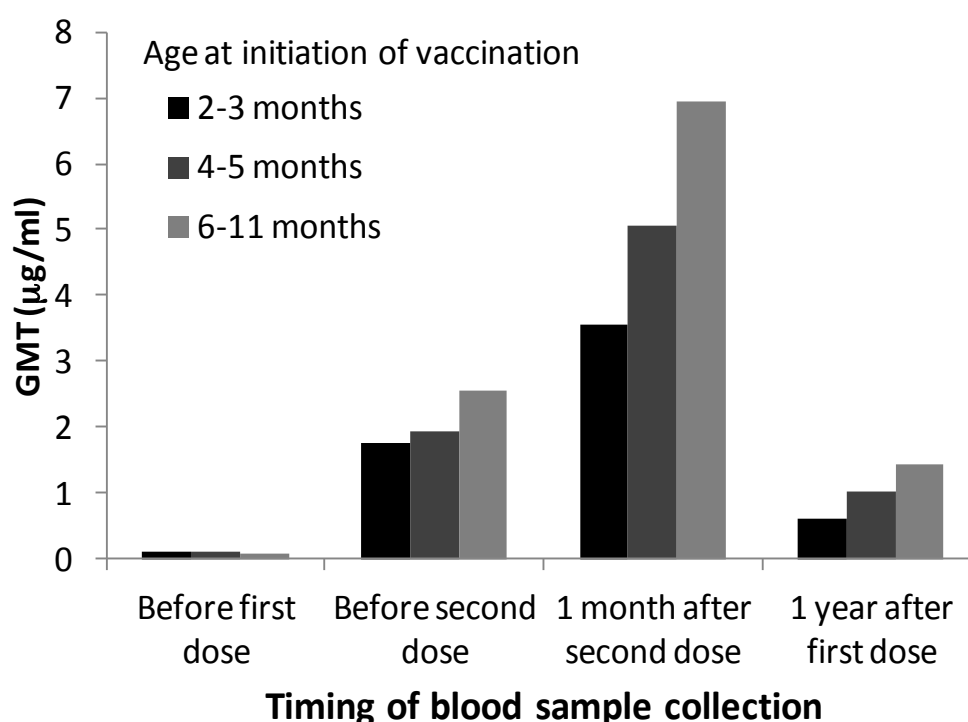
3.5.1. Number of doses in the primary series

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 ⁶ (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 ⁶. (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 ⁷, 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 ⁶ (Figure 6). 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 ⁷. 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

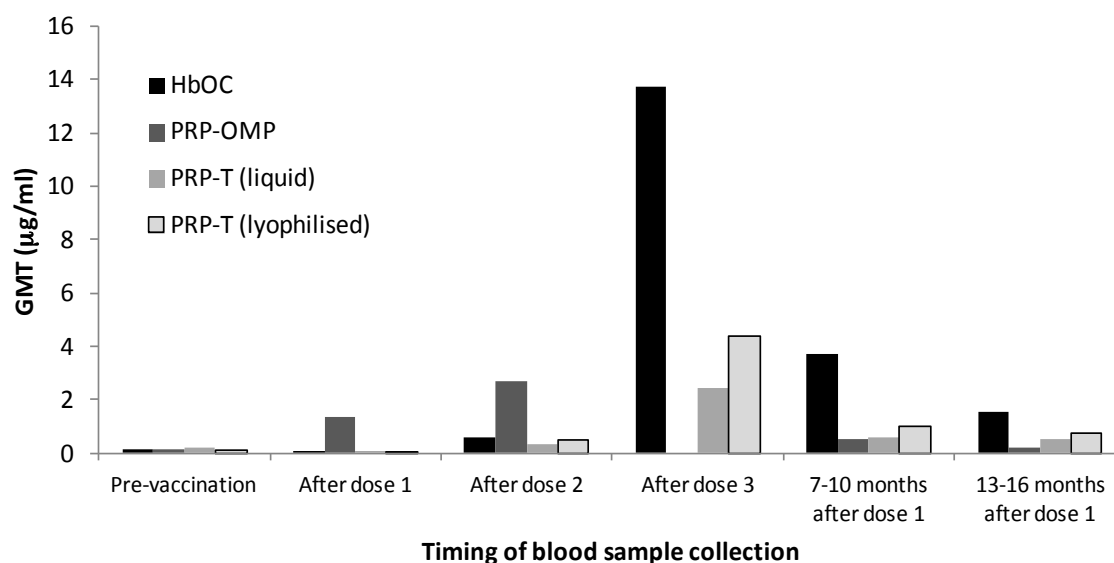
months at vaccination) or the second (91% of children aged <6 months and 92% of children aged 6-11 months) ⁷.

Figure 6: 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 ⁷.



Another study, carried out in Alaska Native infants, compared three different Hib conjugate vaccines and also found that geometric mean 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 7) ⁸. 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, although the results in Figure 7 are influenced by the timing of sample collection (samples were taken 2 months after doses 1 and 2, but 1 month after dose 3). Differences between the types of conjugate vaccines are discussed further below.

Figure 7: Geometric mean anti-PRP antibody titre following vaccination of Alaska Native infants with different Hib conjugate vaccines. Source: Bulkow et al ⁸.



3.5.2. Age at vaccination

In the US study of PRP-OMP given in two doses two months apart ⁷ 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 6). 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) ⁷.

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 age⁵¹. 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 $\geq 0.15\mu\text{g/ml}$ one at that time, and all but three had a titre $\geq 1.0\mu\text{g/ml}$.

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 booster⁶.

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 7)⁸. 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 7). 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 $\geq 0.15\mu\text{g/ml}$. At age 15-18 months (13-16 months after the first dose), the percentage of children with titres $\geq 0.15\mu\text{g/ml}$ was substantial for all vaccines: 91% for HbOC, 71% for PRP-OMP, 86% for PRP-T (liquid) and 88% for PRP-T (lyophilised)⁸.

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) ⁵². 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 ⁵².

A UK study also suggests relatively low immunogenicity of the DTaP-Hib combination ⁵¹. 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 ⁵¹. 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 ⁵¹. 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 ⁵¹.

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 ($p = 0.02$)⁵³. 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 vaccines⁸, 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)^{7, 8}. 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 study⁷, 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)⁵¹, 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.

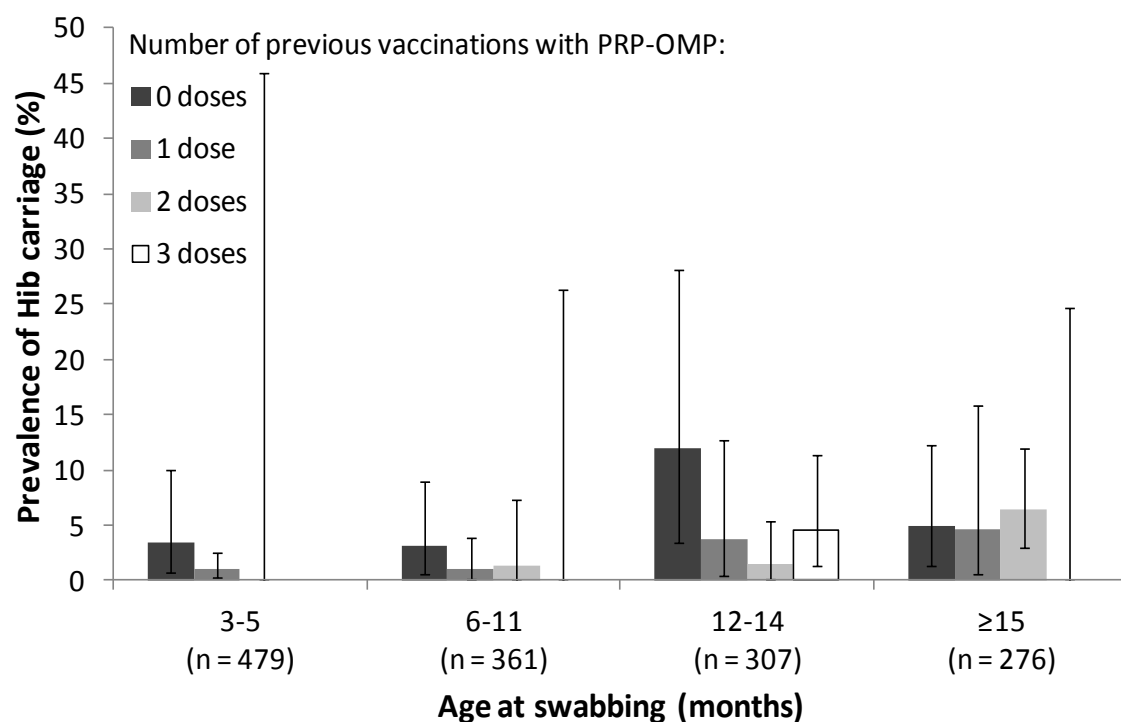
A case-control study conducted in three rural Alaskan villages found no evidence of an effect of vaccination on carriage of Hib⁵⁴. Based on 16 carriers and 32 controls (matched on age and village), 62% of carriers and 62% of controls had received at least one dose of a Hib conjugate vaccine, implying 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)⁵⁵. 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)⁵⁵.

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)⁵⁶. 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 8) 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, $p = 0.05$)⁵⁶. This implies a VE against carriage of 62% (95% CI 0 – 86%).

Figure 8: 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 al⁵⁶.



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-Hib⁵³. 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). Meta-analysis of data from case-control studies using community controls produced estimates of effectiveness after 1, 2 and 3 doses of 55% (95% CI 2-80%), 94% (95% CI 65-99%) and 94% (95% CI 18-100%), respectively, against Hib meningitis. The corresponding estimates of VE against invasive Hib disease were 59% (30-76%) and 99% (77-100%) for 1 and 3 doses (insufficient data were identified to estimate two-dose VE). Based on studies which used hospital controls, VE estimates against Hib meningitis were 53% (95% CI -14-81%), 92% (95% CI 75-97%) and 94% (95% CI 65-99%) for one, two and three doses, respectively. Meta-analysis of data from cohort studies gave a three-dose VE of 96% (95% CI 93-98%) against invasive Hib disease. Although any additional benefit of three doses compared to two may be small, in terms of protective effectiveness, other authors have summarised arguments against recommending a two dose schedule ³: 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 primary doses of DTP) ³.

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 may slightly increase vaccine 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. 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 studies¹⁹. 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).

There was substantial heterogeneity in the three estimates of three-dose VE against invasive Hib disease from case-control studies ($I^2 = 79.8\%$) and moderate heterogeneity in the five estimates of three-dose VE from cohort studies ($I^2 = 34.9\%$). The practical implications of this statistical heterogeneity are unclear, as all of the three-dose estimates which contributed to this pooled estimates were high (>90%). Most of the estimates of dose-specific VE were based on only three, and all on ≤ 5 , studies, which limits the certainty with which conclusions can be drawn. The screening method does not allow adjustment for confounding, so estimates from studies using this method must also be treated cautiously.

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 dosing interval, on effectiveness.

Few of the included studies presented VE following a booster dose, although two cohort studies suggested that a booster dose provided additional protection against invasive Hib disease, compared to a three-dose primary series without booster ^{34, 35}.

This is consistent with incidence data illustrating the impact of Hib vaccination on invasive Hib disease in the UK ⁵⁷. Hib vaccination was introduced in a 2, 3, 4 month schedule (without a booster) in the UK and, together with a catch-up campaign, substantially reduced disease incidence. Nine years after vaccine introduction, incidence began to rise, leading to a booster campaign targeting children aged 6 months to 4 years. A routine booster dose at age 12 months was subsequently introduced and the incidence of Hib disease in the UK has remained low ⁵⁷.

However, other factors besides the absence of a booster dose (including the temporary effects of the catch-up campaign and a change from DTwP-Hib to DTap-Hib) may have contributed to the observed increase in incidence ⁵⁷. A booster dose also appears to be important for HIV-infected children, as discussed in a recent systematic review of Hib epidemiology and vaccination in children with HIV ⁵⁸.

There were too few vaccine failures reported to support firm conclusions regarding waning of immunity following the Hib primary series, and thus to inform the timing of a booster. A screening study in the UK (covering periods of use of both DTap-Hib and DTwP-Hib) reported higher VE within two years of the intended age at the final dose of the primary series than more than two years since vaccination ⁴⁷. This suggests that a booster may be best given within two years of the final dose of the primary series.

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 ⁵⁰ 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 ⁵⁹. The antibody level required for protection may also vary between populations ⁵⁹. 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, manual screening of a 10% random sample of observational studies which did not pass electronic screening identified no additional eligible papers. 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.

Data on vaccine failures were examined in case they provided an indication of waning of protection over time following Hib vaccination. There are several caveats to the use of such data in this way. Firstly, time since vaccination is confounded by age. Secondly, the timing of disease onset in vaccinated children may simply reflect periods of intense transmission in the community; comparable data on the timing of disease in unvaccinated children would be needed to assess this. Thirdly, immunisation (i.e. successful vaccination) of a proportion of the population reduces

the exposure of vaccinated and unvaccinated individuals to Hib; the extent of this reduction increases with the population vaccination coverage and acts to increase the average age at infection. Comparison of vaccine failures between settings in which vaccine coverage may differ is therefore not straightforward. Finally, we did not systematically identify papers which reported data on vaccine failures (e.g. case series were not eligible for inclusion) but extracted data on vaccine failures from those studies which met the inclusion criteria relevant to assessing VE. As discussed above, the interpretation is further complicated by the small numbers of vaccine failures reported in the included studies, which prevent us drawing firm conclusions about the waning of vaccine-derived immunity and the optimum timing of a booster dose.

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. The evidence also indicates, albeit less strongly, that:

- A three dose primary series followed by a booster dose may confer slightly better protection than the same primary series without a booster (based on two cohort studies from Germany)
- A booster may also compensate for an incomplete primary series (based on one cohort study from Germany)
- Hib vaccines administered in combination with DTaP appear to be less effective against clinical outcomes than Hib vaccines administered with DTwP (based on two case-control studies from the UK). This is consistent with data suggesting lower immunogenicity of DTaP-Hib compared to DTwP-Hib vaccines.

We note that these conclusions are tentative, being based on few studies which often included small numbers of cases. The results of this review must be considered together with results of trials and impact studies, as well as with reference to programmatic considerations.

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
Invasive Hib disease													
USA ³⁰	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 ²⁶	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 ²⁸	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 ¹¹	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 ²⁷	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 ¹²	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
USA ¹⁸	2004	1 or more doses vs no Hib vaccine. Intended schedule not stated.	≥18 months	29 total; unclear how many received PRP vaccine so are not included in the analysis of conjugate vaccine.	C	4:1	3 years	P	Documented only	Not stated	Conditional logistic regression	1 - OR	Matching: age (±2 days), town of birth
The Gambia ²⁵	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 ¹³	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

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
England & Wales ¹⁴	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
Hib meningitis													
Australia ³¹	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 ¹⁸	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 ¹⁹	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 ²²	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

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
Uganda ²⁰	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
Bangladesh ¹⁷	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 ± 1 month), sex, season, distance from hospital Analysis: age, number of doses; household income
The Gambia ²⁵	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 ± 2 weeks), area of residence Analysis: unspecified covariates (data were collected on distance from health centre, overcrowding, mother's education)
Senegal ¹⁵	2011	1 or more or 2 or more doses vs no Hib vaccine. Intended schedule 6, 10, 14 weeks.	1.5-12	24	C	4 to 1	3 years 5 months	P	Verbal and documented	Combined PRP-T or HbOC, DTP, hep B	Not stated	1 - OR	Matching: age (± 28 days), neighbourhood Analysis: maternal education, number of children aged <5 years living in household
Purulent meningitis													
Rwanda ²¹	2007	2 or 3 doses vs no Hib vaccine Intended schedule 6, 10, 14 weeks	0-59	45	H (children with <20 WBC per ml 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

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
Uganda ²⁰	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 ¹⁷	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 ± 1 month), sex, season, distance from hospital Analysis: age, number of doses; household income
Aetiology negative meningitis													
Uganda ²⁰	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 ²¹	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
Radiologically confirmed pneumonia													
Brazil ²³	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 (±4 months), neighbourhood Analysis: age, sex, daycare attendance, previous flu-like illness, smokers at home, home ownership, mother's education

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
Colombia ²⁴	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 (± 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
Bangladesh ¹⁷	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 ± 1 month), sex, season, distance from hospital Analysis: age, number of doses; household income

Appendix Table 2: Estimates of vaccine effectiveness (95% CI) against Hib meningitis, invasive Hib disease and radiologically confirmed pneumonia, for imprecise numbers of doses from case-control studies.

Country	Hib meningitis			Invasive Hib disease	Radiologically confirmed pneumonia	
	≥1 dose	≥2 doses	≥3 doses	≥1 dose	≥1 dose	≥2 doses
Studies using community controls						
Uganda ¹⁹		99 (92 to 100)				
Dominican Republic ²²		94 (60 to 100)				
Brazil ²³						31 (-9 to 57)
Colombia ²⁴					47 (2 to 72)	
USA ³⁰				100 (-37 to 100)		
USA ²⁸				95 (66 to 99)		
USA ²⁷				86 (16 to 98)		
USA ¹¹				100		
Bangladesh ¹⁷	90 (34 to 100)	89 (28 to 100)			24 (-6 to 43)	34 (6 to 53)
Australia ³¹	75 (-266 to 98)					
England ¹³				96 (81 to 99)		
USA ¹⁶	95 (56 to 99)					
Senegal ¹⁵	91 (66 to 98)	96 (68 to 99)				
Studies using hospital controls						
Malawi ¹⁸	73 (39 to 88)	92 (72 to 98)	94 (70 to 99)			
Uganda ¹⁹		94 (74 to 99)				
Uganda ²⁰	65 (41 to 79)	93 (69 to 99)				

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

Country ^{ref}	Number of participants	Method of ascertainment of exposure	Assessment of clinical outcomes	Method of statistical analysis	Factors adjusted for	Main quality concerns
Invasive Hib disease						
Australia ³⁹	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 ³⁶	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	Rate ratio comparing incidence in vaccinated to unvaccinated cohort	None.	No control for confounding.
England & Wales ³³	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 ^m (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 ³⁵	Cases: 36; Non-cases: 667 ⁿ	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. ^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. Unclear how vaccination status of cases was ascertained

^l 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

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

ⁿ 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)

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

Country ^{ref}	Number of participants	Method of ascertainment of exposure	Assessment of clinical outcomes	Method of statistical analysis	Factors adjusted for	Main quality concerns
Invasive Hib disease						
Germany ³⁴	Cases: 32; Non-cases: 2893 ^p	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 ³⁵ , 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 ^{37, 38}	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 ^q	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.
Hib meningitis +/- other outcomes						
Denmark ⁴⁰	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 ^r	Rate of loss to follow-up not reported by exposure group.
Denmark ⁴¹	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 ^s	Age, calendar period, and receipt of other vaccines; age and calendar period interaction. ^t	Rate of loss to follow-up not reported by outcome. Estimates of vaccine effectiveness give in figures only.

^p 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)

^q 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.

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

^s 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.

^t 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.

Appendix Table 4: *Estimates of vaccine effectiveness (95% CI) against invasive Hib disease for imprecise numbers of doses, from cohort studies*

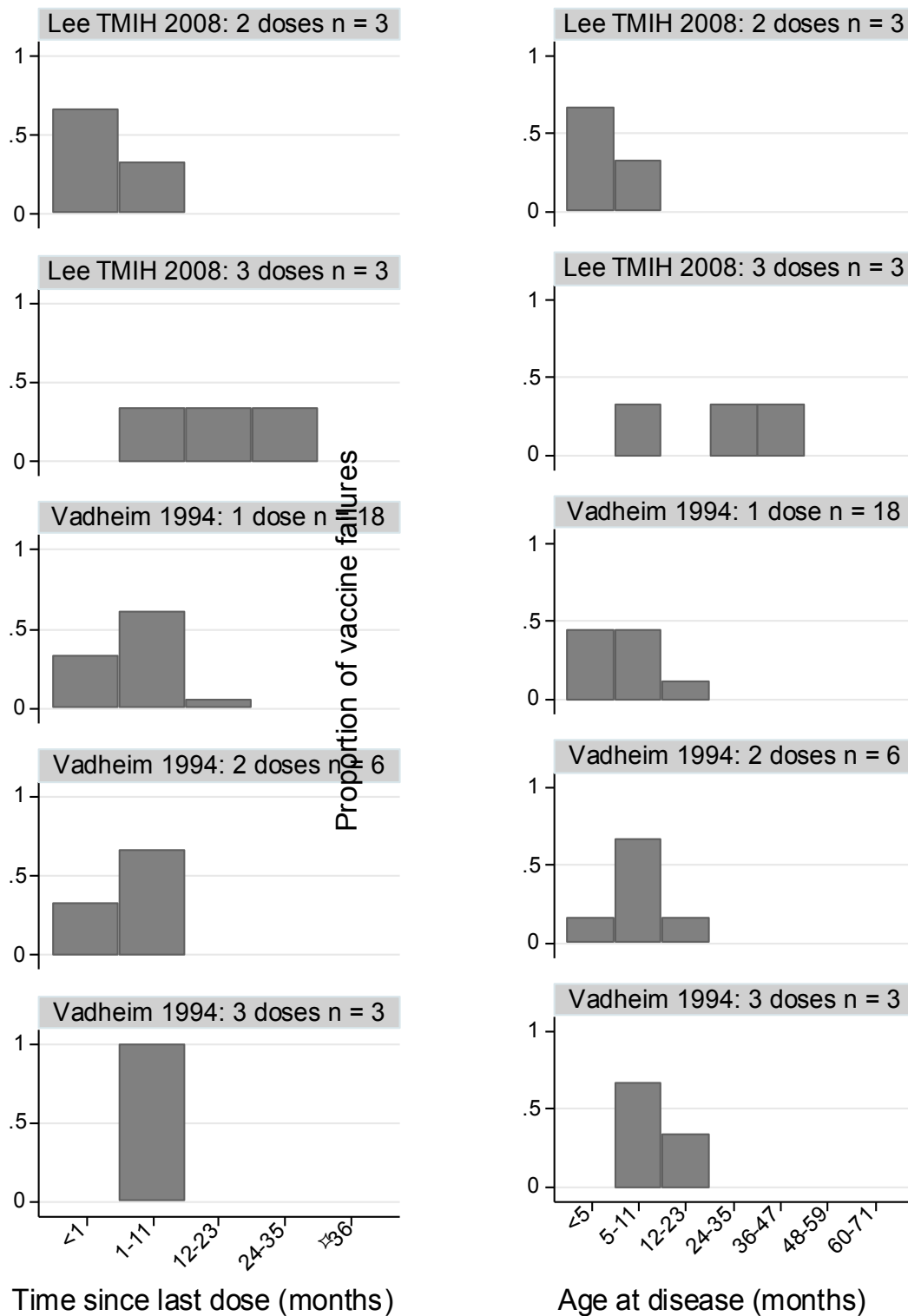
Country	≥1 dose	1-2 doses	≤2 doses	≤3 doses
Australia* ³⁹			92 (80 to 97)	
Germany ³⁵		90 (67 to 97)		
Germany ³⁴		68 (19 to 88)		
South Africa ^{37, 38}	82 (59 to 92) [†] 79 (66 to 88) [‡]			79 (66 to 88)

* ≥2 doses before the age of 12 months, or ≥1 dose after the age of 12 months.

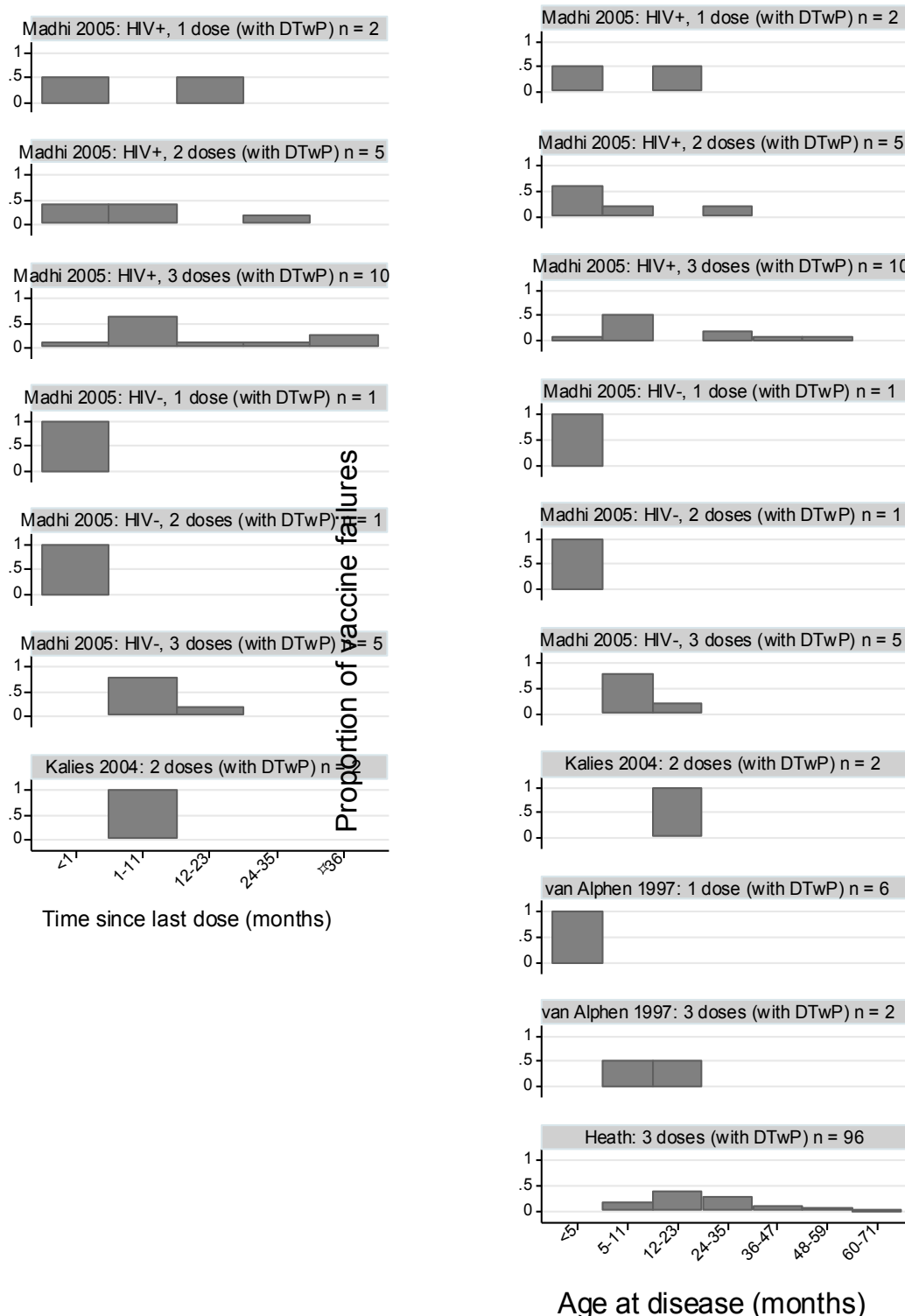
[†] At age <1 year

[‡] At age <2 year

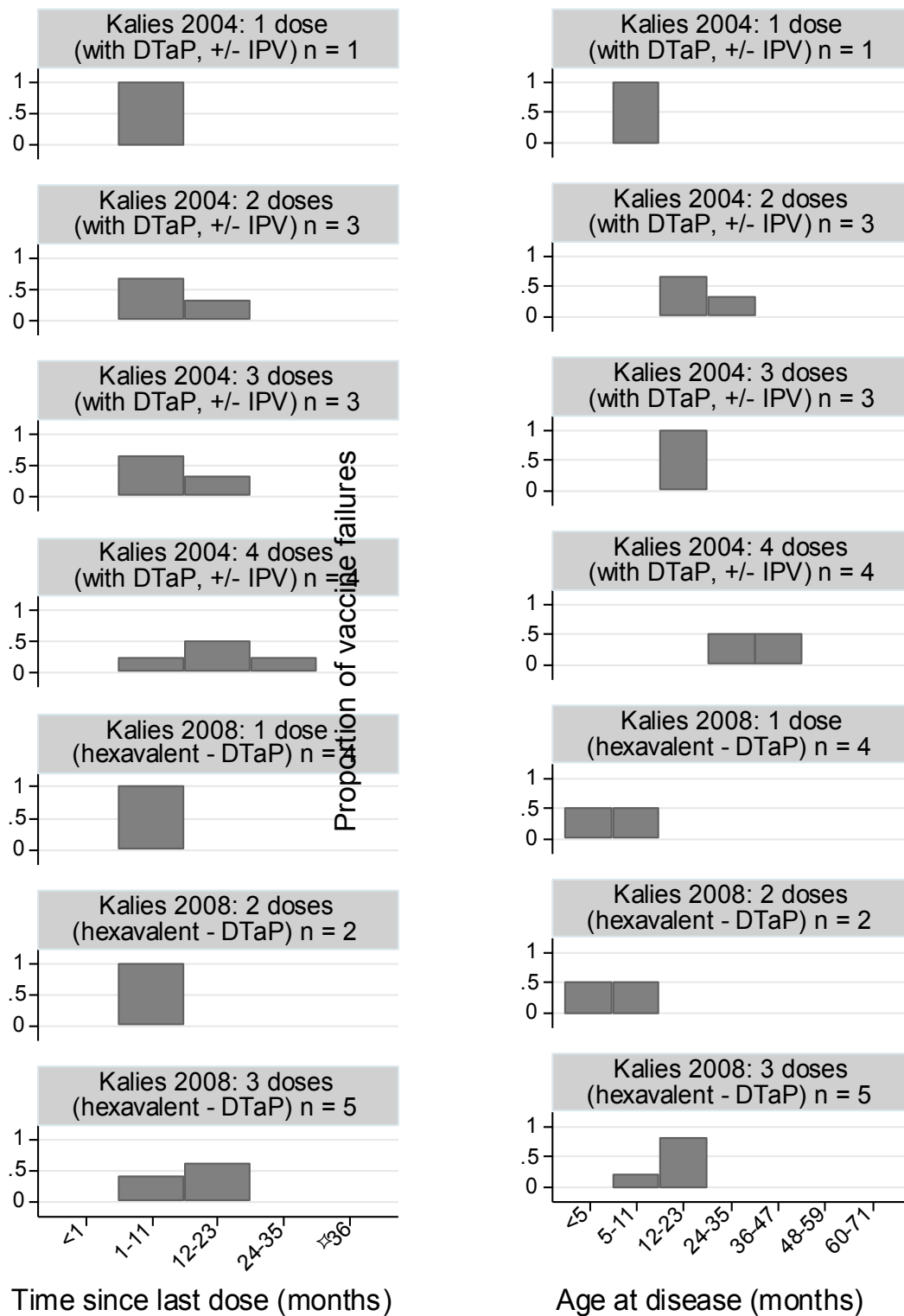
Appendix Figure 1: Distributions of time since last vaccine dose and age at disease onset for vaccine failures reported in case-control studies. Hib vaccine was used with DTWP in the Lee study; other vaccines used in the Vadheim study were not stated.



Appendix Figure 2: Distributions of time since last vaccine dose and age at disease onset for vaccine failures reported in cohort studies in which Hib vaccine was given with DTwP.



Appendix Figure 3: Distributions of time since last vaccine dose and age at disease onset for vaccine failures reported in cohort studies in which Hib vaccine was given with DTaP.



Appendix Figure 4: Distributions of time since last vaccine dose and age at disease onset for vaccine failures reported in cohort studies in which Hib vaccine was given alone or with pertussis vaccines other than DTwP or DTaP.

