EXPANDING THE POTENTIAL IMPACT OF *Haemophilus influenzae type b* VACCINES (Hib) BY OPTIMIZING IMMUNIZATION SCHEDULES

POLICY QUESTION

What are optimal immunization schedules for *Haemophillus Influenzae type b* vaccines (Hib) for children living in different epidemiological settings?

Haemophilus influenzae type b (Hib) conjugate vaccines have been in use for over 20 years with remarkable success. By 2011, 179 (92%) of countries worldwide had introduced Hib containing vaccines with a further 6 (3%) countries planning to introduce them in 2012. An additional 4 (2%) plan to introduce them in 2013. Five (3%) countries (China, Equatorial Guinea, Republic of Korea, South Sudan, Thailand) have no current plans to introduce Hib containing vaccines. However, there are informal reports regarding widespread use of Hib containing vaccines in the private sector of these countries. WHO has estimated that 43% of infants received at least three doses of Hib containing vaccine in 2011.

Number of doses: at least 3 doses

Available evidence suggests that three doses are needed to achieve high vaccine efficacy and effectiveness. These can be administered as three primary doses without a booster (3p+0) or as two primary doses plus a booster (2p+1). The marginal increase in effectiveness is considerably greater between first and second, than between second and third dose. Choice of vaccine schedule depends on the age-distribution of Hib disease in infants, the potential to achieve high and timely coverage of each dose and establish contacts for the delivery of vaccines and other health interventions (see further information on page 5).

Age at administration of first dose: at 6 weeks or soon thereafter

Limited available evidence suggest that schedules starting earlier (i.e. at 4-6 weeks of age) are comparable to schedules starting later (i.e. $\geq$ 2 months of age).Trade-offs may exist between initiating vaccination earlier versus later in infancy in settings where Hib disease epidemiology data suggest that a large proportion of cases occur before 8 weeks of age. Another consideration in the choice of the age at first dose is the recognition of delays with the actual age at vaccination. There is no evidence to firmly determine the age limit for initiating vaccination but three years seems appropriate as it is in line with the evidence on the age distribution of Hib disease cases in the pre-vaccine era (see further information on page 21).

Interval between doses: 4-8 weeks between primary doses

There is no strong evidence that effectiveness is significantly different in schedules with short (i.e. 4 weeks) versus longer (> 8 weeks) intervals between primary doses. There is no evidence of significant differences in effectiveness with various intervals between the primary doses and the booster dose. Trade-offs exist as schedules with shorter interval may allow children to complete primary series earlier, which may be important if appreciable Hib disease occurs in very young infants (see further information on page 24).

Immunization of children in emergency settings

Limited data for children < 12 months of age suggest that at least one dose should be given and, if conditions permit an additional dose should be provided. For young infants (< 6 months of age) OMP has reported higher immunogenicity and therefore is preferable (see further information on page 28).

Immunization of HIV infected children

Limited evidence suggest that they would benefit from receiving a booster dose regardless of the number of primary doses received and irrespective of whether or not the child is receiving anti-retroviral therapy. There is no evidence to firmly determine the upper age limit for additional booster doses but five years seems appropriate as it is in line with the evidence on the age distribution of Hib disease cases in the pre-vaccine era (see further information on page 30).

Type of evidence: randomized clinical trials (RCTs), observational studies, studies to assess disease epidemiology, coverage surveys and impact evaluation studies post vaccine introduction, mathematical model estimates
Quality: Varies across studies. Not formally assessed for the mathematical model.
Caution: Limited evidence from studies including direct comparisons between schedules; limited data from studies including Hib disease as one of the outcomes. Model estimates include the effect of waning of immunity and of herd immunity, but it is not a dynamic model.

This summary includes

X THIS SUMMARY DOES NOT INCLUDE DETAILED INFORMATION ON OPERATIONAL ISSUES

Burden of Hib disease[1]

Haemophilus influenzae type b (Hib) is a common cause of serious diseases in children worldwide. Its most frequent manifestations are pneumonia and meningitis, but it can also cause infections of the epiglottis, soft tissues, bones, joints, and other sites.

It has been estimated that in 2000, Hib caused 8.13 million serious illnesses (UR 7·33–13·2 million) and 371 000 deaths (247 000–527 000) in children younger than 5 years. Of the deaths, 8100 (5600 – 10 000) occurred in HIV-infected children. Hib disease accounted for 5·6% (3·9–7·7%) of the estimated 6·6 million post-neonatal child deaths and 16% of the estimated 1·8 million pneumonia deaths in HIV-negative children.

Because most estimated deaths occurred in developing countries in Africa and Asia, Hib disease contributed to the disparity in child mortality between developed and developing countries. Just ten countries, all in Asia or Africa, account for an estimated 61% of childhood Hib deaths. These countries include those with high-mortality rates but small populations and those with moderate-mortality rates but large populations. Hib is also a major cause of child morbidity. It was estimated that, in the absence of vaccination, 1·3% of children younger than 5 years (1·2–2·1%) would have had an episode of Hib pneumonia each year—about 5·0% of cases of clinical pneumonia in 2000.

Epidemiology of Haemophilus influenzae type b (Hib) meningitis in the pre-vaccine era[2]

In 2002, WHO published a comprehensive literature review on *Haemophilus influenzae* type b (Hib) meningitis in the pre-vaccine era. Overall, Hib contributed an average of 42.4% to all < 5 year bacterial meningitis cases with known aetiology, ranging from 9% of neonatal meningitis cases to 44.2% of meningitis cases in children < 2 years of age. It should be noted that the majority of cases of Haemophilus meningitis in neonates are caused by non-capsulated strains of H. influenzae.

The cumulative distribution shows that nearly 60% of all cases in children < 5 years occurred before age 12 months and that 35.6% of all < 5 year Hib meningitis cases occurred in children 6–11 months of age, with roughly equivalent contributions of the age groups 1–5 months and 12–23 months (22.6% and 23.8%, respectively). Only 1.6% of < 5 year cases occurred in neonates.

The percentage of studies with > 60% of cases in children 0–11 months of age was 100% in SEAR (n=5), 92% in EMR (n=13), 90% in AFR (n=19), 53% in WPR (n=19), 50% in AMR (n=24), and 8% in EUR (n=38). The mean case-fatality rate for children with Hib meningitis was 13.8%, with a median of 10%, and a range of 0% to 65%. The mean case-fatality rate was 17.3% for developing countries, compared with 3.2% for industrialized countries. By region, mean case-fatality rates ranged from a low of 4.1% in EUR to a high of 27.6% in AFR.

Age at Hib disease, and the impact of vaccination.[3]

Aim: To seek existing data on age at invasive Hib disease and Hib meningitis, with age groups small enough for assessment of the population impact of vaccination according to different schedules.

Methods: 1: Age at Hib disease i) Re-examine an earlier literature review of the burden of Hib disease covering the period 1980-2005, and conduct a literature review for the period 2005-12; ii) identify papers with relevant data on age at Hib and/or authors' contact details; iii) seek authors' cooperation in supplying age distributions or raw data; iv) tabulate %s aged < 6m and < 12m if available; v) for finely stratified datasets, fit gamma distributions to summarise results from each population and deal with reporting anomalies; vi) fit regression models for each gamma parameter with independent variables such as GDP (World Bank); and vii) use these models to estimate age distributions in countries without data. A case of invasive Hib disease was defined as a child <5 years of age with H. influenzae type b isolated from a normally sterile site (i.e., blood, cerebrospinal fluid (CSF), or pleural fluid, etc.). A case of Hib meningitis was defined as a child <5 years of age with laboratory-confirmation by culture or identification (i.e. by Gram stain or antigen detection methods) of Hib in the CSF or from the blood, in a child with a clinical syndrome consistent with bacterial meningitis (WHO, 2003).

Methods 2: Age at vaccination: i) Obtain data from recent DHS and MICS surveys; ii) impute missing data and carry out survival analyses to estimate age-specific coverage; iii) fit lognormal curves to the age-coverage curves; iv) fit regression models for each lognormal parameter, with independent variables including GNI & skilled birth attendants (World Bank), the difference between coverage of DPT1 and DPT3, and WHO-CHOICE subregion (WHO); v) use these models to estimate timeliness in countries without surveys.

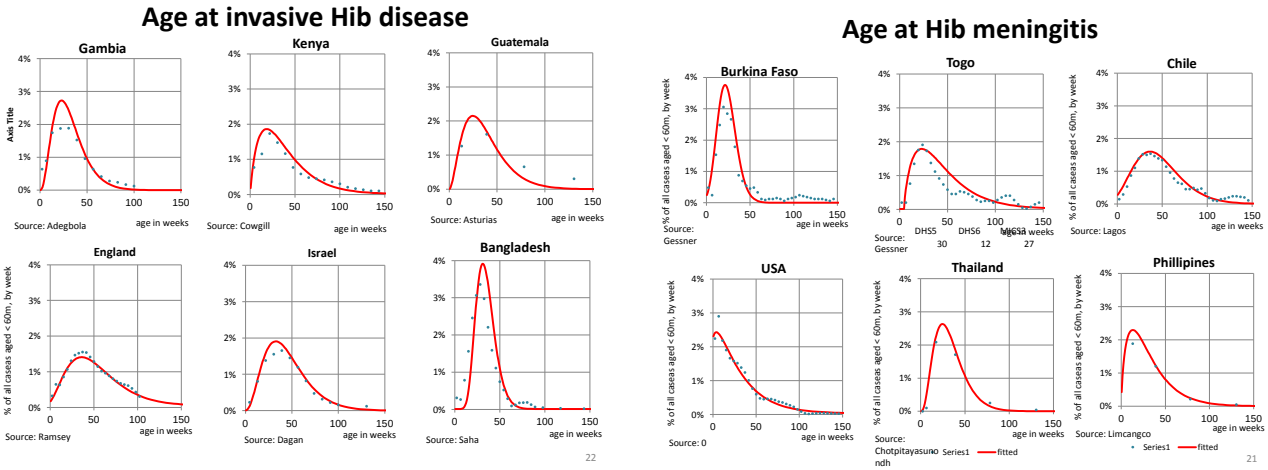
Methods 3: Impact of schedules: Use an Excel model to estimate the implications of changes in the vaccination schedule (2 + 0, 2+1, 3+0) and timeliness (observed delays vs on time) for numbers of deaths saved, using different scenarios for vaccine effectiveness, waning and herd immunity.

Results 1: age at Hib disease. The earlier literature review included 209 studies, of which 97 had relevant data on Hib and 35 had author contact details. The new review produced 1492 studies, 28 with relevant Hib data and 11 with author contact details. A further 14 investigators were identified as having unpublished data. Attempts were made to contact 60 authors/investigators, and 7 (12%) sent more detailed data. We found 16 published studies, and 6 unpublished datasets, with age bands <=3m, and 17 of these included more than 100 cases aged < 60m.
In 67 studies there were data from studies with n > 30 on the percentages of all cases aged < 60m who were also aged < 6m and < 12m. Results from these are shown below (table (*i*) and figure (a)).

Table (i) Age at invasive Hib disease and Hib meningitis: studies reporting % < 6m and % < 12m

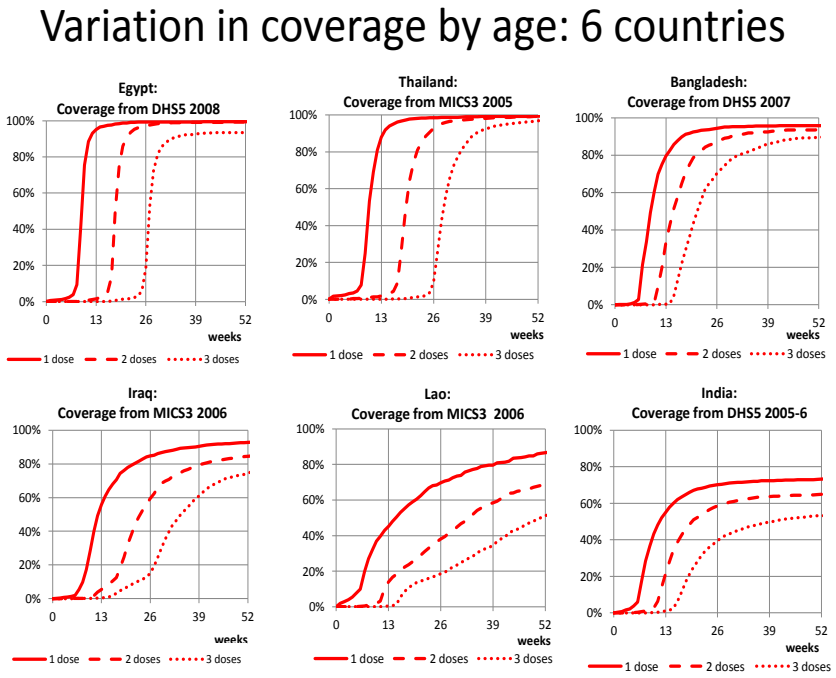
				median n of cases aged < 60m	*of all cases aged < 60m*	
	Region	*number of studies*	*median year study started*		*median % aged < 6m*	*median % aged < 12m*
Invasive Hib	*AMRO*	*1*	*1992*	*180*	*41.5%*	*74.4%*
	EMRO	*3*	*1993*	*258*	*39.5%*	*75.0%*
	EURO	*8*	*1990*	*193*	*17.0%*	*35.3%*
	SEARO	*1*	*1993*	*517*	*39.3%*	*92.5%*
	WPRO	*5*	*1992*	*212*	*19.2%*	*41.0%*
	overall	*18*	*1990*	*196*	*22.0%*	*60.4%*
Hib meningitis	*AFRO*	*10*	*1990*	*52*	*37.0%*	*73.1%*
	AMRO	*10*	*1989*	*200*	*26.0%*	*60.2%*
	EMRO	*3*	*1999*	*51.5*	*39.7%*	*84.6%*
	EURO	*7*	*1981*	*151*	*15.3%*	*46.3%*
	SEARO	*4*	*1993*	*64*	*26.5%*	*85.5%*
	WPRO	*5*	*1994*	*79*	*26.8%*	*59.3%*
	overall	*39*	*1989*	*81*	*26.5%*	*69.7%*

Figure (a): Age at invasive Hib disease & meningitis: studies with age bands of 2m or less, and fitted curves.



Results 2: age at vaccination. There were usable data in 42 DHS and 25 MICS surveys. Examples of the age-coverage are shown in Figure (b).

Figure (b): Age at vaccination: data from selected DHS and MICS surveys



Summary of the evidence

The information in this section was extracted from: (T) randomized clinical trials[4]; (O) observational studies[5] and; (L) long-term impact evaluations[6].

In the tables below ITT = "intention to treat". In each cell the findings are reported in this order. The overall conclusion on the available evidence for each outcome of interest is presented at the top of each cell in bold. Full details of analyses and studies descriptions are available in each individual review report.

Effect of number of doses of Hib vaccine on selected outcomes: Available evidence suggests that 3 doses are needed to achieve high vaccine efficacy and effectiveness[1]. These can be administered as three primary doses without a booster (3p) or as two primary doses plus a booster (2p+1). There is no evidence to firmly determine the upper age limit for initiating vaccination but three years seems appropriate as it is in line with the evidence on the age distribution of Hib disease cases in the pre-vaccine era.

Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Invasive Hib disease	**Limited evidence to conclude on the superiority of either schedule** **(T)** No data from RCTs that directly compare these 2 schedules. Data from RCTs that compared 2p vs. 0 (USA1)[7] and 3p vs. 0 (USA2[8], USA3[9], Gambia4[10] and Chile3[11]) suggest that there is no clear evidence on the superiority of either schedule. Reported VE from ITT analyses (figure 1) for 2p vs. 0 are 95% (95%CI 72-99) and, for 3p vs. 0 were 84% (95%CI 59, 94) and 90.2% (95%CI 74.5, 100). Similar results were reported in per protocol analyses (figure 2) in USA1[7], Gambia 4[10] and Chile3[11] trials.	**Limited evidence to conclude on the superiority of either schedule** **(T)** No data from RCTs	**Limited evidence to conclude on the superiority of either schedule** **(T)** No data from RCTs	**Two or three doses of Hib vaccines are highly efficacious and effective against invasive Hib disease** **(T)** 4 RCTS: Gambia4[10], USA2[8], USA3[9] and Chile3[11]. Reported VE from ITT analyses for 3p vs. 0 were 84% (95%CI 59, 94) and 90.2% (95%CI 74.5, 100). The combined VE estimate for ITT analyses (figure 1) was 83% (95% CI 72, 89). Reported VE from per protocol analyses range from 92% to 95% (figure 2). However, it is important to note that the 2p vs. 0 studies used only PRP-OMP[2]. NB: Chile3 has an element of randomisation and therefore was not excluded from the RCT review. However, randomisation in this case would not have contributed to balancing the groups and therefore this study is assessed as being at risk of bias. Additionally, the clustered assignment of this study means it will measure direct and indirect effects of vaccination, so its results are

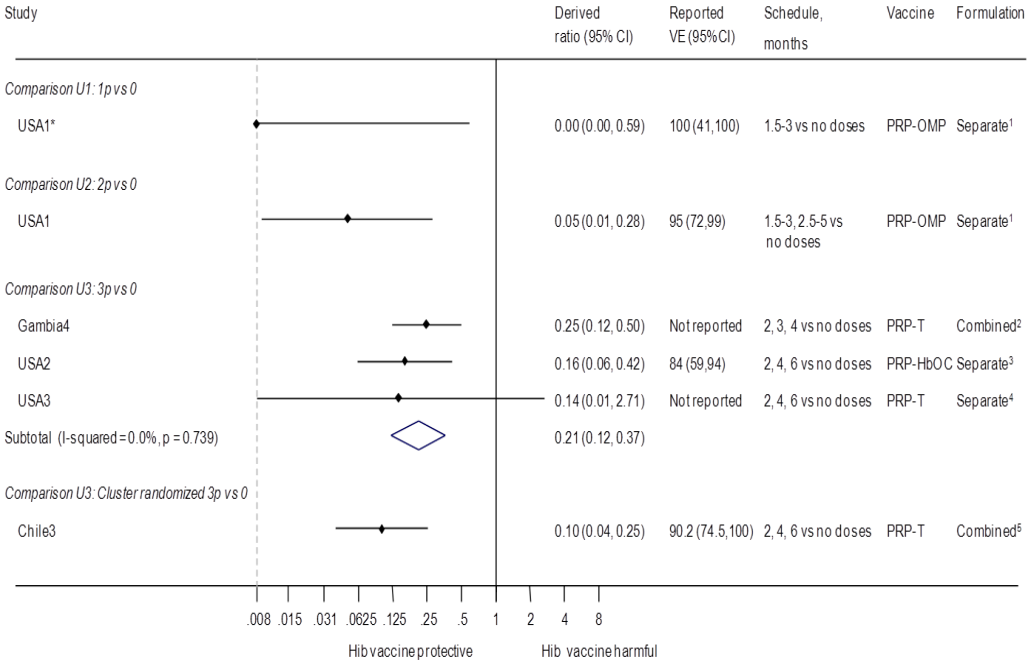
[1] However, one study randomized infants to 2 doses of Hib vaccine (PRP-OMP) or placebo[7], and followed participants until 18 months of age. This study reported ITT VE against invasive Hib disease of 95% (95%CI 72, 99) and PP VE against invasive Hib disease of 93% (95%CI 53, 98). ITT VE against Hib meningitis was calculated by reviewers to be 96% (95%CI 37, 100). Pneumonia was not reported in this study as a separate outcome". Other additional information: invasive disease with pneumonia was reported, but vaccine efficacy against pneumonia (with or without invasive disease) was not assessed in this study; vaccine doses were intended to be given at 1.5-3m and 2.5-5m; this study was in a population of Navajo and Apache infants.

[2] Chile3 has an element of randomisation and therefore was not excluded from the RCT review. However, randomisation in this case would not have contributed to balancing the groups and therefore this study is assessed as being at risk of bias. Additionally, the clustered assignment of this study means it will measure direct and indirect effects of vaccination, so its results are reported separately from the individually randomised trials (see figure1). The VE for the individually randomised studies (measuring direct effects) is 79% (95%CI 63-88) as compared to the 83% (95% CI 72, 89) reported here. The former value might be more appropriate to report here although it does not differ greatly to the estimate including Chile3.

Outcome of interest	Number of doses			
	3p vs. 2p	3p vs. 2p+1	3p vs. 3p+1	3p vs. 0
				reported separately from the individually randomised trials (see figure1). The VE for the individually randomised studies (measuring direct effects) is 79% (95%CI 63-88) as compared to the 83% (95% CI 72, 89) reported here. The former value might be more appropriate to report here although it does not differ greatly to the estimate including Chile3. One study randomized infants to 2 doses of Hib vaccine (PRP-OMP) or placebo7, and followed participants until 18 months of age. This study reported ITT VE against invasive Hib disease of 95% (95%CI 72, 99) and PP VE against invasive Hib disease of 93% (95%CI 53, 98). ITT VE against Hib meningitis was calculated by reviewers to be 96% (95%CI 37, 100). Pneumonia was not reported in this study as a separate outcome". Other additional information: invasive disease with pneumonia was reported, but vaccine efficacy against pneumonia (with or without invasive disease) was not assessed in this study; vaccine doses were intended to be given at 1.5-3m and 2.5-5m; this study was in a population of Navajo and Apache infants.

Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Invasive Hib disease	**(O)** No data from observational studies that directly compare these 2 schedules. In case control studies, VE after two or more doses ranged from 86% (95% CI 16-98%)[12] to 100% (95% CI 68-100%)[13]. In cohort studies, VE after 3 doses ranged from 90.4% (95% CI 64.8-100%)[14] to 97.6% (95% CI 96.9-98.1%)[15] (figure3). **(L)** No data.	**(O)** No data from observational studies that directly compare these 2 schedules. Data from one cohort study suggested that a booster dose could compensate for an incomplete primary schedule (within a three dose primary schedule)[14]: VE was 100% for booster after incomplete primary series vs. 0 doses compared with VE of 68.4 % for incomplete primary series without booster vs. 0 doses. In 4 cohort studies, VE after 3 doses ranged from 90.4% (95% CI 64.8-100%)[14] to 97.6% (95% CI 96.9-98.1%)[15]. **(L)** 2p+1 has been used effectively in a few European countries and 3p schedules have been used in several African and Latin American countries but there are no specific impact data on Hib invasive disease.[6]	**(O)** No data from observational studies that directly compare these 2 schedules. **(L)** 3p+1 has been used effectively in a many industrialized countries. Limited data on the effectiveness of 3p against invasive disease. Most studies have used Hib meningitis as the primary endpoint. 3p schedules have shown good effectiveness against meningitis in several African and Latin American countries.[6]	**(O)** Effectiveness after two or more doses ranged from 86% (95% CI 16-98%)[12] to 100% (95% CI 68-100%)[13]in 4 case-control studies Two case-control studies reported 3-dose VE against invasive Hib disease; both estimates were 94% (95%CI 62-99% and 68-99%)[13,16] (figure 4). In cohort studies, VE after 3 doses ranged from 90.4% (95% CI 64.8-100%)[14] to 97.6% (95% CI 96.9-98.1%)[15] (figure3). **(L)** No data.

Figure 1: Invasive Hib disease, intention to treat analyses, all available schedules, from RCTs

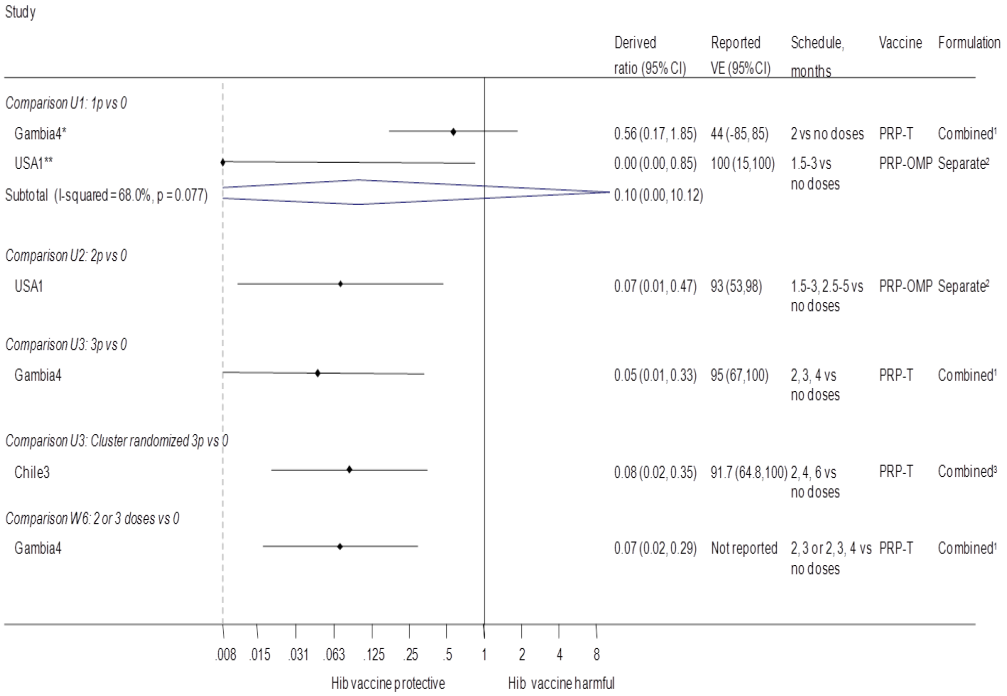


For the purposes of this graph, "intention to treat" is used to mean analyses where no individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – Haemophilus influenzae type b vaccine; VE - vaccine efficacy

* USA1 - onset before second dose

1 DTP and oral polio given at the same time but separately from Hib vaccine; 2 DTP/Hib. Not stated if aP or wP; 3 Other vaccines not described; 4 DTP/Hib. Not stated if aP or wP; 5 DTP/Hib. Not stated if aP or wP

Figure 2 : Invasive Hib disease, per protocol analyses, all available schedules, from RCTs



For the purposes of this graph, "intention to treat" is used to mean analyses where no individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – Haemophilus influenzae type b vaccine; VE - vaccine efficacy

*Gambia 4 - onset after one dose. Onset before second dose also available: "Efficacy against all invasive disease after a single dose of vaccine was 44% (PRP-T vaccinees five, controls nine [95% CI 85, 85]). Amongst children who had received one dose only less than 56 days before their admission there were two cases of invasive disease in the vaccine group and seven in the control group. Thus, the short-term vaccine efficacy after one dose was 71% (CI 50,97)."

** USA1 - onset before second dose. 1 DTP/Hib. Not stated if aP or wP; 2 DTP and oral polio given at the same time but separately from Hib vaccine; 3 DTP/Hib. Not stated if aP or wP. OPV at same time.

Figure 3: Estimates of effectiveness of 3 doses of Hib vaccine against invasive Hib disease, from cohort studies.

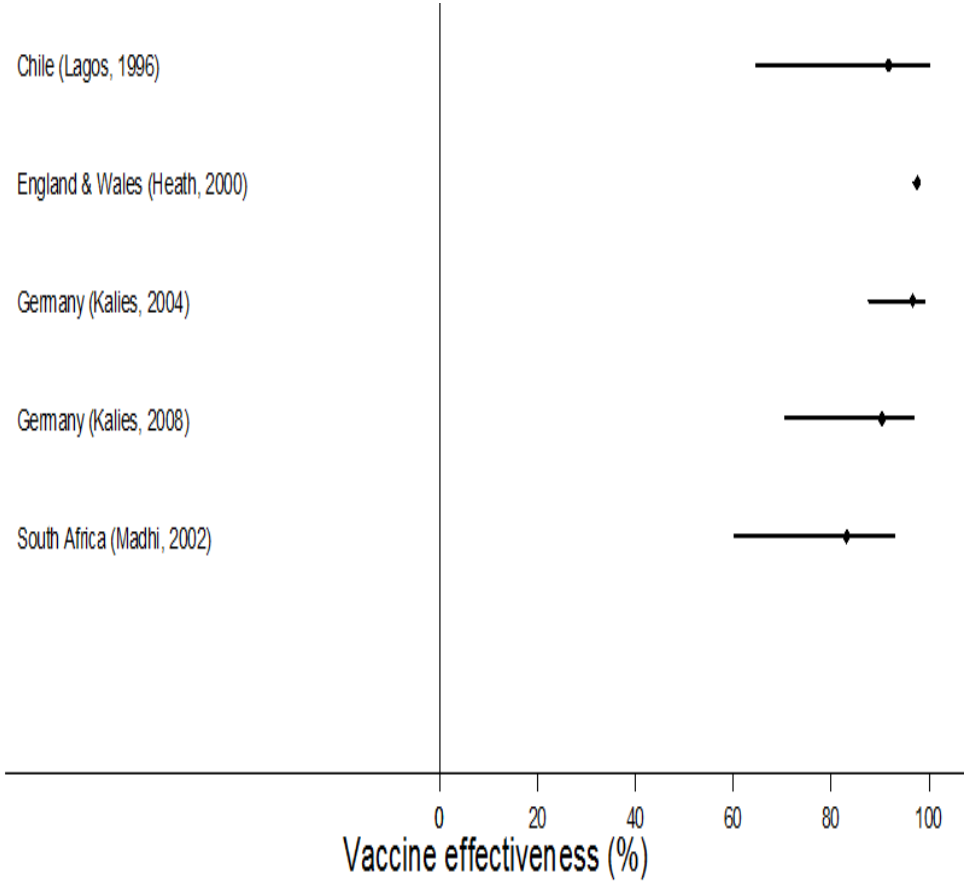
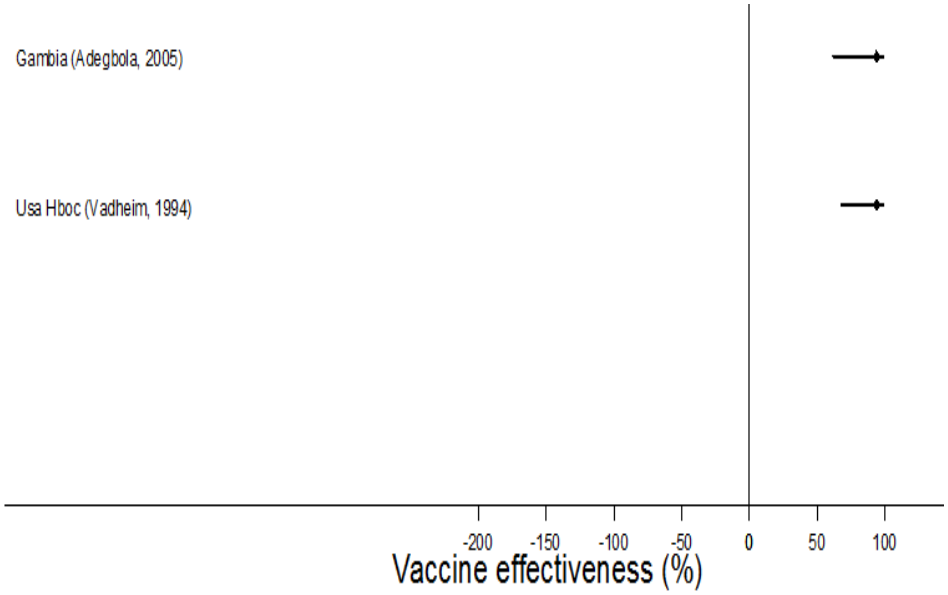
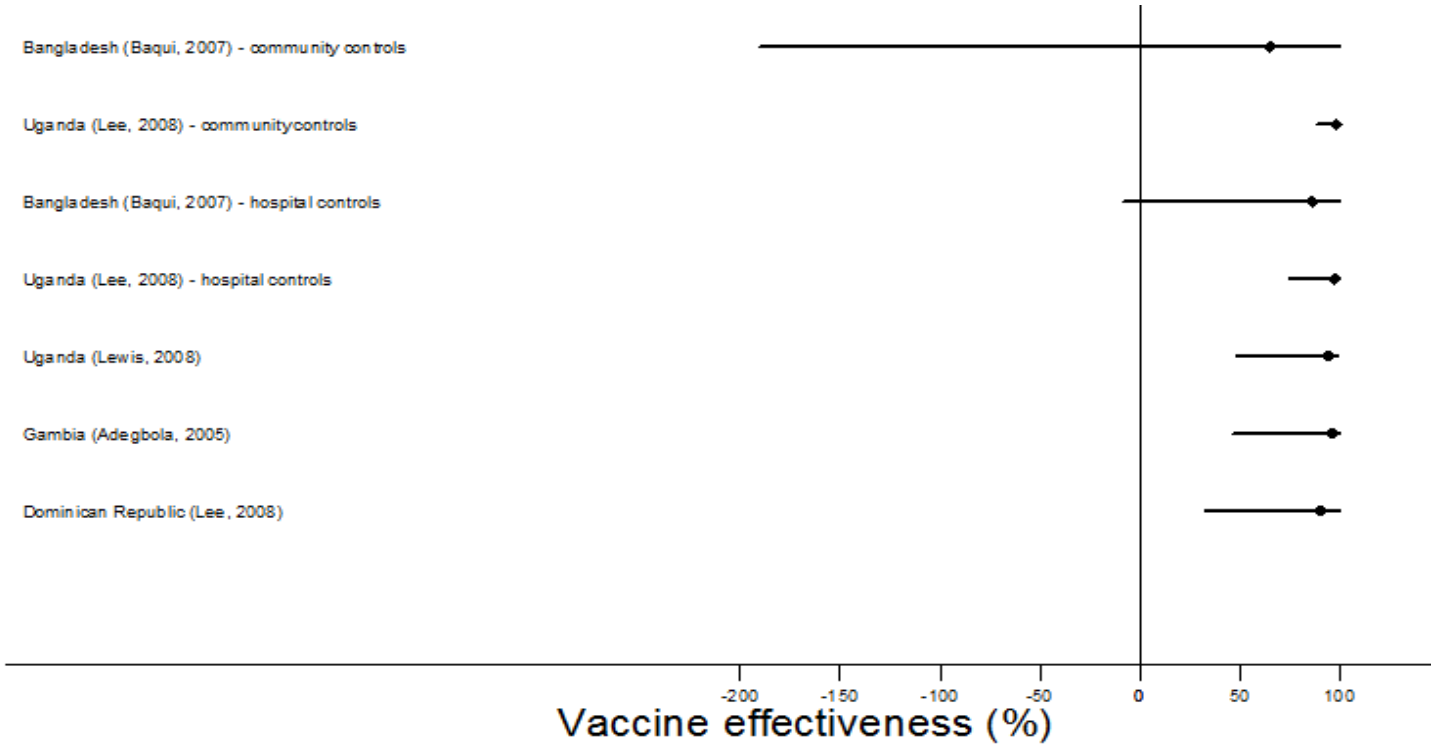


Figure 4: Estimates of effectiveness of 3 doses of Hib vaccine against invasive Hib disease, from case-control studies.



Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Hib Meningitis	**Limited evidence to conclude on the superiority of either schedule** (**T**) No data from RCTs that directly compare these schedules. One study randomized to 2p vs. 0 (USA1)[7] but did not report VE. ITT VE calculated by reviewers was 96% (95%CI 37-100%). Three RCTs randomized to 3p vs. 0. Two of these reported ITT VE and values were 86%[17] and 91%[11] (no confidence intervals reported). The ITT VE calculated by the reviewers for the remaining study examining 3p vs. 0 was 67% (95%CI 22-86)[10]. **(O)** In 6 datasets from 5 case-control studies, 2-dose VE ranged from 87% (95% CI 14-100%)[18] to 99% (95% CI 90-100%)[19.] In 7 datasets from 5 case-control studies, 3-dose VE ranged from 65% (95% CI -190 to 100%) [22] to 98% (95% CI 89-100%)[19]. In one cohort study, 3-dose VE was 99% (95% CI 95–100%) and 2-dose VE 99% (96-100%)[20]. (**L**) No data.	**Very limited evidence to conclude on the superiority of either schedule** (**T**) No data from RCTs (**O**) No data from observational studies (**L**) 2p+1 has been used effectively in a few European countries. 3p schedules have shown good effectiveness against meningitis in several African and Latin American countries. [6]	**Very limited evidence to conclude on the superiority of either schedule** (**T**) No data from RCTs (**O**) No data from observational studies **(L)** 3p+1 has been used effectively in a many industrialized countries. Limited data on the effectiveness of 3p against invasive disease. Most studies have used Hib meningitis as the primary endpoint. 3p schedules have shown good effectiveness against meningitis in several African and Latin American countries.[6]	**Two or three doses of Hib vaccines are highly efficacious and effective against invasive Hib meningitis** (**T**) Three RCTs randomized to 3p vs. 0. Two of these reported ITT VE and values were 86%[21] and 91%[11] (no confidence intervals reported). The ITT VE calculated by the reviewers for the remaining study examining 3p vs. 0 was 67% (95%CI 22-86)[10]. (**O**) The estimated effectiveness after two or more doses ranged from 65% (95% CI -190 to 100%)[22] to 99% (95% CI 92-100%)[19]against Hib meningitis, in 8 datasets from 6 case-control studies (figure 5). Excluding the estimate of 65%, the lowest reported effectiveness against Hib meningitis after 2 or 3 doses was 87% (95% CI 14-100%)[18]. One cohort study[20] reported VE against Hib meningitis: 1 dose: 97.74% (90.77–99.45%); 2 doses 98.94% (95.71–99.74%); 3 doses 99.29% (94.87–99.90%). (**L**) 3p schedules have shown good effectiveness against meningitis in several African and Latin American countries. [6]

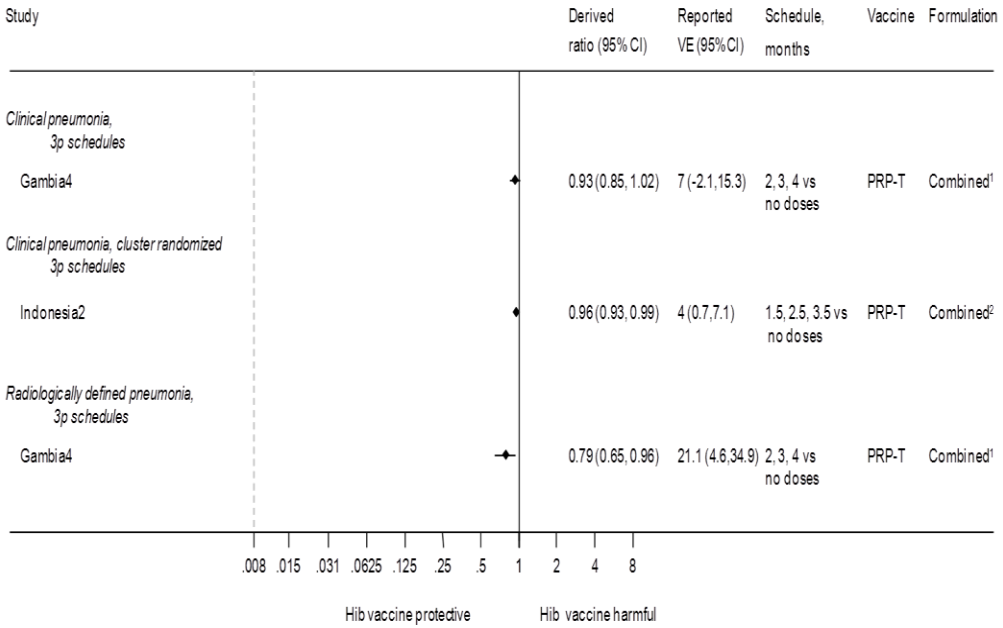
Figure 5: Estimates of effectiveness of 3 doses of Hib vaccine against confirmed Hib meningitis, from case-control studies.



Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Hib pneumonia	**No data to compare these 2 schedules** (**T**) No data from RCTs.	**No data to compare these 2 schedules** (**T**) No data from RCTs	**No data to compare these 2 schedules** (**T**) No data from RCTs	**Limited data indicate that Hib vaccine is protective against Hib specific pneumonia, and hence can reduce all cause pneumonia.** (**T**) Two RCTs: Gambia4[10] (all clinical pneumonia and X ray pneumonia) and Indonesia2[23] (all clinical pneumonia), reported that VE from ITT analyses range from 7% to 21% (figure 6-8). One RCT (Chile 3)[11] reported Hib vaccine was protective against radiologically-defined pneumonia after 2p or 3p doses. (PP VE 23% 95%CI 1, 40). One RCT (Gambia4)[10] reported Hib vaccine was protective against definitive Hib pneumonia after 2p or 3p doses (PP VE 100%, 95%CI 55, 100). All used PRP-T. NB:Unfortunately the VE estimates from Indonesia, Lombok trial for radiological pneumonia were published without confidence intervals and therefore could not be included in meta-analysis. Reviewers assessed the data presented to see if they could calculate VE with confidence intervals but could not do so without making substantial assumptions. The reported VE point estimates were -4.9 (ITT) and -12.0 (PP).

Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Hib pneumonia	(**O**) One case-control study[24] reported VE for three doses (55% [95% CI 7-78%]) and two doses (52% [3-76%]). (**L**) no data	(**O**) No data from observational studies (**L**) no data	(**O**) No data from observational studies (**L**) 3p+1 has been used effectively in a many industrialized countries.[6] However, there is no data available to directly compare these schedules.	(**O**) Two case-control studies reported the effectiveness of 3p against radiologically confirmed pneumonia (figure 9). In a study in Colombia[24] VE was reported to be 55% (95% CI 7-78%). In Bangladesh, 3p were estimated to be 44% (95% CI 16-63%) or 32% (95% CI -2 to 54%) effective against radiologically confirmed pneumonia[22.] One further study, from Brazil, reported the effectiveness of 2p or 3p against radiologically confirmed pneumonia as 31% (95% CI -9 to 57%), using HbOC[25] . (**L**) no data

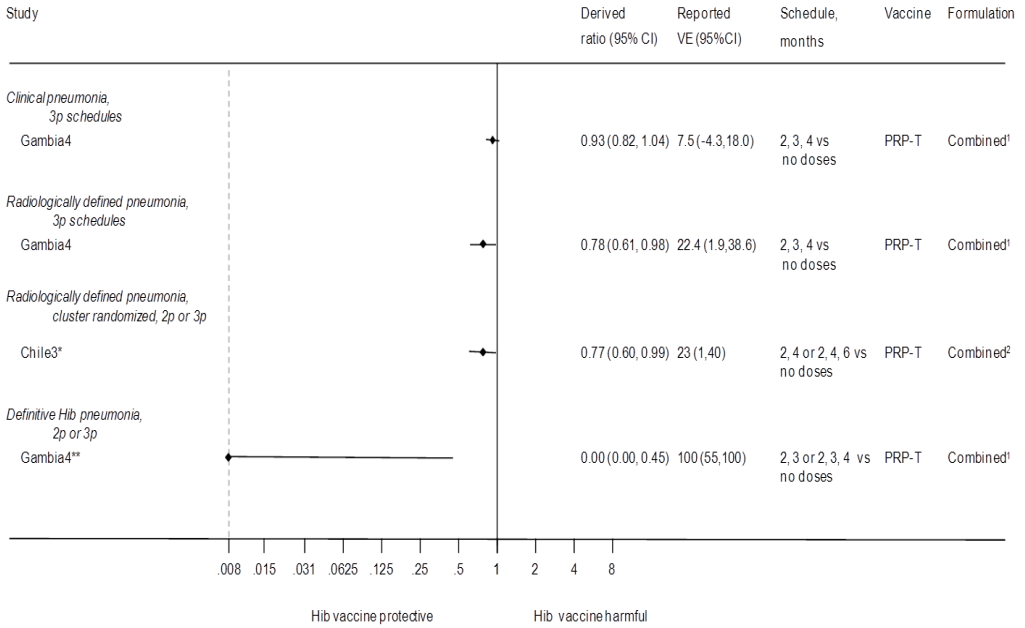
Figure 6: Pneumonia, intention to treat analyses, all available schedules, from RCTs[3]



For the purposes of this graph, "per protocol" is used to mean analyses where some individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – Haemophilus influenzae type b vaccine; VE - vaccine efficacy

1 DTP/Hib. Not stated if aP or wP; 2 DTP-Hib. Not stated if aP or wP

Figure 7: Pneumonia, per protocol analyses, all available schedules, from RCTs



For the purposes of this graph, "per protocol" is used to mean analyses where some individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – *Haemophilus influenzae* type b vaccine; VE - vaccine efficacy. * Chile3 - data presented is for pneumonia with consolidation, effusion or erythrocyte sedimentation rate ≥40mm/hour. 98% of include individuals had chest radiography performed[4].

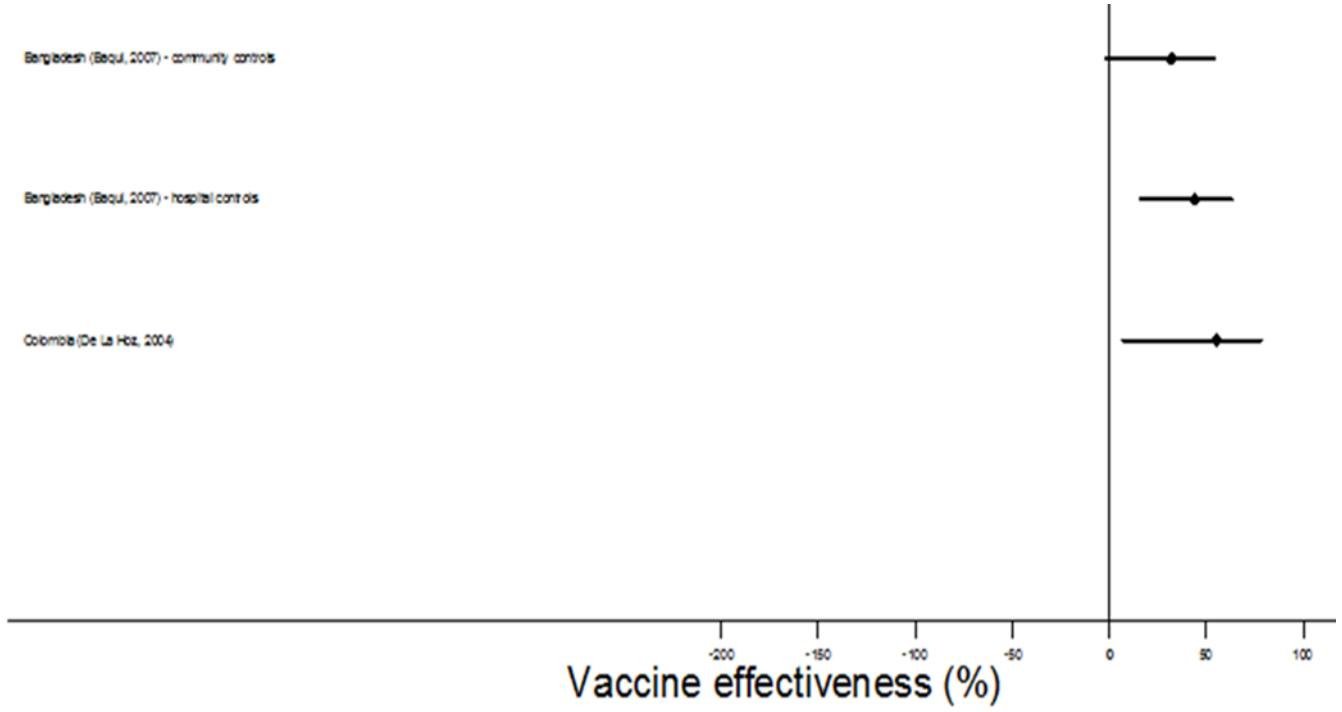
**Gambia4 - analysis performed on a sub-group of individuals receiving either 2 or 3 doses of vaccine.

1 DTP/Hib. Only wP; 2 DTP/Hib. Only wP. OPV at same time.

[3] Unfortunately the VE estimates from Indonesia Lombok trial for radiological pneumonia were published without confidence intervals therefore they could not be included in meta-analysis. Reviewers also assessed the data presented to see if they could calculate VE with confidence intervals but could not do so without making substantial assumptions. The reported VE point estimates were -4.9 (ITT) and -12.0 (PP).

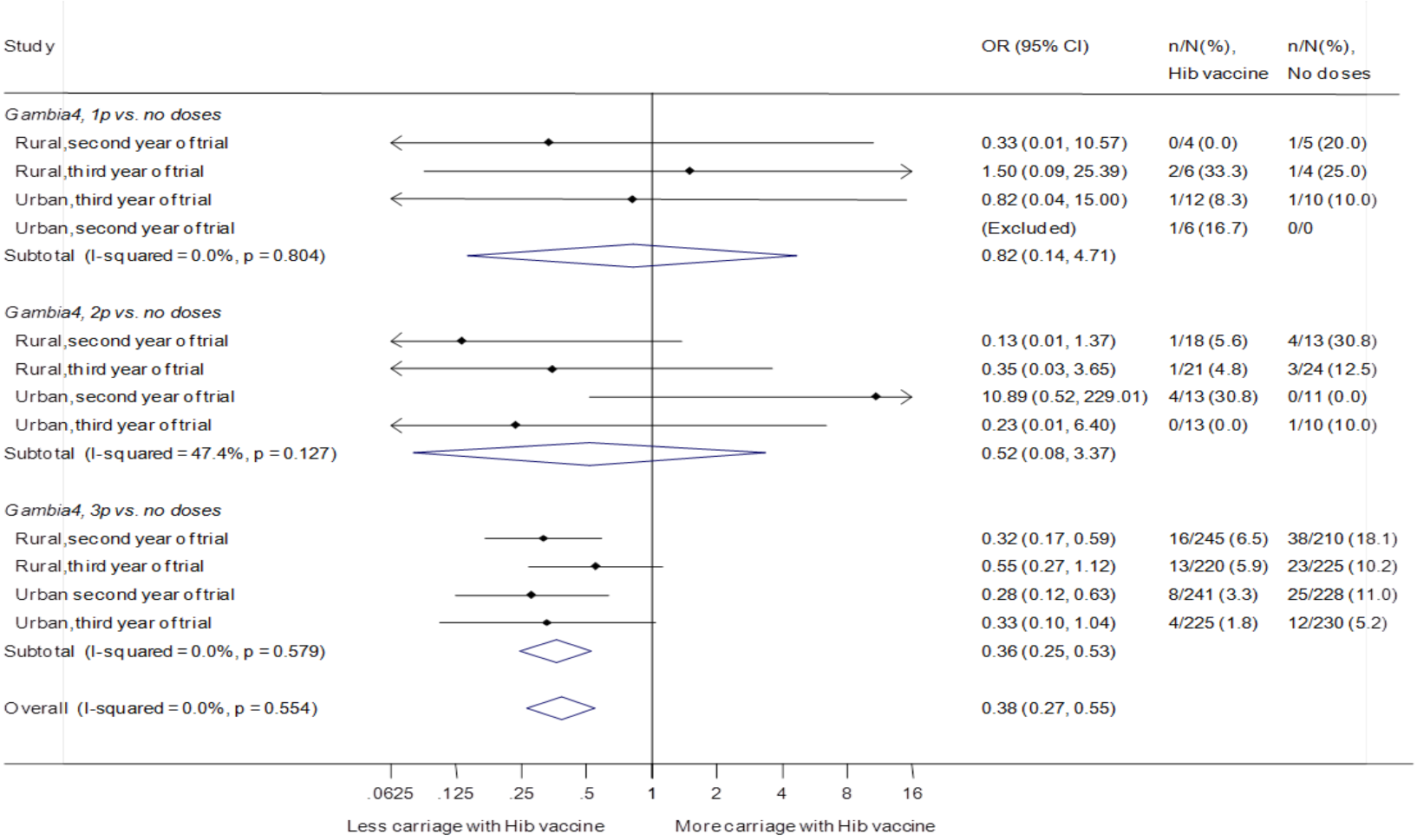
[4] The reviewers selected these data (for pneumonia with consolidation, effusion or erythrocyte sedimentation rate ≥40mm/hour). However other results were not much different: 1) Consolidation or effusion 22(-7, 43); 2) Consolidation, effusion or bronchial breath sounds 26 (4, 44); 3) Consolidation, effusion, bronchial breath sounds or ESR >=40mm/hr 26 (7, 44). Multiple definitions for pneumonia are provided in Levine, O.S., et al., Defining the burden of pneumonia in children preventable by vaccination against Haemophilus influenzae type b. Pediatr Infect Dis J, 1999. 18(12): p. 1060-4.

Figure 8: Estimates of effectiveness of 3 doses of Hib vaccine against radiologically confirmed pneumonia, from case-control studies.



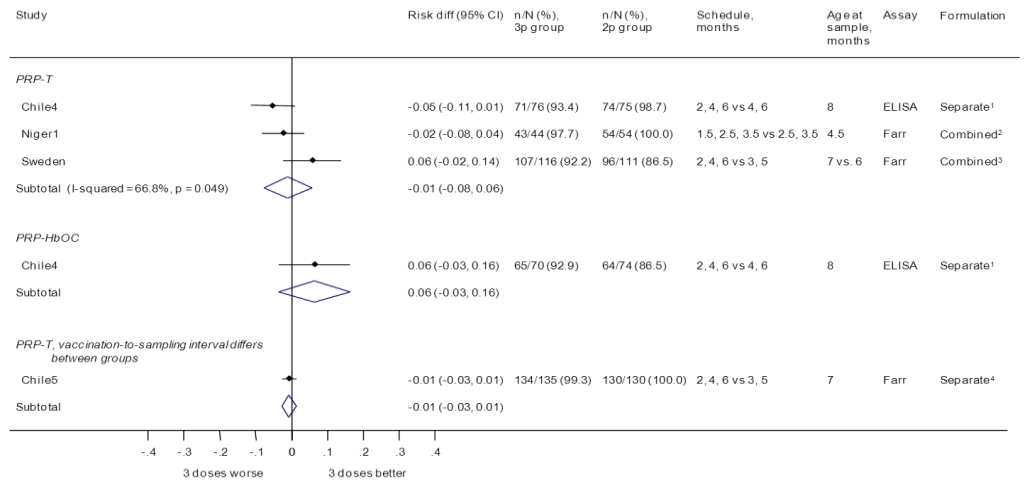
Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Carriage data	**No data to compare these 2 schedules** (**T**) No RCTS directly compared these schedules. There are data from a single trial (Gambia4)[10] comparing 3p vs. 0 and 2p vs. 0. The pooled OR for 2p vs. 0 was 0.52 95%CI 0.08-3.37) and for 3p vs. 0 the pooled OR was 0.36 (95%CI 0.25-0.53) (figure 9). (**O**) Limited observational data (reviewed non-systematically) showed no clear relationship between prevalence of carriage and number of doses received. **(L)** No data.	**No data to compare these 2 schedules** (**T**) No data from RCTs (**O**) No data from observational studies (reviewed non-systematically). **(L)** No data.	**No data to compare these 2 schedules** (**T**) No data from RCTs (**O**) No data from observational studies (reviewed non-systematically). **(L)** No data.	**Limited data shows less carriage after Hib vaccine.** (**T**) There are data from a single trial (Gambia4)[10] comparing 3p vs. 0 and 2p vs. 0. The pooled OR for 2p vs. 0 was 0.52 95%CI 0.08-3.37) and for 3p vs. 0 the pooled OR was 0.36 (95%CI 0.25-0.53) (figure 9). (**O**) Three observational studies reported effectiveness of 13% (95% CI -1000 to 93%) of at least one dose[26] , 73% (95% CI 38-89%) of three doses plus booster[27] or 62% (95% CI 0-86%) for age-appropriate vaccination[28]. **(L)** No data.

Figure 9: Hib carriage, all available schedules



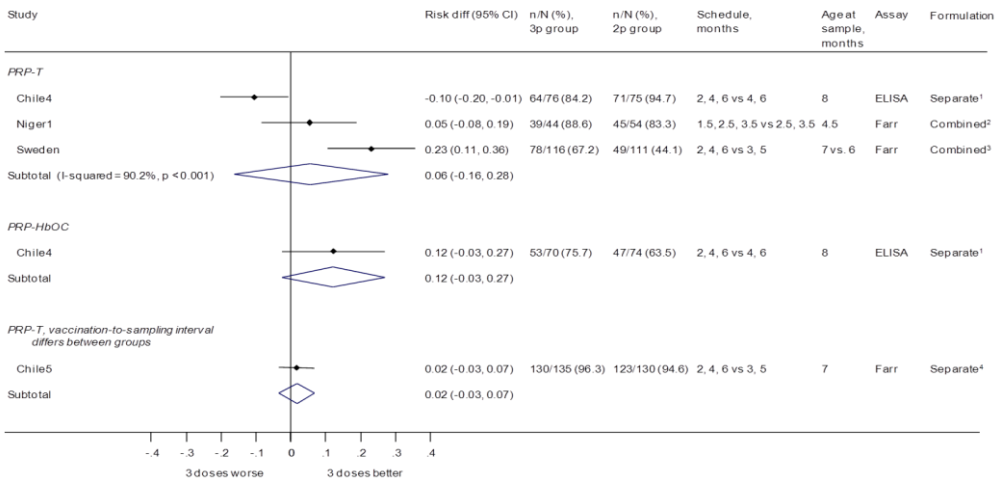
Outcome of interest	Number of doses			
	3p vs. 2p	**3p vs. 2p+1**	**3p vs. 3p+1**	**3p vs. 0**
Immunogenicity	**Limited evidence that both schedules are comparably immunogenic** (**T**) Comparisons of proportions seropositive at 0.15ug/ml. (RD = "risk difference" in proportions seropositive: [3p – 2p]): a) *1 month post primary*-(figures 10-11) Three RCTs compared 3p vs. 2p PRP-T (Chile4[29], Niger1[30], Sweden[31]): RD was -0.01 (95%CI -0.08, 0.06). One RCT (Chile4[29] compared 3p vs. 2p PRP-HbOC: RD was 0.06 (95%CI -0.03, 0.16). b) *6 month post primary* –(figures 13-14) Three RCTs compared 3p vs. 2p PRP-T (Chile4[29], Niger1[30,] Sweden[31]): RD was 0.02 (95%CI -0.10, 0.14). One RCT (Chile4[29]) compared 3p vs. 2p PRP-HbOC: RD was 0.06 (95%CI 0.07, 0.19). Three RCTs (Guatemala[32], Guatemala[32] and Netherlands[33]) compared 3p vs. 2p PRPT: RD -0.01 (95%CI -0.13, 0.11). Similar results were reported for 1.0 ug/ml threshold for 1 month and 6 months post-primary doses. (**O**) In one observational study[34] identified through non-systematic review, HbOC and PRP-T required 3 doses for a substantial rise in GMT. **(L)** No data.	**Limited evidence that both schedules are comparably immunogenic** (**T**) Comparisons of proportions seropositive at 0.15ug/ml. (RD = "risk difference" in proportions seropositive: [3p] – [2p+1]): One RCT (Sweden[31] compared 3p vs. 2p+1 PRP-T at 13 months of age (figure 15). The RD was -0.20 (95%CI -0.27— 0.13). Seropositivity at 1 or 6 month after 3p or after 2p+1. Three RCTs reported the proportions seropositive 1 month after 3p (Chile5[35], Niger1[30], Sweden[31]): the proportions seropositive were all above 92% (figure 16). All studies included PRP-T. Six RCTs reported the proportions seropositive 6 months after 3p (Chile4[29], Guatemala[32], Guatemala[32], Niger1[30], Netherlands[33,] and Sweden[31]): the proportions seropositive were all above 80% (figure 17). All studies included PRP-T except Chile which also included PRP-HbOC. Two RCTs reported the proportions seropositive 1 month after 2p+1 (Netherlands[33] and Sweden[31]): the proportions seropositive were both above 98%. Both studies used PRP-T. Considerable variation observed for studies reporting data on the proportion seropositive at 1.0 ug/ml. (**O**) No data and **(L)** No data.	**Some evidence that 3p+1 more immunogenic than 3p** (**T**) Comparisons of proportions seropositive at 0.15ug/ml or 1.0 ug/ml (RD = "risk difference" in proportions seropositive: [3p+1]-[3p]): One RCT (Europe[36]) compared 3p+1 vs. 3p PRP-T. The RD one month after the booster dose was 0.16 (95%CI 0.11, 0.22) for 0.15 ug/ml and 0.59 (95%CI 0.52, 0.67) for 1.0 ug/ml. (**O**) No data from non-systematic review of observational studies. **(L)** No data.	**Good data on immunogenicity of 3p schedule** (**T**) Assessment of proportion seropositive at 0.15 ug/ml Seropositivity at 1 or 6 month after 3p or after 2p+1 (figures 10-13). Three RCTs reported the proportions seropositive 1 month after 3p (Chile5[35], Niger1[30], Sweden[31]): the proportions seropositive were all above 92%. All studies included PRP-T. Six RCTs reported the proportions seropositive 6 months after 3p (Chile4[29]Guatemala[32], Guatemala[32], Netherlands[33], Niger1[30] and Sweden[31]): the proportions seropositive were all above 80%. All studies included PRP-T except Chile which also included PRP-HbOC. Considerable variation observed for studies reporting data on the proportion seropositive at 1.0 ug/ml. (**O**) No data from non-systematic review of observational studies. **(L)** No data.

Figure 10 : 3p vs 2p, approx. 1m post primary, 0.15µg/ml, from RCTs



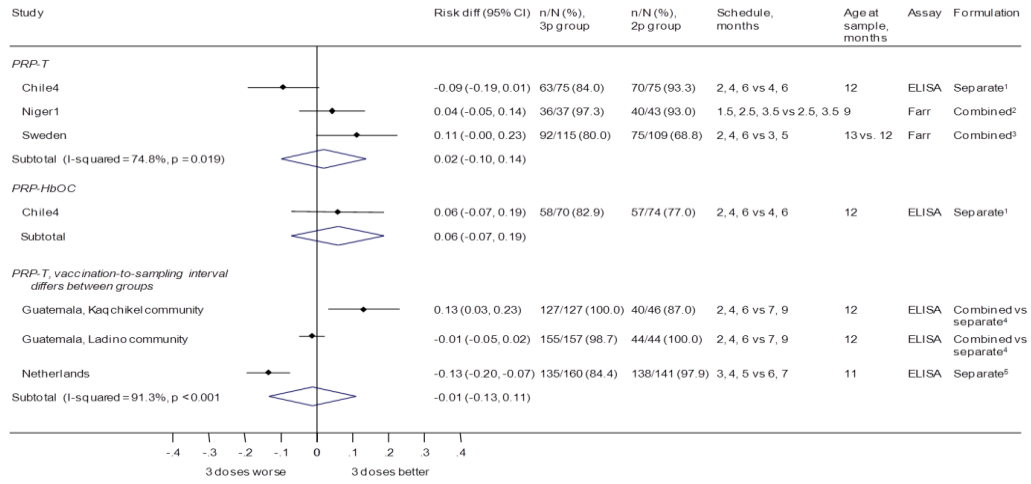
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5 . Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTaP 2, 4, 6 both groups

Figure 11: 3p vs 2p, approx. 1m post primary, 1.0µg/ml, from RCTs



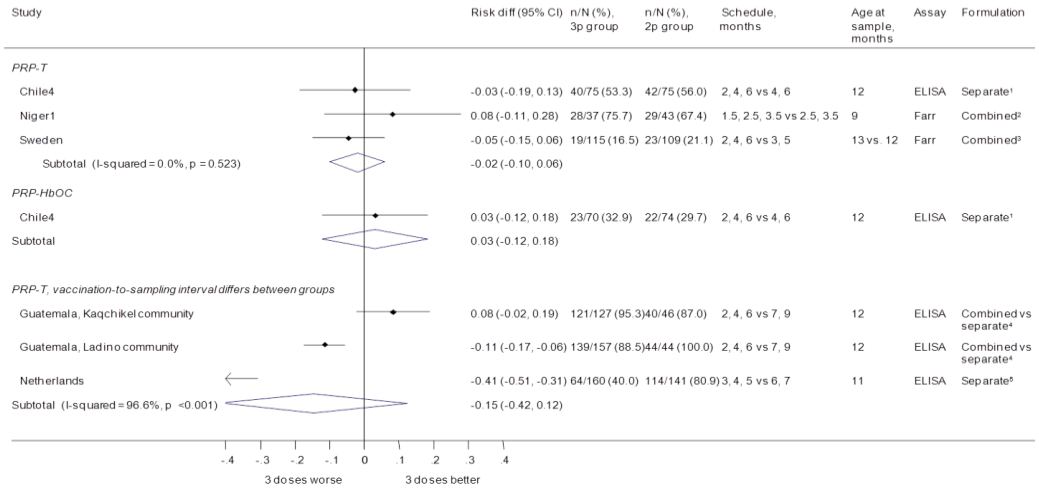
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTaP 2, 4, 6 both groups

Figure 12: 3p vs 2p, approx. 6m post primary, 0.15µg/ml, from RCTs



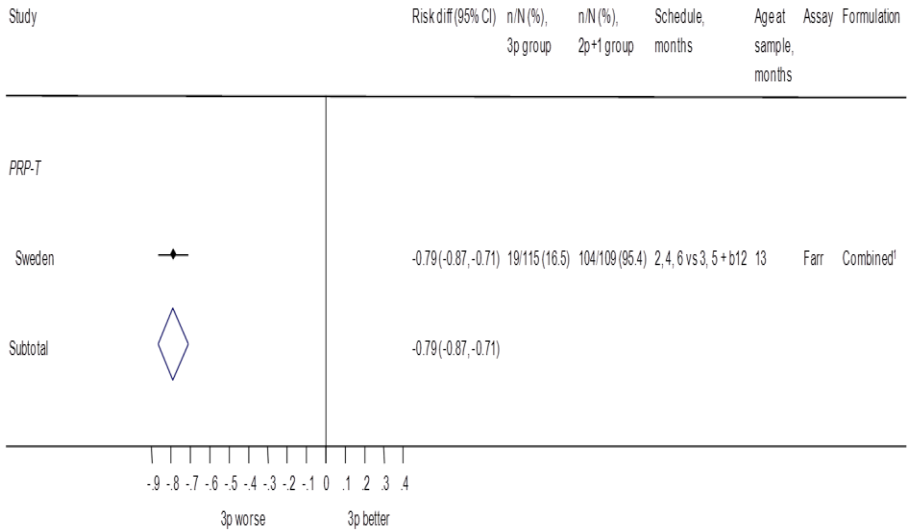
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 5 DTwP-IPV both groups at 3, 4, 5

Figure 13: 3p vs 2p, approx. 6m post primary, 1.0µg/ml, from RCTs



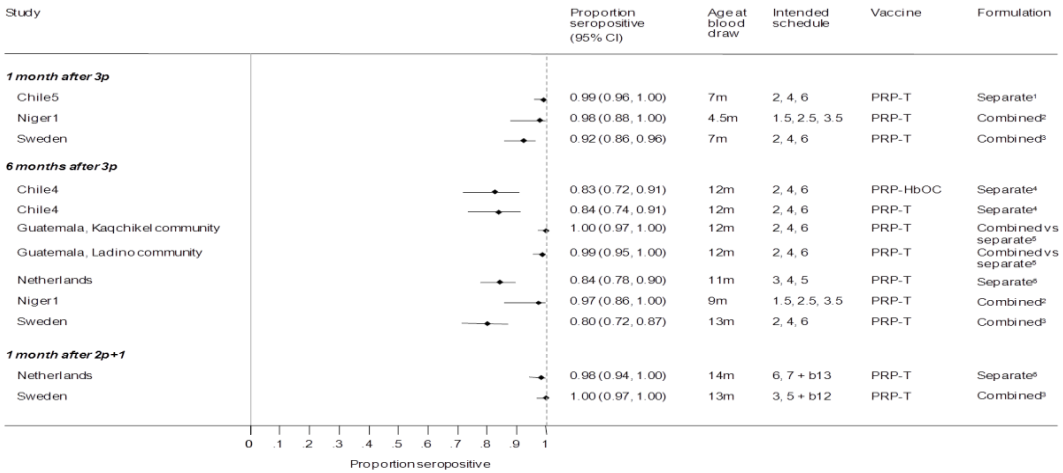
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTP both groups at 2, 4, 6. Unclear if aP or wP ; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 5 DTwP-IPV both groups at 3, 4, 5

Figure 14: 3p vs 2p+1, 13 months of age, 1.0µg/ml, from RCTs



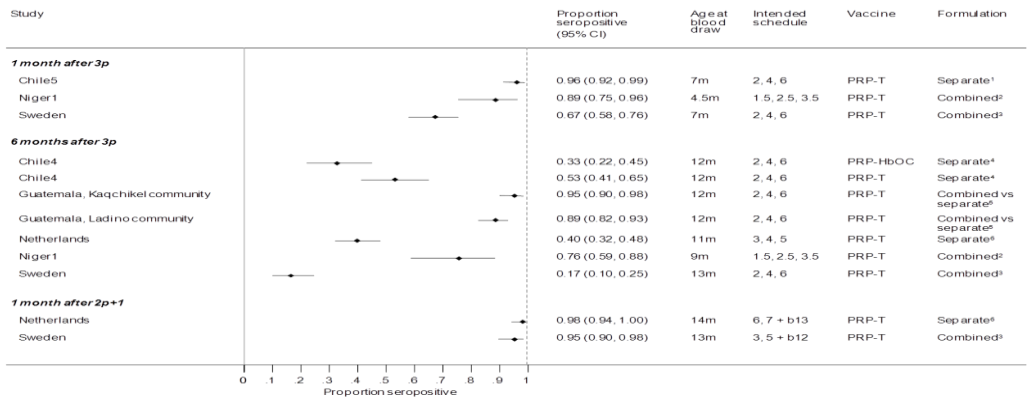
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-IPV/Hib both groups

Figure 15: Seropositivity after 3p and 2p+1, 1 and 6 months after 3p and 1 month after 2p+1, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP 2, 4, 6 both groups; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTP both groups at 2, 4, 6. Unclear if aP or wP; 5 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 6 DTwP-IPV both groups at 3, 4, 5

Figure 16: Seropositivity after 3p and 2p+1, 1 and 6 months after 3p and 1 month after 2p+1, 1.0µg/ml, from RCTs



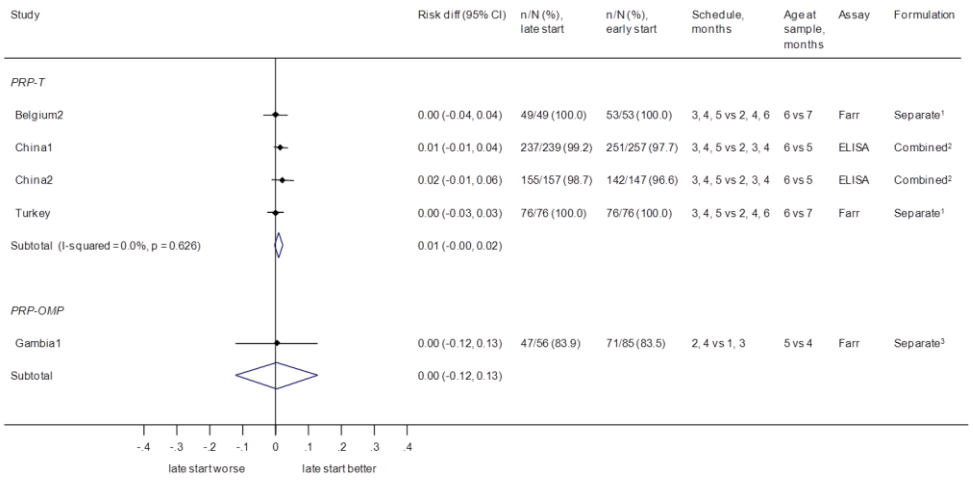
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP 2, 4, 6 both groups; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTP both groups at 2, 4, 6. Unclear if aP or wP; 5 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 6 DTwP-IPV both groups at 3, 4, 5

Effect of age at administration of first dose of Hib vaccine on selected outcomes: Limited available evidence suggest that schedules starting earlier (i.e. at 4-6 weeks of age) are comparable to schedules starting later (i.e. > 2 months of age). Trade-offs may exist between initiating vaccination earlier versus later in infancy in settings where Hib disease epidemiology data suggest that a large proportion of cases occur before 8 weeks of age. Another consideration in the choice of the age at first dose is the recognition of delays with the actual age at vaccination. There is no evidence to firmly determine the age limit for initiating vaccination but three years seems appropriate as it is in line with the evidence on the age distribution of Hib disease cases in the pre-vaccine era.

Comparison	Evidence
Immunization schedules starting later (i.e. $\geq$ 2 months of age) vs immunization schedules starting earlier (i.e. at 4-6 weeks of age)	**(T)** There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data. Seropositivity results are presented in figures 17-22, stratified by conjugate type. A study which reported only GMC (Gambia2[50]) examined PRP-T and compared doses at 2 and 4 months of age to doses at 1 and 3 months of age. GMC was measured 1 month after the last dose of vaccine. The GMC was 0.41µg/ml (95%CI 0.28-0.61) in the 2 and 4 month group and 0.26µg/ml (95%CI 0.19-0.35) in the 1 and 3 month group. There a few additional studies assessing the immunogenicity of neonatal doses of Hib vaccines. In a Finnish[37] study Hib capsular polysaccharide (PS)-tetanus toxoid conjugate vaccine (PRP-T) was given to 120 neonates at 2 days of age, followed by PRP-T or the Hib PS vaccine at 4 months and a PRP-T booster at 14 months. Their anti-Hib PS concentrations were compared with those in children receiving PRP-T at 2 and 4 months or at 4 months.TS: The geometric mean concentration of anti-Hib PS at the age of 2 days was 0.34 micrograms/mL and at 4 months was 0.12 micrograms/mL. This was significantly more than the concentration in unimmunized infants at this age and 3.5 times more than expected, taking into account the natural decay of transplacentally acquired antibodies. Such a response was not seen in infants with a high (greater than 3.0 micrograms/mL) neonatal antibody concentration. The PRP-T vaccine given at 4 months elicited an antibody response in all infants and Hib PS in 62%, indicating immunologic priming. At 14 months, a higher percentage of the infants who had received PRP-T at 2 days and 4 months than of those who had received PRP-T at 4 months only had anti-Hib PS concentrations greater than 0.15 micrograms/mL. All infants responded well to the booster at 14 months. There was no evidence of immunologic tolerance. A study in Papua New Guinea[38] evaluated the safety and immunogenicity of a lyophilized and a liquid form of Hib polysaccharide-tetanus toxoid conjugate vaccines (PRP-T) given in the same syringe as diphtheria-tetanus-pertussis (DTP) vaccine (Lehmannmexy D, Kakazo M, Saleu G, Tame J, Javati A, Namuigi P, Alpers M, Wegmüller B, Zellmeyer M et al. Safety and immunogenicity of two Haemophilus influenzae type b polysaccharide-tetanus toxoid conjugate vaccines (PRP-T) given with diphtheria-tetanus-pertussis vaccine to young Papua New Guinean children PNG Med J 2001 Mar-Jun;44(1-2):6-16.). As part 1 of the study 209 children were randomized to receive at ages 1, 2 and 3 months either DTP alone or a liquid formulation of DTP/PRP-T or lyophilized PRP-T dissolved in DTP suspension. A further 75 children were given the liquid DTP/PRP-T formulation at ages 2, 3 and 4 months as part 2 of the study. 54 children aged 15-18 months were given a booster of the same preparation of PRP-T/DTP as they had received during Part 1. Blood for antibody assays was collected at enrolment, before (Part 1 only) and one month after the third dose, then just before and 3 weeks after the booster dose. Results. Follow-up to age of 12 months showed that PRP-T was safe with no evidence of impaired response to individual vaccine components when combined with DTP.

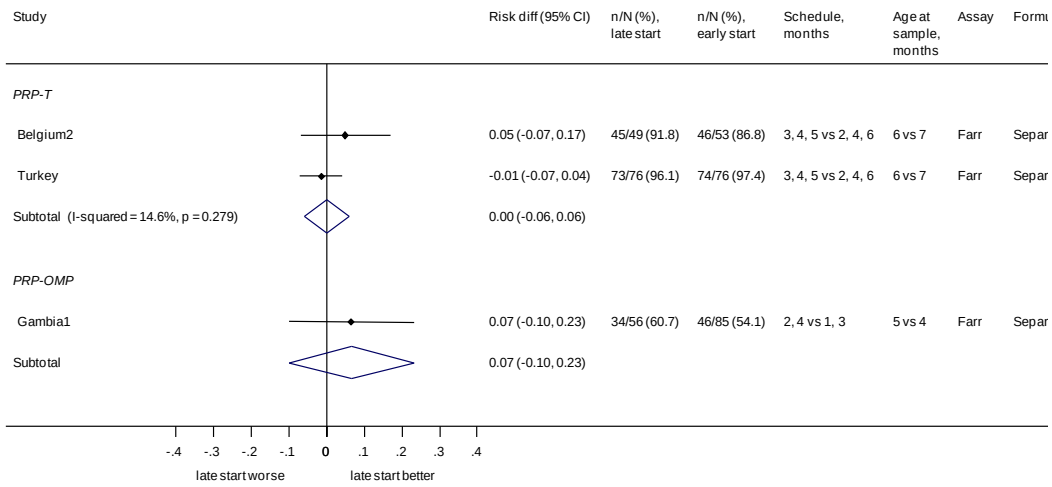
Comparison	Evidence
	Geometric mean titres (GMTs) of anti-PRP antibody before vaccination (n=64, mean age 41 days), after 2 doses (mean age 99 days) and after 3 doses (mean age 132 days) of the lyophilized formulation were 0.21, 1.48 and 5.04 μg/ml, respectively, with 58% and 89% having anti-PRP antibody titres ≥1.0 μg/ml after 2 and 3 doses, respectively. Anti-PRP antibody responses to the liquid Hib vaccine formulation were lower (GMT post-dose 3 = 0.48 μg/ml) than to the lyophilized formulation, but better responses were elicited from older children (Part 2; GMT post-dose 3 = 0.78 μg/ml, with 79% ≥0.15 μg/ml). Both PRP-T preparations elicited excellent booster responses suggesting that children are likely to be protected if exposed to Hib infection. The liquid DTP/PRP-T formulation showed a lower immunogenicity than in earlier studies with this vaccine, which might have been due to exposure to low temperature during shipment or the younger age at immunization.Serum antibody responses to three Hib capsular polysaccharide protein conjugate vaccines (PRP-OMP HbOC and PRP-T) were evaluated in 102 Filipino infants[39]. Vaccination was carried out at 6, 10 and 14 weeks of age based on the national Expanded Programme on Immunization (EPI) schedule together with diphtheria-tetanus-pertussis, hepatitis B and oral poliomyelitis vaccines. Sera were collected at 6 weeks and I month after each vaccination. Anti-Hib polysaccharide antibody concentrations were determined by Farrtype radioimmunoassay (RIA) and enzymeimmunoassay (EIA). Following the first dose, the geometric mean concentrations (GMC, pgml-') for PRP-OMP HbOC and PRP-T were 0.69, 0.27 and 0.38, respectively After two doses, there was a significant response (PcO.05) to PRP-OMP and PRP-T (0.89 and 1.47) but not for HbOC (0.37). Differences in the GMC after the primary series were significant (pair-wise PcO.05): GMC was highest for PRP-T (4.0) followed by HbOC (1.6) and PRP-OMP (1.1). All three Hib vaccines were immunogenic when given in the local EPI schedule in Filipino infants although significant differences in the kinetics and magnitude of antibody responses were noted. The anti-Hib antibody concentrations determined by RIA and EL4 were also compared in order to validate the latter for use in laboratories where it is feasible. There was a good correlation (r' = 76%; P = 0.0001) in the Hib antibody titres obtained by both assays. **(O)** There is limited evidence. Six cohort studies with intended age at initiation ranging from 6 weeks to 2-5 months provided VE estimates. Estimated VE may increase slightly with intended age at initiation. In Denmark, the intended age at initiation of vaccination 3 or 5 months of age, as opposed to 2 months of age in the other cohort studies which reported the intended schedule[20, 40]. In the Danish study 3-dose vs 0 dose VE for PRP-T against Hib meningitis was 99.3% (94.87–99.90%)[20]. In the South African study, in which age at initiation of vaccination was intended at 6 wks, 3- dose vs 0 dose VE against invasive Hib was estimated to be 83.2 % (60.3–92.9%); there was a high prevalence of HIV infection in the children in this study and effectiveness of 3 doses vs none was estimated as 96.5% (74.4–99.5%) in children who were not HIV-infected[41]. The 3-dose (vs 0 dose) VEs against invasive Hib from the Chilean, English and German studies, which all had intended age at initiation of 2 months, were slightly higher than the overall estimate from the South African study (ranging from 90.4 to 97.6%)[11, 14,15,42]. **(L)** There is limited variability in first dose timing in currently used schedules. Developing countries recommend the first dose at 6 or 8 weeks. Industrialized countries recommend the first dose mainly at 8 weeks with a few at 12 weeks. Hib continues to cause disease in all countries reviewed, with incidence highest in the first year of life. This suggests ongoing risk in young infants. No clear evidence of the superiority of either schedule.[6]

Figure 17: Immunization schedules starting later vs earlier start, 1m post primary, 0.15µg/ml, from RCTs



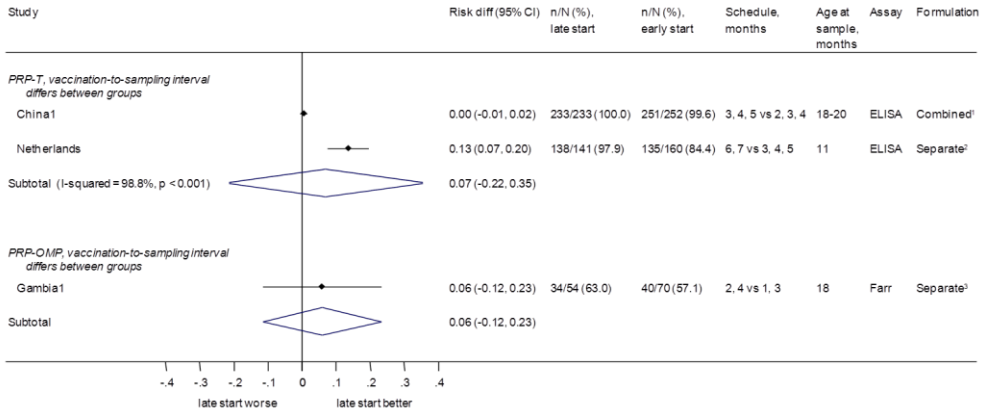
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 DTaP-IPV/Hib; 3 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 18: Immunization schedules starting later vs earlier start, 1m post primary, , 1.0µg/ml, from RCTs



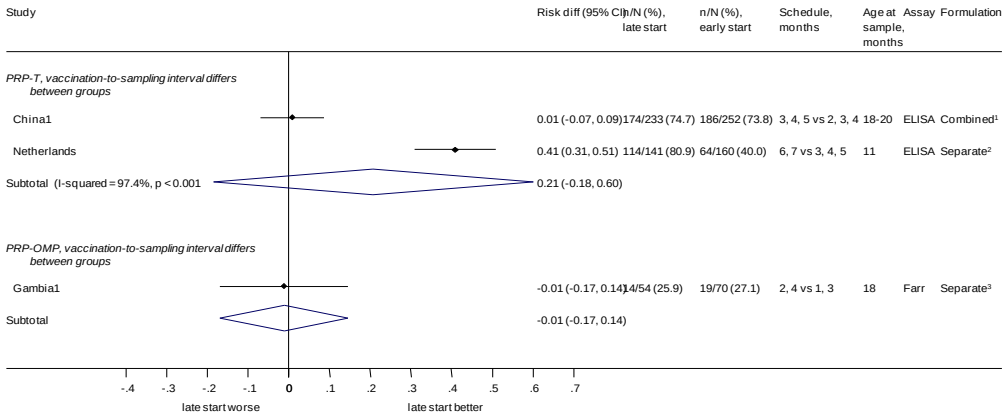
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time fro vaccine.
1 DTaP at same time as Hib in separate syringe; 2 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 19: Immunization schedules starting later vs earlier start, pre-booster, 0.15µg/ml, from RCTs



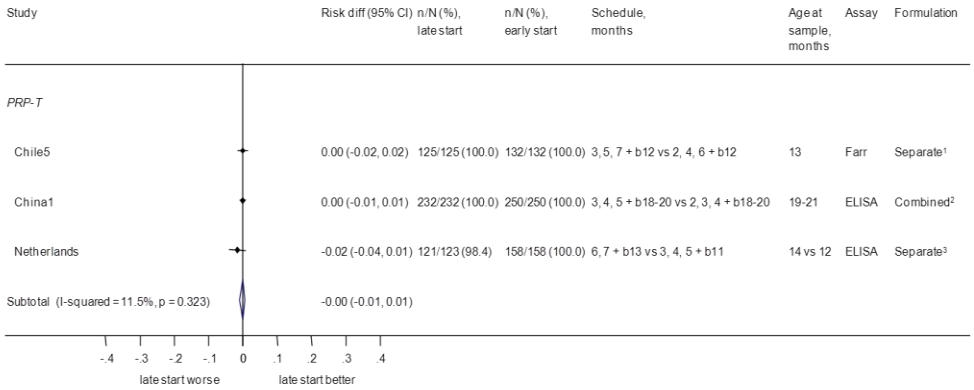
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-IPV/Hib; 2 DTwP-IPV both groups at 3, 4, 5; 3 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 20: Immunization schedules starting later vs earlier start, pre-booster, 1.0µg/ml, from RCTs



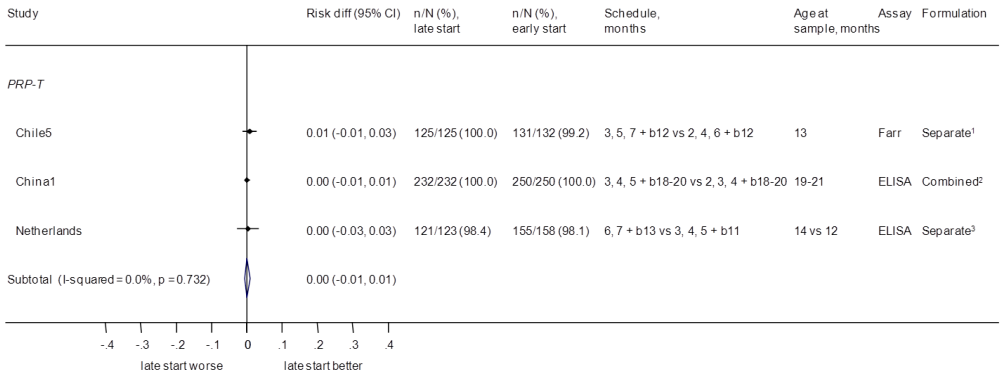
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-IPV/Hib; 2 DTwP-IPV both groups at 3, 4, 5; 3 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 21: Immunization schedules starting later vs earlier start,, 1m post booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP 2, 4, 6 both groups; 2 DTaP-IPV/Hib; 3 DTwP-IPV both groups at 3, 4, 5

Figure 22: Immunization schedules starting later vs earlier start,, 1m post booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP 2, 4, 6 both groups; 2 DTaP-IPV/Hib; 3 DTwP-IPV both groups at 3, 4, 5

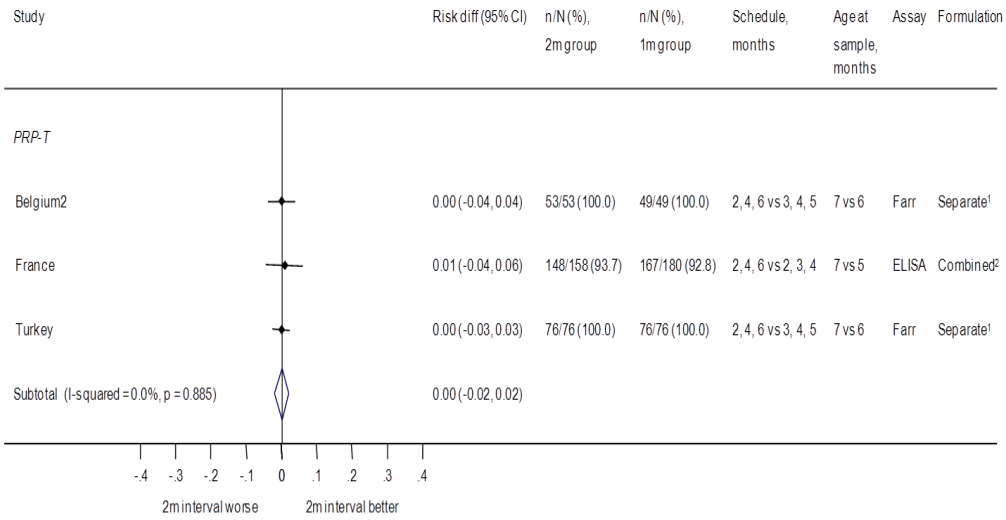
Effect of the interval between primary doses of Hib vaccine on selected outcomes: there is no strong evidence that effectiveness is significantly different in schedules with short (i.e. 4 weeks) versus longer (> 8 weeks) interval between primary doses[5]

Comparison	Evidence
Immunization schedules with short (i.e. 4 weeks) versus longer (> 8 weeks) intervals between primary doses	**(T)** There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data. Seropositivity results are presented in figures 23-26, stratified by conjugate type. The trial which compared two-month intervals to one-month intervals using PRP-OMP[6] reported GMC results only and could not be included in seropositivity graphs. This study used alternation for assignment of interventions and was therefore quasi-randomized. The mean age at first vaccination was unintentionally older in the two-month-interval group than in the one-month-interval group (4.1 months and 3.2 months respectively). Age adjusted GMCs one month after the second vaccinations were 3.95µg/ml (95%CI 2.63-5.92) in the two-month-interval group and 2.32µg/ml (95%CI 1.48-3.64) in the one-month-interval group. The reviewers concluded that it has methodological problems (e.g. randomization was not effective) which should be mentioned noted. **(O)** In most reported case control studies, 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

[5] However, it is important to note that this statement is based on evidence from studies using PRP-T vaccine..
[6] Lenoir, A.A., P.D. Granoff, and D.M. Granoff, Immunogenicity of Haemophilus influenzae type b polysaccharide-Neisseria meningitidis outer membrane protein conjugate vaccine in 2- to 6-month-old infants. Pediatrics, 1987. 80(2): p. 283-7.

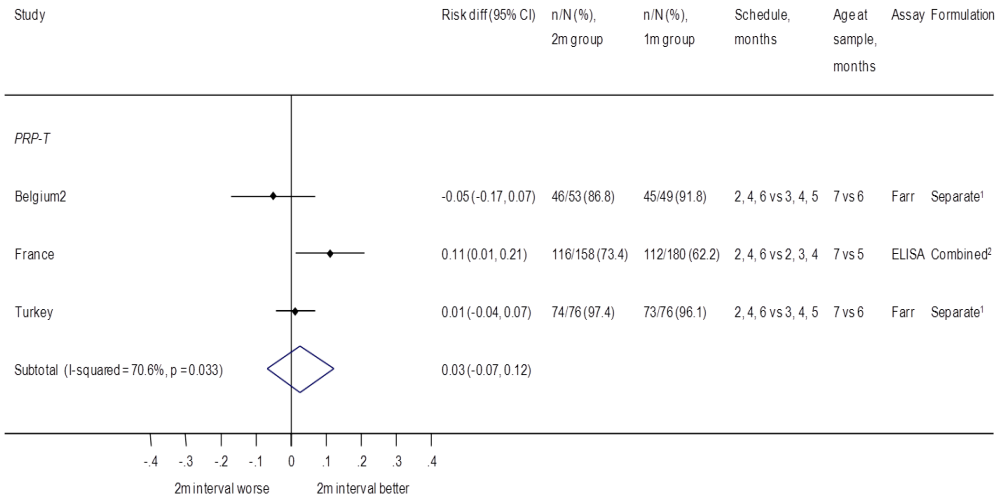
Comparison	Evidence
	or radiologically confirmed pneumonia between studies using different intended dosing intervals. A study carried out in Colombia compared the time between doses of Hib vaccine in pneumonia cases and controls [24]. The median delay between both doses 1 and 2 and doses 2 and 3 was 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[24]. There are limited data from cohort studies to inform the optimal interval between doses. A Chilean had a schedule with 2-month intervals: the VE for 3 doses vs 0 doses, quadrivalent vaccine, was 91.7% (64.8 - 100%)[11]. A German, English and South African studies included schedules that have 1-month intervals and report VE for 3 doses vs 0 doses which ranges from 83.2% and 97.6 %[14, 15, 42, 43]. 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. **(L)** Both 4 week and 8 week intervals have been used in a number of countries with good sustained long term impact. [6]

Figure 23: Immunization schedules with 2m vs 1m interval in primary course, 1m post primary, 0.15µg/ml, from RCTs



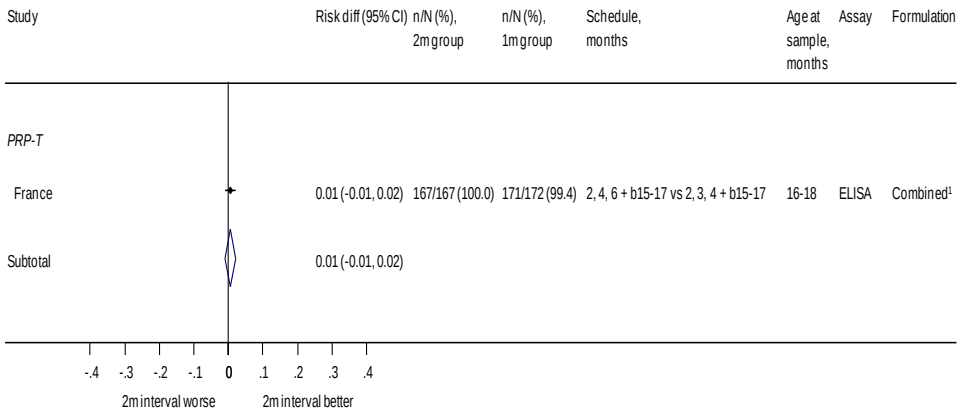
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 DTaP-hepB-IPV/Hib

Figure 24: Immunization schedules with 2m vs 1m interval in primary course, 1m post primary, 1.0µg/ml, from RCTs



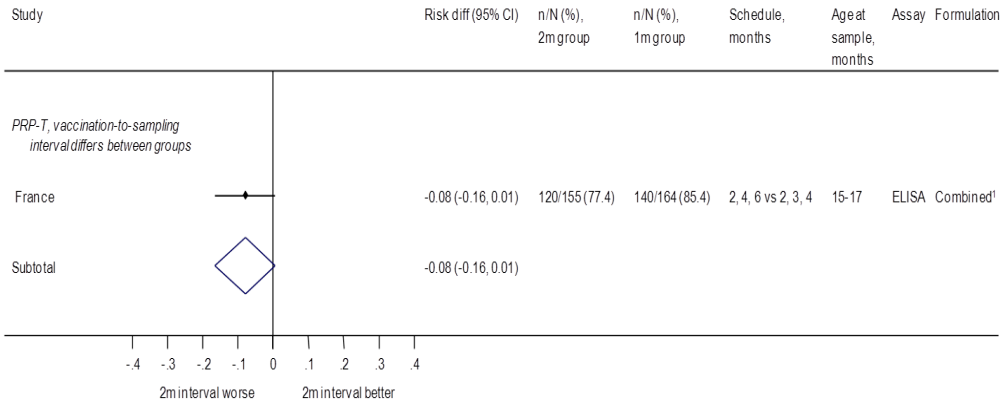
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 DTaP-hepB-IPV/Hib

Figure 25: Immunization schedules with 2m vs 1m interval in primary course, 1m post booster, 0.15µg/ml, from RCTs



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib

Figure 26: Immunization schedules with 2m vs 1m interval in primary course, pre-booster, 1.0µg/ml, from RCTs

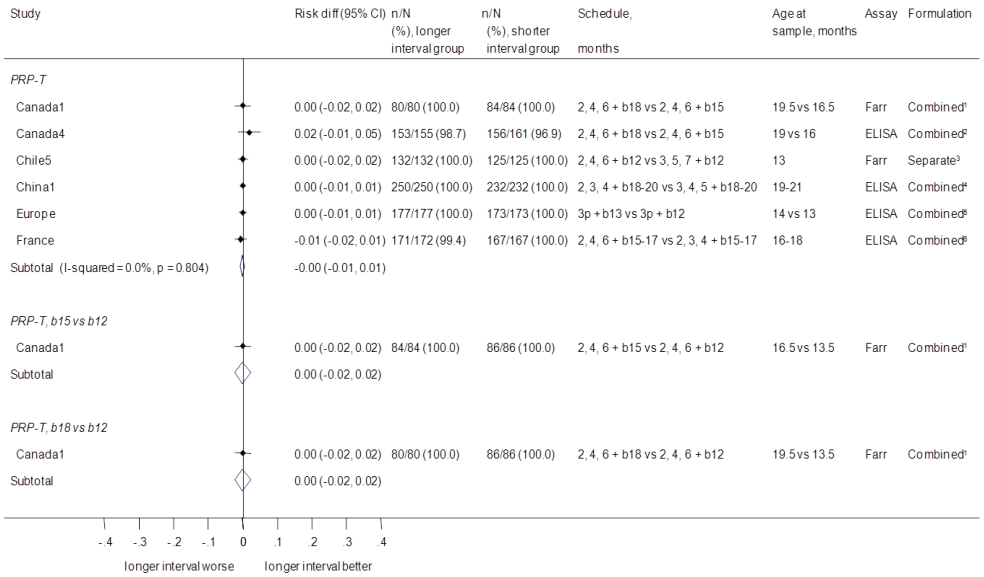


Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib

Interval between last primary dose and booster dose: There is no evidence of significant differences in effectiveness with various intervals between the primary doses and the booster dose

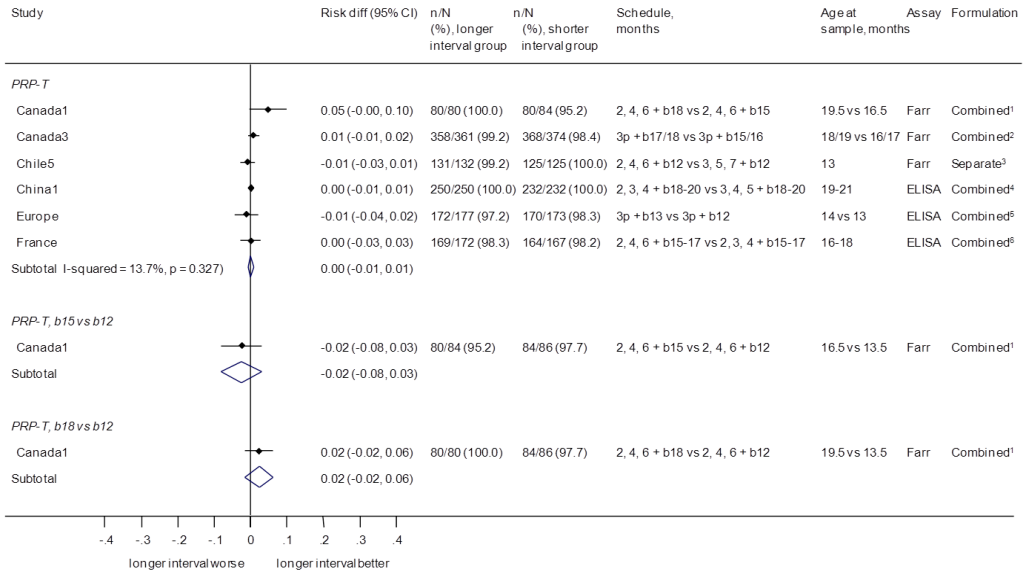
Comparison	Evidence
Immunization schedules with long (> 8 weeks) vs short (i.e. 4 weeks) intervals between primary doses	**(T)** Immunological data: Minimal difference seen between the schedules (figures 27-28). **(O)** No data available **(L)** Schedules with a booster dose given in the second year of life have shown good sustained long term impact. Schedules with the booster dose ranging from 11 months to 18 months of age have all been successful. No clear evidence of the superiority of booster dose timing between 11 months and 18 months of age.[6]

Figure 27: Long vs short interval between primary and booster, 1m post-booster, 0.15µg/ml, from RCTs



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTP-IPV/Hib. Not stated if aP or wP. MMR given separately at 12m; 2 DTaP-IPV/Hib. PCV7 given at the same time but separate to other vaccines; 3 DTaP 2, 4, 6 both groups; 4 DTaP-IPV/Hib; 5 DTaP-hepB-IPV/Hib. Men ACWY given at 12m in both groups; 6 DTaP-hepB-IPV/Hib

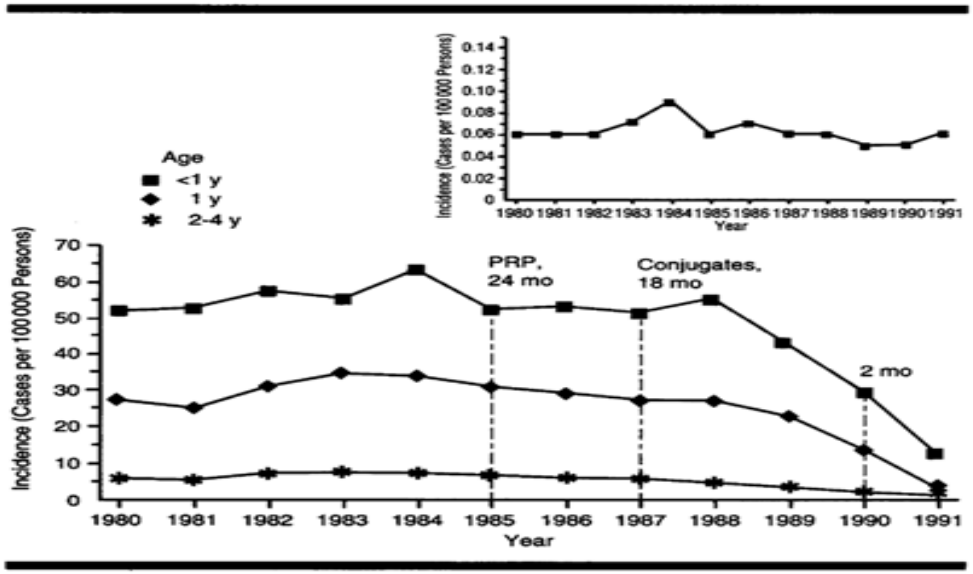
Figure 28: Long vs short interval between primary and booster, 1m post-booster, 1.0µg/ml, from RCTs



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTP-IPV/Hib. Not stated if aP or wP. MMR given separately at 12m; 2 DTaP-IPV/Hib; 3 DTaP 2, 4, 6 both groups; 4 DTaP-IPV/Hib; 5 DTaP-hepB-IPV/Hib. Men ACWY given at 12m in both groups; 6 DTaP-hepB-IPV/Hib

Schedules for children in special circumstances

Emergency settings: Limited data for children < 12 months of age suggest that at least one dose should be given and, if conditions permit an additional dose should be provided. For young infants (< 6 months of age) OMP has reported higher immunogenicity and therefore is preferable

Setting	Evidence
Emergency settings **Figure 29: Decline of childhood reported Hib meningitis cases after toddler vaccine use in the USA**  Fig 2.—*Haemophilus influenzae* meningitis cases by age in children less than 5 years old and at least 12 years old (inset) according to the National Bacterial Meningitis Reporting System, 1980 through 1991 (20 continuously reporting states). Licensure dates of polyribosyl-ribitol phosphate (PRP) and conjugate vaccines are indicated.	**(T)** There were no RCTs that directly compared these schedules and reported invasive disease, pneumonia or carriage data. Clinical data from trials comparing 2p to no Hib vaccine and 1p to no Hib vaccine are presented in figures 1-2. Carriage data from a single trial comparing 2p to no Hib vaccine and 1p to no Hib vaccine are presented in figure 9. **(o)** In general in case control studies, the effectiveness of a single dose of Hib vaccine was reported to be lower (point estimates were ≤63% against any of the included outcomes) than that of two or three doses. Two studies carried out in the USA were exceptions to this, reporting 100% (95% CI 39 – 100%) [13] and 92% (95% CI 45 – 100%)[44] effectiveness of one dose of PRP-OMP against invasive Hib disease, although with wide CIs. It is important to note that the 1p efficacy observed is for the short interval of about 2 months between first and second doses. No data on whether one dose alone would maintain high efficacy if the second or third doses were not given. There are limited data from cohort studies. The Danish study published in 2004 reports VE for 1, 2 or 3 doses(VE 1 dose: 97.74% (90.77–99.45%); 2 doses 98.94% (95.71–99.74%)) [20] while the German studies present separate estimates of VE for <3 doses and 3 doses (VE 1-2 doses vs 0 doses: 89.6% (67.0-96.7%) and; VE 1-2 doses vs 0 doses: 68.4 % (19-87.6 %), VE 57% in sensitivity analysis) [14, 42]. 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[40]. **(L)** An impact evaluation in the USA[45], reported a decline on reported Hib meningitis cases among infants during the period 1980 to 1981 during which Hib PRP and conjugate vaccine were used in children older than 18 months of age. This marked declined was observed among infants 'too young to be immunized' (figure 29).

Immunological data after one dose of Hib conjugate vaccine, by vaccine and ascending age

Data from trials with immunological data that qualified for analysis in the ISPM review (i.e. that examined eligible schedule vs. schedule comparisons), plus Mulholland et al 1996[46]. Note: this is NOT systematically collected data. Other trials and cohort studies will have collected immunological data after one dose of vaccine in individual groups but are not reported here.

Study	vaccine	time of dose and sample	>0.15µg/ml n/N (%)	>1.0µg/ml n/N (%)	GMC, µg/ml (95%CI)
USA5[47]	PRP-HbOC	0m dose (GMC at 2m)	NR	NR	0.06 (0.05-0.09)
USA5[47]	PRP-HbOC	2m dose (GMC at 4m)	NR	NR	0.05 (0.02-0.08)
Gambia1[48]	PRP-OMP	1m dose (SP and GMC at 2m)	62/85 (73)	28/85 (33)	0.53 (0.41-0.70)
Gambia1[48]	PRP-OMP	2m dose (SP and GMC at 3m)	44/56 (79)	29/56 (52)	0.82 (0.57-1.18)
USA4 [49]	PRP-OMP	2m dose (SP and GMC at 6m)	NR	14/36 (39)	0.53 (0.32-0.85)
Gambia2[50]	PRP-T	1m dose (GMC at 2m)	NR	NR	0.18 (0.15-0.22)
Niger1[30]	PRP-T	1.5m dose (SP and GMC at 2.5m)	26/47 (55)	8/47 (17)	0.19 (0.11-0.34)
Gambia2[50]	PRP-T	2m dose (GMC at 3m)	NR	NR	0.17 (0.14-0.22)
Mulholland et al[46] "separate" group	PRP-T	2m (SP and GMC at 3m)	41/79 (52)	14/79 (18)	0.18 (0.12-0.27)
Mulholland et a al[46] "combined" group	PRP-T	2m (SP and GMC at 3m)	26/77 (34)	8/77 (10)	0.06 (0.04-0.10)
Niger1[30]	PRP-T	2.5m dose (SP and GMC at 3.5m)	37/37 (100)	27/37 (73)	2.40 (1.70-3.39)
Belgium1[51]	PRP-T	14m dose			
		(SP and GMC at: 15m)	40/42 (95)	38/42 (90)	5.43 (3.04-9.66)
		(SP and GMC at: 48-72m)	34/36 (94)	25/36 (69)	2.59 (1.43-4.65)
Indonesia1[52]	PRP-T	15-18m dose (SP and GMC at 16.5-19.5)	60/60 (100)	57/60 (95)	20.7 (NR)

HIV infected children: Limited evidence suggest that they would benefit from receiving a booster dose regardless of the number of primary doses received and irrespective of whether or not the child is receiving anti-retroviral therapy. There is no evidence to firmly determine the upper age limit for additional booster doses but five years seems appropriate as it is in line with the evidence on the age distribution of Hib disease cases in the pre-vaccine era.

Setting	Evidence
HIV infected children	Limited data suggest HIV infected children are at higher risk of Hib disease. Very limited data suggest that Hib vaccine is lower in HIV infected children. A systematic review of the literature on the epidemiology of Hib disease and the effectiveness of Hib conjugate vaccine (HibCV) in HIV-infected children was recently conducted.[53] The review concluded that HIV-infected children have an almost 6-fold higher risk of Haemophilus influenzae type b (Hib) invasive disease than HIV-uninfected children and HibCV effectiveness is lower in this population. HIV-related Hib containing vaccine failures are difficult to detect without well-functioning surveillance systems and HIV testing of cases. Breakthrough Hib cases have been noted in vaccinated HIV-infected children in South Africa.

Limitations of the evidence

Number of doses of Hib vaccine

(T) Clinical and carriage data: no direct RCTs with comparisons within individual trials between these 2 schedules. Studies randomizing to 2p schedules are PRP-OMP, and those to 3p are PRP-T and PRP-HbOC.

(O) Limited control for confounding (particularly in cohort studies).

(L) There is no direct comparison of the two schedules. Few countries use a 2p+1 schedule. Comparisons must be made between countries which may result in confounding. Comparisons are difficult because there are no long term data from developing countries using a 2p+1 schedule and few developing countries are using a booster dose at all. Also, no industrialized countries reviewed are currently using a 3p schedule. Likely long term effectiveness must be inferred from immunogenicity and efficacy data. Reasons for increases in incidence in countries using 3p are not known. There are no impact data on use of a booster dose prior to 11 months of age**.**

Age at first dose

(T) Clinical and carriage data: no data. Immunological data: Only PRP-T and PRP-OMP in comparisons of seropositivity. Few data about birth dose and conclusions about birth dose differ depending on control group used (e.g. Lieberman 1995, HbOC)

(O) Studies mainly reported intended schedules rather than actual age at vaccination. Limited range in intended age at first dose (6 weeks, 2 months or 2-5 months).
The one study with intended age at initiation of 6 weeks and relatively low three-dose VE (83%) was carried out in a population with a high prevalence of HIV infection.

(L) There is limited variability in first dose timing in currently used schedules. Developing countries recommend the first dose at 6 or 8 weeks. Industrialized countries recommend the first dose mainly at 8 weeks with a few at 12 weeks. Hib continues to cause disease in all countries reviewed, with incidence highest in the first year of life. This suggests ongoing risk in young infants. No clear evidence of the superiority of either schedule.

Interval between doses

(T) Clinical and carriage data: no data. Immunological data: Only seropositivity data from PRP-T studies. One study (Lenoir 1987, PRP-OMP) showed 2m interval better but 2m group vaccinated later.

(O) Limited evidence. Comparison of VE estimates between studies. One case-control study compared intervals between doses in cases and controls. No evidence to favour any particular interval based on intended schedules. The one case-control which provided actual dosing intervals found no evidence of a different in the median interval between doses in cases and controls, but found an increased risk of pneumonia with a longer interval between doses (OR 2.1 if >90 days interval between doses 1 and 2 in a three-dose schedule).

(L) Both 4 week and 8 week intervals have been used with good sustained long term impact. There are no direct comparisons of different age at first dose using long term impact as an outcome. Data on the age and vaccine receipt in cases that persist in countries using vaccine for >5 years has not been systematically assessed.

Interval between last primary dose and booster dose

(T) Clinical and carriage data: no data. Immunological data: Data about PRP-T only.

(O) No data are available on earlier use of the booster dose. Few countries recommend a booster dose prior to the first birthday. Comparisons must be made between countries which could result in confounding.

(L) Schedules with a booster dose given in the second year of life have shown good sustained long term impact. Schedules with the booster dose ranging from 11 months to 18 months of age have all been successful. No clear evidence of the superiority of booster dose timing between 11 months and 18 months of age.

Emergency settings- Very limited data overall. No data from studies in emergency settings

HIV infected children-

Limited data to inform policy. There are not studies to assess various immunization schedules

Research needs

Additional studies are needed (e.g. observational studies) to further assess vaccine effectiveness after various immunization schedules in low and middle income countries including: number of doses with or without booster, early vs late start schedules, interval between doses and; duration of protection of primary series with and without booster. In addition, supplementary evidence on the immunogenicity of 1st dose at 4 weeks would be informative.

Moreover, studies are required to further assess the effect on Hib vaccine efficacy and effectiveness of co-administration with acellular Pertussis (aP) vaccines (by type of aP). In particular, studies assessing immunogenicity achieved using schedules including 1, 2, 3 months versus 2,3,4 months and/or versus 1,3, 4.

It is important to conduct special studies to further monitor disease impact and evaluate disease surveillance systems. This evidence will help to inform policy as it will provide evidence on any changes on the age distribution of the cases and would provide further evidence on the impact of Hib immunization in various epidemiological settings. There is a need to expand ongoing review of Hib disease surveillance data to assess vaccine impact by schedule. Planning of such studies should bear in mind the opportunities offered by ongoing or planned research including but not limited to carriage studies on Streptococcus pneumonia.

As the data on Hib vaccination in emergency settings are absent, generating such evidence is important. It is proposed that the SAGE Working Group dealing with immunization in emergency settings should consider promoting relevant research, together with the evaluation on the feasibility and appropriateness of a vaccine stockpile to address the needs of children living in such conditions. Evaluation of potential role of Hib vaccines should be conducted together with the evaluation of the impact of other health interventions. Lastly, evaluation should consider the effectiveness of different Hib vaccines.

Given the limited data on the Hib disease epidemiology and Hib vaccine response among HIV infected individuals studies to assess both elements are critical to define future immunization schedules. In order to determine whether a booster dose should be given to HIV-infected children in developing countries, well-designed studies need to be conducted to better determine the persistence of protective antibody concentrations, response to booster doses of vaccine as well as timing of and risk factors for vaccine failure in HIV-infected children both treated and naive to antiretroviral drug therapy (ART).

Impact and Cost Effectiveness Analysis of Hib Vaccines: by schedule, coverage and by epidemiological setting.

Economic evaluations of *Haemophilus influenzae* type b vaccine: systematic review of the literature

A systematic review[54] aimed to identify and evaluate the published evidence on the cost–effectiveness of the Hib vaccine, with particular emphasis on low- and middle-income countries. It was concluded that there were only few studies available from resource-poor countries and some of those are of low quality.

The 17 papers included in the review cover a total of 14 countries. According to the 2007 World Bank classifications, seven of the countries can be described as high income (2007 GNI per capita of >US$11,456), two as upper middle-income (US$3706–US$11,455), three as lower middle-income (US$936–US$3705) and two as low-income countries (<US$935).

Direct comparison of most of the study results is not possible owing to the different methods used for valuing health states. Five of the cost–benefit studies presented a positive benefit–cost ratio while it was negative in South Korea. In three of the cost–benefit studies a ratio was not calculated. Instead, the difference between the annual costs of Hib vaccination and Hib disease were presented, illustrating cost savings in both settings (Sweden and the Philippines). The two Australian studies presented results in terms of costs per QALY gained and these values are comparable. The costs per QALY gained were higher in the French study, probably owing to the lower disease incidence and higher vaccine prices assumed. The Moscow study estimated considerably higher costs per DALY averted than the studies from Kenya and Indonesia. Again, this is arguably due to a combination of a higher vaccine price and a lower Hib disease incidence used in this analysis. The two cost–effectiveness studies from Papua New Guinea and Colombia produced widely different results. However, none of these estimates can be considered reliable. The overall quality of the study from Papua New Guinea is weak and many of the parameter assumptions do not seem reliable. While the parameter assumptions in the Colombia study can be considered valid, the cost–effectiveness results are reported in a confusing and incorrect way. All of the papers except the ones from South Korea and Moscow concluded that Hib vaccine was good value for money and recommended introduction of the vaccine into the routine vaccination schedule.

The findings of the review suggest that there are important limitations with the existing literature, both in terms of methodological quality and general level of reporting. Eight studies from low- and middle-income countries were included in the review, but three of these were of such poor quality with respect to data inputs and presentation of results that their results are either unlikely to be useful for decision-making purposes or could lead to erroneous policy decisions. The most important limitation with regard to Hib disease incidence was that the multifaceted impact of Hib vaccine on pneumonia was not adequately included in the studies. While the studies reported widely different incidence rates of Hib meningitis, it is debatable whether this is a reflection of reality or instead an indication of variation in the quality of the bacterial meningitis surveillance studies that have been used to estimate this parameter. Treatment cost estimates were identified as the weakest factor among the studies, as only few of them presented the unit costs and quantities that were used for generating estimates of the average treatment costs per case. It is, however, possible that this deficiency is more due to poor reporting than inadequate cost estimates. A similar problem was seen with regard to Hib vaccine delivery costs. Nine of the studies included the costs of vaccine delivery in addition to the vaccine costs; however, none of these specified a data source or explained how the figure was derived.
Half of the studies included in the review were cost–benefit studies in which mortality and morbidity were valued and expressed in monetary terms.
Two out of eight cost–benefit studies used the human capital approach and assigned either the average annual wage or GDP per capita as a monetary value on death or disability. None of the studies reviewed presented a dynamic model of Hib disease transmission. Hence, herd immunity was not accurately depicted and the impact of the vaccine was therefore underestimated. In total, 15 out of the 17 studies reviewed concluded that Hib vaccine is a cost-effective intervention. However, this conclusion was arrived at for widely different reasons.

WHO Recommendations for Routine Immunization (2006)[55]

National immunization schedules differ depending upon local epidemiological and programmatic considerations. In general, three-dose primary series is given at the same time as the primary series of DTP (table 1). The first dose may be given to infants as young as 6 weeks of age, and the second and third doses may be given at 4–8-week intervals along with DTP. For children aged 12–24 months who have not received their primary series of immunizations, a single dose of the vaccine is sufficient. When Hib vaccine is introduced into a country, the implementation of catch-up vaccination of children aged 12–24 months will likely result in a more rapid decline of disease incidence. The vaccine is not generally offered to children aged >24 months owing to the limited burden of Hib disease among them. In most developed countries, a booster dose is recommended at 12–18 months of age; in developing countries, the need for and timing of booster have not yet been defined. Although immunization against Hib disease is not routinely recommended for individuals aged >24 months, older children and adults who are at an increased risk for invasive Hib infection should be vaccinated where resources are available. Such high-risk individuals include those with HIV infection or immunoglobulin deficiency, recipients of stem cell transplants, patients undergoing chemotherapy for malignant neoplasms and those with asplenia (for example, due to sickle-cell disease or splenectomy). Although vaccines are generally less immunogenic in immunocompromised individuals, people who have not previously been vaccinated and who have one of the aforementioned conditions or similar immunodeficiency should be given at least 1 dose of a conjugate Hib vaccine. Liquid Hib vaccines are used directly from the vial, whereas freeze-dried vaccines must be reconstituted before administration, either with diluent or with another vaccine that has been specifically identified and indicated for this purpose by the manufacturer, such as DTP. All conjugate Hib vaccines are given intramuscularly: in infants, they are administered into the anterolateral aspect of the thigh or in older children into the deltoid muscle. The standard dose is 0.5 ml. Hib vaccine can be given safely and effectively at the same time as routine vaccines included in national immunization programmes. If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it has been manufactured as a combined product (such as DTP–Hib or DTP–hepatitis B–Hib) or regulatory authorities have approved that the mixture induces an immune response that is not inferior to separate injections of the respective antigens. Evidence suggests that an immunization series started with one type of conjugate Hib vaccine may be completed using another formulation of conjugate Hib vaccine. Hib vaccine has not been associated with any serious adverse effects. However, redness, swelling and pain at the site of injection may occur in as many as 25% of those who have been vaccinated. Such reactions usually start within 1 day after immunization and last for 1–3 days. Less commonly, children may develop a fever or be irritable for a short period. When the Hib vaccine is given at the same time as DTP, the rate of fever or irritability, or both, is no higher than when DTP is given alone.

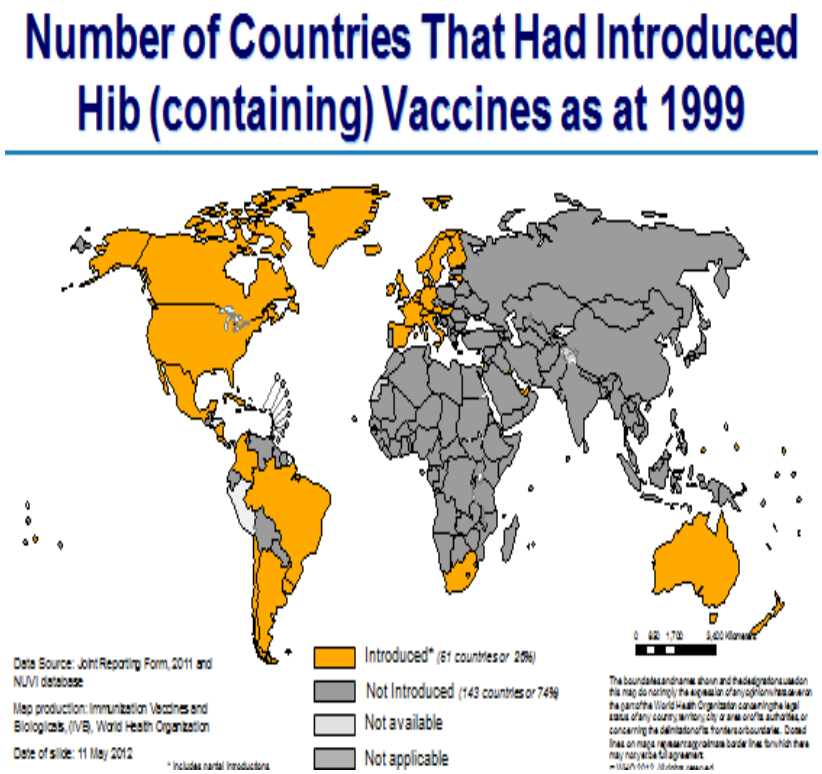
Table 1. Recommended Routine Immunizations for Children (http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

Antigen	Age at 1st dose	Doses in primary series	Interval between doses		Considerations (see below
			1st to 2nd	2nd to 3rd	
Haemophilus influenza type b[7]	6 weeks (min) with DTP1, 24 months (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3	Single dose if > 12 months of age. Delayed/ interrupted schedule.

[7] Position paper reference: Weekly Epid. Record (2006, 81: 210-220)
Immunization should start as early as possible after the age of 6 weeks. The 3-dose primary series is given at the same time as the DTP primary series often in combination vaccines. The vaccine is not generally offered to children aged >24 months owing to the limited burden of Hib disease among children older than that age. Delayed series - if a child 12-24 months of age has not received their primary vaccination series, a single dose of the vaccine is sufficient. Booster dose may be administered to children aged between 12-18 months although there is no WHO recommendation on this yet.

Progress with the introduction of Hib containing vaccines

In 1999,[56] 51 (26%) countries had introduced or partially introduced Hib containing vaccines. Mainly in the region of the Americas and Europe; South Africa, Australia and New Zealand also introduced the vaccine by that year. 31 of them are high income countries and 18 middle income countries. By 2011, 179 (92%) of the countries introduced Hib containing vaccines and 6 (3%) countries planned to introduce it in 2012 and 4 (2%) in 2013. 5 (3%) countries (China, Equatorial Guinea, Republic of Korea, South Sudan, Thailand)have not introduced nor have plans to introduce Hib containing vaccines.



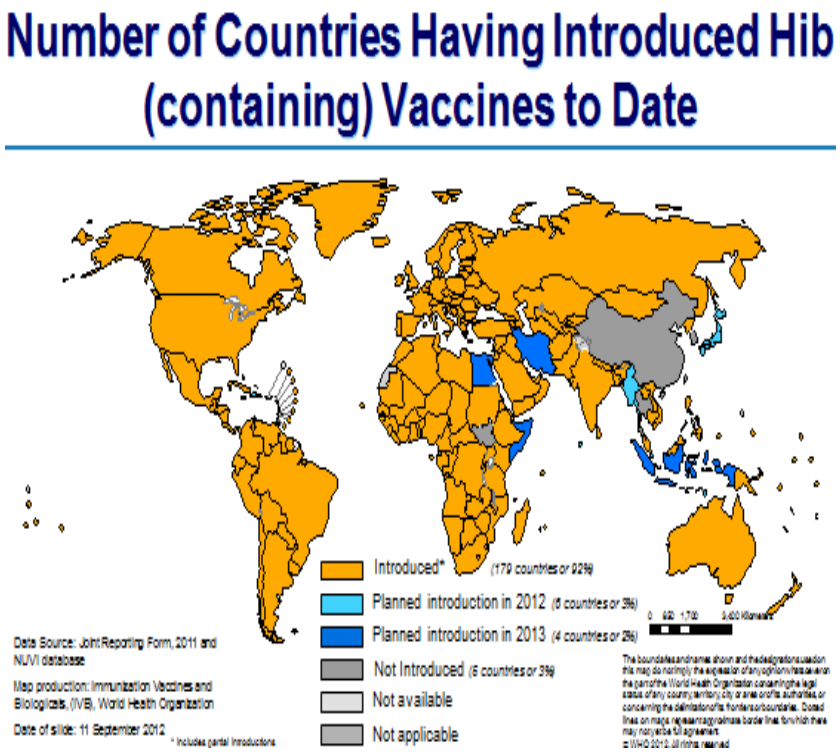


Table 2. List of WHO Prequalified pentavalent (DTP-HepB-Hib vaccines) and licensed schedules [57]

Vaccine name	Vaccine	Presentation	Components and (type of Hib vaccine)	Number of doses	Age primary dose in infants	Age booster dose	Co administration
Quinvaxem Berna Biotech Korea Corporation a Crucell Company	Fully liquid	1 dose vial	DTwP-HepB-Hib-(HbOC)	3	At least one month apart, starting as early as 6 weeks of age	Reinforcing vaccination of toddlers (13-24 months after birth): one booster dose	With other vaccines
Biologcial E India	Fully liquid	1 and 10 dose vials	DTwP-HepB-Hib-(PRP-T)	Product insert not yet been supplied by the manufacturer			
SII India	Fully liquid	1, 2 and 10 dose vials	DTwP-HepB-Hib-(PRP-T)	3	First dose at 2 months or as early as 6 weeks Interval of 4 weeks between doses.	A booster dose can be given at 15-18 months A reinforcing injection should be administered at 5 years	As with other intramuscular injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive.

Vaccine name	Vaccine	Presentation	Components and (type of Hib vaccine)	Number of doses	Age primary dose in infants	Age booster dose	Co administration
Biological E	Lyo-liquid	1 and 10 dose vials	DTwP-HepB-Hib-(PRP-T)	Product insert not yet been supplied by the manufacturer			
Tritanrix™HB+Hib GSK Belgium	Lyo-liquid	1 and 2 dose vials	DTwP-HepB-Hib-(PRP-T)	Product insert not yet been supplied by the manufacturer			
SII India	Lyo-liquid	1 and 10 dose vials	DTwP-HepB-Hib-(PRP-T)	3	First dose at 2 months or as early as 6 weeks Interval of 4 weeks between doses.	A booster dose can be given at 15-18 months A reinforcing injection should be administered at 5 years	As with other intramuscular injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive.
Eufrovac-Hib LG Life Sciences LTD	Lyo-liquid	1 and 2 dose vials.	DTwP-HepB-Hib-(PRP-T)	3	Not for birth dose First dose as early as 6 weeks . Interval of 4 weeks between doses.		With BCG, measles, polio (POV or IPV), yellow fever and Vitamin A

Vaccine name	Vaccine	Presentation	Components and (type of Hib vaccine)	Number of doses	Age primary dose in infants	Age booster dose	Co administration
Quattvaxem™ Novartis Vaccines and Diagnostics S.R.L	Liquid	1 and 10 dose vials	DTwP-Hib-(HbOC)	3	2, 5, 11-2 months of age; 2, 3, 4 months of age or 2, 4, 6 months of age. In countries where pertussis is of particular danger for young infants, the combined vaccine should be administered as soon as possible with the first dose given as early as 6 weeks, and two subsequent doses given at 4-week intervals.		Can be administered simultaneously with other vaccines (like OPV, HBV, BCG measles, IPV or yellow fever) or with human immunoglobulin.
TETRAct-Hib Sanofi Pasteur	Lyo-liquid	1 and 10 dose vials	DTwP-Hib –(PRP-T)	3	2, 3, 4 months or 2, 4, 6 months of life.	Booster 1 year after third dose	There is no known contraindication to the simultaneous administration of this vaccine with other standard vaccines during the same vaccination session. In order to avoid possible interactions between several medicinal products, any other ongoing treatment should be systematically

Vaccine name	Vaccine	Presentation	Components and (type of Hib vaccine)	Number of doses	Age primary dose in infants	Age booster dose	Co administration
							reported to your doctor or to your pharmacist.
SII India	Lyo-liquid	1 dose vial	DTwP-Hib-(PRP-T)	3	Infants and pre-school children with an interval of four weeks between doses. First dose as early as 6 weeks of age	A booster can be given at 15-18 months of age. A reinforcing injection should be given at 5 years of age.	As with other intramuscular injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive.
Quimi-Hib Center for Genetic Engineering and Biotechnology	Liquid	1 dose	Hib	Product insert not yet been supplied by the manufacturer			
Hiberix GSK	Lyophilized	1, 2 and 10 dose and vials	Hib-(PRP-T)	Product insert not yet been supplied by the manufacturer			

Vaccine name	Vaccine	Presentation	Components and (type of Hib vaccine)	Number of doses	Age primary dose in infants	Age booster dose	Co administration
Pevdax Hib Merck	Liquid	1 dose vial	Hib-(PRP-OMP)	2	First dose at 2 months of age. Interval between doses: 2 months.	Booster at 12-15 months of age.	Can be administered concomitantly with DTP, OPV, eIPV, VARIVAX (Varicella Virus Vaccine Live), MMR II or RECOMBIVAX HB (Hepatitis B vaccines)
Vaxem HIB Novartis Vaccines and Diagnostics	Liquid	1 and10 dose vials	Hib-(HbOC)	3	First dose at 2 months of age with interval of four weeks between doses. Vaxem Hib is not recommended for healthy children more than 4 years	According to official recommendations.	In clinical studies, concomitant administration of Vaxem Hib with various vaccines containing the following antigens did not affect immune responses to these other antigens: diphtheria and tetanus toxoids, whole cell or acellular pertussis components, polioviruses (live attenuated), hepatitis B, or live attenuated measles, mumps and rubella viruses.
Act-HIB Sanofi Pasteur	Lyophilized	1 and 10 dose vials	Hib-(PRP-T)	Before 6 months: 3 doses Between 6 and 12 months: 2 doses	Before 6 months: Doses 1 or 2 month apart Between 6 and 12 months: one month apart	Before 6 months: Booster 1 year after the third dose. Between 6 and 12 months: booster at 18 months of age.	

Vaccine name	Vaccine	Presentation	Components and (type of Hib vaccine)	Number of doses	Age primary dose in infants	Age booster dose	Co administration
Serum Institute of India	Lyophilized	1 dose vial	Hib-(PRP-T)	3	First dose at 6 weeks. Doses at 4 weeks of intervals Unvaccinated children older than 7 months should receive two doses approximately 2 months apart.	Vaccinated children should receive a booster at 12-18 months of age but not less than 2 months after the previous dose.	Individuals receiving immunosuppressive may have a diminished antibody response to immunization with Hib polysaccharide conjugate vaccine.

World Health Organization
Global Vaccine Safety,
Immunization, Vaccines and Biologicals
20, avenue Appia, Ch-1211 Geneva 27

INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
HAEMOPHILUS INFLUENZAE TYPE B (HIB) VACCINE

April 2012

The Vaccines

Monovalent Hib vaccine

Several *Haemophilus influenzae* type b (Hib) conjugate vaccines have been developed and licensed. All vaccines contain the polyribosylribitol phosphate (PRP) isolated from the Hib capsule. The immunogenicity of PRP is limited in children under 2 years of age and requires conjugation to a protein carrier. Four different carrier types have been used – diphtheria toxoid (PRP-D), tetanus toxoid (PRP-T), CRM_{197} (a non-toxic variant of diphtheria toxin HbOC), and the outer membrane protein complex of serogroup B *Neisseria meningitidis* (PRP-OMP). Thiomersal and adjuvants have been used in some preparations.

Although the vaccines differ in the protein carrier used, the size of the polysaccharide, the type of linkage, and immunogenicity there are no marked differences in the adverse event profile between Hib vaccines (Ward & Zangwill, 1999).

Combination Hib vaccines

Hib is combined with a number of antigens which include DTaP, DTwP, Hep B, IPV and meningococcal conjugate vaccines.

Adverse events with monovalent Hib vaccines

Mild adverse events

Local adverse events; Injection site reactions are common following administration of Hib vaccines. Within 24 hours of vaccination, 20-25% of recipients may experience pain and tenderness at the injection site (Institute of Medicine, 1994). These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required (Fritzell & Plotkin, 1992).

Systemic adverse events; Fever occurs in 2% of vaccinees (Valdheim et al., 1990).

Severe adverse events

Severe adverse events following administration of Hib vaccine are uncommon, making it one of the safest vaccines currently available. In a study of >4000 infants, there were no differences in the type and frequency of severe adverse events occurring among those receiving Hib conjugate vaccine and those receiving a placebo (CDC, 1991).

Adverse events with combination Hib vaccines

Hib–DTP: A combination of *Haemophilus influenzae* type b vaccine–diphtheria toxoid conjugate with diphtheria–tetanus–acellular pertussis (DTaP) vaccine did not result in significant differences in safety (Kovel et al., 1992) compared to DTaP alone. The rates of local and systemic adverse events did not differ according to the site of injection, arm versus thigh, or the concurrent or combined administration of DTwP (Scheifele et al., 1992).

The safety profile of combined HbOC–DTwP is comparable to that of the vaccines co-administered at separate injection sites. The incidence of local and systemic reactions is similar (Madore et al., 1990; Paradiso et al., 1993; Black et al., 1993; CDC, 1993). One exception is for swelling, not associated with increased tenderness or fever, after the first dose, which was more common (8.0% vs. 4.3%) with the combined product Hb–OC products in one study (Black et al., 1993).

The administration on the same day of either MMR vaccine or DTwP+OPV vaccine together with PRP-OMPC results in an increase in the rates of fever or irritability from 35% to 71% (Dashefsky et al., 1990). After PRP-T vaccine, no severe side-effects were observed and the rate of adverse reactions was consistent with the concurrent administration of diphtheria–tetanus–pertussis vaccine infants (Mulholland et al., 1994), children (Fritzell & Plotkin, 1994), and in an accelerated schedule (Booy et al., 1992; Begg et al., 1995).

Hib–DTwP–IPV: PRP-T vaccine mixed in the same syringe with diphtheria–tetanus–pertussis–enhanced inactivated poliovirus vaccine resulted in the same rate of local and systemic side-effects as for children receiving DTwP–IPV only, except for irritability and use of acetaminophen after the second dose. These were slightly but significantly more frequent in the DTP–IPV–PRP-T group (Dagan et al., 1994). PRP-T was given concurrently or combined with DwTP and IPV to healthy children at two, four and six months (Gold et al., 1994). Combination resulted more significantly in local redness (18% vs. 11%) but there were no differences in other local symptoms and systemic reactions occurred at similar rates in both groups.

Hib-MenCY-TT:
Haemophilus influenzae type b-*Neisseria meningitidis* serogroups C and Y-tetanus-toxoid conjugate vaccine (Hib-MenCY-TT) has been shown to have similar reactogenicity profile to separately administered Hib and Meningococcal C vaccines (Nolan et al 2007, Schmitt et al., 2007).

Other safety issues

Immunocompromised individuals including HIV: Hib vaccines are safe in HIV-infected individuals (Leroy et al., 1996; Dockrell et al., 1998) and studies show that vaccination of persons with human immunodeficiency virus infection was well tolerated except for mild soreness at the site of injection in some individuals (Kroon et al., 1997).

Anaphylaxis: Anaphylaxis was not reported during the pre-licensure clinical trials. Since then, post-marketing surveillance has identified very few cases of anaphylaxis (Milstien et al., 1987; Stratton et al., 1994). However, no reports of anaphylaxis following Hib vaccination have been published. After reviewing available data, the Institute of Medicine (IOM) concluded that there is not enough evidence to accept or reject a causal relationship between Hib vaccines and anaphylaxis (Stratton et al., 1994).

Guillain–Barré syndrome: No controlled studies have been conducted to explore the risk of GBS following Hib vaccination. GBS was not reported in any of the pre-licensure clinical trials. The Institute of Medicine identified seven cases of GBS that occurred following Hib vaccination, however, three of the individuals had received multiple vaccines and one had an implausible onset interval. Therefore, the IOM concluded there was inadequate evidence to accept or reject a causal relationship between Hib vaccines and GBS (Stratton et al., 1994).

Thrombocytopenia: During one Hib conjugate vaccine trial, a case of thrombocytopaenia was reported; however, a subsequent study found the vaccine had no effect on platelet count (Lepow et al., 1984; Stratton et al., 1994). Since that time, post-marketing surveillance has identified several possible cases of thrombocytopenia following Hib vaccination (Milstien et al., 1987; Stratton et al., 1994). The Institute of Medicine reviewed available data and concluded that evidence was not adequate to accept or reject a causal relationship between Hib vaccines and thrombocytopenia (Stratton et al., 1994).

Transverse myelitis: The vaccine adverse event reporting system has identified, in the USA, three possible cases of transverse myelitis (TM) following Hib vaccination. However, there have been no reports of TM following Hib vaccination published in the literature and no cases of TM were reported in pre-licensure trials. Therefore, the Institute of Medicine concluded that the data was inadequate to accept or reject a causal relationship between Hib vaccines and TM (Stratton et al., 1994).

Diabetes: The association between Hib vaccination (HbOC) and Type 1 juvenile diabetes was investigated by examining existing data from participants and refusers from a large controlled prospective Phase III clinical efficacy trial conducted within the Northern California Kaiser Permanente between 1988 and 1990. Amongst >50,000 children who were assessed between 10 to 12 years of age there was no evidence that vaccination with Hib conjugate vaccine in infancy was associated with risk of diabetes later in life (Black et al., 2002).

Summary of mild and severe adverse events after Hib vaccine vaccine

Nature of Adverse event	Description	Rate/doses
Mild	Local reactions	
	Injection site reactions	1 per 10
	Systemic	
	Fever	1 per 50
Severe	None	

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al 2008, Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words "vaccine antigen", "Safety" and "adverse events". An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomised controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: http://www.who.int/vaccine_safety/vaccrates/en/index.html

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vaccsafety@who.int

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