EXPANDING THE POTENTIAL IMPACT OF

Haemophilus influenzae type b vaccines (Hib)

BY OPTIMIZING IMMUNIZATION SCHEDULES

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

March 26, 2013

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IMPLICATIONS FOR IMMUNIZATION POLICY

Hib conjugate vaccine 2p+1, 3p+0 and 3p+1 schedules are likely to provide direct protection from Hib disease but the optimal schedule, and overall impact population is likely to depend on setting characteristics. For example, in countries where the burden of severe Hib disease lies in young infants it is more appropriate to provide three doses of Hib vaccine early in life. The first dose should be given at 6 weeks of age or soon after and the interval between primary doses should be at least 4 weeks. However, in settings where the greatest disease morbidity and mortality occur later, in the presence of herd immunity or, where a resurgence of Hib cases is seen after the introduction of Hib vaccine, it might be advantageous to use a schedule where the third dose is given as a booster e.g. at 11 months of age or during the second year of life. Programmatic considerations are also likely to influence the choice of Hib vaccine schedule, as most Hib vaccines are administered as combined vaccines, which mean that the scheduling of the other co-administered vaccines must also be taken in to account when choosing a Hib vaccine schedule.

SUMMARY

Selecting the optimal schedule for Hib containing vaccines is a complex process. It requires understanding of the efficacy and effectiveness of various schedules from clinical trials and observational studies. Choice of vaccine schedule depends on the age-distribution of Hib disease and the potential to achieve high and timely coverage of each dose. The choice of schedule should also take into account programmatic considerations including but not limited to: (i) vaccine presentation in use (especially since many countries are using Hib vaccines in combination forms, often as pentavalent with DTwP and HepB), (ii) potential to administer all recommended doses on time and achieve high coverage and, (iii) contact opportunities for provision of other health interventions and other vaccines. In addition, the experience to date in various countries has demonstrated that the interplay between carriage rates in the pre-vaccine era, reduction of carriage and potential for natural boosting after vaccine introduction, herd immunity and the force of infection, and immunological memory are also key factors to determine the potential impact on disease and immunological outcomes of various immunization schedules. Moreover, Hib vaccine effectiveness may be reduced as a result combining it with certain vaccines.

Hib conjugate vaccines have been in use for over 20 years with remarkable success. Hib vaccine has been recommended for universal introduction by WHO since 2006. The current WHO recommendation for Hib includes a three doses primary schedule with no booster (3p+0) and states that immunization should start as early as possible after the age of 6 weeks and that in countries where the vaccine is being introduced, consideration should be given to offering a one-time dose to all eligible children aged 12-24 months.

Countries are currently using Hib vaccines in routine immunization programmes as part of a combination product (often as pentavalent presentation e.g. Hib-DTwP-HepB). The Hib containing immunization schedules (as reported in the JRF, data as 31st December 2011) can be summarized as follows. 8.8% countries out of 194 reporting countries have not introduced Hib vaccine in the routine immunization programme, 56.2% countries (mostly non-industrialized countries representing 76.9% of the global birth cohort of ~135 million infants) use 3 primary doses without booster schedule(3p+0); 28% of countries (most of them industrialized countries) use 3 primary doses plus a booster (3p+1) and, 5.7% of countries (most of them industrialized countries representing 1.4% of the global birth cohort) use 2 primary doses plus a booster (2p+1). There are 41 countries using a combination that includes acellular pertussis (aP) vaccine, 36 of them with a schedule that includes a booster dose in the second year of life (6 as 2p+1 and 30 as 3p+1), the majority of which are from industrialized countries, (see further information on page 18). However in practice the actual age at vaccination may vary from recommended ages[1] .

NUMBER OF PRIMARY DOSES

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two primary doses?	
Conclusion	**Data suggest that at least three doses of Hib vaccine are required to achieve high effectiveness**. (See further information on pages 18-28).
Summary statement	**From the studies identified, data available do not clearly favour a 3p+0 or 2p+0 schedule in terms of disease outcomes or immunogenicity for various Hib vaccine types [except for PRP-OMP].** The observed marginal increase in efficacy and effectiveness was considerably greater between the first and second dose, than between second and third dose, when assessed as part of the primary series. The data found did not show significant differences by type of Hib vaccine conjugate (except PRP-OMP conjugate as reported efficacy and effectiveness with one or two doses was reported as > 90%) or for combination vaccines using wP or aP. Data available from RCTs suggest that a booster dose after a 2p primary series results in high levels of proportion above a set threshold (i.e. > 1.0 ug/ml)). If a two primary doses schedule is selected, evidence suggests that efficacy and effectiveness over time will be high. There is some evidence that DTaPHib vaccines may be less effective and less immunogenic that DTwPHib vaccines.
Quality of evidence	**We are uncertain about the estimate of the effect.** We were unable to identify data from RCTs or observational studies reporting direct comparison between 2 and 3 primary doses for disease outcomes for any of the conjugates, and using different vaccine combination types such as aP containing vaccines. In terms of immunological outcomes, seven RCTs provided immunological data to compare two doses versus three primary doses. There was also information from observational studies.

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two primary doses?	
Caution	Estimates of vaccine efficacy from different trials in terms of immunogenicity cannot be compared directly as evidence of equivalence or superiority of one particular schedule and there were too few trials for a network metanalysis which would allow such a comparison. It is important to note that most of the evidence on effect on disease outcomes is drawn from observational studies and few RCTs comparing schedule versus no vaccination. The observational studies took place when the vaccine was in routine use and other children in the community may have received 3 or more doses. There is no experience from any country using a 2p+0 schedule.

NEED FOR A BOOSTER DOSE

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
Conclusion	**In some countries, administering a booster dose during the child's second year of life has been deemed necessary to sustain overall disease control in population and direct protection of toddlers. However, the need for booster doses in non-industrialized countries requires further evaluation.** (See further information on pages 30-35).
Summary statement	Available data suggest that after 5 years of vaccine introduction using a 3p+0 schedule a significant reduction in meningitis in young children was observed in a number of developing countries. A recent evaluation from four South American countries reported that Hib meningitis rates were similar 6-10 years post introduction in countries with and without boosters. There is similar data from a dozen of non-industrialized countries that have used a 3p+0 schedule for at least 6 years. However, the UK had a different experience: after the introduction of a 3p+0 schedule (2, 3, 4 months) in 1992 with PRPT-conjugate alongside a catch-up campaign for toddlers 12-48 years of age (with HbOC conjugate vaccine), the UK had an initial decline in cases, but started observing an increase in Hib over a decade after an initial decline in cases. As a result of this, a Hib vaccination booster campaign using (PRP-T conjugate) was conducted between May and September 2003, offering one dose of vaccine to all children who were aged between 6 months and 4 years on 1 April 2003 and to those children who reached 6 months of age during the campaign. A routine booster dose in the vaccine schedule was introduced in 2006. Following these interventions cases declined again. Data from industrialized countries suggest that immunogenicity may be lower with PRPT conjugate and aP containing vaccine and this could have an impact on duration of protection. Emerging reports on some resurgence of Hib cases in older children in The Gambia (3p + 0) highlight the need for further evaluation of duration of protection and of the role of a booster dose in non-industrialized country settings [e.g. 10 years after introduction of Hib vaccine in combination with whole cell pertussis vaccine]. If boosters are deemed necessary (i.e. as

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
	part of a 2p+1 or 3p+1 schedule), an alternative to routine booster at 11 months or later may be to implement catch-up campaigns targeting toddlers. The UK experience suggests that they have resulted in important reductions of overall carriage
Quality of evidence	**We are moderately confident on the estimate of the effect. 3primary doses vs 2p+1→ low quality of evidence (GRADE table 6)** Assessment of the need for booster doses is challenging because (a) there are no data directly comparing clinical effectiveness between similar primary schedules with and without booster No data are currently available from developing country settings using aP containing combination vaccines without a booster dose.
Caution	The situations in which a booster dose should be used remain unclear, and it would depend on various factors including local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

INTERVAL BETWEEN DOSES

Does using Hib conjugate vaccine schedule with a longer interval between primary doses (e.g. 8 weeks or more) have a greater effect on disease or immunological outcomes than a schedule with a shorter interval (i.e. 4 weeks) between doses?	
Conclusion	**Limited data available showed no consistent or clinically relevant differences between shorter (e.g. 4 weeks) and longer (e.g. ≥ 8 weeks) intervals between primary doses of Hib vaccines.** (See further information on page 55-57).
Summary statement	In most reported schedules, 3 primary doses were separated by either one month (e.g. 6, 10, 14 weeks and 2, 3, 4 months) or two months (e.g. 2, 4, 6 months) whereas 2-dose schedules essentially included 8-weeks intervals. Available data on proportion achieving a set threshold (i.e. ≥ 0.15mcg/ml and ≥1.0 mcg/ml) show no significant difference between short interval [e.g. 4 weeks] vs. longer interval [e.g. ≥ 8 weeks] in the primary series on immunogenicity outcome for different types of Hib conjugates. There was no clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between observational studies using different dosing intervals or different Hib conjugates. Two months intervals between doses in the primary schedule were not shown to be consistently more immunogenic than one month interval in the observational studies. From long term impact studies both a 4 week and 8 week interval have been used in a number of countries with good sustained long term impact.
Quality of evidence	**We are moderately confident on the estimate of the effect.** There were no RCTs or observational studies that compared various intervals and, types of vaccine conjugate and that reported effect on various disease outcomes.
Caution	Not enough evidence on schedules using 2p+1 at short intervals (e.g. 4 weeks)

DURATION OF PROTECTION

Does using 2 or 3 primary doses plus a booster of Hib conjugate vaccine has a greater effect on duration of protection than using three primary doses without a booster?	
Conclusion	**Although there is some evidence for decrease over time in the proportion above a set threshold (i.e. >0.15mcg/ml and >1.0 mcg/ml) there is limited evidence for this decline being associated with an increase in disease.** (See further information on page 37-39).
Summary statement	The rationale for the 3p+0 schedule is predicated on the induction of sufficient primary antibody responses after three doses in infancy to reduce carriage and thus confer indirect protection through the early childhood years when susceptibility is greatest. In the UK over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, using PRP-T conjugate) and at the same time a catch up campaign with single dose of Hib (HbOC conjugate) given to those aged 13 months to 4 years, vaccine failures were observed primarily in children age 1-4 years who completed the primary vaccination series, despite the induction of immune memory. An increased in disease in previously non immunized children over 15 years of age was also seen, confirming the resurgence of Hib circulation. Enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign conducted when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis . This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant
Quality of evidence	**We are uncertain about the estimate of the effect** Although there is some evidence for decrease over time in proportion above a set threshold there is limited evidence to date for this decline being associated with increase in disease, except in the UK
Caution	As mentioned above, available data from developing countries on long-term duration of protection requires further evaluation. This is a complex issue. With high sustained vaccine coverage with a highly effective vaccine and a low force of infection, carriage may be reduced to a low level which results in less opportunity for boosting antibody levels by exposure but also a very low risk of disease. If VE in children drops then this might allow Hib to re-emerge. In countries, such as those in the developing world, with lower coverage and a higher force of infection, carriage of Hib may be still likely to be sufficiently common to result in continued boosting and maintenance of antibody levels and thus longer duration of direct protection in an individual but no indirect protection.

Hib combination vaccines: The above statements are based on evidence related to all the currently available Hib conjugate vaccines and to both combination and monovalent vaccines. There are limited data comparing the effect on Hib disease between vaccination schedules that include acellular vs. whole cell vaccine combinations. There is some evidence of lower immunogenicity (and limited data on lower clinical effectiveness outside the UK) when Hib vaccines are combined with acellular pertussis as compared to whole cell pertussis combinations. (See further information on page 55).

Sources of evidence

Although the systematic reviews used to inform this summary assessed several schedules with different numbers of primary doses and boosters, the summary below focus on information from studies that used 3p+0, 2p+1 and 3p+1. Full details of analyses and studies descriptions are available in each individual systematic review report. Hib conjugate vaccines of the following types were eligible for inclusion in this summary: PRP-HbOC (diphtheria CRM 197 protein conjugate), PRP-OMP (outer membrane protein (Neisseria meningitides conjugate) and PRP-T (tetanus toxoid conjugate).

Table 1. List of main articles used to inform this summary of evidence

Author (Year)	Title	Type of review	Number of studies included [time period]
Scott, P. et al. (2013)[2]	*Haemophilus influenzae* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules	Systematic review and meta-analysis	40 randomized clinical trials [earliest citation - June, 2012]
Griffiths, U. et al. (2012)[3]	Dose-specific efficacy of *Haemophilus influenzae* type b conjugate vaccines: a systematic review and meta-analysis of controlled clinical trials	Systematic review and meta-analysis	8 randomized clinical trials [not stated, search conducted March, 2011]
Jackson, C. et al. (2013)[4]	Systematic review of observational data on effectiveness of *Haemophilus influenzae* type b vaccines to allow optimization of vaccination schedules	Systematic review and meta-analysis	33 observational studies (20 case-control, 9 cohort, 4 other) [earliest citation - June, 2012]
Watt, J. et al. (2012)[5]	*Haemophilus influenzae* type b conjugate vaccine: review of observational data on long-term impact to inform recommendation for vaccine schedules	Systematic review	38 studies including data from 34 countries [earliest citation - June, 2012]
Garcia, S. et al.	Impact of vaccination against *Haemophilus influenzae* type b with and	Descriptive	Sentinel site surveillance data and

Author (Year)	Title	Type of review	Number of studies included [time period]
(2012)[6]	without a booster dose on meningitis in four South American countries	review	cross-sectional carriage surveys [not stated]

In addition, to ensure completeness we consulted the following reviews and individual articles:

Author (Year)	Title	Type of review	Number of studies included [time period]
Sanderson, C. et al. (2013)	Age at Hib disease, and the impact of delayed vaccination - report to WHO 2012 [7]	Systematic review	17 studies
Bar-On, E. (2012)[8]	Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, Hepatitis B and *Haemophilus influenzae* B (HIB) (Review)	Systematic review and meta-analysis	20 randomized clinical trials [Jan, 1966 - Nov, 2011]
Dhillon, S. et al. (2008)[9]	DTaP/IPV/Hib Vaccine (Pentacel)	Descriptive review	8 randomized clinical trials [not stated]
Chandran, A (2012)[10]	*Haemophilus influenzae* vaccines, in Vaccines 6th ed.	Textbook chapter	
Decker, M. et al. (2012)[11]	Combination vaccines, in Vaccines 6th ed.	Textbook chapter	
Peltola, H. et al. (1999)[12]	A five-country analysis of the impact of four different *Haemophilus influenzae* type b conjugates and vaccination strategies in Scandinavia	Descriptive review	Routine surveillance data from 5 countries [not stated]
Ladhani S. et al. (2010)[13]	Invasive *Haemophilus influenzae* disease, Europe 1996-2006	Descriptive review	
Mc Vernon J. et al (2007)[14]	Understanding the impact of Hib conjugate vaccine on transmission, immunity and disease in the UK	Mathematic model	
Mc Vernon J. et al (2004)[15]	Trends in *Haemophilus influenzae type b* infections in adults in England and Wales: surveillance study	Descriptive review	
Ladhani S. et al. (2009)[16]	*Haemophilus influenza* serotype b conjugate vaccine failure in twelve countries with established national childhood immunisation programmes	Descriptive review	

Burden of Hib disease[17]

Estimated Hib and pneumococcal deaths, children under 5 years of age for year 2008

In March 2012, the World Health Organization released estimates for global and regional year 2008 deaths from Haemophilus influenzae and Streptococcus pneumoniae among children under 5 years of age that update the estimates from year 2000. It is estimated that in 2008 globally there were 203,000 (uncertainty range: 139,000 - 287,000) child deaths due to Hib (*Haemophilus influenzae* type b) among those under 5 years, of which 199,000 (uncertainty range: 136,000 - 281,000) occurred among HIV-negative children. It is also estimated that there were 541,000 (uncertainty range: 376,000- 594,000) global child deaths due to pneumococcal (Streptococcus pneumoniae) infections among those under 5 years, of which 476,000 (uncertainty range: 333,000 – 529,000) occurred among HIV-negative children. Hib and pneumococcal global and regional mortality estimates by syndrome and HIV infection status are provided in Annex I. An update of the year 2000 pneumococcal and Hib case estimates has not been done for year 2008; Hib and pneumococcal case fatality ratios combining year 2008 deaths and year 2000 cases should not be done as there are important methodologic and key input differences in the year 2000 and year 2008 models. Based on the World Health Organization estimates of 8.8 million deaths among children under 5 years of age globally in the year 2008, (of which 5.2 million occurred in the non-neonatal period), Hib is estimated to cause 2% of all cause-child mortality under five and 4% of non-neonatal mortality while pneumococcus is estimated to cause 5% of all cause-child mortality under five and 9% of non-neonatal mortality. The year 2000 and 2008 Hib and pneumococcal mortality values are shown in Annex II. Although part of the reduction in number of deaths from Hib can be attributed to the introduction of Hib vaccine into the national immunization schedule of 68 countries between 2000 and 2008, the change in values should not be interpreted as a time-series or used as the values to infer the impact of Hib vaccine. Although the Hib mortality differences do include the effect of vaccine introduction, differences in the mortality estimates between the two time periods are deeply impacted by significant changes in the value of model input parameters (e.g. population size, child mortality, pneumonia mortality). Specifically the all-cause pneumonia death estimates by WHO declined from 1.8 million in 2000 to 1.2 million in 2008. This change is attributable to changes in estimation methods and model input values. The year 2008 Hib and pneumococcal mortality estimates, like the year 2000 estimates, do not incorporate any impact from PCV, which was not yet in use in the developing world by 2008.

Epidemiology of *Haemophilus influenzae* type b (Hib) meningitis in the pre-vaccine era [7]

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.

Age at Hib disease i) Re-examine an earlier literature review of the burden of Hib disease covering the period 1980-2005 (Watt et al 2009), 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

summarize 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, pleural fluid or from the blood, in a child with a clinical syndrome consistent with bacterial meningitis (WHO, 2003).

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.

Results 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 in Table 2.

Table 2: Age at invasive Hib disease and Hib meningitis: studies reporting % < 6m and % < 12m

					of all cases aged < 60m	
	Region	*n of studies*	*median year study started*	*median n of cases aged < 6m*	*median % aged < 6m*	*median % aged < 12m*
Invasive Hib	AMR	1	1992	180	41.5%	74.4%
	EMR	3	1993	258	39.5%	75.0%
	EUR	8	1990	193	17.0%	35.3%
	SEAR	1	1993	517	39.3%	92.5%
	WPR	5	1992	212	19.2%	41.0%
Hib meningitis	AFR	10	1990	52	37.0%	73.1%
	AMR	10	1989	200	26.0%	60.2%
	EMR	3	1999	51.5	39.7%	84.6%
	EUR	7	1981	151	15.3%	46.3%
	SEAR	4	1993	64	26.5%	85.5%
	WPR	5	1994	79	26.8%	59.3%

Figure 1: Age at invasive Hib disease & meningitis: studies with age bands of 2m or less, and fitted curves.

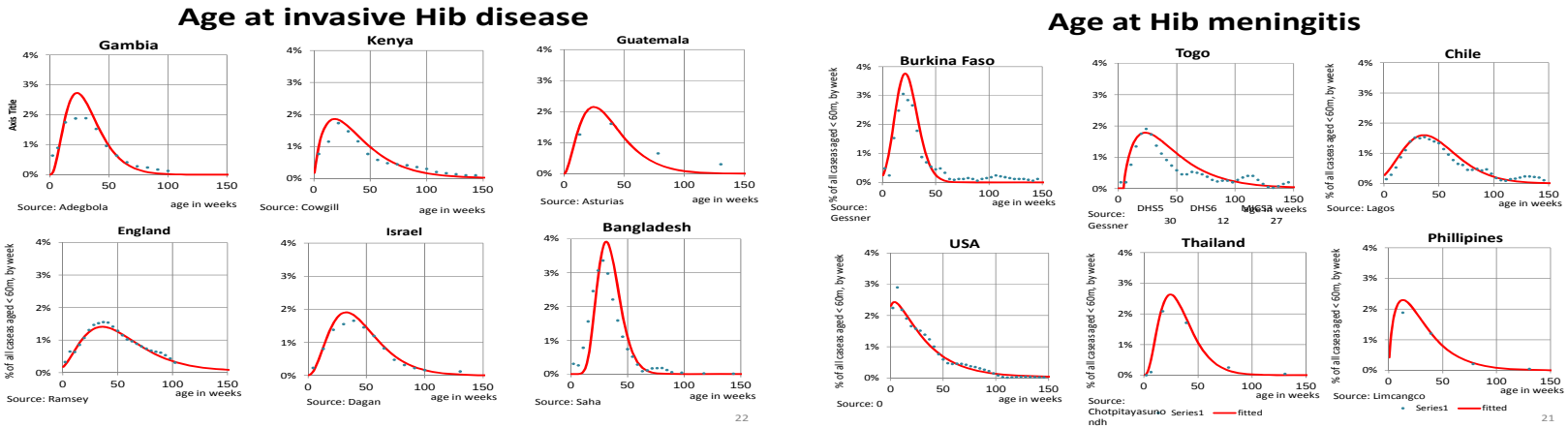
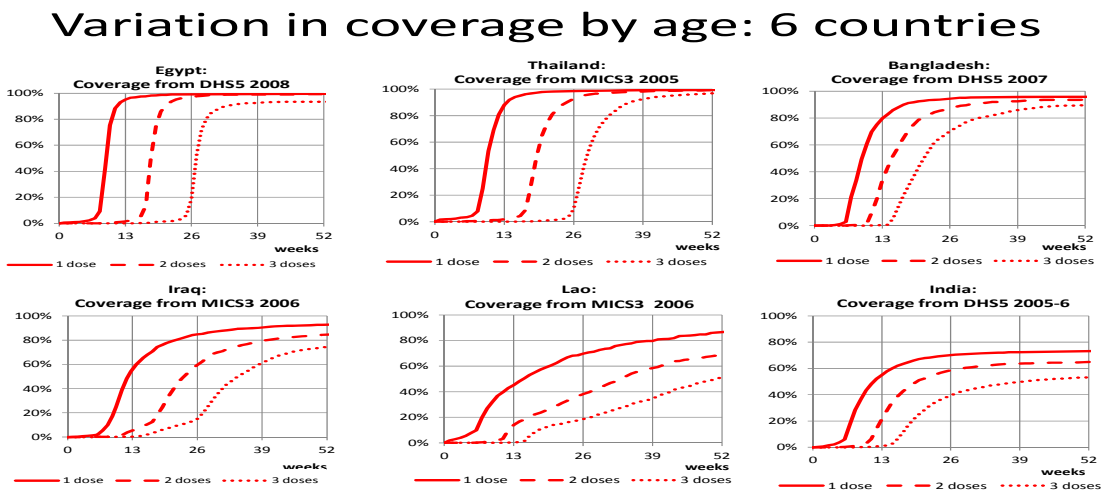


Figure 2: Age at vaccination: There were usable data in 42 DHS and 25 MICS surveys



WHO Recommendations for Routine Immunization (2006)[18]

"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. 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 has 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. (…). 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. "

Table 3. Recommended Routine Immunizations for Children (http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

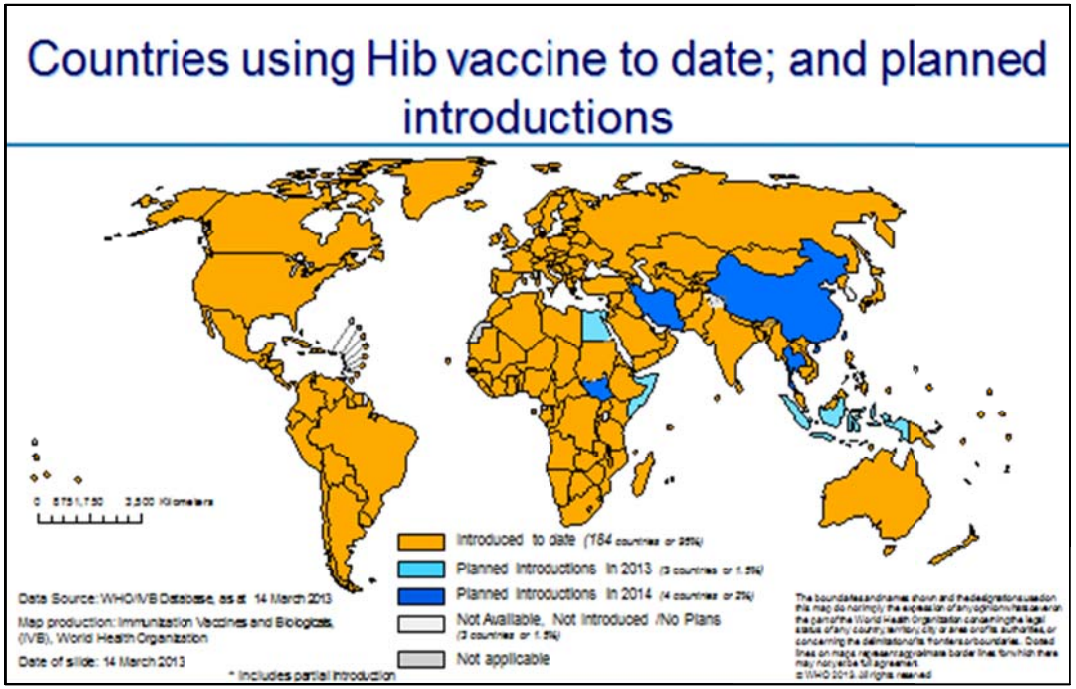
Antigen	Age at 1st dose	Doses in primary series	Interval between doses		Considerations (see footnote)
			1st to 2nd	2nd to 3rd	
Haemophilus influenza type b[1]	6 weeks (min) with DTP1, 24 months (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3	Single dose if > 12 months of age. Delayed/ interrupted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

[1] 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 vaccines globally and vaccines and schedules in use

In 1997, 31 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 March 2013, 184 (95%) of the countries introduced Hib containing vaccines, 3 countries are planning introduction in 2013 and 4 countries are planning introduction in 2014 (Figure 2). Data is not available or there are no introduction plans from 3 countries. Note that on a global level only 74% of all infants are receiving Hib vaccine.



Countries are currently using Hib vaccines in routine immunization programmes as part of a combination product (often as pentavalent vaccine presentation) using one of 3 different schedules:

- 56.2% of countries (mostly developing countries) use 3 primary doses (3p+0),
- 28% of countries (most of them industrialized countries) use 3 primary doses plus a booster (3p+1),
- 5.7% of countries (most of them industrialized countries) use 2 primary doses plus a booster (2p+1).

There are 41 countries using a combination that includes acellular pertussis vaccine, all with a schedule that includes a booster dose in the second year of life, the majority of which are from the European Region.

Table 4. Summary of Hib containing vaccine delivery as reported in the JRF, data as at 31st December 2011

	Total		AFR		AMR		EMR		EUR		SEAR		WPR	
	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort
No Hib	17	34,785,830	2	6,484,206	1	266,231	5	4,700,496	0	-	6	6,376,862	3	16,958,035
3 doses	109	77,103,805	41	23,143,673	23	6,607,251	10	9,730,506	14	1,790,237	5	31,224,881	16	4,607,256
2 doses + 1 booster	11	1,410,202	0	-	0	-	0	-	9	1,406,360	0	-	2	3,842
3 doses + 1 booster	55	20,008,149	3	1,781,140	11	8,629,986	7	1,323,878	28	6,249,073	0	-	6	2,024,072
other	2	1,689,399	0	-	0	-	0	-	2	1,689,399	0	-	0	-
use with combination of aP	41	8,197,901	2	1,068,886	2	461,012	1	23,405	32	5,693,936	0	-	4	950,662
use with combination of Wp	117	83,207,665	42	23,855,927	29	10,435,040	14	10,855,856	11	2,228,704	5	31,224,881	16	4,607,256
Other (some doses with ap and others with wp) * see notes	10	5,390,841	0	-	3	4,341,185	2	175,123	5	874,533	0	-	0	-
Hib mono only	8	1,726,195	0	-	0	-	0	-	4	648,943	0	-	4	1,077,252
ap combination Hib only	35	6,985,332	2	1,068,886	2	461,012	1	23,405	29	4,852,907	0	-	1	579,122
wp combination Hib only	115	82,603,869	42	23,855,927	28	10,325,398	14	10,855,856	10	1,734,551	5	31,224,881	16	4,607,256
ap combination Hib + Hib mono for booster	5	451,499	0	-	0	-	0	-	2	79,959	0	-	3	371,540
wp combination Hib + Hib mono for booster	2	603,795	0	-	1	109,642	0	-	1	494,153	0	-	0	-
other	12	7,840,865	0	-	3	4,341,185	2	175,123	7	3,324,557	0	-	0	-

Notes:

1. The list of countries that have introduced Hib includes the ones that have introduced in some parts of the country, which are Belarus, India and the Philippines. This explains the large birth cohort for SEAR that is for the entire country for India

2. The 17 countries not having introduced Hib are: China, Egypt, Equatorial Guinea, Haiti, Indonesia, Iran (Islamic Republic of), Iraq, Republic of Korea (the), Democratic People's Republic of Korea (the), Maldives, Myanmar, Nigeria, Singapore, Somalia, Thailand, Timor-Leste, South Sudan. Since then, the following countries introduced (but did not yet report to WHO their JRF with the schedule): Haiti, Iraq, DPRK, Maldives, Myanmar; Nigeria (in some parts of the country) and Timor-Leste.

3. Are not counted here the 8 countries that are using Hib monovalent only + Russia that is using Hib mono only with only 2 doses schedule

Number of primary doses

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two primary doses?	
Conclusion	**Data suggest that at least three doses of Hib vaccine are required to achieve high effectiveness**.
Summary statement	**From the studies identified, data available do not clearly favour a 3p+0 or 2p+0 schedule in terms of disease outcomes or immunogenicity for various Hib vaccine types [except for PRP-OMP].** The observed marginal increase in efficacy and effectiveness was considerably greater between the first and second dose, than between second and third dose, when assessed as part of the primary series. The data found did not show significant differences by type of Hib vaccine conjugate (except PRP-OMP conjugate as reported efficacy and effectiveness with one or two doses was reported as > 90%) or for combination vaccines using wP or aP. Data available from RCTs suggest that a booster dose after a 2p primary series results in high levels of proportion above a set threshold (i.e. > 1.0 ug/ml)). If a two primary doses schedule is selected, evidence suggests that efficacy and effectiveness over time will be high. There is some evidence that DTaPHib vaccines may be less effective and less immunogenic that DTwPHib vaccines.
Quality of evidence	**We are uncertain about the estimate of the effect.** We were unable to identify data from RCTs or observational studies reporting direct comparison between 2 and 3 primary doses for disease outcomes for any of the conjugates, and using different vaccine combination types such as aP containing vaccines. In terms of immunological outcomes, seven RCTs provided immunological data to compare two doses versus three primary doses. There was also information from observational studies.
Caution	Estimates of vaccine efficacy from different trials in terms of immunogenicity cannot be compared directly as evidence of equivalence or superiority of one particular schedule and there were too few trials for a network metanalysis which would allow such a comparison. It is important to note that most of the evidence on effect on disease outcomes is drawn from observational studies and few RCTs comparing schedule versus no vaccination. The observational studies took place when the vaccine was in routine use and other children in the community may have received 3 or more doses. There is no experience from any country using a 2p+0 schedule.

Effect of 3p+0 and 2p+0 schedules on selected disease outcomes

Table 5. Summary of studies reporting on Hib vaccine efficacy (PRPT-conjugate) and effectiveness on Hib disease: studies comparing 3p+0 or 2+0 schedule versus no vaccination

We found no data from RCTs or observational studies that directly compare 3p+0 vs. 2p+0 schedules.

PRP-T vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
RCTs- two RCTs (Gambia –Mulholland 1997[19] and Chile – Lagos 1996[20]) **Observational studies** – four studies (Gambia–Adegbola 2005[21], Chile-Lagos 1996[20], Germany–Kalies 2008[22] and Germany-Kalies 2004[23]). All used combined Hib vaccines including wP vaccine with the exception of the German studies that used aP.	**RCTs-** no RCTs **Observational studies** – six studies (Uganda-Lee 2008[24], Dominican Republic-Lee 2008[25], Uganda-Lewis-2008[26], Malawi-Daza 2006[27], The Gambia-Adegbola 2005[21], Bangladesh-Baqui 2007[28]). All used combined Hib vaccines including wP vaccine.	**RCTs**- two RCTs (Gambia-Mulholland 1997[19], Chile-Lagos 1996[20], reported on radiologically defined pneumonia and one RCT (Indonesia - Gesner 2005[29]) reported on clinical pneumonia. **Observational studies –** two studies (Colombia-de la Hoz 2004[30] and Bangladesh-Baqui 2007[28]) after 3p+0. All used combined Hib vaccines including wP vaccine except for Colombia which used monovalent Hib vaccine.
The Gambia -Mulholland 1997[19] reported PP VE after 3p+0 was 95% (95%CI 67-100). Chile-Lagos 1996[20] reported PP VE after 3p+0 was 91.7% (95%CI 64.8, 100). A case control study that compared 2p+0 vs. 3p+0 (The Gambia-Adegbola 2005[21]) reported no statistically significant difference between both schedules. Cohort studies (Chile-Lagos 1996[20], [2]Germany–Kalies 2008[22] and Germany-Kalies 2004[23]) reported VE against invasive Hib disease as follows: 90.4 (95% CI 70.6-96.8) (Germany 2008[22]),	In the observational studies, VE against Hib meningitis after two or more doses ranged from 65% (95% CI-190 to 100%)[28] to 99% (95% CI 92-100%)[24]. Excluding the estimate of 65%, the lowest reported effectiveness against Hib meningitis after 2 or 3 doses was 87% (95% CI 14-100%)[25]. Meta-analysis (Jackson C et al 2012)[4] using community controls produced estimates of VE against Hib meningitis of 55% (95% CI 2-80%), 94% (95% CI 65-99%) and 94% (95% CI 18-100%) for 1, 2	In the RCTs, the reported PP VE against radiologically defined pneumonia was 22.4% (95%CI -1.9, 38.6) for the individually randomized trial (Gambia –Mulholland 1997[19]) and 23% (95%CI1, 40) in the cluster-randomized trial (Chile-Lagos 1996 [20]). ITT VE estimates were similar to PP estimates. In the RCT that reported ITT VE against clinical pneumonia was 4% (95%CI 0.7,7.1) In an observational study in Colombia [30]

[2]

PRP-T vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
91.7 (95% CI 64,8-100) (Chile 1996[20]) and, 96.7 (95% CI 87.7-99.1) (Germany 2004[23]) for 3p+0. Acellular pertussis was used in the two German studies, all studies used combination vaccines. VE for 1-2 doses ranged from 68.4 (95% CI 19-87.6) in Germany 2008[22] to 89.6% (95% CI 67-96.7) in Germany 2004[23]. Based on the screening method, in England & Wales during 1993-2003, when the intended schedule was 3p+0 (at 2, 3, 4 months) and PRPT was used, VE against invasive Hib disease for full primary vaccination or a single catch-up dose at age $\geqslant$13 months was estimated to be 57% (95% CI 42 to 67%), or 72% in a sensitivity analysis which assumed that vaccination coverage in the population was 2% than reported (UK – Ramsay 2003[31]). VE against invasive Hib disease was only 49% (95% CI 32 to 64%) when vaccinees were defined only as children who received their 3 primary doses. VE overall (full primary vaccination plus catch up) and VE restricted to full primary vaccinees only were both higher within two years of scheduled vaccination (66%, 95% CI 51-76%) than after two years (37% 95% CI 3-62%). VE was estimated to be higher in children vaccinated at	and 3 doses, respectively. The estimates using hospital controls were similar: 53% (95% CI -14-81%), 92% (95% CI 75-97%) and 94% (95% CI 65-99%). There was no or very limited heterogeneity between studies using community controls; in studies using hospital controls, the one-dose estimates were moderately heterogeneous (I^2 = 35.8%). For Hib meningitis, one Danish study (published in 2004 and using data from 1991-1999), which used various schedules over the study period and which did not specify what vaccines were used, presented dose specific VE which suggest high VE was achieved after a single dose: VE 1 dose: 97.74% (90.77–99.45%); 2 doses 98.94% (95.71–99.74%); 3 doses 99.29% (94.87–99.90%)[33]	effectiveness of 3p+0 was reported to be 55% (95% CI 7-78%). In Bangladesh [28], VE after 3p+0 were estimated to be 44% (95% CI 16-63%) or 32% (95% CI -2 to 54%) effective against radiologically confirmed pneumonia, based on hospital and community controls, respectively[3].

[3] These estimates are based on cases of pneumonia diagnosed both by study personnel and by an independent paediatrician who reviewed the radiograph. If the VE estimate is instead based on cases diagnosed by only study personnel or by only the independent paediatrician, then the estimate is lower than that stated above, potentially as low as 16% (95% CI -11 to 37%) based on community controls diagnosis by the independent paediatrician.

PRP-T vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
more than one year of age compared with those vaccinated during infancy (HbOC vaccine was predominantly used in the catch-up campaign in the UK). It is important to note that during the 2000-2002 period approximately half of the conjugate Hib vaccine was in combination with aP vaccine. This later vaccine has reportedly associated with lower Hib immunogenicity. A German screening method study[32] reported VE against invasive Hib disease during 1998 and 1999, when the intended schedule was DTaP-Hib or DTaP-IPV-Hib given at 2, 3 and 4 months followed by a booster at 11-15 months. VE estimates were, 95.4% (92.7; 97.2) for two doses and 98.9% (98.3; 99.3) for three doses, compared to 0 doses).		

Table 6. Summary of studies reporting on Hib vaccine (PRP-OMP conjugate) efficacy and effectiveness on Hib disease: studies comparing 3p+0 or 2p+0 schedule versus no vaccination

We found no data from RCTs or observational studies that directly compare 3p+0 vs. 2p+0

PRP-OMP vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
RCTs –one RCT (USA-Santosham 1991[34]) using monovalent wP **Observational studies**- two (USA- Harrison 1994[35] and USA-Vadheim-1994[36]) .	**RCTs**- one RCTs (USA- Santosham 1991[34]) **Observational studies -** no observational studies	**RCTs**- no RCTs **Observational studies-** no observational studies
Data from the RCT in the USA-Santosham 1991[34] was collected from individuals with onset of invasive Hib disease before their second dose. This trial reported PP VE 100% (95%CI 15,100) for one dose and 93% (95%CI 53, 98) for two doses. One case control study (USA-Harrison 1994[35]) reported not statistically significant difference between 2p+0 (99% 95%CI 69-100) and 3p+0 (99% 95%CI -57-100) schedules. Another case control study (USA-Vadheim 1994[36]) reported not statistically significant difference between 1p+0 (100% 95%CI 39-100) and 2p+0 (100% 95% CI -68-100) schedules.	No data found	No data found

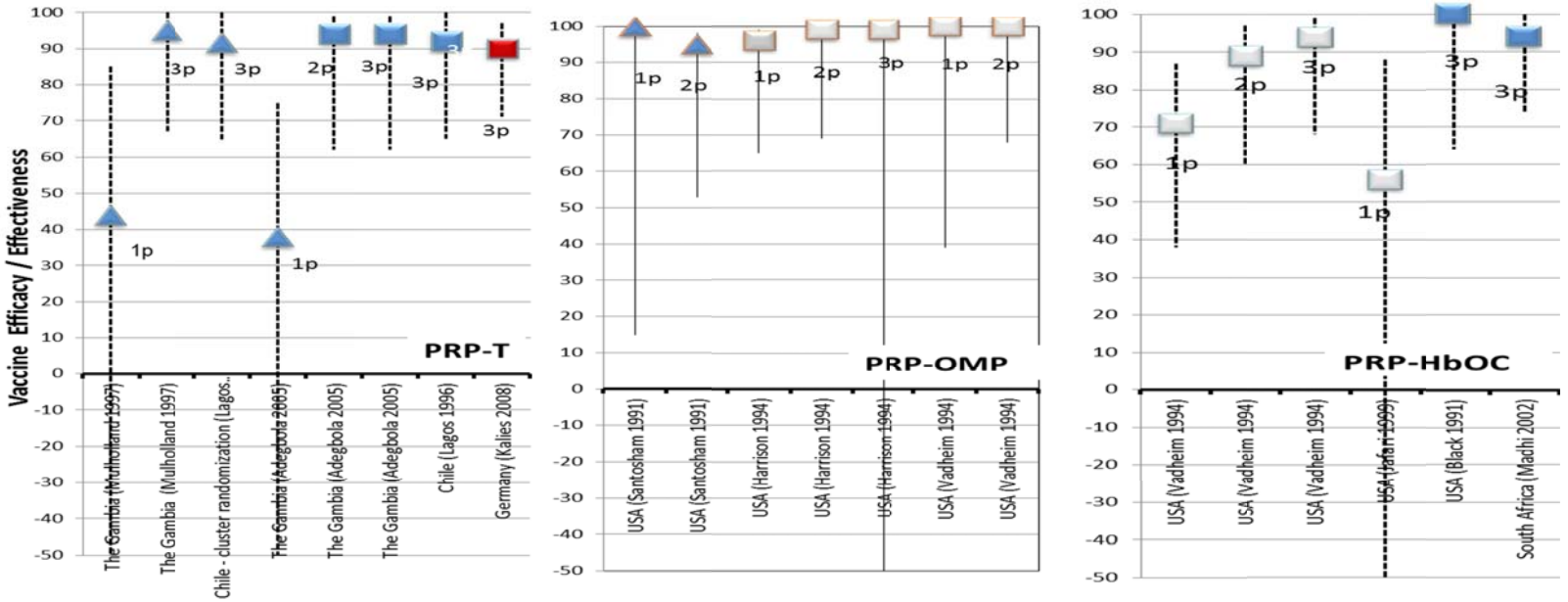
Table 7. Summary of studies reporting on Hib vaccine (HbOC conjugate) efficacy and effectiveness on Hib disease: studies comparing 3p+0 or 2p+0 schedule versus no vaccination

We found no data from RCTs or observational studies that directly compare 3p+0 vs. 2p+0

PRP-HbOC-vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
RCTs– no RCTs **Observational studies** – Four studies (USA-Vadheim 1994[36], USA –Jafari 1999[37], USA-Black 1991[38] and South Africa-Madhi 2002[39]).	**RCTs–** no RCTs **Observational studies- -** no observational studies	**RCTs–** no RCTs **Observational studies-** one observational study (Brazil-de Andrade 2004[40]).
The observational studies that compared 3p+0 vs. no vaccination reported vaccine effectiveness above 94% and one study that compared 2p+0 vs. no vaccination reported vaccine effectiveness of 89%. One study (USA-Vadheim 1994) reported not statistically significant difference between 2p+0 and 3p+0. The pooled estimates from meta-analysis (Jackson C et al 2012[4]) of studies that used PRP-T or PRP-HbOC vaccines were 59% (95% CI 30-76%) for one dose and 99% (95% CI 77-100%) for three doses (only two studies which used PRP-T or PRP-HbOC vaccines reported two-dose VE against invasive Hib disease, so meta-analysis was not performed). There was high heterogeneity in the three-dose estimates (I2 = 79.8%) but not in the one-dose estimates (I2 = 0%). Sufficient data for meta-analysis of vaccine effectiveness from cohort studies that used PRP-T or PRP-HbOC were identified only for three doses against invasive Hib disease. The South African study [39] stratified VE estimates by HIV status; only the estimate for HIV-uninfected children is included in the meta-analysis. The pooled VE estimate was 94% (95% CI 88-97%),	No data found	The observational study from Brazil [40] reported the effectiveness of two or more doses against radiologically confirmed pneumonia as 31% (95% CI -9 to 57%), based on an intended schedule of 2, 4, 6 months and using HbOC. All of these estimates of effectiveness against radiologically confirmed pneumonia [28 30 40]are lower than those of the effectiveness of two or three doses against invasive Hib disease and Hib meningitis. 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[29]. 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.

PRP-HbOC-vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
with little heterogeneity (I2 = 0%).		The reported VE point estimates were -4.9 (ITT) and -12.0 (PP).

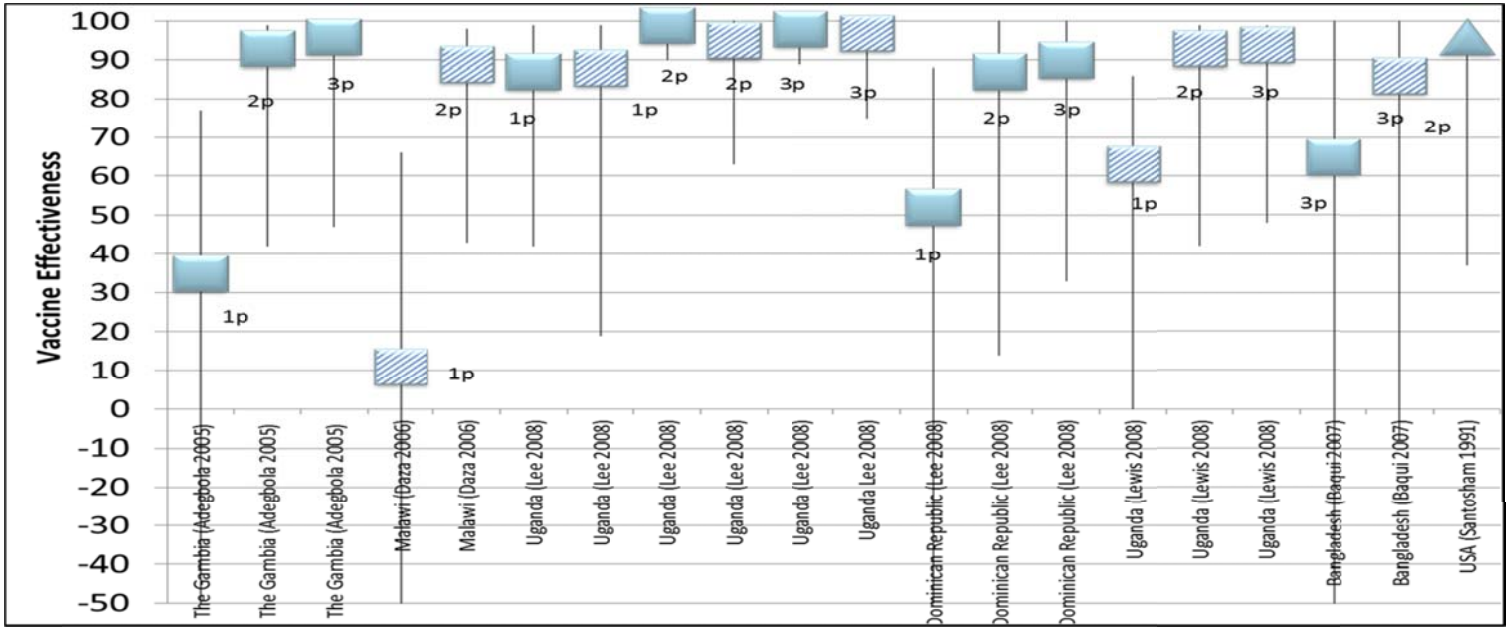
Figure 3. Studies reporting on Hib vaccine efficacy and effectiveness on invasive Hib disease - studies comparing schedule versus no vaccination



Triangle = RCT, Square = Observational study, Blue= wP, Red= aP, Grey= not stated.NB: Data from the RCT in the USA-Santosham 1991 was collected from individuals with onset of invasive Hib disease before their second dose. The Gambia -Mulholland 1997 data for 1p+0 is reported for outcomes with onset after one dose. Onset before second dose also but not included in this summary.

Figure 4. Studies reporting on Hib vaccine effectiveness on Hib meningitis - studies comparing schedule versus no vaccination

All studies are case control studies except Santosham which is an RCT. All studies used PRP-T conjugate combined with wP (shown in squares) except the USA-Santosham 1991[34], which used monovalent Hib PRP-OMP conjugate vaccines (shown in triangle).

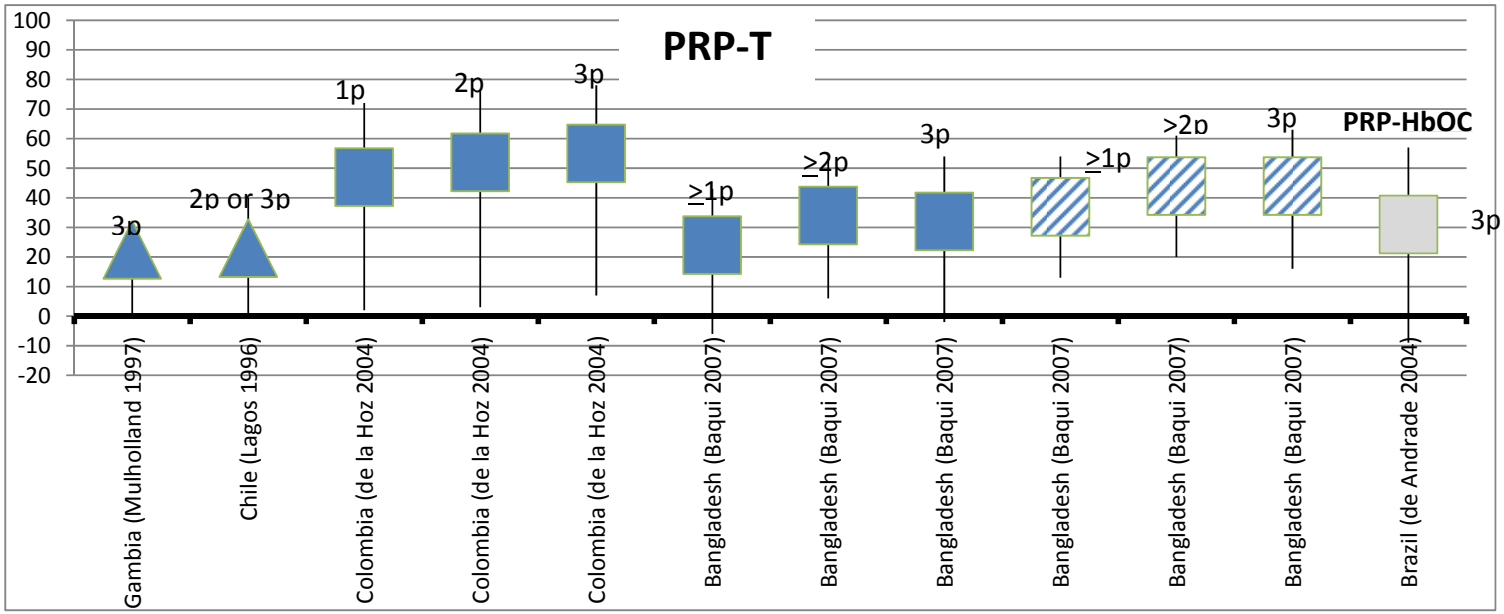


Solid marker = Community controls; Striped marker = Hospital control

Blue= wP
Red= aP
Grey= not stated

Figure 5. Studies reporting on Hib vaccine efficacy and effectiveness on radiologically defined pneumonia - studies comparing schedule versus no vaccination

All studies used PRP-T conjugate combined with wP except the Colombia-De la Hoz 2004[30] that used monovalent Hib PRPT and Brazil-de Andrade 2004[40], which used monovalent Hib PRP-HbOCvaccine .



Triangle = RCT, Square = Observational study, Blue= wP, Red= aP, Grey= not stated, solid= community control, hatches= hospital control

Effect of 3p+0 or 2p+0 on selected immunological outcomes

Table 8: Summary of studies reporting proportion above a set threshold (i.e. ≥1.0 ug/ml) and/or risk difference at the set threshold after 1 or 6 month post primary and/or geometric mean Concentrations (GMCs)

Three primary doses (3p) vs. two primary doses (2p)
PRP-T vaccines - six trials provided immunological data for this comparison (Chile –Lagos 1998[41], Chile Lagos 1998[42], Guatemala-Asturias 2009[43], Netherlands-Labadie 1996[44], Niger Campagne 1998[45], Sweden Carlsson 1998[46]). In three trials examining (Chile4 –Lagos 1998[41], Niger Campagne 1998[45], Sweden Carlsson 1998[46]), the proportion above a set threshold around 1m after vaccination was high for both 3p and 2p schedules at 0.15µg/ml. The proportions above a set threshold were lower at the 1.0µg/ml threshold and at 6m after last dose in the primary schedule. Neither the 2p nor the 3p schedule was consistently favored in analyses. By six months after the last primary dose, there was no statistical evidence of a difference between the schedules at the 1.0µg/ml threshold (pooled risk difference -0.02, 95%CI -0.10, 0.06, I^2 0%) but it remained high at the 0.15µg/ml threshold (pooled risk difference 0.02 95%CI -0.10, 0.14, I^2 75%). A case-control study performed at the time demonstrated an increased risk of vaccine failure in those who received the DTaP-Hib combination (Ramsay et al., 2003[31]). Despite intensive study and the supposition that Hib carriage must have increased in the period, associated with increased disease, adequately powered studies of Hib carriage in various age groups failed to reveal significant Hib carriage in the United Kingdom population during this period (Heath & McVernon, 2002[47]). Trotter and colleagues (Trotter et al., 2003[48]) studied serum samples obtained from different birth cohorts and showed that Hib antibody titres beyond the first year of life in cohorts immunized after the catch-up campaign did not differ significantly from titres in similarly aged children in the pre-vaccine era. McVernon and colleagues (McVernon et al., 2004b[49]) analysed anti-PRP IgG titres in the serum stored from adults in the United Kingdom, spanning the period 1991 to 2003, and showed that titres in adults declined and remained low following the introduction of Hib conjugate. This was presumably as a result of reduced exposure to Hib due to the reduction in carriage associated with the introduction of conjugate. Low circulating titres in toddlers and adults may thus explain the increase in invasive disease in the United Kingdom between 1999 and 2002, which suggests that immune memory alone in a vaccinated child is unable to provide robust protection against invasive Hib disease. A catch-up campaign was undertaken in the United Kingdom in 2003 for all children under the age of five years, and the incidence of invasive Hib disease reduced. A routine Hib booster dose was introduced into the United Kingdom schedule in 2006[50]. A UK study (Southern 2007[51]) recruited, through immunisation clinics, 388 children aged 6 months to 4 years who had previously received their full primary Hib vaccine series and were given a booster dose in a catch-up campaign. Amongst these children, the GMC before the booster decreased with time since

Three primary doses (3p) vs. two primary doses (2p)
vaccination, and thus age. Despite this, the post-booster GMC increased with age at boosting: 29.87µg/ml, 68.41µg/ml and 182.36µg/ml in each group one month after booster. All but one of the 344 participants who had a blood sample taken one month after the booster had a titre ⩾0.15µg/ml one at that time, and all but three had a titre ⩾1.0µg/ml.
PRP-OMP vaccines – we did not find RCTs for this vaccine type. An observational study in the USA (Shehab 1991[52]) which used PRP-OMP vaccine did find an increase in GMT after a single dose. The GMT increased from 0.11 to 1.75 µg /ml after a single dose administered at the age of 2-3 months. The GMT increased further in all age groups following the second dose, e.g. to 3.5 µg /ml in those vaccinated at 2-3 months of age. The fold increases in GMT were 15-31, depending on age group after the first dose and 2-3 after the second. There was little difference between age groups in the percentage of children whose antibody titres reached 1.0 µg /ml after the first dose (76%, 75% and 72% of children aged 2-3 months, 4-5 months and 6-11 months at vaccination) or the second (91% of children aged <6 months and 92% of children aged 6-11 months).
PRP-HbOC vaccines – two trials examined PRP-HbOC (USA Lieberman 1995[53] and Chile –Lagos 1998[41]). One trial (Chile –Lagos 1998[41]) examined PRP-HbOCand presented seropositivity data. Point estimates favored the 3p group but the confidence interval crossed the null effect at both two and six months after the last dose and for both thresholds. The trial which reported only GMC (USA Lieberman 1995[53]) examined PRP-HbOCand compared a birth dose plus doses at 2 and 4 months of age to doses at 2 and 4 months of age. Two months after the last dose, the GMC in the 3p group (birth-dose group) was 0.93µg/ml (95%CI 0.48, 1.69) and 0.20µg/ml (95%CI 0.10, 0.29) in the 2p group. In an observational study of the immunogenicity of HbOC and PRP-D vaccines carried out in Finland (Käyhty 1989[54]), 46 children received HbOC at ages 4 and 6 months, and 25 of these received a booster dose at 14 months. Blood samples were taken before each vaccination and one month after the second and third doses, and anti-PRP antibody titres measured. There was no increase in GMT after the first dose of HbOC (0.07µg/ml before, 0.09µg/ml after); after the second dose, GMT increased to 4.32µg/ml and all children had a titre >0.15µg/ml.

Use of Hib vaccines and observation of their clinical efficacy in practice has questioned the relevance of the ≥0.15 ug/ml and ≥1.0 ug/ml (ref)concentration as surrogates of protection following conjugate vaccination (Eskola et al., 1999[55]) although they are still widely used today for licensure purposes.
The fact that conjugate vaccines induce memory, suggests that irrespective of the antibody concentrations achieved after vaccination, priming for memory responses may provide protection of longer duration, particularly if ongoing exposure to Hib is able to maintain circulating antibody concentration.
Protection against invasive Hib disease in the face of vaccine induced memory but the absence of circulating antibody is not clearly established (Galil et al., 1999[56]) and is illustrated with experience in the United Kingdom.

An increase in antibody avidity following primary immunization and boosting has been demonstrated in Hib conjugate immunogenicity trials (Goldblatt, Vaz & Miller, 1998[57]; Anttila et al., 1999[58]). Avidity measurements have thus been proposed as a surrogate marker for the successful generation of immunological memory. The relative importance of memory versus circulating antibody levels for clinical protection by conjugate vaccines is unclear. During the development and evaluation of Hib conjugate vaccines, two thresholds were identified, one that predicted short-term and one that predicted long-term protection respectively (i.e. $\geq$0.15 ug/ml and $\geq$1.0 ug/ml).

Need for a booster dose

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
Conclusion	**In some countries, administering a booster dose during the child's second year of life has been deemed necessary to sustain overall disease control in population and direct protection of toddlers. However, the need for booster doses in non-industrialized countries requires further evaluation.**
Summary statement	Available data suggest that after 5 years of vaccine introduction using a 3p+0 schedule a significant reduction in meningitis in young children was observed in a number of developing countries. A recent evaluation from four South American countries reported that Hib meningitis rates were similar 6-10 years post introduction in countries with and without boosters. There is similar data from a dozen of non-industrialized countries that have used a 3p+0 schedule for at least 6 years. However, the UK had a different experience: after the introduction of a 3p+0 schedule (2, 3, 4 months) in 1992 with PRPT-conjugate alongside a catch-up campaign for toddlers 12-48 years of age (with HbOC conjugate vaccine), the UK had an initial decline in cases, but started observing an increase in Hib over a decade after an initial decline in cases. As a result of this, a Hib vaccination booster campaign using (PRP-T conjugate) was conducted between May and September 2003, offering one dose of vaccine to all children who were aged between 6 months and 4 years on 1 April 2003 and to those children who reached 6 months of age during the campaign. A routine booster dose in the vaccine schedule was introduced in 2006. Following these interventions cases declined again. Data from industrialized countries suggest that immunogenicity may be lower with PRPT conjugate and aP containing vaccine and this could have an impact on duration of protection. Emerging reports on some resurgence of Hib cases in older children in The Gambia (3p + 0) highlight the need for further evaluation of duration of protection and of the role of a booster dose in non-industrialized country settings [e.g. 10 years after introduction of Hib vaccine in combination with whole cell pertussis vaccine]. If boosters are deemed necessary (i.e. as part of a 2p+1 or 3p+1 schedule), an alternative to routine booster at 11 months or later may be to implement catch-up campaigns targeting toddlers. The UK experience suggests that they have resulted in important reductions of overall carriage
Quality of evidence	**We are moderately confident on the estimate of the effect.** Assessment of the need for booster doses is challenging because (a) there are no data directly comparing clinical effectiveness

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
	between similar primary schedules with and without booster No data are currently available from developing country settings using aP containing combination vaccines without a booster dose.
Caution	The situations in which a booster dose should be used remain unclear, and it would depend on various factors including local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Effect of 3p+1 and 2p+1 on selected disease outcomes

We did not identify RCTs or observational studies that compared these schedules to a 3p+0 schedule. The conclusions below are based on data from long term impact post vaccine introduction (Watt J et al 2012[5]) that are described in page 38 of the 3p+1 or the 2p+1 regimens.

In some countries, administering a booster dose during the child's second year of life has contributed to sustain overall disease control in population and direct protection of toddlers. However, the need for booster doses in non-industrialized countries requires further evaluation. Data from industrialized countries suggest that immunogenicity is lower with an aP containing vaccine and this could have an impact on duration of protection.

No data are currently available from developing country settings using aP containing combination vaccines without a booster dose. Available data suggest that after 5 years of vaccine introduction using a 3p+0 schedule a significant reduction in meningitis in young children has been observed in a number of developing countries.

A recent evaluation from four South American countries reported that Hib meningitis rates were similar 6-10 years post introduction in countries with and without boosters. However, the UK after the introduction of a 3p+0 schedule (2, 3, 4 months) with the PRPT-conjugate alongside a catch-up campaign for toddlers 12-48 years of age (with HbOC conjugate) experienced an increase in Hib cases several years after an initial decline in cases. Cases again declined after two booster campaigns and the introduction of a routine booster dose to the vaccine schedule. (see pages 31-36).

The situations in which a booster dose should be used remain unclear, and might relate to local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Emerging reports on cases of Hib disease from the Gambia highlight the need for further evaluation of duration of protection and of the role of a booster dose in some settings [e.g. 10 years after introduction of Hib vaccine in combination with whole cell pertussis vaccine]. See pages 39-48.

If boosters are deemed necessary, an alternative to routine booster is to implement catch-up campaigns targeting toddlers. The UK experience suggests that they have resulted in important reductions of overall carriage. See page 49.

Table 9. Summary of studies reporting on Hib vaccine efficacy and effectiveness on selected disease comparison of 3p+0 versus schedules including a booster dose.

Hib invasive disease	Hib meningitis	Hib pneumonia
Three primary doses (3p+0) vs. two or three primary doses and a booster (2p+1 or 3p+1)		
No data from RCTs or observational studies that directly compared three primary doses with other primary doses and a booster schedules	No data from RCTs or observational studies that directly compared three primary doses with other primary doses and a booster schedules	No data from RCTs or observational studies that directly compared three primary doses with other primary doses and a booster schedules
Two or three primary doses and a booster vs. no vaccination (2p+1 or 3p+1 vs. no vaccination)		
PRP-T vaccines – No data from RCTs or observational studies	**PRP-T vaccines** – No data from RCTs or observational studies	**PRP-T vaccines** – No data from RCTs or observational studies
PRP-OMP vaccines – No data from RCTs or observational studies	**PRP-OMP vaccines –** No data from RCTs or observational studies	**PRP-OMP vaccines –** No data from RCTs or observational studies
PRP-HBOC vaccines – No data from RCTs or observational studies	**PRP-HBOC vaccines –** No data from RCTs or observational studies	**PRP-HBOC vaccines –** No data from RCTs or observational studies

Effect of 3p+1 or 2p+1 on selected immunological outcomes

A booster dose after a primary series of either two or three doses of Hib conjugate vaccine results in high levels of seropositivity. There was no evidence from trials that the age at which the booster dose is given, or the interval between the primary series and the booster dose affect the level of seropositivity. Proportion above a set threshold levels in children after a booster dose are much higher than in children who received the same primary schedule without a booster. The interval between the last vaccine dose and blood draw is, however, shorter in children receiving the booster than in those who received only the primary schedule, and it is not clear if differences in antibody levels can be interpreted as differences in protection from Hib disease. The UK experienced an increase in Hib cases several years after an initial decline in cases subsequent to the introduction of a 3p+0 schedule (2, 3, 4 months) alongside an early catch-up campaign. Cases again declined after two booster campaigns and the introduction of a routine booster dose to the vaccine schedule.

Table 10. Summary of studies reporting on Hib vaccine efficacy on selected immunological outcomes: comparison of 3p+0 versus for schedules including a booster dose.

Three primary doses (3p+0) vs. two primary doses and a booster (2p+1)	Three primary doses (3p+0) vs. three primary doses and a booster (3p+1)
PRP-T vaccines - One trial provided immunological data for this comparison (Sweden-Carlsson 1998[46]) using PRP-T. This trial reported seropositivity and GMC data. At 13 months of age (seven months after the 3p group received their last primary dose and one month after the 2p+1 group received their booster); the 2p+1 schedule resulted in higher proportions above a set threshold than the 3p schedule at both the 0.15µg/ml and 1.0µg/ml thresholds. The risk difference was -0.79 (95%CI -0.87, -0.71) at the 1.0µg/ml threshold (favors the 2p+1 schedule) and -0.20 (95%CI -0.27, -0.13) at 0.15µg/ml. The proportion above the 0.15µg/ml threshold	**PRP-T vaccines -** two trials provided immunological data for this comparison (Canada-Scheifele 2005[59], Europe- Knuf 2011[60]). Both examined PRP-T, and one reported seropositivity data (Europe-Knuf 2011[60]). Both trials reported GMC. At 13 months of age (one month after the 3p+1 group received their booster dose), the 3p+1 schedule resulted in higher proportions above a set threshold than the 3p schedule at both the 1.0µg/ml (risk difference 0.59, 95%CI 0.52, 0.67) and 0.15µg/ml thresholds (risk difference 0.16, 95%CI 0.11, 0.22).

Three primary doses (3p+0) vs. two primary doses and a booster (2p+1)	Three primary doses (3p+0) vs. three primary doses and a booster (3p+1)
remained high at around 6 months after a 3p schedule. This proportion was lower at the 1.0µg/ml threshold. Additionally, six trials included in this review reported data for an individual trial arm receiving a 3p schedule or a 2p+1 schedule (Chile4 –Lagos 1998[41], Chile5-Lagos 1998[42], Guatemala-Asturias 2009[43], Netherlands-Labadie 1996[44], Niger-Campagne 1998[45], Sweden-Carlsson 1998[46]). High proportions of individuals remained above the 0.15µg/ml threshold 6 months after a 3p schedule. The proportion was lower at the 1.0µg/ml threshold but there was variability between trials.	One trial reported only GMC (Canada-Scheifele 2005[59]). At 16 months of age a group which received a 3p schedule with a booster dose at 15 months of age achieved a GMC of 29.2µg/ml (95%CI 24.58, 36.43) and a group which had received a 3p schedule with no booster dose by 16 months of age achieved a GMC of 0.32µg/ml (95%CI 0.25, 0.41). A UK study (Southern 2007[51]) recruited, through immunisation clinics, 388 children aged 6 months to 4 years who had previously received their full primary Hib vaccine series and were given a booster dose in a catch-up campaign. Amongst these children, the GMC before the booster decreased with time since vaccination, and thus age. Despite this, the post-booster GMC increased with age at boosting: 29.87µg/ml, 68.41µg/ml and 182.36µg/ml in each group one month after booster. All but one of the 344 participants who had a blood sample taken one month after the booster had a titre ≥0.15µg/ml one at that time, and all but three had a titre ≥1.0µg/ml.
PRP-OMP vaccines – We did not find RCTs for this vaccine type. A study, carried out in Alaska Native infants (Bulkow 1993), compared three different Hib conjugate vaccines and also found that geometric mean antibody titres were increased after one dose of PRP-OMP intended to be given at the age of 2 months, and increased further after a second dose intended to be given at 4 months. However, vaccination with HbOC or PRP-T required 3 doses (intended to be given at 2, 4 and 6 months) for a substantial rise in GMT, although the results are influenced by the timing of sample collection (samples were taken 2 months after doses 1 and 2, but 1 month after dose 3.)	**PRP-OMP vaccines –** We did not find RCTs for this vaccine type.

Three primary doses (3p+0) vs. two primary doses and a booster (2p+1)	Three primary doses (3p+0) vs. three primary doses and a booster (3p+1)
PRP-HbOC vaccines – We did not find RCTs for this vaccine type. In the Finnish study (Käyhty 1989[54]) of 25 children given a primary series of HbOC at 4 and 6 months with a booster at 14 months, the GMT immediately prior to the booster dose was 1.12µg/ml. This increased to 58.3µg/ml following the booster.	**PRP-HbOC vaccines –** We did not find RCTs for this vaccine type.

Impact of Hib vaccines on carriage

The mechanism of protection against carriage is not well understood, but high levels of serum anti-PRP IgG (>5 lg/mL) have been associated with protection against carriage, and the presence of anti-PRP antibodies in saliva is associated with high serum levels of anti-PRP antibody. Vaccination strategies that elicit higher post-vaccination anti-PRP levels may therefore be more effective in reducing Hib carriage and transmission. The reduction in Hib carriage directly determines herd immunity and significantly contributes to the protection of the vaccinated population. However, in a non-vaccinated population, Hib encountered in the course of childhood may contribute to immunity by repeated stimulation of antibody production thereby inducing both individual and herd immunity. Thus in a vaccinated population reduction in carriage results in a decrease in natural boosting and, in the absence of further doses of vaccine, serum antibody concentrations wane. Initial efficacy trials, involving only a subset of the population may have underestimated this effect (reference Goldblatt et al 2007[61]).

There were no eligible carriage outcome data from trials that compared different schedules of Hib vaccination. One trial presented data about carriage for 1p1= vs. no doses (Gambia-Mulholland 1997[19]). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was low (I2 0%). The point estimate showed slightly less carriage with one dose of PRP-T compared to no doses but confidence intervals were very wide (pooled odds ratio 0.82, 95%CI 0.14, 4.71). This trial also reported about carriage for 2p+0 vs. no doses although it was randomized trial of a 3p schedule (Gambia-Mulholland 1997[19]). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was moderate (I2 47%). The point estimate showed less carriage with two doses of PRP-T compared to no doses but confidence intervals were very wide (pooled odds ratio 0.52, 95%CI 0.08, 3.37). Again, this trial, comparing three primary doses of PRP-T at 2, 3 and 4 months with no Hib doses, reported carriage data (Gambia-Mulholland

1997[19]). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was low (I2 0%). The combined odds ratio comparing three doses of PRP-T to no doses was 0.36 (95%CI 0.25, 0.53, I2 0%).

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

A study in Turkey compared the prevalence of carriage in fully vaccinated, partially vaccinated and unvaccinated children (the intended vaccination schedule was 2, 4, 6 and 18 months, using PRP-T) 53. 19/57 (33%) fully vaccinated children carried Hib in the oropharynx, compared to none of 17 partially vaccinated and 46/85 (54%) unvaccinated children. After adjusting for previous respiratory infection, having a sibling aged <5 years, breastfeeding and recent antibiotic use, the OR comparing unvaccinated to fully vaccinated children was 3.76 (95% CI 1.61 – 8.80). This implies a VE of 73% (95% CI 38-89%). This estimate is not adjusted for age, time since vaccination or socioeconomic status (although the authors state that there was no association between carriage and parental job)[84]

A study in Native American children[63] reported the prevalence of carriage in relation to age and the number of doses of PRP-OMP received (intended to be given in 3 doses at ages 2, 4 and 12-15 months). Overall, 65% of carriers and 80% of non-carriers had received at least one dose before the swab was taken; 13% of carriers and 36% of non-carriers had received the intended number of doses for their age. The point estimate of the prevalence of carriage was highest in unvaccinated children in all age groups (Figure 6) but confidence intervals were wide (the number of carriers was <10 in each group) and there was no apparent dose-response relationship. After adjusting for age and the presence of a respiratory infection at the time of swabbing, the OR comparing children who were not age-appropriately vaccinated to those who were, was 2.66 (95% CI 1.00 – 7.05, p = 0.05) 54. This implies a VE against carriage of 62% (95% CI 0 – 86%).

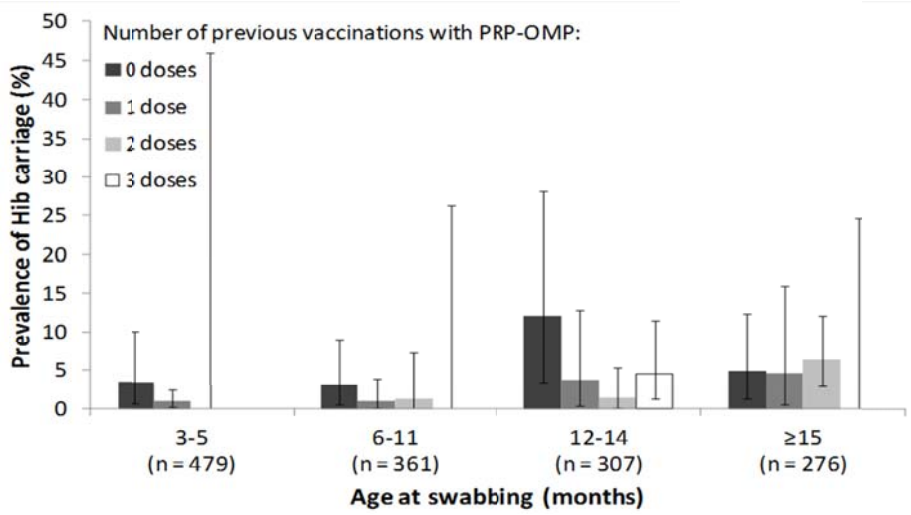


Figure 6: Prevalence of oropharyngeal carriage of Hib by Native American children, by age and number of previous doses of PRP-OMP. Error bars show 95% exact binomial CIs (or one-sided 97.5% CIs if the point estimate is zero) [63]

In the UK, carriage was assessed in 143 children (recruited via computerised immunisation records) who had received three doses of Hib-containing vaccine in relation to the number of doses given as DTaP-Hib 51. Only three carriers were identified: one had received no doses of DTaP-Hib and two had received three doses. These small numbers do not allow a comparison of the effects of DTaP-Hib versus other vaccines on effectiveness against carriage. The studies included here which report the prevalence of carriage according to the number of vaccine doses received did not suggest an obvious dose-response relationship, but the number of carriers was usually small. However, these studies of Hib vaccination indicate some reduction in carriage, perhaps with an effectiveness of 60-70%. They are thus consistent with population data showing dramatic impacts of Hib vaccines against invasive disease in several populations.

Duration of protection and considerations for immunization schedule selection

Does using 2 or 3 primary doses plus a booster of Hib conjugate vaccine has a greater effect on duration of protection than using three primary doses without a booster?	
Conclusion	**Although there is some evidence for decrease over time in the proportion above a set threshold (i.e. >0.15mcg/ml and >1.0 mcg/ml) there is limited evidence for this decline being associated with an increase in disease.**
Summary statement	The rationale for the 3p+0 schedule is predicated on the induction of sufficient primary antibody responses after three doses in infancy to reduce carriage and thus confer indirect protection through the early childhood years when susceptibility is greatest. In the UK over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, using PRP-T conjugate) and at the same time a catch up campaign with single dose of Hib (HbOC conjugate) given to those aged 13 months to 4 years, vaccine failures were observed primarily in children age 1-4 years who completed the primary vaccination series, despite the induction of immune memory. An increased in disease in previously non immunized children over 15 years of age was also seen, confirming the resurgence of Hib circulation. Enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign conducted when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis . This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant
Quality of evidence	**We are uncertain about the estimate of the effect** Although there is some evidence for decrease over time in proportion above a set threshold there is limited evidence to date for this decline being associated with increase in disease, except in the UK
Caution	As mentioned above, available data from developing countries on long-term duration of protection requires further evaluation. This is a complex issue. With high sustained vaccine coverage with a highly effective vaccine and a low force of infection, carriage may be reduced to a low level which results in less opportunity for boosting antibody levels by exposure but also a very low risk of disease. If VE in children drops then this might allow Hib to re-emerge. In countries, such as those in the developing world, with lower coverage and a higher force of infection, carriage of Hib may be still likely to be sufficiently common to result in continued boosting and maintenance of antibody levels and thus longer duration of direct protection in an individual but no indirect protection.

The rationale for the 3p+0 schedule is predicated on the induction of sufficient primary antibody responses after three doses in infancy to reduce carriage and thus confer indirect protection through the early childhood years when susceptibility is greatest.

In the UK over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, using PRP-T conjugate) and at the same time a catch up campaign with single dose of Hib (HbOC conjugate) given to those aged 13 months to 4 years, vaccine failures were observed primarily in children age 1-4 years who completed the primary vaccination series, despite the induction of immune memory. An increased in disease in previously non immunized children over 15 years of age was also seen, confirming the resurgence of Hib circulation. Enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign conducted when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis . This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant. Although there is some evidence for decrease over time in proportion above a set threshold (i.e. >0.15mcg/ml and >1.0 mcg/ml) there is limited evidence for this decline being associated with increase in disease, except in the UK.

As mentioned above, available data from developing countries on duration of protection requires further evaluation. In the UK, over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, mostly PRP-T conjugate), vaccine failures were occurring primarily in children aged one to four years who completed the primary vaccination series, but an increase in disease in those over 15 years of age was also seen.

In addition to the information on proportion above the set thresholds over time described above, we reviewed data on vaccine failures from observational studies.

Furthermore, we discussed recent information from vaccine failures in the UK, South Africa and The Gambia in the section on experience with Hib vaccines use and long term impact of various schedules.

Two case-control studies presented data on children who developed Hib disease despite having been vaccinated[24 36]. In one of these studies, from Uganda[24], three children developed Hib meningitis after receiving two doses of Hib vaccine with DTwP, all within one year of the second dose. Three children who had received three doses developed Hib meningitis within three years of the third dose.
These six vaccine failures ranged in age from 17 to 157 weeks (Lee et al 2008[24]).

The second case-control study to include data on vaccine failures was from the USA and reported 27 vaccine failures in total (Vadheim 1994[36]). Eighteen children were diagnosed with invasive Hib disease after a single vaccine dose, all within one year of vaccination. Six and three children developed disease after two and three doses, respectively, again within one year of the most recent dose.

Three cohort studies included data on the time since the last vaccine dose in vaccine failures (Kalies 2008[22], Kalies 2004[23], Madhi 2005[64] and Madhi 2002[39]). In two of these studies (from South Africa and Germany), Hib vaccine was given with DTwP [34, 36, 37.] All children in the German study, and all but one of the South African children not infected with HIV, developed disease within a year of receipt of their final dose of Hib vaccine (irrespective of the total number of doses). In the South African study, children infected with HIV appeared to develop disease later than vaccine failures who were not HIV-infected, e.g. four HIV-infected children developed disease $\geqslant$2 years after receiving two or three doses (Madhi 2005[64] and Madhi 2002[39]).

Amongst cohort studies in which Hib vaccine was given with DTaP[22 23], almost all vaccine failures occurred within two years of receipt of the last dose of vaccine. Vaccine failures also occurred in two children who received two doses of monovalent Hib vaccine (12-23 months after the second dose) and one child who received two doses of DT-Hib.

Experience with Hib vaccine use and impact of various schedules

Observational studies in countries using Hib conjugate vaccine for at least five years suggest that various Hib vaccination schedules in use worldwide have been very effective (Watt J et al 2012[5]). There are limited data available to assess the interaction of different epidemiologic settings and vaccination schedule. Because instances of diminished vaccine effectiveness are few, there are limited data available to assess the relationships between different epidemiologic settings, vaccination coverage levels, vaccination schedules and vaccine effectiveness. To illustrate the impact of various vaccination schedules in different parts of the world we summarized the experience from a selected number of countries in each region.

Table 11. Summary of evidence on long term impact of Hib vaccines with schedules with and without a booster dose

	Schedules without a booster dose	Schedules including a booster dose
Non – industrialized countries	Most developing countries have implemented a primary series only (3p+0), with good effectiveness. In Kenya Hib disease incidence has declined since vaccine introduction. Reports indicate that Anti-PRP Geometric Mean Concentration has declined and yet nasopharyngeal carriage prevalence of H. influenzae has remained low. In The Gambia preliminary reports of an increase in number of cases of Hib disease have led local investigators to ponder whether Hib disease protection may be waning 15 years after introduction. In South Africa following vaccine introduction, there was a substantial decrease in the number of Hib cases, however, from 2003-2009 investigation on vaccine failures suggested a possible resurgence of Hib disease. South Africa introduced a booster dose in 2010.	Data from four Latin American countries found no difference in vaccine impact in the two countries which use a booster dose (Argentina and Uruguay) compared with the two which do not (Chile and Colombia).
Industrialized countries	Limited data are available on the use of a schedule without a booster dose (3p+0) in industrialized countries. The United Kingdom, experienced a resurgence of Hib disease approximately 6 years after vaccine introduction using a 3p + 0 schedule. While multiple factors likely contributed to this resurgence, addition of a booster dose resulted in decreased disease incidence.	With a few exceptions, industrialized countries have implemented schedules that include a primary series and a booster dose (3p+1). In general, schedules used in industrialized countries have been highly effective. Data from Finland and other Scandinavian countries suggest that two vaccine doses in early infancy, followed by a late booster (2p+1), are efficacious in protecting children from *Haemophilus influenzae* type b (Hib) infection, and will practically eliminate Hib meningitis. In Italy, Hib vaccination using a 2p+1 schedule has been in use since 1999. Overall, pediatric H. influenzae disease has become less common whereas there has been a slight increase of disease in the elderly. Among industrialized countries in Watt et al 2012, all but Italy (2p+1) and the Czech Republic (3p+0) reported higher disease incidence among children less than one year of age compared with children 1-4 years of age.

Watt J and colleagues (2012[5]) reviewed data on invasive Hib disease at least 5 years following vaccine introduction[4]. They limited the analysis to countries with at least 100,000 live births per year so that disease incidence estimates for young children would be stable. One hundred two countries introduced Hib conjugate vaccine into their routine infant immunization schedule on or before January 1, 2006. Of these, 50 (49%) had at least 100,000 live births in 2010. Data on Hib disease at least 5 years after vaccine introduction were available from 34 (68%) of these 50 countries. By WHO region, data were available from 4 countries in the African region, 18 countries in the Americas, 11 in the European region, and 1 in the Western Pacific region. Data on disease incidence at least 5 years after vaccine introduction was available from 21 countries. Data on case characteristics from sentinel sites was available from an additional 13 countries.

Table 12. Description of Hib vaccine schedules in selected countries with data on Hib disease at least 5 years following vaccine introduction.

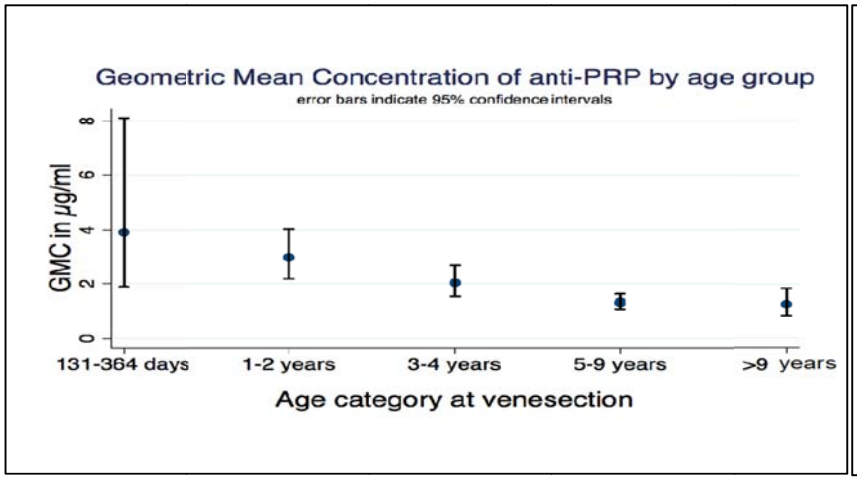
Country	WHO region	Year of introduction	Vaccine presentation	Current type of pertussis vaccine	Schedule	Primary schedule	Booster dose	DATA TYPE AVAILABLE
Kenya	AFRO	2001	DTP/HepB/Hib	wP	3p+0	6, 10, 14 wks.	None	Incidence
The Gambia	AFRO	1997	DTP/HepB/Hib	wP	3p+0	2, 3, 4 mos	None	Incidence
Malawi	AFRO	2002	DTP/HepB/Hib	wP	3p+0	6,10,14 wks	None	Case
Uganda	AFRO	2002	DTP/HepB/Hib	wP	3p+0	6,10,14 wks	None	Case
South Africa	AFRO	1999	DTP/Hib until 2008. DTaP/Hib/IPV from 2009	aP	3p+1	6, 10, 14 wks.	Booster dose added 2010.	Incidence
Chile	AMRO	1996	Hib until 2006. DTP/HepB/Hib from 2007.	wP	3p+0	2, 4, 6, mos	None	Incidence
Colombia	AMRO	1998	Hib until 2002. DTP/HepB/Hib from 2003.	wP	3p+0	2, 4, 6, mos	None	Incidence
Brazil	AMRO	1999	Hib until 2002. DTP/Hib from 2003.	wP	3p+0	2, 4, 6, mos	None	Incidence
Canada	AMR	1986	DTaP/Hib/IPV	aP	3p+1	2, 4, 6, mos	18 mos	Incidence
United States of America	AMR	1991	Various	aP	3p+1	2, 4, 6, mos	12-15 mos	Incidence

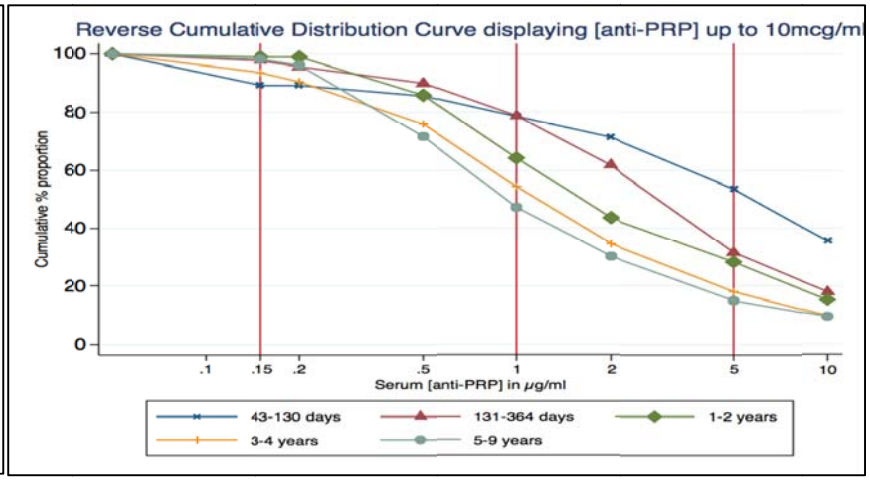
[4] This time range was selected based on the experience in the United Kingdom where disease resurgence was observed beginning 6 years after vaccine introduction. Five years was selected as the threshold to increase the amount of data for review.

Country	WHO region	Year of introduction	Vaccine presentation	Current type of pertussis vaccine	Schedule	Primary schedule	Booster dose	DATA TYPE AVAILABLE
Uruguay	AMR	1994	DTP/HepB/Hib	wP	3p+1	2, 4, 6, mos	12 mos	Incidence
Argentina	AMR	1997	DTP/Hib	wP	3p+1	2, 4, 6, mos	18 mos	Incidence
Sweden	EUR	1992	Various		2p+1	3, 5 mos	12 mos	Incidence
Italy	EUR	1999	Various DTaP/Hib combinations	aP	2p+1	3, 5 mos	11-12 mos	Incidence
Czech Republic	EUR	2001	Hib monovalent until 2006. DTaP/Hib/HepB/IPV from 2007	wP	3p+0	9, 13, 17 wks.	18 mos	Incidence
United Kingdom	EUR	1992	DTP/Hib until 1999. DTaP/Hib combinations from 1999	aP	3p+1	2, 3, 4 mos	12 mos (added in 2003)	Incidence
Netherlands	EUR	1993	Hib monovalent until 2002. Switched to DTP/Hib/IPV in 2003. Switched to DTaP/Hib/IPV or DTaP/Hib/HepB/IPV in 2005	aP	3p+1	2, 3, 4 mos	11 mos	Incidence
Israel	EUR	1994	DTP/Hib/IPV until 2001. DTaP/Hib/IPV from 2002 onwards.	aP	3p+1	2, 4, 6 mos	12 mos	Incidence
Australia	WPR	1993	DTaP/Hib/HepB/IPV Hib/HepB (PRP-OMP, indigenous children)	aP	3p+1	2, 4, 6 mos and 2,4 mos	12 mos	Incidence

Kenya (3p+0)[5]

In November 2001, Kenya, Hib vaccine was introduced as part of a pentavalent using a 3p+0 schedule (at 6, 10, and 14 weeks of age). A catch-up campaign was not conducted. Coverage with three doses of vaccine by 12 months of age was estimated to be 87% in 2004 (Ndirtu BMC Pub Health 2006). Culture-based surveillance for invasive Hib disease at Kilifi District Hospital has been conducted from 2000 through present. Antibodies to Polyribosylribitol Phosphate (PRP), were assessed by ELISA on serum samples collected in 2009, from 471 children aged 0 to 15 years residing in the KDHSS. Long-term protective anti-PRP titres (>1mcg/ml) were detected amongst 75.8% (95% CI 57.7-88.9) of children aged <1 year, 71.3% (64.0-77.7) of children aged 1-5 years and 52.9% (46.4-59.4) of children aged 5-15 years. Anti-PRP Geometric Mean Concentration declined from 3.9mcg/ml (95% CI 1.9-7.8) amongst children aged <1 year to 2.4mcg/ml (2.0-3.0) amongst children aged 1-5 years to 1.3mcg/ml (1.1-1.6) amongst children aged 5-15 years (preliminary analyses). (See GMC values and reverse cumulative distribution curves (below.). Analysis of anti-PRP antibodies is ongoing for ~1000 serum samples collected from children in 1998 – 2007. Nasopharyngeal carriage prevalence of H. influenzae has been assessed in cross-sectional surveys conducted in the KHDSS in 2004, 2009, 2010, 2011, and 2012. The prevalence of Hib carriage in children <5 years of age in the KHDSS was 6 (1.7%)/349 in 2004 (Abdullahi PIDJ 2006) and 1(0.2%)/623 in 2009-2012 (preliminary analysis, personal communication A Scott and L Hermit[65]).





[5] Summary courtesy of Dr L Hammit Johns Hopkins Bloomberg School of Public Health, USA and Dr A Scott London School of Hygiene and Tropical Medicine, UK

South Africa (3p+0 and then 3p+1)[6]

South Africa introduced Hib conjugate vaccine in 1999 as a 3 dose primary series without a booster dose. The initial vaccine was a PRP-T combination vaccine with a whole cell pertussis component. In 2009, this vaccine was replaced with a combination vaccine containing an acellular pertussis component and inactivated polio vaccine (IPV).(Von Gottberg, 2012[66]) Following vaccine introduction, there was a substantial decrease in the number of Hib cases identified by the national surveillance system (Von Gottberg, 2006[67]) However, from 2003 through 2009, despite high vaccination coverage, detection rates of Hib disease in children <5 years increased from 0.7 per 100,000 population in 2003 to 1.3/100,000 in 2009 ($p < 0.001$). Among 263 episodes of invasive Hib disease among children with known vaccination status, 135 (51%) were classified as vaccine failures. Of vaccine failures, 55% occurred among case patients ⩾18 months old. HIV status was documented for 90 children with vaccine failure; 53% were not HIV infected. Vaccine failures, which occurred in both HIV-infected and -uninfected children, comprised half of the rise in invasive Hib disease. In November 2010, children in South Africa began receiving a booster dose of HibCV as part of a pentavalent vaccine (Von Gottberg 2012[66]). The introduction of the booster dose was driven by polio prevention since IPV was being used and not a response to change in Hib disease incidence.

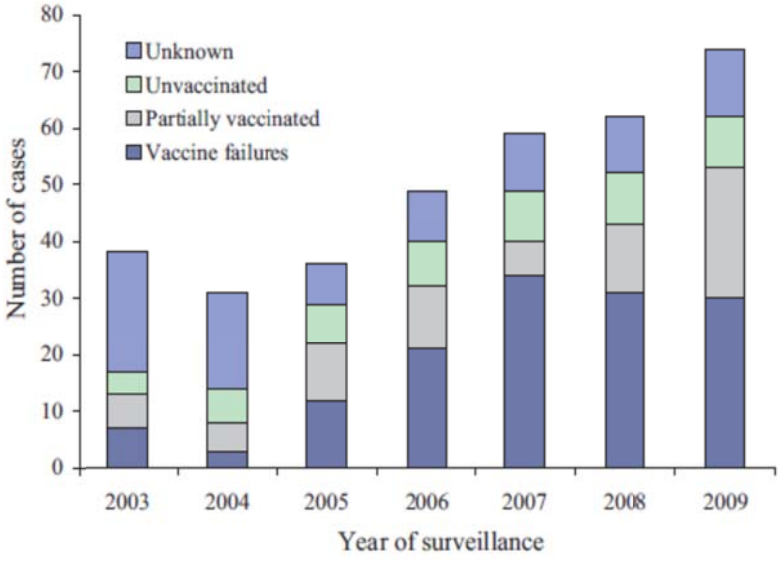


Fig. 2. Number of children <5 years with confirmed invasive *Haemophilus influenzae* serotype b disease (n=349) by vaccination history and year, South Africa, 2003–2009.

[6] Summary prepared using information kindly provided by Dr A von Gottberg, Centre for Respiratory Disease and Meningitis, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service, South Africa

Figure 10: Number of reported cases of invasive Haemophilus influenzae (Hi) disease in children <5 years (n=1455), by serotype and year, South Africa, 2003-2009.

Invasive pneumococcal disease (IPD) documented for children <5 years is depicted for the same time period. Serotype b = *H. influenzae* serotype b; Non-typeable = non-encapsulated H. influenzae; other encapsulated Hi = *H. influenzae* serotypes a, c, d, e, and f.

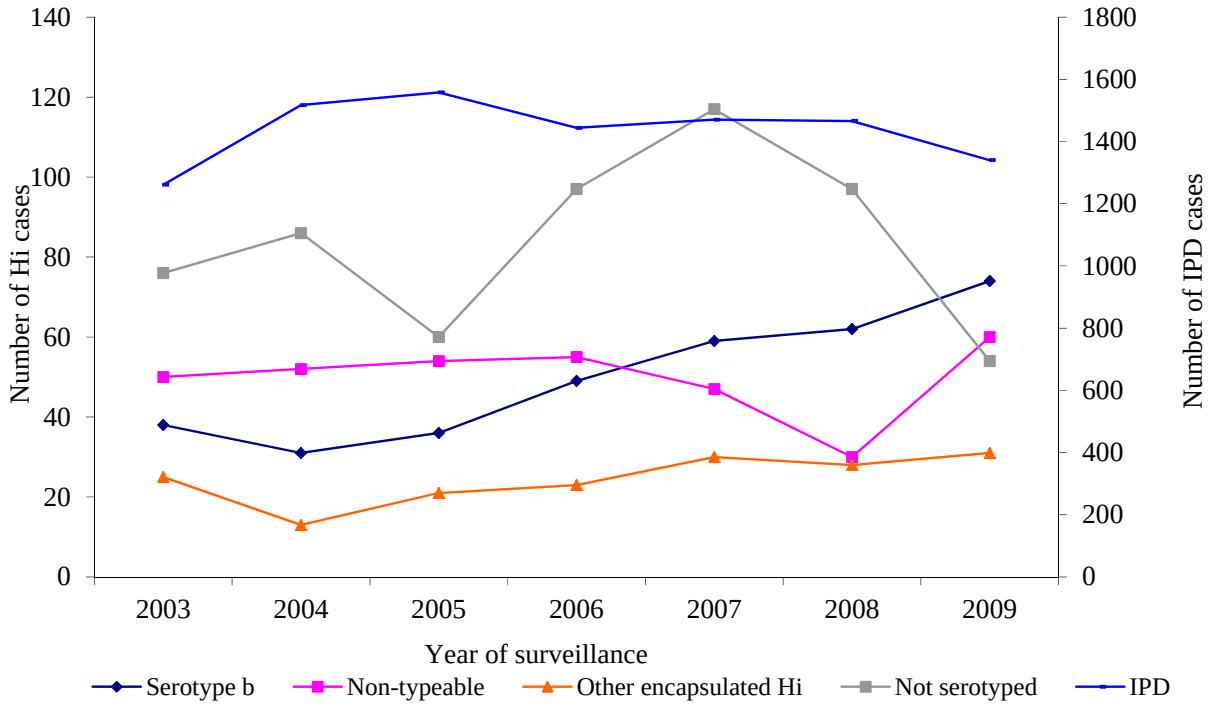


Figure 11: Number of children <5 years with confirmed invasive *Haemophilus influenzae* serotype b disease (n=349) by vaccination history and year, South Africa, 2003-2009

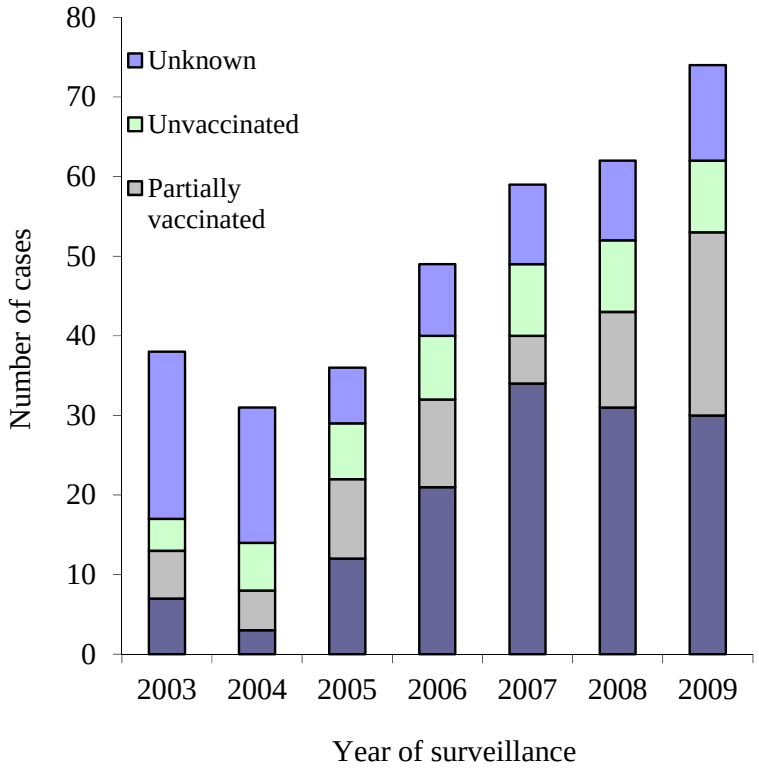


Figure 12: Number of children with confirmed invasive *Haemophilus influenzae* serotype b disease, reported by age and known vaccination status (n=263), South Africa, 2003-2009

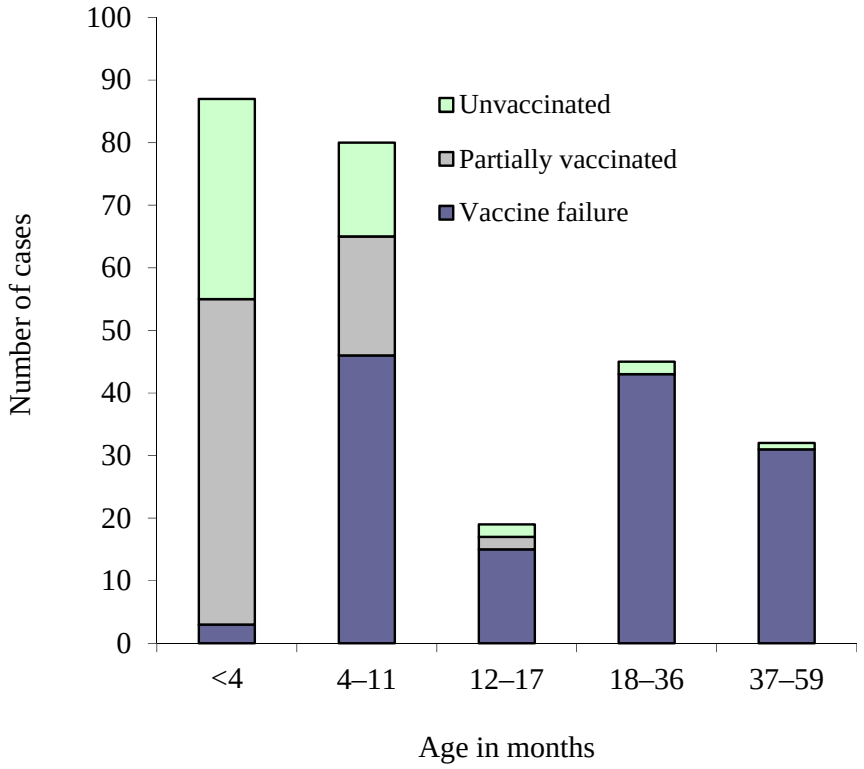
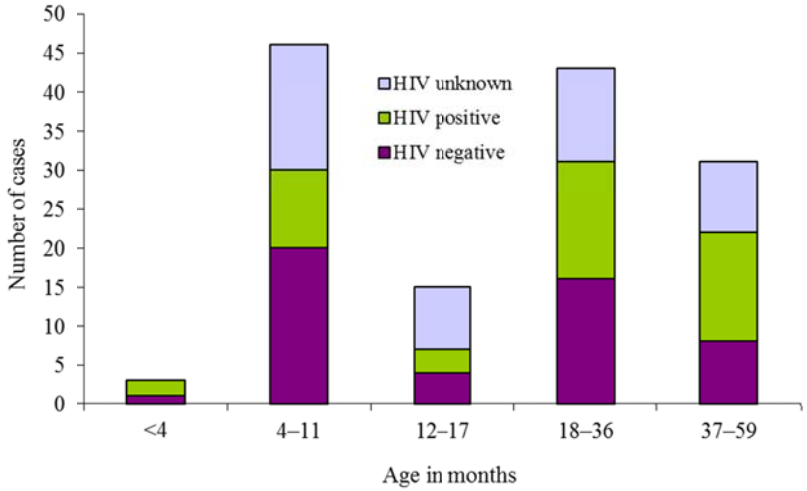


Figure 13: Number of *Haemophilus influenzae* serotype b vaccine failures (n=138) by age and HIV infection, South Africa, 2003-2009



The Gambia- (3p+0) Routine conjugate Hib vaccination with a 3-dose primary series was introduced into The Gambia in 1997, the first introduction in Africa, with virtual elimination of Hib disease by 2002. Sporadic cases were observed thereafter through incidental detection in hospitals but formal surveillance in The Western Region from 2007-2010, extending 14 years after introduction, confirmed a low incidence of invasive disease (Hib meningitis <3 per 100,000 under 5), a low rate of carriage (0.9% in 1 year olds), high community seroprotection (99.3% of 2-5 year olds with protective antibody levels), and high

vaccine coverage (92% having 3 doses at 1 yo). These observations were not suggestive that a booster dose was required. In 2011 and 2012 formal clinical and microbiological surveillance in Eastern Gambia associated with PCV introduction (Aug 2009) detected over 20 cases, having detected one in the previous 2 years; this was accompanied by incidentally detected hospital cases in the Western Region where formal surveillance had stopped in 2010. Around half had had 2 or more doses of vaccine and half were under 1 year of age. Local investigators suggest that this resurgence raises the question of the need for a booster dose, and reinforces the need for continuing high quality surveillance of Hib disease

Table 13. Overview of key milestones in the Hib immunization programme of The Gambia

Time period	Vaccination coverage	Surveillance system	Hib disease incidence	Age distribution of cases	Carriage
Before 1997	Pre-routine vaccination	Western Region (formal clinical/microbiological surveillance)	meningitis 70 per 100,000 children <5 years (1990)	80% <12 months of age	12% (1-2 year olds)
2002, 5 years after introduction,	2000 for 1-2 yo: 3 doses 68%, 2 doses 84%, 1 dose 94%; Median age at 1st, 2nd, 3rd doses (2000): 3.4m, 6.5m, 8m	Western Region (formal clinical/microbiological surveillance)	meningitis 0 per 100,000 children <5 years		0.25% (1-2 year olds)
2006		no formal surveillance		Western Region, hospital cases detected incidentally	Cases: N=5 ; median age 15 months
2007-2010	1-2 yo - 3 doses 92% Median age at 1st, 2nd, 3rd doses: 2.6m, 4.3m, 6.0m	Western Region formal clinical/microbiological surveillance (funded by Hib Initiative)	meningitis 0.8-2.3 per 100,000 children <5 years (all invasive Hib 0.8-3.7/100k)		0.9% (1-2 year olds)
2009 Introduction pentavalent DPT-HepB-Hib vaccine					
2011-2012 Provisional data		Eastern Gambia formal clinical/microbiological surveillance, Western Region (no formal surveillance)	>20 culture +ves cases in Eastern Gambia with latex agglutination typing (only 1 case 2009/10,), half with 2+ doses a handful of incidentally detected cases Western Gambia	half <1 yo;	

South America – (3p+1 or 3p+0)

To evaluate potential impact of use of a booster dose, we used surveillance data to compare trends in Hib meningitis incidence among children <5 years in four countries, two of which had a 3p+0 schedule (Chile and Colombia) and two of which had a 3p+1 schedule (Argentina and Uruguay). Surveys of nasopharyngeal carriage were conducted among children in Argentina and Colombia to compare prevalence of Hib colonization several years after introduction of Hib conjugate vaccines (Garcia S et al 2012[6]). Following Hib vaccine introduction, rates of Hib meningitis declined and were sustained at low levels through the study period in all four countries. Incidence of Hib meningitis during the post-vaccine study period varied from 2.3 to 1.2 cases per 100,000 among children <1 year and 0.5 to 0 cases per 100,000 among 1–4 year olds. Surveillance data from all four countries demonstrated that Hib meningitis cases continued to occur, albeit at low levels, 6–10 years following vaccine introduction. Contrasting Hib meningitis incidence during the post-vaccine period with the prevaccine base-line period, relative rates were similar in countries with and without booster doses.

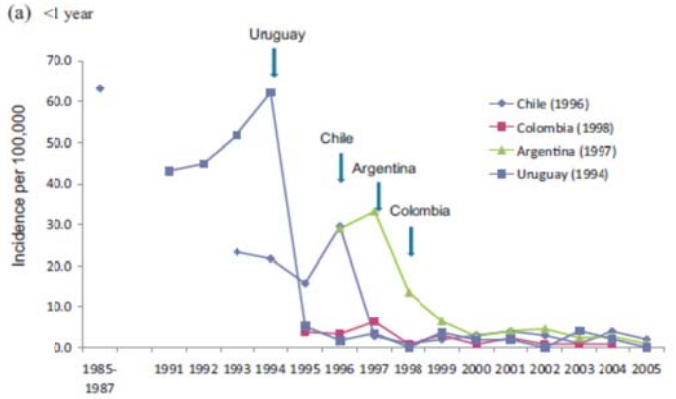


Fig. 1. Trends in Hib meningitis incidence in 4 South American countries before and after introduction of Hib vaccines in national immunization programs: (a) <1 year; (b) 1–4 years of age. *In 2005 the age groups used for reporting changed: from 2005 to 2009 the cases among children aged 48–59 are included in the 1–4-year-old group.

United States (3p+1)

In the United States prior to Hib vaccine introduction, the annual incidence of H. influenzae meningitis was approximately 50-60/100,000, 25-35/100,000 and 5/100,000 for children <1 year of age, 1 year of age and 2-4 years of age, respectively.(Adams, 1993[68]) Hib conjugate vaccine was introduced as a single dose at 18 months of age in 1987. Following vaccine introduction, there were declines in the incidence of Hib disease in vaccinated age groups. Incidence also declined in infants who were too young to be vaccinated, reflecting an indirect impact of the vaccine. (Adams, 1993[68]) Infant vaccination was introduced in 1990. In the United States, a number of different vaccines and combinations and schedules have been used. However, since 1990, the basic approach to scheduling has been to use a 3p+1 schedule. Disease incidence has remained low. Of note, there was a resurgence of invasive Hib disease among Alaska Native children reported in 1996 associated with a change in Hib conjugate vaccine. Prior to vaccine introduction, Alaska Native children had among the highest rates of invasive Hib disease reported worldwide. Use of PRP-OMP vaccine, which is more immunogenic after a single dose than other Hib conjugate vaccines, resulted in a large decline in disease incidence. However, disease incidence increased after a switch to PRP-CRM197 vaccine, which is less immunogenic until the third dose of the primary series. The resurgence of Hib disease in Alaska Native children was associated with ongoing circulation of the organism in pre-school and school aged children, despite several years of routine vaccination. (Galil, 1999[56]; Singleton, 2000[69]) Disease incidence declined following reinstitution of a PRP-OMP based schedule.

Italy- (2p+1)

In Italy, Hib vaccination using a 2p+1 schedule (at 3, 5, and 11 months of age) was introduced in 1999 and coverage by 24 months of age was estimated to be 95.6% in 2009. An "Active Surveillance of Invasive H. influenzae Disease" was carried out in a sample of Italian regions during the period 1997–2002 and extended nationally following the rapid decline in Hib incidence. From 2003 to 2006, data on cases of invasive H. influenzae disease were detected through the National Surveillance Network of Bacterial Meningitis but, since January 2007, they have been collected as a part of the National Surveillance of Invasive Bacterial Disease. Both the latter surveillances used a passive reporting system. Ten years after Hib vaccination was introduced, the annual incidence of invasive H. influenzae infection was 0.06/100,000 in 2007, 0.08/100,000 in 2008 and 0.09/100,000 in 2009 in all age groups. A slight increase in disease incidence has been observed in adults ⩾65 years since 2007 (Giufre M et al 2011)[70].

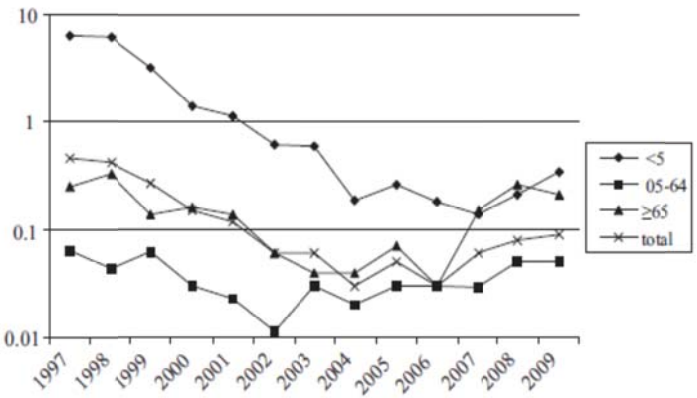


Fig. 1. Age-specific incidence (cases per 100,000 inhabitants, semi-logarithmic scale) for invasive disease caused by *Haemophilus influenzae* in Italy, during the period 1997–2009.

United Kingdom – (3p+0 the 3p+1)[7]

Prior to the introduction of routine vaccination, the incidence of invasive Hib disease in children aged <5 years in the UK was estimated to be 21–44/100,000. In October 1992, the UK introduced the Hib conjugate vaccine into the national immunisation programme. A Hib-tetanus toxoid conjugate vaccine (Hib-PRP-T) was offered to infants at 2, 3 and 4 months of age alongside DTwP. At the same time, a catch-up campaign lasting 12 months took place, where three dose of Hib-PRP-T vaccine were offered to infants and a single dose of Hib CRM197 conjugate vaccine (HbOC) was given to those aged 13 months to 4 years. Unlike many other industrialised countries, a Hib booster in the second year of life was not recommended. Coverage of over 90% was rapidly achieved in infants and coverage in the catch up campaign was above 85% in most cohorts. This Hib vaccination programme led to a rapid decline in the incidence of invasive Hib disease within two years, initially in the age group targeted for vaccination, but soon followed by a reduction in all other age groups through indirect (herd) protection. In 1996, a Hib-OC conjugate vaccine was licensed to be mixed with DTwP but, in 1997, a combination vaccine containing Hib-PRP-T with DTwP was introduced.

By 1998, invasive Hib incidence fell to its lowest level: 0.63/100,000 in children aged <5 years. From 1999, however, enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign that was offered to children up to 4 years of age when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis (aP). This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant.

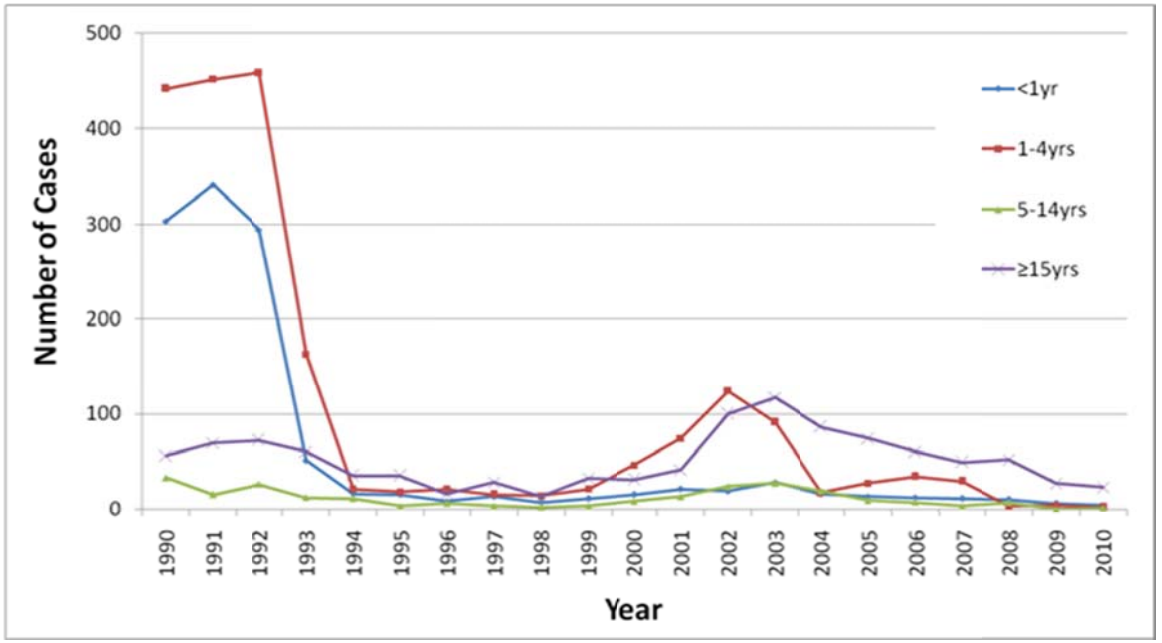
As a result of the increase, a number of control measures were taken. The implicated DTaP vaccine was withdrawn and DTwP vaccines were resumed. In addition, a Hib vaccination booster campaign using PRP-T was conducted between May and September 2003, offering one dose of vaccine to all children who were aged between 6 months and 4 years on 1 April 2003 and to those children who reached 6 months of age during the campaign. In September 2004, the infant combination vaccine was changed to one containing DTaP, inactivated polio and Hib. This vaccine has a different acellular pertussis component to the one previously used and was shown to have a satisfactory immune response against Hib. Together, these measures resulted in a rapid reduction in cases, initially in toddlers, but soon followed by a reduction in the other age groups.

[7] Summary courtesy of Drs M Ramsay and S Ladhani, Immunisation, Hepatitis and Blood Safety Department, Health Protection Agency , UK

From September 2006 onwards, a routine 12-month Hib booster administered as a Hib-MenC-PRP-T was introduced. After the 2003 booster campaign, however, an increase in Hib cases among 1–3-year-old children was noted (from 13 cases in 2004 to 32 cases in 2006), children too young to be vaccinated in the 2003 booster campaign and too old for the routine 12-month booster in September 2006. This group of approximately 1.5 million children, was subsequently targeted in a separate programme when a dose of Hib was given at pre-school age (3 years 4 months to 5 years of age) between September 2007 and 3 March 2009,

Currently, control of Hib in the UK is the best that has ever been achieved. In 2010, there were only 30 invasive Hib disease cases across all age groups, with only 6 cases in children under 5 years. Hib cases in adults were also at their lowest levels since 1998 (n=23).

Figure 16. Number of cases of invasive Hib disease in different age-groups diagnosed in England and Wales (1990-2010).
Source: Health Protection Agency Centre for Infection



Australia (3p+1 and 2p+1)

Australia introduced Hib conjugate vaccine in 1993. Currently, an acellular pertussis PRP-T combination vaccine is used with a schedule of 2, 4, 6 and 12 months for non-indigenous children. Indigenous children receive PRP-OMP vaccine at 2, 4, and 12 months of age. Horby et al. reported national surveillance data showing that invasive Hib disease incidence fell sharply following vaccine introduction and remained low (<2/100,000 children less than 5) from mid-1996 through mid-2000.(Horby, 2003[71]) Australia also participated in the EU-IBIS surveillance system from 1999-2006. Between these years, reported Hib disease incidence in children less than 5 years of age remained low, ranging from 0.5-1.6 cases per 100,000. Of note, incidence rates in indigenous populations living in Northern Australia who had very high levels of disease in the pre-vaccine era have fallen considerably, but remain higher than in non-indigenous persons (Menzies, 2008[72]).

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.

Immunization schedules starting later (i.e. > 2 months of age) vs. immunization schedules starting earlier (i.e. at 4-6 weeks of age)

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

A study which reported only GMC (Gambia- Mulholland 1994[19]) 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[73] (Kurikka 1995) 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 µg/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 µg/mL. All infants responded well to the booster at 14 months. There was no evidence of immunologic tolerance.

A study in Papua New Guinea 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, 2001[74]). 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.

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. 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 (, 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.

There is limited evidence from observational studies. 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[33 75] . In the Danish study 3-dose vs. 0 dose VE for PRP-T against Hib meningitis was 99.3% (94.87–99.90%)[33]. 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[39]. 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%)[20 22 23].

From long term impact studies, we found that 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.

Effect of the interval between doses on selected outcomes

Effect of the interval between primary doses of Hib vaccine on selected outcomes

Does using Hib conjugate vaccine schedule with a longer interval between primary doses (e.g. 8 weeks or more) have a greater effect on disease or immunological outcomes than a schedule with a shorter interval (i.e. 4 weeks) between doses?	
Conclusion	**Limited data available showed no consistent or clinically relevant differences between shorter (e.g. 4 weeks) and longer (e.g. ≥ 8 weeks) intervals between primary doses of Hib vaccines.**
Summary statement	In most reported schedules, 3 primary doses were separated by either one month (e.g. 6, 10, 14 weeks and 2, 3, 4 months) or two months (e.g. 2, 4, 6 months) whereas 2-dose schedules essentially included 8-weeks intervals. Available data on proportion achieving a set threshold (i.e. ≥ 0.15mcg/ml and ≥1.0 mcg/ml) show no significant difference between short interval [e.g. 4 weeks] vs. longer interval [e.g. ≥ 8 weeks] in the primary series on immunogenicity outcome for different types of Hib conjugates. There was no clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between observational studies using different dosing intervals or different Hib conjugates. Two months intervals between doses in the primary schedule were not shown to be consistently more immunogenic than one month interval in the observational studies. From long term impact studies both a 4 week and 8 week interval have been used in a number of countries with good sustained long term impact.
Quality of evidence	**We are moderately confident on the estimate of the effect.** There were no RCTs or observational studies that compared various intervals and, types of vaccine conjugate and that reported effect on various disease outcomes.
Caution	Not enough evidence on schedules using 2p+1 at short intervals (e.g. 4 weeks)

Immunization schedules with short (i.e. 4 weeks) versus longer (> 8 weeks) intervals between primary doses

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

The trial which compared two-month intervals to one-month intervals using PRP-OMP 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.

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 or radiologically confirmed pneumonia between studies using different intended dosing intervals. A study carried out in Colombia[30] compared the time between doses of Hib vaccine in pneumonia cases and controls17. 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. There are limited data from cohort studies to inform the optimal interval between doses. A Chilean[20] had a schedule with 2-month intervals: the VE for 3 doses vs. 0 doses, quadrivalent vaccine, was 91.7% (64.8 - 100%). A German [22 23], English and South African[64] 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 %9 50 10 . 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.

From long term impact studies, both 4 week and 8 week intervals have been used in a number of countries with good sustained long term impact.

Effect of interval between last primary dose and booster dose on selected disease outcomes

We found no evidence of significant differences in effectiveness with various intervals between the primary doses and the booster dose

Immunization schedules with long (> 8 weeks) vs. short (i.e. 4 weeks) intervals between primary doses

No immunological data from RCTs: Minimal difference seen between the schedules. 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[5].

Effect of combination vaccines

The available data do not suggested clinically relevant decreases in Hib efficacy or interference with other antigens with the use of combination vaccines compared with monovalent vaccines. There is some evidence of lower immunogenicity against Hib with the use of aP vaccines compared to wP vaccines, though little evidence of interference with other antigens in either combination. The clinical relevance of lower immunogenicity is unclear, as is the necessity of a booster dose with the use of aP containing vaccines.

Combination vs. monovalent vaccines

A recent COCHRANE meta-analysis[8] including data from twenty RCT's (N=5874 children for immunogenicity analysis, N=5232 for reactogenicity analysis) concluded that the overall level of evidence comparing combination and monovalent vaccines was low, and could not conclude that the immune response to combination vaccines was different from or equivalent to monovalent vaccines. No studies presented data on clinical outcomes. Antibody responses to diphtheria, pertussis, polio, and hepatitis B were not significantly different. Antibody response to Hib and tetanus was lower in children receiving combination vaccines. However, when the results were analyzed distinguishing aP and wP combination vaccines, the differences in immunogenicity were seen only in the aP vaccines; wP vaccines had equivalent of better immune responses, although no differences were statistically significant. There was no significant difference in the number of serious adverse events. A small but statistically significant increase in pain and redness at the injection site was noted for combination vaccines.

A review found in the textbook Vaccine (Plotkin, 6th ed.[76]) concluded that geometric mean titers for Hib/PRP have been seen to be lower in combination vaccines; however, there is no evidence that these differences are clinically meaningful as most (>95%) of children achieve antibody levels >1.0 ug/ml even with combination vaccines and observational and surveillance data do not support the hypothesis of lower effectiveness of combination vaccines.

A review of 41 studies[77] evaluating proportion of vaccine recipients achieving seroprotection, as opposed to GMT levels, found no consistent differences. 13 studies reported a significantly significant difference in seroprotection for one or more antigens; 8 found decreased seroprotection with combination vaccines while 5 found increased seroprotection with combination vaccines.

Acellular vs. whole cell pertussis component

A Cochrane meta-analysis[8] found significantly lower Hib seroprotection in recipients of aP containing vaccines, but not in wP vaccines. Studies have consistently documented this reduced immune response in terms of GMT following the primary series, however, following a booster dose all combination vaccines are highly immunogenic[76]. In general, aP vaccines do not show additional interference with other antigens, although the meta-analysis did note a decrease in seroprotection against tetanus with aP.

Most developed countries use aP vaccines and have effectively controlled Hib disease. The use of a booster dose in most of these countries may serve to augment lower immunogenicity such that the vaccine remains effective.

Hib vaccines and herd immunity

Available data suggest a very strong indirect effect with Hib vaccine, even at medium to low levels of coverage. Hib conjugate vaccines also have been shown to reduce carriage in vaccinated children. Widespread use of conjugate vaccines has led to decreases in disease incidence that were greater than rates of vaccination coverage and to decreases in Hib disease in unvaccinated age groups.

The impact of herd effect can be seen by the tenfold reduction in Hib disease rates in the United Kingdom in unvaccinated children <1 year of age in 1998 compared with rates in similarly aged children before vaccination began (Heath et al., 2000b[78]). Another reflection of herd effect is the impact of childhood Hib vaccination on adult Hib disease. A review of adult cases of Hib disease in five English regions between 1990 and 1995 showed a halving of case numbers between the first three-year period and the last two-year period (Sarangi et al., 2000[79]). Ongoing surveillance for Hib disease by Moulton and colleagues (Moulton et al., 2000[80]) demonstrated that immunization of 40% of Navajo Indian infants (USA) between the years 1988 to 1992 resulted in a 75% reduction of Hib disease among infants that were living in the same community. This demonstrates that countries that implement Hib immunization programmes may receive greater benefits at the community level than those hitherto seen due to the direct protection conferred on the individual through vaccination.

In Canada after several Hib vaccines were introduced within the last two decades. In Ontario, Canada authors reported that the incidence of invasive Hib disease in children, reflected in the submission of invasive Hib isolates to Ontario's Public Health Laboratory-Toronto, has fallen sharply since the introduction of the Hib conjugate vaccine (Adam HJ 2010[81]) . Furthermore, they concluded that herd effects were acting on all age groups in the population; using data to document a reduction in the risk of invasive Hib infection in older (unvaccinated) adults following vaccine introduction. Authors argued that this is a result of a reduced force of infection due to less Hib colonization among children.

A systematic literature search for studies which included impact data (pre- and post-introduction measure(s) of disease), vaccine coverage, and sufficient methodology detail to judge study quality was conducted (Walker N et al 2012-personal communication[82]). Direct effect of vaccine was calculated as efficacy x coverage; indirect effect was calculated as study observed effect - calculated direct effect. Eight out of 10 included studies showed higher observed impact on Hib disease than would be expected given coverage levels of the vaccine, suggesting indirect effects (herd immunity). Excluding the studies with a negative effect, the calculated indirect effects ranged from 7% to 63%, representing 13% to 76% of the total vaccine impact in some settings. The lowest level of vaccine coverage was in Brazil in 1999, at 8%. At this coverage level a 26% reduction in Hib meningitis was observed. Most studies which showed a negative indirect effect (observed impact was lower than would be expected at the given coverage levels) were conducted in the first year of vaccine introduction and reported maximum coverage levels for that year, as opposed to median-year coverage. This likely caused an over-estimation of the true coverage for most of that year, and thus an overestimation of the expected direct effect.

Limitations of the evidence

Number of doses of Hib vaccine: 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. Limited control for confounding (particularly in cohort studies). There is no direct comparison of the two schedules from impact studies. 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: Clinical and carriage data: no data from RCTs, immunological data only: Only PRP-T and PRP-OMP in comparisons of proportion above a set threshold. Few data about birth dose and conclusions about birth dose differ depending on control group used (e.g. Lieberman 1995[53], HbOC).Observational 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. Regarding impact studies, 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

Clinical and carriage data from RCTs: no data. Immunological data: Only proportion above a set threshold data from PRP-T studies. One study (Lenoir 1987[83], PRP-OMP) showed 2m interval better but 2m group vaccinated later. Limited evidence from observational studies. 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). 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

Clinical and carriage data from RCTs: no data. Immunological data: Data about PRP-T only. No data are available on earlier use of the booster dose from observational studies. Few countries recommend a booster dose prior to the first birthday. Comparisons must be made between countries which could result in confounding. 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.

HIV infected children

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

Research needs

Main research priorities include: ongoing surveillance for impact and possible disease resurgence in a small number of high quality surveillance sites; Evaluation of need for booster in HIV infected children; assessment of any impact on disease of switching to aP with various conjugate Hib vaccines, especially PRP-T.

In addition, we list below additional research questions that will help address some of the identified evidence gaps are listed below:

Studies are required to further assess the effect on Hib vaccine efficacy and effectiveness as well as carriage of co-administration with acellular pertussis vaccines (by type of aP), schedules, including assessing the need for a booster. 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.

Over the long term, there is a need further assess the impact of various schedules, particularly looking at disease at later ages, ad secondarily serotype replacement. Therefore, 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.

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. In addition, we need to better understand the effect of vaccine coverage and force of infection on the optimal schedule. For example, some argue that in the UK they may have experienced and increase in Hib disease among older people because coverage was too high relative to baseline Hib carriage, leading to a lack of natural boosting. However, maybe in developing countries, a lower coverage with occasional boosting using a 3p+0 schedule will result in acceptable levels of Hib disease control.

Over the short term, it is also important to assess what vaccine coverage is necessary and with what distribution through the population to achieve elimination or near elimination.

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), though these studies are becoming more difficult to conduct due to prenatal ART programs.

As the data on Hib vaccination in emergency settings are absent, generating such evidence is important. 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.

APPENDIX 1 Hib and pneumococcal global and regional mortality estimates by syndrome and HIV infection status

Table 1: Estimated Hib deaths for children under 5 years of age, 2008

	GLOBAL			AFR			AMR			EMR			EUR			SEAR			WPR		
	Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range	
		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound
TOTAL																					
Deaths	203,000	139,000	287,000	98,600	68,200	135,000	1,400	900	2,000	31,600	21,700	45,700	2,600	1,800	3,700	51,700	34,300	74,900	17,300	11,800	25,800
§ Total Deaths in HIV +	4,300	3,000	5,400	4,100	2,800	5,100	<100	<100	<100	<100	<100	<100	<100	<100	<100	100	<100	100	<100	<100	<100
§ Total Deaths in HIV -	199,000	136,000	281,000	94,500	65,400	129,000	1,400	900	1,900	31,600	21,600	45,700	2,600	1,800	3,700	51,600	34,300	74,700	17,300	11,800	25,800
Pneumonia																					
Deaths	161,000	113,000	234,000	72,600	51,100	105,000	1,200	800	1,700	26,500	18,600	38,600	2,000	1,400	2,900	43,300	30,400	63,100	15,300	10,800	22,300
§ Deaths in HIV +	3,200	2,200	3,900	3,000	2,100	3,700	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	100	<100	<100	<100
§ Deaths in HIV -	158,000	111,000	230,000	69,600	49,000	102,000	1,200	800	1,700	26,400	18,600	38,600	2,000	1,400	2,900	43,200	30,300	63,000	15,300	10,700	22,300
Meningitis																					
Deaths	42,100	25,400	52,400	25,900	17,100	29,100	200	<100	200	5,100	3,000	7,100	600	400	800	8,400	3,900	11,700	2,000	1,000	3,500
§ Deaths in HIV +	1,200	700	1,400	1,100	700	1,400	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	40,900	24,700	50,900	24,800	16,300	27,700	200	<100	200	5,100	3,000	7,000	600	400	800	8,300	3,900	11,600	2,000	1,000	3,500
NPNM																					
Deaths	200	100	300	<100	<100	100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV +	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	200	100	300	<100	<100	100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100

Global and regional results are the sum of country results. Global and regional totals have been rounded and reported with three significant digits, and never more specific than hundreds of cases or deaths.

Table 2: Estimated Pneumococcal deaths for children under 5 years of age, 2008

	GLOBAL			AFR			AMR			EMR			EUR			SEAR			WPR		
	Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range	
		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound
TOTAL																					
Deaths	541,000	376,000	594,000	309,000	208,000	336,000	13,700	9,400	15,900	68,900	49,700	75,900	6,800	5,000	7,800	108,000	79,400	119,000	33,700	23,900	39,400
§ Total Deaths in HIV +	64,900	44,500	72,800	62,300	42,700	69,900	400	300	400	600	400	600	<100	<100	<100	1,400	1,000	1,400	300	200	300
§ Total Deaths in HIV -	476,000	333,000	529,000	247,000	167,000	274,000	13,400	9,200	15,500	68,300	49,400	75,300	6,800	5,000	7,800	107,000	78,500	118,000	33,400	23,600	39,100
Pneumonia																					
Deaths	485,000	354,000	526,000	273,000	200,000	296,000	10,300	7,300	10,900	64,100	46,900	69,700	5,700	4,100	6,100	101,000	73,600	109,000	31,200	22,900	33,900
§ Deaths in HIV +	57,400	42,000	62,400	55,000	40,300	59,800	300	200	300	500	400	500	<100	<100	<100	1,300	900	1,300	300	200	300
§ Deaths in HIV -	427,000	312,000	464,000	218,000	159,000	237,000	10,000	7,100	10,500	63,600	46,600	69,100	5,700	4,100	6,000	99,400	72,700	108,000	30,900	22,600	33,600
Meningitis																					
Deaths	38,800	12,900	43,600	28,100	6,100	28,300	1,700	1,100	2,600	3,300	1,800	4,100	600	500	900	3,900	2,900	4,900	1,300	500	2,700
§ Deaths in HIV +	5,600	1,800	7,600	5,500	1,700	7,400	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	33,200	12,900	43,600	22,600	6,100	28,300	1,700	1,100	2,600	3,200	1,800	4,200	600	500	900	3,800	2,900	4,900	1,200	500	2,700
NPNM																					
Deaths	17,400	8,400	24,500	8,600	2,600	11,500	1,700	1,000	2,400	1,500	1,000	2,100	600	400	800	3,700	2,900	4,900	1,200	500	2,800
§ Deaths in HIV +	1,900	700	2,800	1,800	600	2,700	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	15,500	7,700	21,600	6,800	2,000	8,800	1,700	1,000	2,400	1,500	1,000	2,000	600	400	800	3,700	2,800	4,800	1,200	500	2,700

Global and regional results are the sum of country results. Global and regional totals have been rounded and reported with three significant digits, and never more specific than hundreds of cases or deaths.

APPENDIX 2 –OVERVIEW OF STUDIES INCLUDED IN THIS SUMMARY

Table 1. Results of studies reporting on Hib vaccine efficacy and effectiveness on invasive Hib disease Hib-PRPT conjugate): studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
The Gambia (Mulholland 1997)[19]	RCT	-85	85	44	1p vs. 0	1 vs. no doses	PRP-T	Combined[1], wP*
The Gambia (Adegbola 2005)[21]	Case control - community	-58	75	38	1p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Germany (Kalies 2008)[22]	Cohort	19	88	68	1p or 2p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined aP
Germany (Kalies 2004)[23]	Cohort	67	97	90	1p or 2p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined aP
The Gambia (Adegbola 2005)[21]	Case control - community	62	99	94	2p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
The Gambia (Mulholland 1997)[19]	RCT	67	100	95	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined[1], wP*
Chile - cluster randomization (Lagos 1996)[20]	RCT	65	100	92	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined[3], wP*
The Gambia (Adegbola 2005)[21]	Case control - community	62	99	94	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Chile (Lagos 1996)[20]	Cohort	65	100	92	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Germany (Kalies 2008)[23]	Cohort	71	97	90	3p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined, aP
Germany (Kalies 2004)[23]	Cohort	88	99	97	3p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined aP

Table 2. Results of studies reporting on Hib vaccine (PRP-OMP conjugate) efficacy and effectiveness on Hib invasive disease: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
USA (Santosham 1991)[34]	RCT	15	100	100	1p vs. 0	1.5-3 vs. no doses	PRP-OMP	Monovalent, wP*
USA (Harrison 1994)[35]	Case control - community	65	99	96	1p vs. 0	not stated	PRP-OMP	Not stated
USA (Vadheim 1994)[36]	Case control - community	39	100	100	1p vs. 0	2, 4, 12 months	PRP-OMP	Not stated
USA (Santosham 1991)[35]	RCT	53	98	95	2p vs. 0	1.5-3, 2.5-5 vs. no doses	PRP-OMP	Monovalent,, wP*
USA (Vadheim 1994)[36]	Case control - community	68	100	100	2p vs. 0	2, 4, 12 months	PRP-OMP	Not stated
USA (Harrison 1994)[35]	Case control - community	69	100	99	2p vs. 0	not stated	PRP-OMP	Not stated
USA (Harrison 1994)[35]	Case control - community	-57	100	99	3p vs. 0	not stated	PRP-OMP	Not stated

Table 3. Results of studies reporting on Hib vaccine (PRP-HbOC conjugate) efficacy and effectiveness on Hib invasive disease: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
USA (Vadheim 1994)[36]	Case control - community	38	87	71	1p vs. 0	2, 4, 6, 15 months	PRP-HbOC	Not stated
USA (Jafari 1999)[37]	Case control - community	-63	88	56	1p vs. 0	2, 4, 6 vs. no doses	PRP-HbOC	Not stated
USA (Vadheim 1994)[36]	Case control - community	60	97	89	2p vs. 0	2, 4, 6, 15 months	PRP-HbOC	Not stated
USA (Vadheim 1994)[36]	Case control - community	68	99	94	3p vs. 0	2, 4, 6, 15 months	PRP-HbOC	Not stated
USA (Black 1991)[38]	Case control -community	64	100	100	3p vs. 0	2, 4, 6 vs. no doses	PRP-HbOC	wP
South Africa (Madhi 2002)[39]	Cohort	74	100	97	3p vs. 0	6, 10, 14 weeks vs. no doses	PRP-HbOC	wP

Table 4. Results of studies reporting on Hib vaccine (PRPT and PRP-OMP conjugates) efficacy and effectiveness on Hib meningitis: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
USA (Santosham 1991)[34]	RCT	37	100	96	2p vs. 0	1.5 - 3 or 2.5 -5 vs. no doses	PRP-OMP	Monovalent ,wP
The Gambia (Adegbola 2005)[21]	Case control - community	-84	77	35	1p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - community	42	99	87	1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - hospital	19	99	88	1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Dominican Republic (Lee 2008)[25]	Case control -community	-63	88	52	1p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Uganda (Lewis 2008)[26]	Case control - hospital	0	86	63	1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Malawi (Daza 2006)[27]	Case control - hospital	-151	66	11	1p vs0	6, 10, 14 weeks	PRP-T	Combined, wP
The Gambia (Adegbola 2005)[21]	Case control - community	42	99	93	2p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Malawi (Daza 2006)[27]	Case control - hospital	43	98	89	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - community	90	100	99	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - hospital	63	100	95	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Dominican Republic (Lee 2008)[25]	Case control -community	14	100	87	2p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Uganda (Lewis 2008)[26]	Case control - hospital	42	99	93	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
The Gambia (Adegbola 2005)[21]	Case control - community	47	100	96	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - community	89	100	98	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda Lee 2008)[24]	Case control - hospital	75	100	97	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Dominican Republic (Lee 2008)[25]	Case control -community	33	100	90	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Uganda (Lewis 2008)[26]	Case control - hospital	48	99	94	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - community	-190	100	65	3p vs. 0	6, 10 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	-8	100	86	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP

Table 5. Results of studies reporting on Hib vaccine (PRP-T and PRP-OMP conjugates) efficacy and effectiveness on radiologically defined pneumonia: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
Colombia (de la Hoz 2004)[30]	Case control	2	72	47	1p vs. 0	2, 4, 6 vs. no doses	PRP-T	Monovalent
Bangladesh (Baqui 2007)[28]	Case control - community	-6	43	24	≥1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	13	54	37	≥1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - community	6	53	34	≥ 2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	20	61	44	≥ 2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Chile (Lagos 1996)[20]	RCT	1	40	23	2p or 3p vs. 0	2, 4 or 2, 4, 6 vs. no doses	PRP-T	Combined[2], wP*
Colombia (de la Hoz 2004)[30]	Case control	3	76	52	2p vs. 0	2, 4, 6 vs. no doses	PRP-T	Monovalent
Colombia (de la Hoz 2004)[30]	Case control	7	78	55	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Monovalent
Gambia (Mulholland 1997)[19]	RCT	0.61	0.98	22.4	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined[1], wP*
Bangladesh (Baqui 2007)[28]	Case control - community	-2	54	32	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	16	63	44	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Brazil (de Andrade 2004)[40]	Case control -	-9	57	31	≥ 2p vs. 0	2, 4, 6 vs. no doses	PRP-HbOC	Monovalent

Table 6. Results of studies reporting proportion above a set threshold (i.e. ≥1.0 ug/ml) at different time points after vaccination with Hib vaccines containing PRP-T conjugate.

Study	Schedule	Time since vaccination	Proportion above set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Niger1[45]	2p + 0	1m after	83	71	92	4.5 m	2.5, 3.5	PRP-T	Combined, wP
Sweden[46]	2p + 0	1m after	44	35	54	6 m	3, 5	PRP-T	Combined, 2 component aP
Chile4[41]	2p + 0	2m after	95	87	99	8m	4, 6	PRP-T	Separate, wP
Chile5[42]	2p + 0	2m after	95	89	98	7m	3, 5	PRP-T	Separate, 2 component aP
Guatemala Kaqchikel[43]	2p + 0	3m after	87	74	95	12 m	7, 9	PRP-T	Separate, wP 2, 4, 6 m
Guatemala Ladino[43]	2p + 0	3m after	100	92	100	12 m	7, 9	PRP-T	Separate, wP 2, 4, 6 m
Netherlands[44]	2p + 0	4m after	81	73	87	11 m	6, 7	PRP-T	Separate, wP
Niger1[45]	2p + 0	5.5 m after	67	51	81	9 m	2.5, 3.5	PRP-T	Combined, wP
Chile4[41]	2p + 0	6 m after	56	44	67	12 m	4, 6	PRP-T	Separate, aP
Sweden[46]	2p + 0	7 m after	21	14	30	12 m	3, 5	PRP-T	Combined, 2 component aP
Belgium[84]	3p + 0	1m after	87	75	95	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
Belgium[84]	3p + 0	1m after	92	80	98	6 m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile5[42]	3p + 0	1m after	96	92	99	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
France[85]	3p + 0	1m after	62	55	69	5 m	2, 3, 4	PRP-T	Combined, 2 component aP
France[85]	3p + 0	1m after	73	66	80	7 m	2, 4, 6	PRP-T	Combined, 2 component aP
Niger1[45]	3p + 0	1m after	89	75	96	4.5 m	1.5, 2.5, 3.5	PRP-T	Combined, wP
Sweden[46]	3p + 0	1m after	67	58	76	7 m	2, 4, 6	PRP-T	Combined, 2 component aP
Turkey[84]	3p + 0	1m after	97	91	100	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
Turkey[84]	3p + 0	1m after	96	89	99	6m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile4[41]	3p + 0	2m after	84	74	92	8 m	2, 4, 6	PRP-T	Separate, wP
Niger1[45]	3p + 0	5.5 m after	76	59	88	9 m	1.5, 2.5, 3.5	PRP-T	Combined, wP
Chile4[41]	3p + 0	6 m after	53	41	65	12 m	2, 4, 6	PRP-T	Separate, wP
Guatemala	3p + 0	6 m after	95	90	98	12 m	2, 4, 6	PRP-T	Combined, wP

Study	Schedule	Time since vaccination	Proportion above set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Kaqchikel[43]									
Guatemala Ladino[43]	3p + 0	6 m after	89	82	93	12 m	2, 4, 6	PRP-T	Combined, wP
Netherlands[44]	3p + 0	6 m after	40	32	48	11 m	3, 4, 5	PRP-T	Separate, wP
Sweden[46]	3p + 0	7 m after	17	10	25	13 m	2, 4, 6	PRP-T	Combined, 2 component aP
Europe[60]	3p + 0	unclear time after	39	32	47	13 m	3p	PRP-T	Combined, 3 component aP
France[85]	3p + 0	9-11 m after	26	19	33	15-17 m	2, 4, 6	PRP-T	Combined, 2 component aP
France[85]	3p + 0	11-13 m after	40	32	48	15-17 m	2, 3, 4	PRP-T	Combined, 2 component aP
China1[86]	3p + 0	13-15 m after	75	69	80	18-20 m	3, 4, 5	PRP-T	Combined, 2 component aP
China1[86]	3p + 0	14-16 m after	74	68	79	18-20	2, 3, 4	PRP-T	Combined, 2 component aP
Netherlands[44]	2p + 1	1m after	98	94	100	14 m	6, 7 + b13	PRP-T	Separate, wP
Sweden[46]	2p + 1	1m after	95	90	98	13 m	3, 5 +b12	PRP-T	Combined, 2 component aP
Sweden[46]	2p + 1	4.5 year after	44	33	55	5.5 y	3, 5 +b12	PRP-T	Combined, 2 component aP
Canada3[59]	3p + 1	1m after	98	97	99	17/18 m	3p + b16/17	PRP-T	Combined, 5 component aP
Canada3[59]	3p + 1	1m after	99	98	100	18/19	3p +b17/18	PRP-T	Combined, 5 component aP
Chile5[42]	3p + 1	1m after	99	96	100	13 m	2, 4, 6 +12	PRP-T	Separate, 2 component aP
Chile5[42]	3p + 1	1m after	100	97	100	13 m	3, 5, 7 +b12	PRP-T	Separate, 2 component aP
China1[86]	3p + 1	1m after	100	99	100	19-21 m	2, 3, 4 + b18-20 m	PRP-T	Combined, 2 component aP
China1[86]	3p + 1	1m after	100	98	100	19-21 m	3, 4, 5 + b18-20	PRP-T	Combined, 2 component aP
Europe[60]	3p + 1	1m after	98	95	100	13 m	3p + 12	PRP-T	Combined, 3 component aP
Europe[60]	3p + 1	1m after	97	94	99	14 m	3p + 13	PRP-T	Combined, 3 component aP
France[85]	3p + 1	1m after	98	95	100	16-18 m	2, 3, 4 + b15-17	PRP-T	Combined, 2 component aP
France[85]	3p + 1	1m after	98	95	100	16-18 m	2, 4, 6 + b15-17	PRP-T	Combined, 2 component aP
Netherlands[44]	3p + 1	1m after	98	95	100	12 m	3, 4, 5 + b11	PRP-T	Separate, wP
Sweden[46]	3p + 1	1m after	99	95	100	14 m	2, 4, 6 + b13	PRP-T	Combined, 2 component aP
Canada1[87]	3p + 1	1.5m after	98	92	100	13.5 m	2, 4, 6 + b12	PRP-T	Combined wP

Study	Schedule	Time since vaccination	Proportion above set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Canada1[87]	3p + 1	1.5m after	95	88	99	16.5 m	2, 4, 6 + b15	PRP-T	Combined, wP
Canada1[87]	3p + 1	1.5m after	100	95	100	19.5 m	2, 4, 6 +b18	PRP-T	Combined, wP
Europe[60]	3p + 1	2m after	97	93	99	14 m	3p +12	PRP-T	Combined, 3 component aP
Sweden[46]	3p + 1	4.5 year after	38	27	49	5.5 y	2, 4, 6 + b13	PRP-T	Combined, 2 component aP

Table 7. Results of studies reporting proportion above a set threshold (i.e. >1.0 ug/ml) at different time points after vaccination with Hib vaccines containing PRP-OMP and PRP-HbOC conjugates.

Study	Schedule	Time since vaccination	proportion above a set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Gambia1[88]	2p + 0	1m after	54	43	65	4m	1, 3	PRP-OMP	Separate, wP 2, 3, 4 m
Gambia 1[88]	2p + 0	1m after	61	47	74	5m	2, 4	PRP-OMP	Separate, wP 2, 3, 4 m
USA4[89]	2p + 0	1m after	58	41	74	7m	3, 6	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	3m after	38	23	55	7m	2, 4	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	9m after	22	9	40	15m	3, 6	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	11m after	9	2	24	15m	2, 6	PRP-OMP	Separate, wP according to guidelines
Gambia1[88]	2p + 0	14m after	26	15	40	18m	2, 4	PRP-OMP	Separate, wP 2, 3, 4m
Gambia1[88]	2p + 0	15m after	27	17	39	18m	1, 3	PRP-OMP	Separate, wP 2, 3, 4m
Chile4[41]	2p + 0	2m after	64	52	74	8m	4, 6	PRP-HbOC	Separate, wP
Chile4[41]	2p + 0	6m after	30	20	41	12m	4, 6	PRP-HbOC	Separate, wP
Chile4[41]	3p + 0	2m after	76	64	85	8m	2, 4, 6	PRP-HbOC	Separate, wP
Chile4[41]	3p + 0	6m after	33	22	45	12m	2, 4, 6	PRP-HbOC	Separate, wP

APPENDIX 3 - GRADE TABLES

GRADE Table No 1: Hib vaccination schedules: three primary doses versus two primary doses

PICO Question: Does using three primary doses of Hib have a greater effect on proportion above a set immunological threshold than using two primary doses?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		6 RCTs	4
	Factors decreasing confidence	Limitation in study design	serious[8]	-1
		Inconsistency	Very serious[9]	-2
		Indirectness	None	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			1
Summary of Findings	Statement on quality of evidence			We are uncertain about the estimate of effect
	Conclusion			There is no clear difference in effect on proportion above a set threshold of a three primary dose schedule over a two primary dose schedule

[8] All studies either lacked blinding of participants or failed to report it. Most studies did not report allocation concealment

[9] High level of hetereogeneity: I-squared greater than 75% (96.6%)

References

1. Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules Trials graded;

2. Chile 4 Lagos, R., et al., *Economisation of vaccination against Haemophilus influenzae type b: a randomised trial of immunogenicity of fractional-dose and two-dose regimens.* Lancet, 1998. **351**(9114): p. 1472-6.

3. **Chile 5** Lagos, R., et al., *Clinical acceptability and immunogenicity of a pentavalent parenteral combination vaccine containing diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type b conjugate antigens in two-, four- and six-month-old Chilean infants.* Pediatr Infect Dis J, 1998. **17**(4): p. 294-304.

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5. Netherlands: Labadie, J., et al. *Multi-center study on the simultaneous administration of DPT-IPV and Hib PRP-T vaccines. Rijksinst*Lituut *voor Volksgezondheid en Milieu RIVM*. 1996 [accessed 2013 Jan 24]; Available from: http://www.rivm.nl/bibliotheek/rapporten/124001003.html

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GRADE Table 2: Hib vaccination schedules: three primary doses versus two primary doses plus one booster dose

PICO Question: Does using three primary doses of Hib have a greater immunological effect than using two primary doses plus one booster dose?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT	4
	Factors decreasing confidence	Limitation in study design	serious[10]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	serious[11]	-1
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence			Our confidence in the estimate of the effect on the health outcome is low
	Conclusion			One trial has found that the 2p+1 schedule resulted in higher proportion above a set threshold than the 3p schedule but further research is needed to confirm whether this is a true effect.

[10] Randomization unclear, participants not blinded
[11] Only one study-low number of events

Six trials measured examined proportion above a set threshold after either 3p or 2p+1 in individual trial arms but only one trial provided a direct comparison.

References:

Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules

Trials graded;

Sweden: Carlsson, R.M., et al., *Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatr Infect Dis J, 1998. **17**(11): p. 1026-33.

GRADE Table 3: Hib vaccination schedules: three primary doses plus one booster dose versus two primary doses plus one booster dose

PICO Question: Does using three primary doses of Hib plus one booster dose have a greater immunological effect than using two primary doses plus one booster dose?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	serious[12]	-1
		Inconsistency	Not serious	0
		Indirectness	none	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			We are moderately confident in the estimate of effect
	Conclusion			Both schedules induced high proportions above a set threshold and there was little difference between the two groups

[12] [12] Randomization unclear or not reported, participants not blinded

References: Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules

Trials graded:

Netherlands: Labadie, J., et al. *Multi-center study on the simultaneous administration of DPT-IPV and Hib PRP-T vaccines. Rijksinst*Lituut *voor Volksgezondheid en Milieu RIVM*. 1996 [accessed 2013 Jan 24]; Available from: http://www.rivm.nl/bibliotheek/rapporten/124001003.html

Sweden: Carlsson, R.M., et al., *Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatr Infect Dis J, 1998. **17**(11): p. 1026-33.

GRADE Table 4: Hib vaccination schedules: three primary doses plus one booster versus three primary doses only

PICO Question: Does using three primary doses of Hib plus one booster dose have a greater immunological effect than using three primary doses only?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	serious[13]	-1
		Inconsistency	None	0
		Indirectness	None	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			We are moderately confident in the estimate of effect
	Conclusion			The 3p+1 schedule induced higher proportion above a set threshold than the 3p schedule

[13] Randomization unclear or not reported, participants not blinded

Notes

Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules

References:Trials graded: Canada3: Scheifele, D.W., et al., *Safety and immunogenicity of a pentavalent combination vaccine (diphtheria, tetanus, acellular pertussis, polio, and haemophilus influenzae type B conjugate) when administered as a fourth dose at 15 to 18 months of age.* Hum Vaccin, 2005. **1**(5): p. 180-6

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