Prevention of *Haemophilus influenzae* type b disease

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Haemophilus influenzae *type b (Hib) is the leading cause of meningitis in children < 5 years of age. The majority of cases of Hib occur in infants < 2 years of age. Until recently the only vaccine available against this disease contained the pure polysaccharide (PRP) of Hib (Hib-PRP vaccine). The Hib-PRP vaccine was demonstrated to be efficacious in infants > 18 months of age but not below that age. This product was licensed for routine use in the USA for children aged 24 months or more. Recently a hyperimmune globulin termed bacterial polysaccharide immune globulin (BPIg) was prepared by immunizing adult donors with Hib-PRP, meningococcal and pneumococcal vaccines. BPIg has been demonstrated to prevent Hib infections when it is administered to infants at 4-month intervals. However, BPIg has not been licensed for routine use in the USA. A number of new Hib conjugate vaccines have also been developed in the last few years by convalently linking the Hib-PRP to different carrier proteins. Four different Hib conjugate vaccines have undergone clinical trials in the USA. Two of these vaccines, HbOC (Hib capsular oligosaccharide linked to CRM197) and Hib-OMPC (Hib capsular polysaccharide linked to* Neisseria meningitidis *outer membrane protein complex) have been demonstrated to protect infants aged 2 months or more from Hib disease. Both HbOC and Hib-OMPC are currently licensed for routine use in the USA. The widespread use of these vaccines should have a substantial impact in reducing morbidity and mortality from Hib disease.*

Keywords: *Haemophilus influenzae* type b; hyperimmune globulin; Hib vaccines

INTRODUCTION

In the past two decades a number of new strategies for the prevention of *Haemophilus influenzae* type b (Hib) disease have been evaluated. Both active and passive immunizations have been evaluated for the prevention of Hib disease. In this review a brief summary of the efficacy trials that have been conducted with the various products will be summarized. Chemoprophylaxis for the prevention of secondary cases of Hib will not be discussed.

In this paper the term systemic Hib disease is defined as a case in which Hib was isolated from blood, cerebrospinal fluid or other normally sterile body fluids. All the products described below have been demonstrated to have minimal side effects and the details have been presented in the respective original publications. Therefore, in this manuscript only data relevant to the efficacy of the different vaccines will be presented.

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VACCINES

Pure polysaccharide vaccine

The first Hib vaccine available for field testing contained the pure polysaccharide (PRP) portion of Hib. This product was field tested in Finland in 1974[1], during a large meningococcal meningitis epidemic. Infants and children aged 3 months to 5 years were given either the Hib-PRP vaccine or the meningococcal type A vaccine in an open randomized trial. Among children aged 18–71 months who received the Hib-PRP or meningococcal vaccines, there were 0 and 11 cases of systemic Hib in the first year of life, respectively. During the second year of the study, two cases occurred in the Hib-PRP group and five cases in the meningococcal vaccine group. The difference in attack rate of disease for the entire 2-year period between the Hib-PRP and meningococcal vaccine groups was statistically significant ($p < 0.005$ by Poisson distribution). Estimates of vaccine efficacy were not reported.

In children < 18 months of age who received the Hib-PRP vaccine, seven Hib cases were seen in the first year and one case was seen in the second year. In recipients of meningococcal vaccine < 18 months of age, there was one case of Hib in year one and three cases in year two. This difference was not statistically significant.

Thus, this study demonstrated that the Hib-PRP was efficacious in children > 18 months of age but not below

Table 1 Comparison of BPIg and placebo in prevention of Hib and pneumococcal bacteraemia and meningitis

	BPIg group	Placebo group	p^a
No. of patients at risk	353	350	
No. of doses	858	838	
Cases of invasive Hib disease			
Before treatment period	0	1	
1–90 days after immunization	0	7	0.007
91–120 days after immunization	1	0	
1–120 days after immunization	1	7	0.04
After treatment period[b]	2	4	
Cases of invasive pneumococcal infections			
Before treatment period	1	0	
1–90 days after immunization	0	4	0.06
91–120 days after immunization	2	0	
1–120 days after immunization	2	4	
After treatment period[b]	6	6	
Combined No. of cases of invasive Hib and pneumococcal infections			
Before treatment period	1	1	
1–90 days after immunization	0	11	<0.001
91–120 days after immunization	3	0	
1–120 days after immunization	3	11	0.03
After treatment period[b]	8	10	
Total No. of cases	12	22	

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[a] By two-sided Fisher's exact test' p value is given only if $p<0.1$

[b] At 121 days to two years after the third dose

that age. This product was licensed in the USA for routine use for children aged 24 months or above in 1985.

Bacterial polysaccharide immune globulin (BPIg)

Since the majority of Hib cases in the USA occurs in infants <24 months of age, we evaluated an alternate strategy–passive immunization. A hyperimmune globulin termed BPIg was prepared by immunizing adult volunteers with Hib-PRP, meningococcal A and C and pneumococcal vaccines[2]. Based on the results of the initial pharmacokinetic and safety studies[3] with BPIg, we designed a study to evaluate the safety and efficacy of this product in preventing Hib disease in a high risk population[4]. From June 1983 to April 1986 infants born to mothers residing among the White Mountain Apache tribe were randomized to receive either BPIg (0.5 ml/kg) or placebo (0.5 ml saline) at 2, 6 and 10 months of age in a double-blind study. A total of 353 infants were randomized to the BPIg group (*Table 1*) and 350 to the placebo group. During the first 90 days after BPIg or placebo injection, no bacteraemic Hib cases were detected in the BPIg group, whereas seven Hib infections were detected in the placebo group ($p = 0.007$). During the entire 4-month period there was one bacteraemic case in the BPIg group and seven in the placebo group ($p = 0.04$). The point estimate of efficacy for the 4-month period after administration of BPIg was 86% (95% confidence interval was −11% to 100%). For the first 3 months after BPIg administration, the point estimate of vaccine efficacy was 100% (95% confidence interval 47–100%).

Even though BPIg was demonstrated to be efficacious, it was not licensed for routine use in USA for reasons discussed below.

Hib conjugate vaccines

In the past 10 years a number of new Hib conjugate vaccines have been produced by covalently linking the PRP portion of the Hib capsule to different protein carriers. The different Hib conjugate vaccines that are currently available, their manufacturers and their trade names are shown in *Table 2*. The preparation of these vaccines and their initial safety and immunogenicity evaluation have been described in previous publications[5–20]. The properties of the new conjugate vaccines differ from that of the pure PRP vaccine in the following respects: they are more immunogenic in infants compared to the pure PRP vaccine and unlike the pure PRP, which induces a T-cell independent response, they induce a T-cell dependent response. Repeated injections with these vaccines produce a booster response. Thus, even if the infant has relatively low antibody levels after initial immunization with these vaccines, when he/she comes into contact with the Hib organism there should be a brisk antibody response which should protect the infant.

Efficacy studies of Hib vaccine conjugated to diphtheria toxoid (PRP-D)

In a prospective double-blind placebo controlled trial, Ward *et al.* evaluated the safety and efficacy of PRP-D (ProHIBit, Connaught) among Alaskan Native infants[21]. Infants were randomized to receive either 0.5 ml vaccine (20 μg ribose per dose) or saline at 2, 4 and 6 months of age. From 7 October 1984 to 30 June 1988, 2102 subjects were recruited and immunized (1054 to the vaccine group and 1048 to the placebo group). The estimates of vaccine efficacy and the number of cases of Hib that occurred in the two groups are shown in *Table 3*. The point estimates of vaccine efficacy (95% confidence interval) were 25% (−233, 83) after first dose, 35% (−288, 89) after second dose and 43% (−43, 78) after third dose.

A second open randomized trial was conducted in Finland to evaluate the safety and efficacy of PRP-D[22] from October 1985 to August 1987. Infants born on odd-numbered days were given 0.5 ml PRP-D vaccine containing 25 μg PRP and 20 μg diphtheria toxoid at 3, 4 and 6 months of age followed by a booster at 14 to 18 months of age. Infants born on even-numbered days were assigned to the control group and were given the PRP-D vaccine at 24 months of age.

Among infants who have received three doses of the vaccine in infancy, there were four cases of systemic Hib disease between the ages 7 and 24 months compared to 64 cases in the control group; the point estimate of vaccine efficacy was 94% (95% confidence interval 83–98).

Based on the results of these studies, the PRP-D was initially licensed in the USA for infants aged 18 months or more in 1987. Subsequently this vaccine was licensed for infants aged 15 months or more.

Hib vaccine conjugated to CRM197 (HbOC)

The efficacy of HbOC (HibTITER, Praxis Biologics) was evaluated in an open trial in a large Health Maintenance Organization in California from February 1988 to June 1990[23]. Infants were offered three doses (at 2-month intervals) of the HbOC vaccine containing 10 μg Hib capsular oligosaccharide. Infants were eligible for the first dose of the vaccine between 6 weeks and 6 months of age and all three doses of the vaccine had to be given

Table 2 *H. influenzae* type b conjugate vaccines

Manufacturer	Abbreviation	Trade name	Carrier protein	Licensed by the FDA (as of Feb. 91)
Connaught Laboratories	PRP-D	ProHIBit®	Diphtheria toxoid	For children ≥ 15 months of age
Praxis Biologics (distributed by Lederle Laboratories)	HbOC	HibTITER™	CRM197 (a non-toxic mutant diphtheria toxin)	For infants & children ≥ 2 months of age
Merck Sharp & Dohme	PRP-OMPC	PedvaxHIB	OMPC (an outer membrane protein complex of *Neisseria meningitidis*)	For infants & children ≥ 2 months of age
Pasteur Merieux Vaccins	PRP-T	–	Tetanus toxoid	Not licensed

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Table 3 Efficacy of PRP-D vaccine in Alaska Native infants immunized at two, four and six months of age

Time	Incidence of disease (No. cases/No. subjects)		
	Vaccine group	Placebo group	Efficacy[a] (%)
After 1 dose[b]	3/1054	4/1048	25(−233,83)
After 2 doses	2/991	3/966	35(−288,89)
After 3 doses			
Excluding 2nd recurrent episode	7/915	12/883	43(−43,78)
Including 2nd recurrent episode	8/915	12/883	35(−57.73)
After any dose			
Including one episode of recurrent case	12/1054	19/1048	37(−29,69)
Including both episodes of recurrent case	13/1054	19/1048	32(−37,66)

Results include definite and probable cases of *H. influenzae* type b disease.
[a] Values in parentheses are 95% confidence limits. No difference was significant
[b] Includes first episode of recurrent case
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Table 4 Follow-up time and Hib incidence by HbOC status, February 1988–June 1990, in children < 18 months of age

HbOC status	No. of children	No. of person-years	Mean age (months)	No. of Hib cases	Incidence/100 000	95% Confidence interval
Unvaccinated age ≥ 225 days	18 862	11 335	12.1	12	105.9	54.7, 184.9
Fully vaccinated (starts 7 days after dose 3)	20 800	12 949	11.9	0	0.0	0.0, 28.5
Unvaccinated age < 225 days	58 222	15 627	3.4	9	57.6	26.4, 109.3
1 dose only	30 400	6 553	4.5	3	45.8	9.4, 133.8
2 doses only	25 481	5 512	7.2	0	0.0	0.0, 67.0
Total study population	61 080	51 935	8.0	24[a]	46.2	29.6, 68.8

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[a] There have been a total of 25 cases in the study population. One case, who was eligible and unvaccinated, was > 18 months of age and therefore is not included

before 1 year of age. Beginning in April 1988, children born on the first 5 days of any month were eligible to receive vaccine; this exclusion interval was increased to 6 days in May 1989 and to 7 days in June 1990. The excluded group was apparently established both to serve as a reference in the evaluation of possible bias and to allow adjustments in the size of the unvaccinated group.

In this trial the primary test of efficacy was the comparison of rates of disease between the children who were fully vaccinated (received three doses) and those who were unvaccinated. In unvaccinated children follow-up began 1 week after the average age at which fully vaccinated children received their third dose of HbOC vaccine, which was 255 days of age. The number of cases of Hib disease that occurred in the fully vaccinated, partially vaccinated (received less than three doses) and unvaccinated groups is shown in *Table 4*. There were 12 cases of Hib disease in unvaccinated infants > 225 days old compared to no cases in the fully vaccinated group; the point estimate of vaccine efficacy was 100% (lower bound of 95% confidence interval 68%). There were no cases of Hib disease among infants who had received two doses of the vaccine. Among infants who had received one dose of the vaccine, three cases of Hib disease occurred.

Table 5 Anti-HbPs antibody concentrations in relation to interval after HbOC dose 3

Interval (months)	*n*	Geometric mean titre (μg/ml)[a]	≥ 1.0 μ/ml (%)
> 0.5–1.5	144	18.91	97
> 1.5–6	60	4.20	83
> 6–12	45	2.88	84
> 12	28	2.03	71
1 month after 18-month dose	39	28.60	97

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The serological responses to immunization with HbOC are shown in *Table 5*[9].

Based on these data HbOC was licensed for routine use in the USA in 1990 for infants beginning at 2 months of age. It is recommended that this vaccine should be given as three doses at 2-month intervals beginning at 2

Table 6 Efficacy analysis of *H. influenzae* type b OMPC vaccine

Type of analysis and time of disease onset	Cases of Hib disease (No./total)		Efficacy estimate (%)	p value	95% confidence interval	
	Vaccine	Placebo			One-sided[c]	Two-sided
Intention-to-treat analysis[a]						
At least 1 dose						
Onset before 18 mo	1/2588	22/2602	95	<0.001	77	72–99
Onset before 15 mo	0/2588	21/2602	100	<0.001	85	81–100
Onset before 2nd dose	0/2588	8/2602	100	0.005	55	41–100
Two doses						
Onset before 18 mo	1/2056	14/2105	93	<0.001	61	53–98
Onset before 15 mo	0/2056	13/2105	100	<0.001	74	67–100
Strict analysis[b]						
Two doses						
Onset before 18 mo	1/1913	14/1929	93	<0.001	61	53–98
Onset before 15 mo	0/1913	13/1929	100	<0.001	74	67–100
Onset before 2nd dose	0/2451	6/2430	100	0.014	35	15–100

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[a] Included all infants enrolled

[b] Included only infants who received the correct first and second doses of vaccine or placebo at the times specified in the protocol

[c] Lower bound

Table 7 Antibody responses in infants vaccinated with *H. influenzae* type b OMPC vaccine or placebo

Time of measurement	Vaccine recipients					Placebo recipients				
	No. of infants	Mean age (mo)	Anitbody levels			No. of infants	Mean age (mo)	Antibody levels		
			>0.15 μg (%)	>1.0 μg (%)	GMT (μg)			>0.15 μg (%)	>1.0 μg (%)	GMT (μg)
Before vaccination	982	1.8	45	10	0.16	991	1.8	44	8	0.16
2 mo after 1st dose	879	4.2	90	51	0.97[a]	905	4.2	19	1	0.09
2 mo after 2nd dose	735	6.3	91	59	1.35[a]	735	6.3	13	1	0.08
8 mo after 2nd dose	331	11.7	76	24	0.40[a]	336	11.8	24	4	0.10
2nd follow-up visit[b]	108	17.7	69	24	0.40[a]	113	17.7	29	6	0.11

Results show the serum antibody response to the capsular polysaccharide of *H. influenzae* type b. GMT denotes geometric mean titre. Reproduced from *New England Journal of Medicine* (1991), **324**, 1767–1772 with permission

[a] $p < 0.001$ for the comparison with placebo values

[b] Serum samples were obtained between 15 and 18 months of age

months of age followed by a booster immunization at 15 months of age[24].

Hib vaccine conjugated to *Neisseria meningitidis* outer-membrane protein complex (Hib-OMPC)

We conducted a double-blind placebo controlled trial to evaluate the safety and efficacy of Hib-OMPC (PedvaxHIB®, Merck, Sharp & Dohme) among Navajo infants[25]. Infants were randomized to receive either 0.5 ml Hib-OMPC containing 15 μg *H. influenzae* type b PRP, 131–272 μg of a group B meningococcal OMPC and 1–2 mg lactose or placebo (2 mg lactose). The vaccine was provided in the lyophilized form. The aluminium hydroxide diluent (1.5 ml per vial) contained 0.4 mg aluminium and 49.8 μg thimerosal per ml. Infants were given the first dose of vaccine/placebo between 42 and 90 days of age and a second dose between 70 and 146 days of age separated by at least 28 days after the first injection. A total of 2588 infants were randomized to the vaccine group and 2602 to the placebo group. The number of cases of systemic Hib infections that occurred in each group and estimates of vaccine efficacy are shown in *Table 6*. There were 22 systemic Hib infections prior to 18 months of age in the placebo group compared to one in the vaccine group ($p < 0.001$; point estimate of efficacy 95%; 95% confidence interval 72–99%). Among infants who received two doses there was one systemic Hib infection out of 2056 vaccine recipients compared to 14 out of 2105 in placebo recipients ($p < 0.001$; point estimate of efficacy 93%, 95% confidence interval 53–98). The only case of Hib infection in the vaccine group occurred at 15.5 months of age in an infant with osteomyelitis. Between the first and second doses there were no Hib cases in the vaccine group and eight in the placebo group ($p < 0.005$; point estimate of efficacy 100%; 95% confidence interval 41–100). The geometric antibody levels at different ages for the two groups are shown in *Table 7*.

Based on these data the Hib-OMPC has been licensed for routine use in infants beginning at 2 months of age[25].

Hib vaccine conjugated to tetanus toxoid (PRP-TT)

PRP-TT (Institut Merieux) has not under gone clinical efficacy testing. It is not currently licensed for routine use in the USA, although the results of immunogenicity studies suggest that this vaccine should be as efficacious as the licensed Hib conjugate vaccines[19,20].

DISCUSSION

Within the past 5 years, two Hib conjugate vaccines and BPIg have been demonstrated to protect infants from systemic Hib infections in infants < 1 year of age.

Although BPIg has been demonstrated to be efficacious, it is not recommended for routine use because it requires repeated injections and a relatively large volume

Table 8 Summary of recommended regimens for the use of *H. influenzae* type b vaccines

Age immunization initiated (months)	Vaccine product used at initiation	Total number of doses to be administered	Currently recommended vaccine regimens (see text)
2–6	HbOC	4	a. Initial 3 doses at 2-month intervals b. Fourth dose at 15 months of age[a] c. HbOC for doses 1–3 d. HbOC, PRP-OMP or PRP-D for dose 4[a]
	PRP-OMP	3	a. Initial 2 doses at 2-month intervals b. Third dose at 12 months of age c. PRP-OMP for all three doses[b]
7–11	HbOC	3	a. Initial 2 doses at 2-month intervals b. Third dose at 15–18 months age[a] c. HbOC, for doses 1–2 d. HbOC, PRP-OMP or PRP-D for dose 3
	PRP-OMP	3	a. Initial 2 doses at 2-month intervals b. Third dose at 15–18 months of age[a] c. PRP-OMP for doses 1–2 d. PRP-OMP, PRP-D or HbOC for dose 3[a]
12–14	HbOC	2	a. 2–3 month interval between doses b. If the second dose is given at or after 15 months HbOC, PRP-OMP or PRP-D may be given[a]
	PRP-OMP	2	a. 2–3 month interval between doses b. If the second dose is given at or after 15 months, PRP-OMP, PRP-D or HbOC may be given[a]
15–59	HbOC PRP-OMP PRP-D	1	HbOC, PRP-OMP or PRP-D[a]
60 and older[c]	HbOC PRP-OMP PRP-D	1	HbOC, PRP-OMP or PRP-D[a]

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[a] The Academy considers that safety and efficacy are likely to be equivalent for PRP-OMP, PRP-D and HbOC for the use in children 15 months of age or older

[b] If the third dose is inadvertently delayed until the child is 15 months of age or older, the Academy considers that the safety and efficacy are likely to be equivalent for PRP-OMP, PRP-D and HbOC for this third dose

[c] Only for children with chronic illness known to be associated with an increased risk for *H. influenzae* tybe b disease (see text).

needs to be given with each injection. It may, however, be useful in protecting immunocompromised infants who are unable to respond to active vaccines. BPIg may also have a role in the prevention of secondary cases of Hib as an alternative to using rifampin prophylaxis[26], since high levels of Hib antibodies are expected to be achieved within a few hours of administering BPIg. Thus, unlike rifampin prophylaxis, BPIg could be given only to susceptible infants. At the present time BPIg is not licensed for this indication.

The Hib-PRP vaccine is no longer routinely used in the USA, since the new conjugate vaccines have been shown to be more immunogenic.

Two of the vaccines, Hib-OMPC and HbOC, are currently licensed for use in infants beginning at 2 months of age. In evaluating the relative merits of these two vaccines, HbOC is clearly efficacious after three doses and probably after two doses, but it has not been shown to protect after a single dose. However, HbOC appears to produce a better booster response after the third dose resulting in relatively high antibody levels after the primary series of vaccination[9]. Thus, infants may be protected for a longer period of time. On the other hand Hib-OMPC begins protection after a single dose in 6 to 8-week-old infants and is known to be efficacious after two doses until 18 months of age. This vaccine produces relatively high antibody levels after the first dose but produces relatively modest increases in antibody levels after the second dose.

Although the Hib antibody levels attained after the primary series of Hib vaccination may be important, caution must be exercised in extrapolating these data to make judgements about vaccine efficacy. It is difficult to compare the antibody levels reported in different studies because of variations in standardization of assays between laboratories. Moreover, as discussed previously, the Hib conjugate vaccines induce a T-dependent immune response. Thus, even though the antibody levels after the primary series may be relatively low, they would be expected to rise to 'protective' levels if the infant came in contact with the organism. This hypothesis is supported by the findings of the recent Hib-OMPC efficacy trial. In that trial only 59% of infants had antibody levels > 1 μg/ml two months after the second dose. However, the vaccine efficacy was estimated to be 93%.

The recommendations of the American Academy of Pediatrics for the routine use of the currently recommended Hib vaccines are given in *Table 8*[24].

Postmarketing evaluations of both HbOC and Hib-OMPC are currently under way. The ability of these vaccines to provide long-term protection can only be determined after these studies are completed. Nevertheless, we now have two highly efficacious vaccines for the protection of infants from Hib disease. The widespread use of these vaccines should have substantial impact in reducing the mortality and morbidity from this disease.

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