Passive Immunization for Infection With *Haemophilus influenzae* Type b

Mathuram Santosham, MD; Ray Reid, MD; G. William Letson, MD; Mark C. Wolff, PhD; and George Siber, MD

From the Division of Geographic Medicine, Department of International Health, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, the Division of Infectious Disease of the Dana Farber Cancer Institute, Harvard University, and the Biologic Laboratories of the Massachusetts Center for Disease Control, Boston, Massachusetts

Haemophilus influenzae type b is the leading cause of meningitis in children younger than 5 years of age in the United States.[1] The incidence of infection with *H influenzae* type b in certain populations, such as Apache and Navajo Indians and Alaskan Eskimos, is 10 to 20 times higher than in the general US population.[2-4] Another important feature of *H influenzae* type b infections in these populations is that more than 80% of the cases occur during the first year of life, with 35% to 45% occurring during the first 6 months.

One of the currently licensed vaccines that contains the capsular polysaccharide of the *H influenzae* type b organism is not reliably immunogenic in infants younger than 18 months of age.[5,6] A number of new *H influenzae* type b vaccines prepared by covalently coupling the *H influenzae* type b capsular polysaccharide with a protein carrier antigen are undergoing clinical evaluation.[7-13] One of these conjugate vaccines was shown to be efficacious in preventing disease caused by *H influenzae* type b in Finnish infants when they were immunized at 3, 4, and 6 months of age.[14] Unfortunately, in a recently concluded trial, the same vaccine was not found to be efficacious in preventing such disease in infants younger than 1 year of age among the Alaskan Eskimo population.[15]

We have evaluated an alternative approach for protecting high-risk infants. A human hyperimmune globulin called bacterial polysaccharide immune globulin (BPIG) was prepared from the pooled plasma of adult blood donors immunized with *H influenzae* type b, pneumococcal, and meningococcal capsular polysaccharide.[16] The pharmacokinetics of antibody to *H influenzae* type b capsular polysaccharide was compared in older children after BPIG and conventional immune serum globulin were administered intramuscularly at a dose of 0.5 to 0.6 mL/kg.[17] Peak antibody concentrations were approximately 10 times higher after BPIG administration, and concentrations thought to confer protection (>0.15 μg/mL) were maintained for approximately 4 months.

Reprint requests to (M.S.) Dept. of International Health, The Johns Hopkins University School of Hygiene and Public Health, 615 N Wolfe St, Baltimore, MD 21205.

PEDIATRICS (ISSN 0031 4005).

We also have evaluated the efficacy of BPIG in preventing disease caused by *H influenzae* type b in the Apache Indian population.[18] In addition, we evaluated the effect of administering BPIG simultaneously with a *H influenzae* type b conjugate vaccine at 2 months of age.[19]

In this brief review we will summarize the findings of these studies and discuss the potential uses of BPIG.

PHARMACOLOGY OF *H INFLUENZAE* TYPE b ANTIBODY AFTER BPIG ADMINISTRATION

Compared with conventional immune globulin prepared from unimmunized donors, BPIG contained approximately 10 times higher concentration of antibody of *H influenzae* type b capsular polysaccharide. The minimum protective level of passively administered IgG to the *H influenzae* type b capsule was estimated to be 0.05 to 0.15 μg/mL. This estimate is based on trough antibody levels in patients with agammaglobulinemia receiving conventional immune globulin prophylaxis.[20] In our studies, administration of BPIG at a dose of 0.5 mL/kg resulted in serum *H influenzae* type b antibody concentrations of >0.15 μg/mL for 4 months in older children and for 3 months in most Apache infants.[17,18]

EFFICACY OF BPIG IN PREVENTING INVASIVE *H INFLUENZAE* TYPE b AND PNEUMOCOCCAL INFECTIONS

Randomizations

A randomized, double-blind trial was conducted at two Apache Indian reservations from June 1983 to April 1986.[18] Infants born to mothers living in the White Mountain and San Carlos Apache reservations were recruited into the study after written informed consent was obtained.

Protocol

Infants were randomly assigned to receive either BPIG (0.5 mL/kg of body weight) or placebo (0.5 mL of saline) at 2, 6, and 10 months of age. At 2 and 6 months of age, BPIG or placebo was given simultaneously with diphtheria, tetanus, and pertussis immunization. At birth, 2, 4, 6, 10, 15, and 18 months of age, 1 mL of blood was obtained for measurement of serum antibody to the *H influenzae* type b capsular polysaccharide. If an infant was taken to one of the hospitals or clinics with temperature ≥39°C, blood was obtained for culture and serum was obtained to detect the presence of *H influenzae* type b antigen. If an infant was thought to have sepsis or meningitis, blood, cerebrospinal fluid, and urine were obtained for bacterial culture and detection of *H influenzae* type b antigen.

Outcome Measures

Invasive *H influenzae* type b, pneumococcal, and meningococcal infections, defined as isolation of one of these organisms from a normally sterile body fluid (blood, cerebrospinal fluid, pleural fluid, or joint fluid) were evaluated. Presence of purulent meningitis, defined as >100 polymorphonuclear cells per cubic millimeter of cerebrospinal fluid together with presence of *H influenzae* type b capsular polysaccharide antigen in the cerebrospinal fluid, was also considered to be invasive disease caused by *H influenzae* type b.

All infants who received at least one dose of BPIG or placebo were included in the analysis. On the basis of previous pharmacology, only outcomes occurring within 4 months of receipt of BPIG or saline were evaluated for assessment of efficacy.

Results

Of 762 newborn infants recruited into the study, 703 (92%) were randomly assigned to receive at least one dose of BPIG or placebo; 353 were assigned to the BPIG group and 350 to the placebo group. Comparison of various characteristics such as the proportion of infants with low birth weight or the geographic distribution of the population did not show any statistically significant difference between the groups.

The frequency of bacteremic *H influenzae* type b and pneumococcal infections during the study period is shown in Table 1. As shown in the table, there were no cases of *H influenzae* type b infections in the BPIG group during the 3-month postimmunization period, whereas seven cases occurred in the placebo group ($P = .007$). During the fourth month, one case of *H influenzae* type b infection occurred in the BPIG group. Thus, during the full 4-month period after immunization, one case of invasive disease caused by *H influenzae* type b occurred in the BPIG group and seven occurred in the placebo group ($P = .04$). Based on these data, the efficacy of BPIG in preventing disease caused by *H influenzae* type b during the first 3 months after vaccination was estimated to be 100%, with a 95% one-sided confidence interval of 46.7% to 100%. For the full 4 months, the efficacy was 85.8%, with a 95% confidence interval of −11.4% to 99.7%. During the subsequent follow-up period of 2 years after completion of BPIG and placebo administration, two additional cases of *H influenzae* type b occurred in the BPIG group and four in the placebo group.

Although fewer cases of invasive pneumococcal disease occurred in the BPIG group compared with the placebo group during the first 3 and 4 months after immunization, these differences were not statistically significant.

We also have estimated a pooled efficacy rate for BPIG in the prevention of *H influenzae* type b bacteremias by comparing the incidence of *H influenzae* type b bacteremias during infancy in all BPIG recipients with that in all untreated individuals. The placebo recipients and all nonparticipating infants were pooled because their *H influenzae* type b bacteremia incidence was similar. The efficacy was approximately 88%, with a 95% confidence interval of 60% to 95%.

Since the completion of this trial, we have provided BPIG to all infants in this population during the first year of life. Because this population continues to experience a high attack rate of pneumococcal disease during the second year of life, we are conducting further studies to evaluate the efficacy of BPIG in preventing pneumococcal infections during the second year.

EFFICACY OF BPIG IN PREVENTING OTHER INFECTIONS

During the first phase of the study,[18] significant reductions were noted in the numbers of children with recurrent pneumonia (more than three episodes) and children hospitalized with fever ≥39°C in the BPIG group. However, the frequency of all roentgenographically documented pneumonia, clinically diagnosed otitis media, or gastroenteritis did not differ significantly between BPIG and placebo groups.

Studies of experimental otitis media in chinchillas suggest that passive immunization with BPIG is effective in the prevention of pneumococcal otitis media.[21] Therefore, a pilot study of BPIG in the prevention of recurrent otitis media was performed in high-risk infants in Cleveland, Ohio.[22] Infants with 1 to 3 prior episodes of otitis media were given

TABLE 1. *Haemophilus influenzae* Type b (Hib) and Pneumococcal Bacteremia in Infants Given Bacterial Polysaccharide Immune Globulin (BPIG) or Placebo

	BPIG Group	Placebo Group	*P* value*
No. of patients at risk	353	350	
No. of doses	858	838	
Cases of invasive disease caused by Hib			
Before treatment period	0	1	
1–90 days after immunization	0	7	.007
91–120 days after immunization	1	0	
After treatment period†	2	4	
Cases of invasive pneumococcal infections			
Before treatment period	1	0	
1–90 days after immunization	0	4	.06
91–120 days after immunization	2	0	
After treatment period†	6	6	
Combined no. of cases of invasive Hib and pneumococcal infections			
Before treatment period	1	1	
1–90 days after immunization	0	11	<.001
91–120 days after immunization	3	0	
After treatment period†	8	10	

* By two-sided Fisher's exact test. *P* value is given only if $P < .1$.
† From 121 days to 2 years after the third dose.

two doses of BPIG (0.5 mL/kg) 1 month apart and observed for a total of 4 months. The bacteriology of otitis media was examined by tympanocentesis. A significant reduction in pneumococcal otitis media was observed in BPIG-treated infants (7 episodes in 37 BPIG patients as compared with 18 episodes in 42 placebo patients). However, the frequency of otitis media associated with *H influenzae* (nontypable), *Branhamella catarrhalis*, or negative cultures was not decreased. As a consequence, the frequency of all episodes of otitis media was not significantly decreased by BPIG prophylaxis.

BPIG AND CONJUGATE VACCINES

We randomly assigned 2-month-old Navajo infants to one of three groups. Group 1 (control group) was not immunized against *H influenzae* type b; group 2 received a new *H influenzae* type b conjugate vaccine termed HbOC (Praxis Biologics, Rochester, NY) at 2, 4, and 6 months of age; and group 3 received HbOC at the same ages as group 2 and also received one dose of BPIG at 2 months of age. (The HbOC vaccine is composed of *H influenzae* type b capsular polysaccharide covalently linked to nontoxic diphtheria toxin cross-reactive material.) Blood samples were drawn from all three groups just before each immunization and at 7 and 12 months of age.[19]

The mean *H influenzae* type b capsular polysaccharide antibody levels and the proportion of infants with *H influenzae* type b capsular polysaccharide levels ≥0.15 μg/mL and ≥1 μg/mL are shown in the Figure and Table 2. Infants who received BPIG simultaneously with their first dose of HbOC

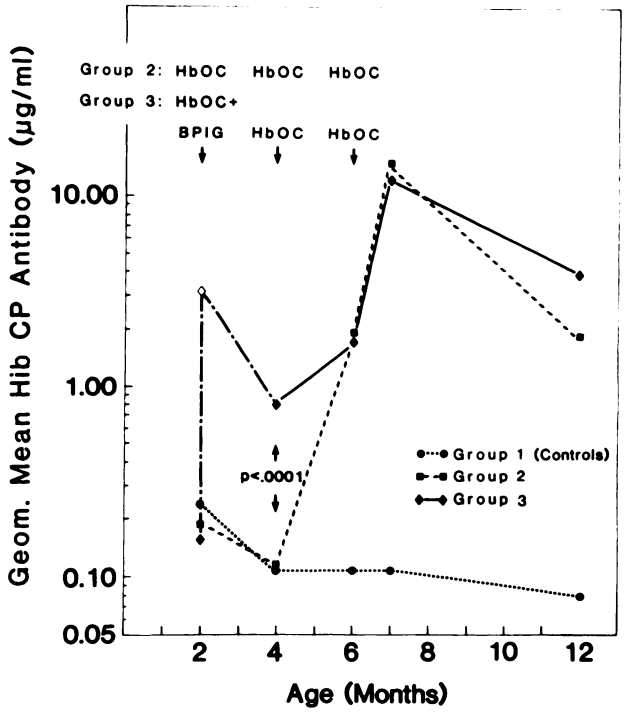

Figure. Mean *Haemophilus influenzae* type b (Hib) capsular polysaccharide (CP) antibody levels and proportion of infants with Hib CP levels ≥0.15 μg/mL and ≥1 μg/mL. Group 1 was not immunized against Hib; group 2 received HbOC at 2, 4, and 6 months of age; and group 3 received HbOC at the same ages as group 2 and also received one dose of bacterial polysaccharide immune globulin (BPIG) at 2 months of age.

at 2 months (group 3) had significantly higher antibody concentrations when compared with the other two groups at 4 months ($P < .001$). The antibody response to the second and third injections of HbOC was similar in the group that re-

TABLE 2. Antibody Response to *Haemophilus influenzae* Type b (Hib) Capsular Polysaccharide (CP) of 2-, 4-, and 6-month-old Navajo Infants Immunized With HbOC Vaccine Alone or Combined With Bacterial Polysaccharide Immune Globulin (BPIG)

Age, mo	Geometric Mean Hib CP Antibody, μg/mL			% With Antibody ≥0.15 μg/mL			% With Antibody ≥1 μg/mL		
	Unimmunized Control (n = 25) Group 1	HbOC Alone (n = 26) Group 2	HbOC + BPIG (n = 24) Group 3	Unimmunized Control (n = 25) Group 1	HbOC Alone (n = 26) Group 2	HbOC + BPIG (n = 24) Group 3	Unimmunized Control (n = 25) Group 1	HbOC Alone (n = 26) Group 2	HbOC + BPIG (n = 24) Group 3
2	0.23	0.19	0.16	56	58	46	24	12	8
4	0.11	0.12	0.76*	36	42	100*	4	4	33†
6	0.11	1.28‡	1.53‡	44	88‡	83§	4	58‡	58‡
7	0.11	10.5‡	8.82‡	42	100‡	100‡	4	92‡	83‡
12	0.075	1.43‡	2.06‡	21	96‡	95‡	0	70‡	73‡

* Differs from HbOC-alone group at $P < .001$.
† Differs from HbOC-alone group at $P < .05$.
‡ Differs from control group at $P < .001$.
§ Differs from control group at $P < .05$.

ceived HbOC alone compared with the group that received HbOC and BPIG. Infants who had received the passive-active immunization regimen had decreases (81% median decrease over 5 months) similar to those of infants who received active immunization alone.

CONCLUSION

Passive immunization with BPIG at a dose of 0.5 mL/kg every 4 months reduced bacteremic *H influenzae* type b infections by approximately 88% in Apache infants. Protection was most reliable during the first 3 months after immunization; breakthrough infections were occasionally observed after 3 months. BPIG did not interfere detectably with the active antibody response to simultaneously administered diphtheria, tetanus, and pertussis vaccine or HbOC conjugate vaccine. The acquisition of antibodies to *H influenzae* type b polysaccharide by natural exposure was not delayed by BPIG administration (G. S., M. S., and R. P., unpublished data, 1987). Similarly, the maturation of the capacity to respond to purified *H influenzae* type b polysaccharide was not affected by passive immunoprophylaxis.

Although it is more expensive than active immunization, BPIG prophylaxis may be cost-effective for the prevention of severe *H influenzae* type b infections in high-risk populations such as American Indian and Eskimo infants. As more immunogenic conjugate vaccines become available, regimens combining passive and active immunization may provide uninterrupted protection at lower cost.

Another potential use for BPIG would be as prophylaxis for the exposed household contacts of patients with primary *H influenzae* type b infection. Currently, rifampin prophylaxis is recommended for all household contacts in this situation.[23] In contrast with rifampin prophylaxis, BPIG prophylaxis could be administered only to the young children who are themselves at risk.

If BPIG is shown to be efficacious in preventing pneumococcal infections, indications for its use may be broadened to include individuals at high risk for these infections, such as children with sickle cell disease and asplenia, or those receiving chemotherapy for cancer.

REFERENCES

1. Schlech WF III, Ward JI, Band JD, et al. Bacterial meningitis in the United States, 1978 through 1981: the National Bacterial Meningitis Study. *JAMA*. 1985;253:1749–1754
2. Coulehan JL, Michaels RH, Hallowell C, et al. Epidemiology of *Haemophilus influenzae* type b among Navajo Indians. *Public Health Rep*. 1984;99:404–409
3. Coulehan JL, Michaels RH, Williams KE, et al. Bacterial meningitis in Navajo Indians. *Public Health Rep*. 1976;91:464–468
4. Losonsky GA, Santosham M, Sehgal VM, et al. *Haemophilus influenzae* disease in the White Mountain Apaches: molecular epidemiology of a high risk population. *Pediatr Infect Dis*. 1984;3:539–547
5. Committee on Infectious Diseases. *Haemophilus influenzae* type b polysaccharide vaccine. *Pediatrics*. 1985;76:322–324
6. Daum RS, Granoff DM. A vaccine against *Haemophilus influenzae* type b. *Pediatr Infect Dis*. 1985;4:355–357
7. Lepow ML, Samuelson JS, Gordon LK. Safety and immunogenicity of *Haemophilus influenzae* type b polysaccharide diphtheria toxoid conjugate vaccine in infants 9 to 15 months of age. *J Pediatr*. 1985;106:185–189
8. Lepow M, Barkin R, Meier K, et al. Studies of safety and immunogenicity of *Haemophilus influenzae* type b polysaccharide vaccine (PRP-D) in children 7–14 months of age. *Pediatr Res*. 1985;19:299A. Abstract
9. Berkowitz CD, Ward JI, Meier K, et al. Safety and immunogenicity of *Haemophilus influenzae* type b polysaccharide and polysaccharide diphtheria toxoid conjugate vaccines in children 16–24 months. *J Pediatr*. 1987;110:509–514
10. Eskola J, Kayhty H, Peltola H, et al. Antibody levels achieved in infants by course of *Haemophilus influenzae* type b polysaccharide/diphtheria toxoid conjugate vaccine. *Lancet*. 1985;1:1184–1186
11. Einhorn MS, Weinberg GA, Anderson EL, et al. Immunogenicity in infants of *Haemophilus influenzae* type b polysaccharide in a conjugate vaccine with *Neisseria meningitidis* outer-membrane protein. *Lancet*. 1986;2:299–302

12. Anderson P, Pichichero ME, Insel RA. Immunization of 2 month old infants with protein-coupled oligosaccharides derived from the capsule of *Haemophilus influenzae* type b. *J Pediatr.* 1985;107:346–351
13. Lenoir AA, Granoff PD, Granoff DM. Immunogenicity of *Haemophilus influenzae* type b polysaccharide-*Neisseria meningitidis* outer membrane protein conjugate vaccine in 2- to 6-month-old infants. *Pediatrics.* 1987;80:283–287
14. Eskola J, Peltola H, Takala AK, et al. Efficacy of *Haemophilus influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. *N Engl J Med.* 1987;317:717–722
15. Ward JI, Brenneman G, Letson G, et al. Limited protective efficacy of an *H. influenzae* type b conjugate vaccine (PRP-D) in Native Alaskan infants immunized at 2, 4 and 6 mo of age. In: Program and abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; Washington, DC: American Society for Microbiology; 1988:309. Abstract
16. Siber GR, Ambrosino DM, McIver J, et al. Preparation of human hyperimmune globulin to *Haemophilus influenzae* b, *Streptococcus pneumoniae*, and *Neisseria meningitidis. Infect Immun.* 1984;45:248–254
17. Ambrosino DM, Landesman SH, Gorham CC, et al. Passive immunization against disease due to *Haemophilus influenzae* type b: concentrations of antibody to capsular polysaccharide in high risk children. *J Infect Dis.* 1986;153:1–7
18. Santosham M, Reid R, Ambrosino DM, et al. Prevention of *Haemophilus influenzae* type b infections in high-risk infants treated with bacterial polysaccharide immune globulin. *N Engl J Med.* 1987;317:923–929
19. Letson GW, Santosham M, Reid R, et al. Comparison of active and combined passive/active immunization of Navajo children against *Haemophilus influenzae* type b. *Pediatr Infect Dis J.* 1988;7:747–752
20. Robbins JB, Parke JC Jr, Schneerson R. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. *Pediatr Res.* 1973;7:103–110
21. Shurin PA, Giebink GS, Wegman DL, et al. Prevention of pneumococcal otitis media in chinchillas with human bacterial polysaccharide immune globulin. *J Clin Microbiol.* 1988;26:755–759
22. Rehmus J, Johnson C, Marchant C, et al. Bacterial polysaccharide immune globulin prophylaxis of otitis media in high-risk infants. In: Program and abstracts of the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; Washington, DC: American Society for Microbiology; 1988:334. Abstract
23. Daum RS, Granoff DM, Gilsdorf J, et al. *Haemophilus influenzae* type b infections in day care attendees: implications for management. *Rev Infect Dis.* 1986;8:558–567

Passive Immunization for Infection With *Haemophilus influenzae* Type b

Mathuram Santosham, Ray Reid, G. William Letson, Mark C. Wolff and George Siber

Pediatrics 1990;85;662

Passive Immunization for Infection With *Haemophilus influenzae* Type b

Mathuram Santosham, Ray Reid, G. William Letson, Mark C. Wolff and George Siber

Pediatrics 1990;85;662