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Comparison of active and combined passive/active immunization of Navajo children against *Haemophilus influenzae* type b

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In a high risk Navajo population we compared the immunogenicity of a new *Haemophilus influenzae* type b mutant-diphtheria toxic conjugate vaccine (HbOC) with simultaneous active (HbOC) and passive immunization with bacterial polysaccharide immunoglobulin prepared from adults immunized with *H. influenzae* b, pneumococcal and meningococcal vaccines.

Only 7 of 26 (27%) 2-month-olds had an increase in *H. influenzae* b capsular polysaccharide antibody after a single dose of HbOC, a proportion similar to that of saline controls (9 of 25, 36%). After a second HbOC dose at 4 months 88% had antibody concentrations of 0.15 μg or more, and after a third dose at 6 months all had antibody levels ≥0.15 μg/ml.

The group receiving both HbOC and bacterial polysaccharide immunoglobulin at 2 months uniformly had *H. influenzae* b CP antibody concentrations of ≥0.15 μg/ml at 4 months ($P < 0.001$ relative to "HbOC alone" group) and subsequently responded similarly to second and third doses of HbOC vaccine as did also the "HbOC alone" group.

We conclude that combined passive/active immunization with bacterial polysaccharide immunoglobulin and HbOC at 2 months maintains antibody at concentrations thought to be protective (≥0.15 μg/ml) without interfering with the active antibody response to second and third doses of HbOC at 4 and 6 months of age.

INTRODUCTION

Incidence rates of invasive *Haemophilus influenzae* type b (Hib) diseases among American Indians are known to be much higher than in the general United States population.[1–4] In children of the Navajo Nation who were younger than 5 years of age, the incidence of all invasive Hib diseases is 214/100 000[1] and the incidence of meningitis alone is 152 to 173/100 000.[1,2] Another important feature of the epidemiology of Hib disease in these populations is that a high proportion of infections occur early in infancy. Among the Navajo and Apache more than 80% of Hib infections occur in the first year of life and 35 to 45% in the first 6 months.[2–5] As a consequence incidence rates of Hib disease during infancy are approximately 10 times higher in Navajo and Apache than in the general United States population.

The currently licensed Hib vaccine consisting of purified capsular polysaccharide (CP) of Hib is not reliably immunogenic in infants less than 18 to 24 months of age.[6,7] New Hib vaccines, prepared by covalently coupling the Hib-CP with a protein carrier antigen, are undergoing clinical evaluations.[8–13] These new conjugate vaccines are more immunogenic than the purified polysaccharide vaccine.[8–13] They may not, however, produce reliable seroresponses in infants younger than 6 months of age. Recently a human hyperimmune globulin called bacterial polysaccharide immunoglobulin (BPIG) was prepared from the pooled plasma of adult donors immunized with Hib, pneumococcal and meningococcal CP vaccines.[14] This globulin has been shown to protect Apache Indian infants younger than 1 year of age from Hib disease when given at 4-month intervals beginning at 2 months of age.[15]

In order to determine the optimal regimen for pro-

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tecting high risk populations such as Navajos, we immunized individuals at various ages with a new conjugate vaccine termed HbOC (Praxis Biologics, Rochester, NY), composed of Hib-CP covalently linked to nontoxic diphtheria toxin cross-reactive material. The effect of administering BPIG simultaneously with HbOC at 2 months of age was also evaluated.

MATERIALS AND METHODS

Study population. Children were recruited from the Navajo Indian population who use the Indian Health Service Hospital at Tuba City, AZ, for their routine health care. Patients were enrolled into the study from July 1, 1985, to June 30, 1987, after written informed consent was obtained. The study protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine, the Indian Health Service and the Tuba City Indian Health Service Hospital Health Board.

Vaccines and immunoglobulin. The Hib conjugate vaccine (HbOC) consisted of oligosaccharides derived from the capsular polysaccharide of Hib covalently linked to a nontoxic diphtheria toxin cross-reactive protein (CRM-197). Lots 5, 9 and 11 of the vaccine were given in a dose of 0.5 ml. Each dose contained 25 μg of protein and 6.5 to 15 μg of oligosaccharide, depending on the lot. The vaccine was dissolved in normal saline containing 0.1 mg/ml of thimerosal.

The Hib-CP vaccine was a licensed lot of b Capsa I® polysaccharide contained in 0.5 ml of saline. Both vaccines were given intramuscularly.

BPIG was prepared from the pooled plasma of adult donors immunized with Hib, pneumococcal and meningococcal vaccines as described previously.[14] BPIG was given in a dose of 0.5 ml/kg body weight intramuscularly divided between two sites.

Schedule of immunization. Eighteen-month-old children were given one dose of HbOC vaccine simultaneously with their fourth diphtheria, tetanus and pertussis (DPT) vaccine in separate sites. Blood samples were drawn just before immunization and 1 and 6 months after immunization, to determine Hib-CP antibodies.

Seven-month-old infants received HbOC vaccine at 7 months of age and a booster dose at 8 months of age. At 11 months of age they were randomized to receive either a second booster dose of HbOC (Group 4) or the Hib-CP vaccine (Group 5). Blood samples were drawn just before each immunization, 1 month after each immunization and at 17 months of age, 6 months after the second booster dose of HbOC or Hib-CP vaccine.

Two-month-old infants were randomized to one of three groups: Group 1 (control group) was not immunized against Hib; Group 2 received HbOC alone at 2, 4 and 6 months of age; Group 3 received HbOC at the same ages as Group 2 and additionally received 1 dose of BPIG at 2 months of age.

Infants in all three groups received DTP immunizations at 2, 4 and 6 months of age in a separate site. Blood samples were drawn from all 3 groups just before each immunization and at 7 and 12 months of age.

Study participants who were more than 1 month delinquent for receiving any of the immunizations or blood samples were discontinued from the study.

Assay for antibody to Hib-CP. Hib-CP antibody was measured by Farr radioimmunoassay[16] with the use of tritiated Hib-CP provided by Porter Anderson (University of Rochester, Rochester, NY) (Lots 4+8/85, C-4/86) and standardized against a standard serum pool containing 70 μg of anticapsular antibody obtained from the Office of Biologics Research and Review (Bethesda, MD). The values used in the analyses reported here were all performed at Praxis Biologics. However, because differences in Hib-CP antibody assays have been reported between laboratories and with different antigen preparations,[17] 44 serum samples were measured in an independent laboratory (George Siber, Dana Farber Cancer Institute, Boston, MA) without knowledge of the concentrations assayed by Praxis Biologics. A different lot of tritiated antigen (Lot B-8/86) provided by Porter Anderson was utilized. Figure 1 shows the correlation between the two assays ($r = 0.98$). The only difference between the assays was that the values obtained by Praxis Biologics were 19% higher than those in Boston ($P < 0.001$ by comparison of slopes).

Data analysis. Antibody concentrations and antibody rises (postimmunization/preimmunization level) were usually nonnormally distributed by the Wilk Shapiro test and were therefore converted to logarithms for analysis. The lower limit of sensitivity of the antibody assay was 0.1 μg/ml. Values falling below this limit were assigned a concentration of 0.05 μg/ml for purposes of calculating geometric means. Geometric means were compared by the the t test.

The apparent serum antibody half-lives were calculated utilizing values in the measurable range by methods previously described.[14]

Antibody concentrations were also analyzed according to the proportion of children who developed concentrations ≥0.15 or ≥1.0 μg of Hib-CP antibody/ml. A concentration of 0.15 μg/ml of Hib-CP antibody was estimated to correlate with protection in agammaglobulinemic patients receiving passive IgG prophylaxis.[18] A concentration of ≥1.0 μg/ml was achieved in >90% of children ages 24 months or older in a large field trial of purified Hib-CP vaccine in Finland.[19] This age group was protected by immuni-

zation for several years; therefore this concentration has been proposed as an estimate for a desired concentration for longterm protection after active immunization.

A two-tailed Fisher exact test was used for a comparison of frequencies and proportions.

RESULTS

Different vaccine lots were tested for differences in antibody response within age groups and no significant differences were found. As a result all the subsequent data reported reflect the grouping together of immune responses to differing lots in each age group.

Eighteen-month-old children. Hib-CP antibody concentrations in 28 eighteen-month-old Navajo children before and after immunization with HbOC vaccine are summarized in Table 1. All developed antibody concentrations ≥0.15 μg/ml and 89% developed concentrations ≥1 μg/ml 1 month after immunization. Antibody concentrations were well-maintained for at least 6 months after immunization.

Seven-month-old infants. Hib-CP antibody concentrations in the 31 seven-month-old children are summarized in Table 2. After a single HbOC immunization 94% developed antibody concentrations ≥0.15 μg/ml and 58% antibody concentrations ≥1.0 μg/ml (Groups 4 and 5 combined). A second dose of HbOC at 8 months produced antibody concentrations ≥1.0 μg/ml in all infants.

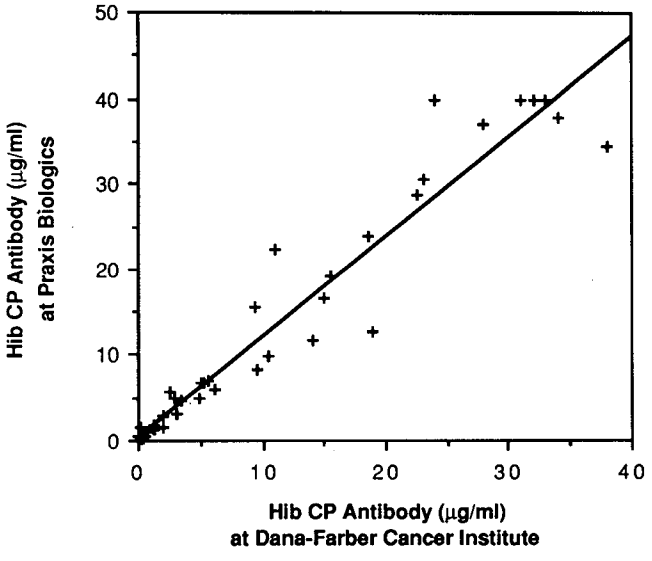

FIG. 1. Correlation of Hib-CP antibody concentrations in 44 sera from Navajo children measured by radioimmunoassay at Praxis Biologics and at the Dana-Farber Cancer Institute. The correlation coefficient was 0.98. The slope was 1.19 which differed from 1.0 at $P < 0.01$.

TABLE 1. Antibody response of 28 eighteen-month-old Navajo Indian children to HbOC vaccine (Group 6)

Time Relative to Immunization	Geometric Mean Hib-CP Antibody (μg/ml)	% with Hib-CP Antibody	
		≥0.15 μg/ml	≥1.0 μg/ml
Before	0.39	89	18
1 month after	2.33	100	89
6 months after	1.62	100	71

To determine whether HbOC had primed children to respond to purified polysaccharide, half of the 7-month-old cohort received 25 μg of b Capsa I® at 11 months of age (Group 5). This group did have a significant increase in Hib-CP antibody from a geometric mean of 6.2 μg/ml to 15.3 μg/ml. The cohort boosted with HbOC (Group 4), however, had a significantly better response as judged by postimmunization antibody concentrations (61.4 *vs.* 15.3 μg/ml, $P < 0.01$). The fold rise in antibody did not differ significantly between the two groups (4.3-fold after HbOC *vs.* 2.4-fold after Hib-CP).

Two-month-old infants. Unimmunized control infants (Group 1) showed a progressive decline in maternally acquired Hib-CP antibody (Table 3; Fig. 2).

Infants immunized with HbOC alone (Group 2) did not respond reliably to the first dose. Only 7 of 26 (27%) had an increase in antibody at 4 months; in 6 of these 7 infants the antibody concentration was ≥0.15 μg/ml. An additional 5 infants with declining antibody concentrations still had concentrations ≥0.15 μg/ml at 4 months. Consequently 11 of 26 (42%) 4-month-olds in Groups 2 had antibody concentrations ≥0.15 μg/ml and one had antibody concentrations ≥1.0 μg/ml (Table 3). These concentrations did not differ from controls in Group 1.

One infant in Group 2 developed Hib meningitis at age 3 months, 6 weeks after his first immunization (Fig. 3). His preimmunization antibody concentration was 0.18 μg/ml and the concentration 1 month after onset of disease was undetectable. He did not generate an antibody response to the first dose of the conjugate vaccine or to natural infection but developed antibody concentrations of 0.33 and 1.56 μg/ml after the second and third doses of the conjugate vaccine, respectively. The patient's antibody response was the fourth lowest in Group 2.

Infants who receive BPIG simultaneously with their first HbOC dose at 2 months (Group 3) had significantly higher antibody concentrations than did infants in Groups 1 and 2 at 4 months (<0.001); all had concentrations ≥0.15 μg/ml and 33% had concentrations ≥1.0 μg/ml. BPIG did not detectably diminish the active antibody response to the second and third doses of HbOC (Table 3; Fig. 2). The differences shown were not statistically significant between Groups 2 and 3.

Persistence of Hib-CP antibody after immunization. The decline in Hib-CP antibody after immunization differed in the three age groups. A comparison of median change in antibody concentrations

TABLE 2. Antibody response of 7-month-old Navajo infants immunized with two doses of HbOC vaccine and a third dose of either HbOC vaccine (Group 4) or purified Hib-CP vaccine (Group 5)

Blood for antibody assays was drawn before administration of vaccines indicated.

Age (Months)	Vaccine	No.	Geometric Mean Hib-CP Antibody (μg/ml)		% with Hib-CP Antibody ≥0.15 μg/ml	% with Hib-CP Antibody ≥1.0 μg/ml
7	HbOC	31	0.114		39	3
8	HbOC	31	1.37		94	58
9	None	31	18.80		100	100
11	Group 4: HbOC	15	12.40	N.S.	100	100
	Group 5: pure CP	16	6.24		100	93
12	Group 4: none	15	61.40	$P < 0.01$	100	100
	Group 5: none	16	15.30		100	100
19	Group 4: none	15	11.70	$P < 0.01$	100	100
	Group 5: none	16	3.71		100	100

N.S., not significant.

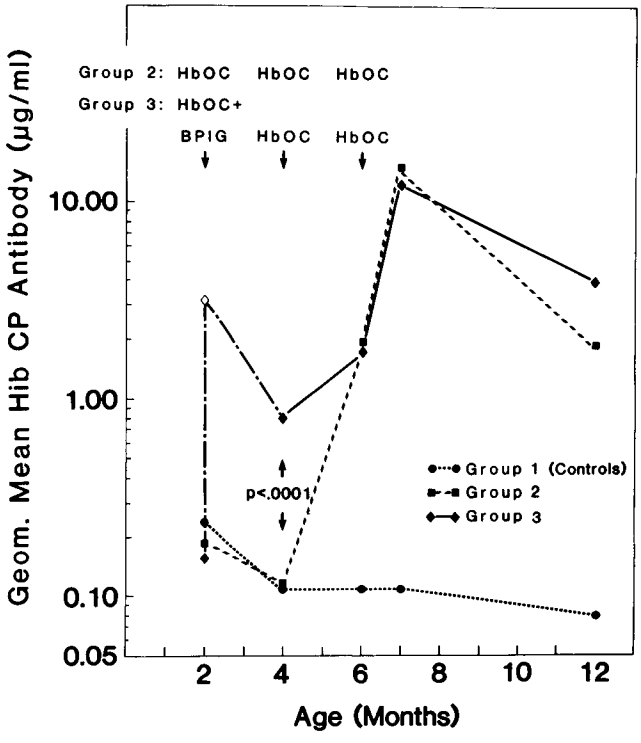

FIG. 2. Geometric mean Hib-CP antibody concentrations in Navajo infants who were unimmunized (Group 1), immunized with HbOC vaccine alone (Group 2) or immunized with HbOC vaccine and BPIG (Group 3). The peak antibody concentration after the BPIG injection at 2 months (◇) in Group 3 was extrapolated from the 4-month-old concentrations assuming a 30-day half-life of passively administered Hib-CP antibody[20].

shows a 43% decrease over 5 months in 19-month-olds (Table 4), a 79% decrease over 7 months in 12-month-olds and an 80% decrease over 5 months in 7-month-olds. The 11-month-old group that had been boosted with pure Hib-CP vaccine did not show better persistence of antibody (78% median decrease over 7 months). 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.

Adverse reactions. Only the results of the reactions reported in the group that received HbOC at 7 and 8 months of age are presented here because all other doses of HbOC vaccine were given simultaneously with DTP injections. Adverse reaction reports were available from 46 of the 85 doses of the HbOC vaccine given to these age groups. Erythema occurred in 11 (23%), pain in 8 (17.4%), fever ≥101°F in 3 (6.5%) and irritability in 15 (32.6%).

DISCUSSION

The major findings of this study are that a single dose of HbOC vaccine induced a "protective" antibody response in 18-month-old Navajo children but that two doses were required in 7-month-old infants and three doses in 2-month-old infants to achieve similar responses. Concurrent passive immunization with BPIG at 2 months maintained antibody concentrations ≥0.15 μg/ml before 6 months of age without detectably impairing the active antibody response to HbOC vaccine.

All 18-month-old children developed serum concentrations of 1.0 μg/ml or greater after a single dose of HbOC vaccine. The geometric mean peak antibody concentration (2.33 μg/ml) appeared substantially higher than the peak concentrations we recently observed in 18-month-old Apache children given the licensed b Capsa I® purified polysaccharide vaccine (0.14 μg/ml).[21]

Seven-month-old infants had geometric mean antibody concentrations of 1.37 μg/ml after their first dose which was not significantly different from 18-month-olds. Although most (29 of 31; 94%) reached antibody concentrations ≥0.15 μg/ml, a lower proportion (18 of 31; 58%) of 7-month-old infants compared with 18-month-old children reached antibody concentrations ≥1.0 μg/ml ($P < 0.01$). After a second dose of HbOC vaccine at 8 months, all infants developed antibody concentrations ≥1.0 μg/ml.

Other investigators have shown that immunization with polysaccharide-protein conjugate vaccines primes infants to respond to purified capsular polysaccharide at an age when they would normally not be expected to respond.[22] Navajo infants primed with

TABLE 3. Antibody response to Hib capsular polysaccharide of 2-, 4- and 6-month-old Navajo infants immunized with HbOC vaccine alone or combined with BPIG

Age (Months)	Geometric Mean Hib-CP Antibody			% with Antibody ≥0.15 μg/ml			% with Antibody ≥1 μg/ml		
	Unimmunized control (Group 1)	HbOC alone (Group 2)	HbOC + BPIG (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[a]	36	42	100[a]	4	4	33[b]
6	0.11	1.28[c]	1.53[c]	44	88[c]	83[d]	4	58[c]	58[c]
7	0.11	10.5[c]	8.82[c]	42	100[c]	100[c]	4	92[c]	83[c]
12	0.075	1.43[c]	2.06[c]	21	96[c]	95[c]	0	70[c]	73[c]

[a] Differs from HbOC alone group at $P < 0.001$.
[b] Differs from HbOC alone group at $P < 0.05$.
[c] Differs from control group at $P < 0.01$.
[d] Differs from control group at $P < 0.05$.

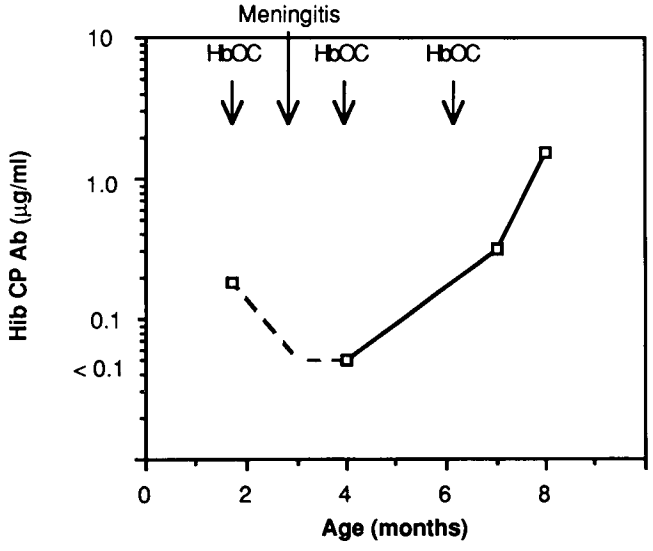

FIG. 3. Antibody concentrations to Hib-CP in an infant who developed Hib meningitis 6 weeks after the first dose of HbOC vaccine.

two doses of HbOC vaccine had a significant antibody response to purified Hib-CP at 11 months. However, the booster response to HbOC in similarly primed infants was significantly better (Table 2).

Two-month-old infants did not respond to their first dose of HbOC vaccine but had modest responses to a second dose at 4 months. A third dose at 6 months produced a substantial booster response resulting in antibody concentrations ≥0.15 and 1.0 μg/ml in 100 and 92%, respectively, of 7 month-old infants.

The occurrence of an episode of Hib meningitis after the first dose of HbOC vaccine provides anecdotal evidence that the vaccine may not be protective after the first dose in 2-month-old infants, nor did the vaccine prime this child for an antibody response to the natural pathogen as documented by a lack of antibody during a convalescence of 1 month between natural infection and his second vaccine dose. Of interest, however, is the fact that this infant was able to produce an antibody response with repeated boosting, indicating that he did not have an absolute deficiency in immune responsiveness to Hib, but rather a relative age-dependent deficiency that was overcome by immune system maturation in the following months.

Simultaneous passive immunization with BPIG and active immunization with HbOC at 2 months of age resulted in antibody levels ≥0.15 μg/ml in 100% of 4-month-olds compared to 42% in infants who received HbOC alone ($P < 0.001$). The active antibody response to the second and third HbOC injections was not impaired by passive immunization at 2 months. In our studies among Apache infants we demonstrated that BPIG given at 2 and 6 months together with DTP immunization did not impair the active response to diphtheria toxoid, tetanus toxoid or pertussis toxin.[15]

The persistence of Hib-CP antibody after HbOC vaccine differed according to the age at immunization. Declines in antibody titers were slowest in 19-month-olds, more rapid in 12-month-olds and most rapid in 7-month-olds (Table 4). Nevertheless all infants immunized at 2, 4 and 6 months maintained concentrations above those likely to be protective at 12 months. However, the median 80% decline from peak concentrations suggests that a booster dose at 15 to 18 months together with other routine immunizations will be necessary to maintain immunity.

We conclude that the HbOC vaccine shows excellent immunogenicity even for young infants in this high risk American Indian population. Because of the high proportion of severe Hib infections in infants younger than 6 months of age and because the HbOC vaccine was not reliably immunogenic in this age range, combined passive and active immunization deserves consideration for such high risk populations.

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TABLE 4. Persistence of Hib-CP antibody after immunization

Age at Initial Dose of Vaccination (Months)	Age at which Maximum Seroresponse Noted (Months)	Immunization	Median % of Decline/Months Post-Maximum Response
18	19	1 dose HbOC	43.5/5
7	12	Group 4: 3 doses HbOC	78.9/7 mos
		Group 5: 2 doses HbOC, 1 dose Hib-CP	78.1/7 mos
2	7	Group 2: 3 doses HbOC	79.5/5 mos
		Group 3: 3 doses HbOC, 1 dose BPIG	80.7/5 mos

Blood Services, Northeast Region, who developed and prepared the bacterial polysaccharide immunoglobulin.

The opinions in this article are those of the authors and do not necessarily reflect the views of the Indian Health Service.

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