Toward Elimination of *Haemophilus influenzae* Type B Carriage and Disease Among High-Risk American Indian Children

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ABSTRACT

Objectives. This report describes the epidemiology of *Haemophilus influenzae* type b (Hib) invasive disease and oropharyngeal colonization among Navajo and White Mountain Apache children younger than 7 years in an era of widespread immunization.

Methods. We conducted active surveillance for invasive *H influenzae* disease from 1992 to 1999 and an oropharyngeal carriage study from 1997 to 1999. The predominant vaccine used was PedvaxHib.

Results. The average annual incidence of invasive Hib disease among children younger than 24 months was 22 cases per 100 000. Of 381 children younger than 7 years, only 1 (0.3%; 95% confidence interval = 0.0%, 1.3%) was colonized with Hib; 370 (97%) had received 2 or more doses of Hib conjugate vaccine.

Conclusions. Among Navajo and White Mountain Apache children, Hib conjugate vaccines have led to a sustained reduction in invasive Hib disease and a reduction in oropharyngeal Hib carriage. The disease incidence among children younger than 24 months remains 20 times higher than in the general US population. Hib elimination will require additional characterization of colonization and disease in these high-risk populations. (*Am J Public Health.* 2000; 90:1550–1554)

Since the introduction of routine immunization against *Haemophilus influenzae* type b (Hib), the incidence of invasive Hib disease among infants and young children in the United States has declined by 98%, from 60 to 100 cases per 100 000 children younger than 5 years to less than 1 case per 100 000.[1] Incidence rates have declined in unvaccinated children as well, indicating that a herd immunity effect has been achieved.[1–4] This effect is likely due to reductions in oropharyngeal colonization among vaccinees and hence reduced transmission to unvaccinated individuals. As a consequence of the tremendous success of Hib conjugate vaccination, Hib disease is being considered as a target for elimination.[5]

In the absence of vaccination, the epidemiology of Hib disease among American Indian (e.g., Navajo and White Mountain Apache) and Alaska Native populations differs from that in the general population of the United States.[6–8] The incidence of disease is 5 to 10 times higher (250–500 cases per 100 000 children younger than 5 years), and the risk of disease peaks at an earlier age (generally 2–6 months vs 6–11 months in the general US population). Data on the prevalence of Hib colonization before vaccination are sparse, but they generally indicate that the prevalence was slightly higher than that observed in the general US population (5%–7% vs 2%–5% of children younger than 5 years). Hib vaccines are highly effective in preventing invasive Hib disease in these populations, and substantial reductions in Hib disease have been observed as a result of routine immunization.[2,9] Nevertheless, a recent resurgence in Hib cases and evidence of persistent Hib colonization among rural Alaska Native children suggest that efforts to eliminate Hib disease in the United States will require special attention to these high-risk populations.[10]

To assess progress in the elimination of Hib disease in a high-incidence population, we evaluated population-based data on the incidence of Hib invasive disease among Navajo and White Mountain Apache children younger than 2 years since 1992 and characterized the cases that continue to occur in the era of Hib immunization. To characterize the epidemiology of Hib colonization, we collected oropharyngeal swabs from 381 children younger than 7 years.

Methods

Surveillance for Invasive Disease

Cases of invasive *H influenzae* were identified through systematic active surveillance of microbiology laboratories serving the Indian Health Service on the Navajo and White Mountain Apache reservations. Hospitals surrounding the reservations, which might serve the population under surveillance, were also contacted on a weekly to monthly basis to identify cases. We defined a case as any Navajo or White Mountain Apache child younger than 24 months of age with *H influenzae* cultured from a normally sterile site. Multiple episodes of disease occurring in an individual were counted if the dates of culture were at least 30 days apart. Information on the clinical and vaccination histories of individual children was

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obtained by reviewing medical charts. Whenever possible, the isolate was collected by study personnel. The isolate was confirmed to be *H influenzae* through standard microbiologic techniques, and serotyping was done by standard antisera methods (Microscan; Baxter Laboratories, West Sacramento, Calif). We used age-specific annual user population estimates obtained from the Indian Health Service (Rockville, Md) as the denominator to calculate rates of disease.

Immunization Regimens

Hib vaccination regimens varied between reservations and over time. During the entire study period, the recommended vaccination schedule for White Mountain Apache Indian children was Hib-OMP (PedvaxHib; Merck & Co, West Point, Pa) at 2, 4, and 12 to 15 months of age. From 1991 to 1994, the recommended vaccination schedule for Navajo Indian children was also PedvaxHib at 2, 4, and 12 to 15 months of age. From 1995 until June 1997, the recommended vaccination schedule for Navajo Indian children was PedvaxHib at 2 months of age followed by 3 doses of Hib-Titer (Wyeth-Lederle Vaccines, West Henrietta, NY) at 4, 6, and 12 months of age. From July 1997 to the present, the recommended vaccination schedule for Navajo Indian children has been PedvaxHib at 2, 4, and 12 to 15 months of age.

Carriage Study

The oropharyngeal Hib carriage study was conducted on the Navajo and White Mountain Apache Indian reservations in New Mexico and Arizona from October 1998 until June 1999. In April 1997, an efficacy trial of the 7-valent protein-conjugate pneumococcal vaccine was initiated that included a nested study of pneumococcal nasopharyngeal (NP) carriage. All children younger than 2 years were eligible to participate in the pneumococcal vaccine efficacy trial and were recruited in the well-child care clinics at Indian Health Service facilities on the reservations. Children enrolled in the efficacy trial who were between 2 and 7 months of age were recruited to participate in the nested NP study. NP study participants included the vaccine trial infants and their household contacts who were younger than 7 years. Oropharyngeal swabs for the detection of Hib were collected from the same children enrolled in the NP study. Children with congenital anomalies of the nasopharynx were excluded from participation. Written informed consent was obtained from the parent or guardian of each study participant.

Parents or guardians of study participants were interviewed to obtain information on a number of household factors and the child's recent exposure to antibiotics. Day care was defined as a place with 5 or more children that the child attended at least 3 days per week and 4 hours per day and included day care centers, Head Start, and preschool. Each participant's immunization history was obtained by medical chart review and, where necessary, through computer record search. The dates of Hib vaccination and product names for each Hib vaccine administered were recorded.

Field-workers and nurses from the Johns Hopkins project on the Navajo and White Mountain Apache Indian reservations were trained in the collection of oropharyngeal specimens. Physicians or nurses with expertise in this technique were present for the first collection by each field-worker and also conducted periodic field visits to ensure technique quality.

One oropharyngeal swab was collected from each study participant by swabbing the tonsils and the posterior pharyngeal wall. Swab specimens were plated directly onto Hib antiserum agar plates (provided by the Centers for Disease Control and Prevention [CDC], Atlanta, Ga). The plates were transported to the local Indian Health Service hospital laboratory within 8 hours and kept at room temperature during inoculation and transport. Plates were incubated at 35°C to 37°C in 5% CO_2 for 24 to 48 hours. Suspected colonies of Hib were identified by the presence of antibody–antigen precipitate "halos" around the colonies. Positive specimens were sent on silica gel packs to the Meningitis and Special Pathogens Branch, CDC, for confirmation. Antiserum agar plates were tested weekly with a laboratory strain of Hib to ensure that they could produce halos and that they were readable by the laboratory technicians.

Statistical Analysis

All analyses were performed with SAS (SAS Institute Inc, Cary, NC) or Excel (Excel 97; Microsoft Corporation, Redmond, Wash).

Ethical Approval

The study was approved by the institutional review boards of the Johns Hopkins University, the CDC, the Indian Health Service, the Navajo Nation, and the White Mountain Apache Tribe.

Results

Invasive Disease

Between January 1, 1992, and December 31, 1999, a total of 19 cases of invasive Hib disease occurred among Navajo and Apache children younger than 24 months, representing 86 197 child-years of observation for an average annual incidence rate of 22 cases per 100 000 child-years of observation (Table 1). The annual incidence rate between 1992 and 1996 was 24.2 cases per 100 000 child-years, compared with 17.6 cases per 100 000 child-years between 1997 and 1999, when the oropharyngeal study was conducted. Annual incidence rates ranged from 46.6 per 100 000 child-years in 1992 to 0 per 100 000 child-years in 1994. One child had 2 episodes of invasive Hib disease 6 weeks apart. Most cases occurred in children aged 7 to 11 months. Since some of the *H influenzae* isolates were not collected for serotyping and may have been serotype b, these reported rates might underestimate the true rates. The remaining *H influenzae* cases were predominantly type a. Rates of disease by year are shown in Table 1.

The charts of 18 children, with 19 episodes of invasive Hib disease, were reviewed for information on clinical syndrome and Hib vaccination. Hib was most commonly isolated from the blood (16 cases), followed by the cerebrospinal fluid (5), joint (2), and pleural fluid (1). The most common clinical syndrome was bacteremia/sepsis (10 cases), followed by meningitis (7), pneumonia (5), cellulitis (2), and arthritis (2). One child died of meningitis, and neurologic sequelae were noted for 2 children. At the time of culture, 3 children had received no Hib vaccine, 5 had received a single dose, 9 had received 2 doses, and 1 had received 4 doses. None of the children had any underlying immunocompromising conditions.

Oropharyngeal Carriage

The characteristics of the 381 study participants are shown in Table 2. The age at time of swabbing ranged from 1.4 months to 82.5 months (median = 12.3 months). There were no significant differences in the age distribution of the children on the 2 reservations. Eighteen of 381 (5%) were receiving antibiotics at the time of swabbing, and 56 (15%) had received antibiotics in the 30 days before swabbing. Amoxicillin was the most frequently used antibiotic. The median interval between time of swabbing and the last Hib vaccination was 6 months.

At the time of swabbing, 370 (97%) of the children had received 2 or more doses of Hib conjugate vaccine. A total of 283 (74.3%) children had received at least 2 doses of PedvaxHib, while 61 (16%) had received a mixed regimen of Hib conjugate vaccines. Twenty-seven (7.1%) had received at least 2 doses of conjugate vaccine before swabbing, but the types were unspecified on the immunization record. One child (0.3%; 95% confidence interval = 0.0%, 1.3%) was colonized with Hib.

TABLE 1—Invasive *Haemophilus influenzae* Disease Among Navajo and White Mountain Apache Children Younger Than 24 Months

	1992	1993	1994	1995	1996	1997	1998	1999	Overall
No. of Hi cases[a]	13	12	11	12	13	11	13	8	93
No. of Hib-infected children	6	3	0	3	2	1	1	3	19
0–6 mo	2	0	0	1	2	0	0	1	6
7–11 mo	4	2	0	2	0	0	1	2	11
12–23 mo	0	1	0	0	0	1	0	0	2
Hib rate/100 000	46.6	24.4	0	27.3	19.3	10.0	10.5	33.3	22.0
No. of Hia cases (rate/100 000)	1 (7.7)	4 (32.6)	4 (35.6)	5 (45.5)	7 (67.5)	6 (60.2)	6 (63.4)	2 (22.2)	35 (40.6)

Note. Hi = *H influenzae*; Hia = *H influenzae* type a; Hib = *H influenzae* type b.
[a]Number of isolates not serotyped: 1992, 4; 1993, 3; 1994, 2; 1995, 4; 1996, 3; 1997, 3; 1998, 4; 1999, 1.

TABLE 2—Characteristics of Navajo and White Mountain Apache Children Enrolled in *Haemophilus influenzae* Type b Oropharyngeal Carriage Study

Characteristic	No. (%) (n = 381)
Age, mo	
0–6	16 (4.2)
7–11	158 (41.5)
12–23	85 (22.3)
24–47	64 (16.8)
>47	58 (15.2)
Tribe	
Navajo	259 (68.0)
White Mountain Apache	122 (32.0)
Sex	
Male	202 (53.0)
Female	179 (47.0)
Ever breastfed	
Yes	277 (72.7)
No	104 (27.3)
Smoker lives in household	
Yes	101 (26.5)
No	280 (73.5)
Wood/coal-burning stove in house	
Yes	198 (52.0)
No	183 (48.0)
Currently attends day care	
Yes	20 (5.3)
No	361 (94.7)
No. of children younger than 6 years living in household	
1	127 (33.3)
2	176 (46.2)
3	66 (17.3)
4	12 (3.2)

The child, a Navajo, was aged 52 months at the time of swabbing and had been vaccinated with PedvaxHib at 2, 4, and 15 months. There was 1 additional swab, which produced a halo, but on further testing it was identified as a staphylococcal species, known to cross-react on the halo plates.

Discussion

These data document that the dramatic reductions in the rate of invasive Hib disease among high-risk American Indian children between 1988 and 1992[2,11] have been sustained and that the rate continues to decrease. Extrapolating from the incidence in the prevaccine era (500–1000 cases per 100 000 children younger than 2 years[12]), approximately 478 to 946 cases of invasive Hib disease would have been expected and yet only 19 were observed, suggesting that between 459 and 927 cases of invasive Hib disease have been prevented by the vaccination of Navajo and White Mountain Apache infants. Previously, others have shown that the decrease in the incidence of Hib disease in these populations and in other groups representative of the general US population was greater than expected on the basis of the proportion of the susceptible population immunized.[1–4] Despite the tremendous declines, the incidence of invasive Hib disease among Navajo and White Mountain Apache children is about 20 times greater than that observed among children of the same age in the general US population (22 cases vs approximately 1 case per 100 000 children younger than 2 years).[1]

The oropharyngeal colonization data suggest that widespread vaccination has reduced Hib carriage among young children in this population of Navajo and White Mountain Apache children to very low levels. Before the widespread introduction of Hib conjugate vaccine, the prevalence of Hib colonization in this population among children younger than 5 years was 4.8%, with children aged 12 to 47 months at highest risk of colonization (7.1%).[13] Reduction of carriage following vaccination with Hib-OMP was most apparent for children aged 3 to 14 months who had received 1, 2, or 3 doses of vaccine, and the effect appeared to wane with increasing time since last vaccination for Hib. However, participants were enrolled in the study soon after the licensure of PedvaxHib in the United States, before high levels of vaccination coverage were achieved in the community.

Similar reductions in the frequency of carriage among vaccinated children have been reported elsewhere, but many of these studies were conducted in populations in which the epidemiology of Hib disease is characterized by lower incidence of disease and an older age at disease onset.[14–17] Among other populations at high risk for invasive Hib disease, studies of the impact of immunization on colonization have yielded mixed results. In Gambia, PRP-T (polyribosylribitol phosphate conjugate to tetanus toxoid; Pasteur-Merieux, Lyons, France) Hib vaccine administered during a vaccine trial led to a 60% reduction in Hib carriage among vaccinees.[18] In Brazil, children in day care who had received adequate vaccination with PRP-T were 4 times less likely to be Hib carriers (1.2% vs 4.8%).[19] However, in a population of rural Alaska Native children aged 12 to 71 months, a recent survey of 5 villages

found carriage rates of 2.2% to 13.2%, despite high rates of vaccination coverage.[10] Rates of colonization increased with increasing age. Conversely, in urban Anchorage, only 1.1% of Alaska Native children aged 1 to 4 years were colonized with Hib.[9] These data suggest that the factors that influence the ability of conjugate vaccines to reduce the transmission of Hib are not entirely clear and that the vaccination regimen, vaccination coverage levels, and characteristics of the population may contribute to the effect.

There are limitations to the current study. The small size of the population means that a single case of Hib invasive disease increases the annual incidence rate in any given year by 10 to 12 cases per 100 000. The cross-sectional design of the oropharyngeal study may not adequately reflect the dynamics of Hib carriage and transmission among infants and children. It is possible that carriage of transient duration or carriage of reduced intensity below the limits of the detection methods currently available may have occurred. Also, the study was limited to young children, and information is not available about carriage rates among older children, adolescents, or adults.

The present study demonstrates that widespread use of Hib conjugate vaccine has reduced oropharyngeal Hib carriage in a population of Navajo and White Mountain Apache children. The proportion of children who have received 3 doses of Hib vaccine by 15 months of age over the past 6 years is over 90% (Diana Hu and Joanette Takehara, Indian Health Service, written communication, June 19, 2000). PedvaxHib was the predominant vaccine used in these populations over the past 10 years; however, our study design does not allow any conclusions to be drawn about the relative effectiveness of different Hib conjugate vaccines against acquisition of Hib carriage. PedvaxHib is unique in its ability to induce high antibody concentrations following a single dose. This is a feature of particular importance for its application among high-risk populations such as the Navajo and White Mountain Apache children, in whom high rates of disease and a younger age at disease onset suggest that infants are exposed to Hib earlier and more intensely. Maintaining high rates of vaccination coverage is essential to ensure adequate protection of infants and young children from invasive Hib disease.

As we consider moving toward the goal of eliminating invasive Hib disease among children in the United States, new strategies may be required, especially among high-risk populations. In spite of the sustained low rate of invasive Hib disease and carriage documented here, cases of invasive Hib continue to occur among Navajo and White Mountain Apache children at a rate several times higher than that observed in the general US population (i.e., 22 cases vs approximately 1 case per 100 000 children younger than 2 years).[1] High rates of vaccination and active surveillance for invasive Hib cases, although necessary, may not be sufficient. One approach to elimination may be to change our response to invasive Hib disease and to consider each case as a sentinel event indicating continued Hib transmission. A greater understanding of the reservoirs of colonization within families and communities and the potential sources of transmission resulting in invasive cases will be needed to identify additional strategies for eliminating Hib disease.

Contributors

E. V. Millar analyzed and interpreted the data and wrote the paper. K. L. O'Brien planned, designed, and conducted the study, analyzed and interpreted the data, and wrote the paper. O. S. Levine planned and designed the study, provided expertise in analysis and interpretation of the data, and contributed to the writing of the paper. S. Kvamme conducted the study and data management. R. Reid conducted the study and contributed to the writing of the paper. M. Santosham planned the study, contributed to the interpretation of the data and the writing of the paper, and provided overall study guidance.

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