Postlicensure effectiveness of the *Haemophilus influenzae* type b polysaccharide–*Neisseria meningitidis* outer-membrane protein complex conjugate vaccine among Navajo children

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The incidence of invasive *Haemophilus influenzae* type b (Hib) infection has decreased significantly among Navajo children since the licensure of Hib conjugate vaccines, even though two lots of Hib (polyribosylribitol phosphate)–meningococcal B outer-membrane protein conjugate vaccine (PRP-OMP) widely used among the Navajo were later found to be of low immunogenicity. We measured the effectiveness of all Hib conjugate vaccines combined, PRP-OMP alone, and the PRP-OMP lots with lower-than-expected immunogenicity among Navajo infants and children. This was a matched case-control study using active, laboratory-based surveillance for the ascertainment of Navajo children 2½ to 59 months of age with invasive Hib infection; 45 patients with infection and 180 control subjects were enrolled. The effectiveness of one, two, and three doses, respectively, of all Hib conjugate vaccines combined was 96% (95% confidence interval (CI) 65%, 99%), 99% (95% CI, 69%, 100%), and 99% (95% CI, −57%, 100%). The effectiveness of one or more doses of PRP-OMP was 95% (95% CI, 66%, 99%). The effectiveness of a single dose of the lots of lower-than-expected immunogenicity was 89% (95% CI, −8%, 99%). The Hib conjugate vaccine coverage increased from 49% during 1991 to 94% during 1992; no control subjects younger than 18 months of age were enrolled during 1993. The occurrence of invasive Hib infections in this population after licensure of Hib conjugate vaccines was the result of gradual vaccine uptake, not poor vaccine effectiveness. The use of PRP-OMP has been highly effective despite concerns about the immunogenicity of several lots. (J PEDIATR 1994;125:571-6)

Before the licensure of efficacious *Haemophilus influenzae* type b vaccines, Hib was the leading cause of invasive bacterial disease among children in the United States, accounting for an estimated 12,000 cases of meningitis per year and an additional 8000 cases of other invasive disease, such as epiglottitis, cellulitis, and primary bacteremia.[1] A randomized, placebo-controlled trial of the Hib polysaccharide (polyribosylribitol phosphate)–meningococcal B outer-membrane protein conjugate vaccine demonstrated a >90% efficacy among Navajo infants beginning at 2 months of age.[2] This study, in conjunction with another trial that demonstrated 100% efficacy of three doses of the Hib

Supported by Merck Research Laboratories.

The opinions expressed herein do not necessarily reflect those of the Indian Health Service.

Submitted for publication Jan. 12, 1994; accepted April 21, 1994.

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9/20/56865

GMT	Geometric mean titer
Hb-OC	Hib (PRP) oligosaccharide conjugate–mutant diphtheria toxoid
Hib	*Haemophilus influenzae* type b
PRP-OMP	Hib polysaccharide (polyribosylribitol phosphate)–meningococcal B outer-membrane protein conjugate vaccine

(PRP)-mutant diphtheria toxoid,[3] led to the licensure of these two Hib conjugate vaccines for use in infants in late 1990.[4] A PRP–diphtheria toxoid conjugate vaccine is licensed for use at 15 to 59 months of age but, because of poor immunogenicity and efficacy, is not licensed for use in young infants.[5] Several PRP-OMP lots that were widely used among the Navajo after licensure were later found to be of relatively low immunogenicity.[6-8]

From 1985 to 1991, the incidence of invasive Hib disease among children younger than 5 years of age declined 82% in the United States.[9] Although the incidence has also declined among Navajo children, invasive Hib infection has continued to occur in this population since vaccine licensure. Previous experience with the purified polysaccharide Hib vaccines showed that the results of prelicensure vaccine efficacy studies[10] are not always confirmed by postlicensure studies.[11-15] To determine whether the continued occurrence of cases among the Navajo was the result of gradual vaccine uptake, less-than-expected effectiveness of Hib conjugate vaccines in general, or the use of the PRP-OMP lots of poor immunogenicity, we enrolled eligible children with invasive Hib disease in a case-control vaccine effectiveness study. This provided the opportunity to measure the postlicensure effectiveness of PRP-OMP in the same population in which a prelicensure randomized, double-blind controlled efficacy trial had recently been performed.[2]

METHODS

Active surveillance for invasive Hib disease. Active, laboratory-based surveillance for Hib disease was conducted by Johns Hopkins University (JHU) research workers who reviewed Indian Health Service (IHS) hospital laboratory logs daily for the presence of *H. influenzae* in cultures of normally sterile body fluids. Available isolates were submitted for confirmatory speciation and serotyping in a JHU reference laboratory in the Whiteriver IHS Hospital. In addition, IHS facilities and IHS contract facilities were contacted monthly to identify additional case children with invasive Hib infection.

Case selection. Case children were ascertained through active surveillance for *H. influenzae* infection from Aug. 3, 1990, the end of the PRP-OMP efficacy trial, through the end of August 1993. A definite case was any Navajo child between 2½ and 59 months of age residing on or near the Navajo reservation from whom Hib was isolated from a normally sterile body fluid and who had clinical signs of infection. Children from whom *H. influenzae* was isolated from a normally sterile body fluid whose isolates were not available for serotyping were also included; children with invasive disease caused by other serotypes or by untypeable *H. influenzae* strains were excluded. The lower age limit was chosen because children younger than 2 months were not eligible for Hib vaccination; an immune response does not develop in those vaccinated until 10 to 14 days later. Sixty months was chosen as the upper cutoff point to be consistent with the recommendations of the Immunization Practices Advisory Committee for vaccine use.[16] A possible case was a child with the detection of Hib antigen in urine, serum, or cerebrospinal fluid, and clinical signs of infection.

After informed consent was obtained, a questionnaire was completed for each case child by interviewing one of the child's parents or guardians. Interviews were completed by Navajo field workers either at the time of a home visit or by telephone. Data collected for each case child included demographic and socioeconomic variables; Hib vaccination status for children who had immunizations documented on an immunization card; information on other potentially confounding variables, such as breast-feeding, access to immunization services, household crowding, and day care attendance; whether the child had any chronic medical conditions that might predispose him or her to infection; and participation in other JHU studies, because children who participate in these studies may be more likely to be up-to-date with their immunizations than children who do not. Vaccination status, including date of vaccination, vaccine lot number, and manufacturer, was ascertained by a review of the child's medical records. Data from the vaccination card provided by the caretaker were used only when the medical record could not be located, which occurred rarely. Only Hib vaccine doses given to case children and control subjects 14 days or more before the case child's date of culture were included in the analysis.

Selection of control subjects. For each case child, four control subjects were selected from the IHS service unit birth logs of the case child's service unit of residence on the date of the Hib culture. To match case children and control subjects closely on age, a caliper method was used, starting with children born on the same date as the case child then moving to the children born the day after, the day before, 2 days after, and so on, until four potential control subjects were identified. Only control subjects whose caretakers were interviewed were enrolled because of the need to collect information on potentially confounding variables, such as day care attendance. However, the Hib vaccination status of eligible control subjects who could not be enrolled because of the lack of a caretaker interview was ascertained from the medical record. Children who had been enrolled in the Hib vaccine efficacy study,[2] who were not Navajo,

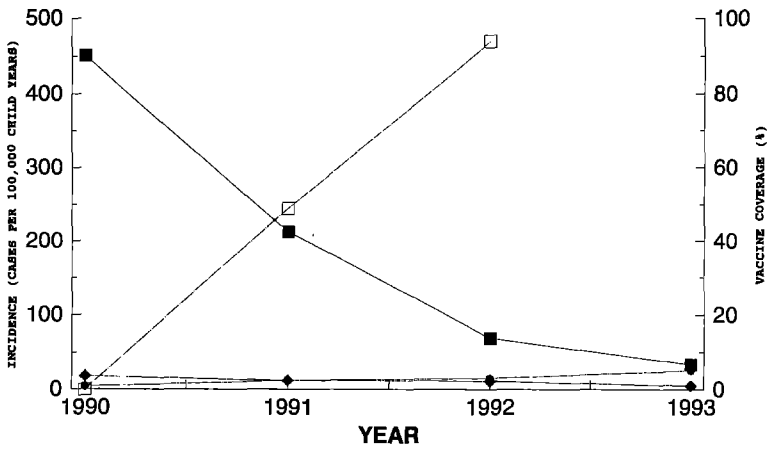

Figure. The incidence of Hib infection among Navajo children younger than 18 months of age *(dark squares)* and 18 to 59 months of age *(diamonds)*, 1990–1993. The incidence of non–type b *H. influenzae* infection is also shown *(circles)*, as is the estimated vaccine coverage among children younger than 3 to 17 months of age *(clear squares)*. Excluded from the figure are seven, two, and three children with *H. influenzae* infection for whom serotype information is not available for 1990, 1991, and 1992, respectively.

who had a documented episode of invasive Hib infection, or who did not live in the same IHS service unit as the case child on the date of the Hib culture were excluded. The same information collected for the case children was collected for each control subject.

Laboratory methods. Sterile-site isolates of *H. influenzae* were characterized by slide agglutination using *H. influenzae* polyvalent capsular antiserum and type-specific antisera for capsular types a through f (Difco Laboratories, Detroit, Mich.).

Statistical methods. Epi Info software, version 5.1 (USD, Inc., Stone Mountain, Ga.), was used for the univariate analyses. Dichotomous variables were analyzed using the match procedure to account for the matched study design. The Kruskal-Wallis test was used for comparison of continuous variables. For the determination of effectiveness, conditional logistic regression was performed with the SAS program for personal computers (SAS Institute Inc., Cary, N.C.). Variables that appeared to be associated with Hib infection in the univariate analyses ($p < 0.1$) were included in the regression model. Estimates of vaccine effectiveness were calculated with the following formula: 1 − matched odds ratio.

RESULTS

The incidence of invasive Hib infection among Navajo children younger than 18 months of age decreased 93% from 1990 through the end of 1993 (Figure). For Hib infection among children 18 to 59 months of age and non–type b *H. influenzae* infection among children 1 to 59 months of age, the rates were low and stable during the same period. Of the 15 children with non–type b *H. influenzae* infection, 10 (67%) had disease caused by serotype a, 2 each (13%) had disease caused by serotype c and non-typeable strains, and 1 (7%) had disease caused by serotype f.

During the study period a total of 62 episodes of invasive *H. influenzae* disease among Navajo children 2½ to 59 months of age were identified. Of these, 45 met the eligibility criteria and were enrolled; 44 were definite cases and one was a possible case. The possible case was an unimmunized 5-month-old child with fatal septicemia and meningitis in whom no cultures were performed; antigen detection for Hib in the urine was positive. Among the 44 definite cases, 38 had serotype b; 6 isolates were unavailable for serotyping. Of the 17 episodes that did not meet the eligibility criteria, 7 were among children who had been enrolled in the efficacy trial.[2] In one of these children invasive Hib infection developed at age 7 months after a single PRP-OMP dose administered at 6 weeks; the other 6 children were unvaccinated at the time of illness. Nine noneligible episodes were caused by other *H. influenzae* serotypes (six serotype a, two serotype c, and one serotype f) and one was a second episode for a child who was already enrolled.

Of the case children, 31 (69%) were younger than 12 months of age, 6 (13%) were 12 to 23 months of age, and 8 (18%) were 24 to 59 months of age. Fourteen (31%) eligible episodes occurred from Aug. 3, 1990, through the end of 1990, 18 (40%) cases occurred in 1991, and 12 (27%) cases occurred in 1992; only 1 (2%) case occurred during the first 9 months of 1993. Of the 45 enrolled children, the clinical syndrome was known for 43: 20 had meningitis, 7 pneumonia, 6 bacteremia/sepsis, 4 cellulitis, 4 otitis media, 2 septic arthritis. *H. influenzae* was isolated from blood in 28 cases, blood and cerebrospinal fluid in 11 cases, cerebrospinal fluid in 4 cases, and joint in 1 case.

A total of 187 control subjects were enrolled; 87% were

Table. Vaccination status of case children and control subjects of all Hib conjugate vaccines combined

	Case children		Control subjects	
No. doses	No.	%	No.	%
0	34	76	89	49
1	6	13	55	31
2	3	7	27	15
3	2	4	9	5
TOTAL	45	100	180	100

Only doses given at least 14 days before the case child's date of culture are included.

among the first 4 eligible control subjects for each case and all were among the first 7. There were no differences in age, sex, and maternal education between case children and control subjects. However, case children were more likely than control subjects to have a chronic illness (11% versus 0%; $p < 0.001$). Of the case children, 17% had a household telephone versus 31% of control subjects ($p = 0.09$), and 29% of case children received immunizations from a private health facility versus 18% of control subjects ($p = 0.06$). Therefore chronic illness, immunization at a private health facility, and presence of a household telephone were included in the logistic regression model.

Of the 45 case children, 11 (24%) had received at least one dose of vaccine in contrast to 91 (51%) of 180 control subjects (Table). Of the 11 case children in whom Hib infection developed despite at least one dose of vaccine, 6 had incomplete Hib infant immunization series. Of the remaining five immunized case children, three had completed a Hib infant immunization series, although one received two doses of one of the PRP-OMP lots with lower-than-expected immunogenicity. Two case children each received a single dose of PRP–diphtheria toxoid conjugate vaccine, one at 17 and the other at 23 months of age. Among 98 first doses given to case children and control subjects for whom the manufacturer was known, 81% were PRP-OMP, 13% were HbOC, and 6% were PRP–diphtheria toxoid conjugate vaccine. Among 40 second doses, 88% were PRP-OMP and 12% were HbOC; among 10 third doses, 60% were PRP-OMP and 40% were HbOC.

For all Hib conjugate vaccines combined, the crude effectiveness of one, two, and three doses, respectively, was 93% (95% CI 68%, 99%), 96% (95% CI 66%, 100%), and 96% (95% CI −84%, 100%). After adjustment for potentially confounding variables, the effectiveness was 96% (95% CI 65%, 99%), 99% (95% CI 69%, 100%), and 99% (95% CI −57%, 100%). The effectiveness did not differ substantially when the 3 case children and 35 control subjects who had received PRP-OMP lots of lower-than-expected immunogenicity were excluded. When the analysis was restricted to case children and control subjects 12 months of age or younger, the effectiveness of a single dose was 94% (95% CI 48%, 99%) and of a second dose, 98% (95% CI 61%, 100%).

Subsequent analyses focused on the effectiveness of PRP-OMP; only children who had received no Hib conjugate vaccines (34 cases, 89 control subjects) or who had received PRP-OMP exclusively (5 cases, 71 control subjects) were included. The effectiveness of a single dose was 92% (95% CI 45%, 100%); this estimate did not change substantially when children who had received lots with lower-than-expected immunogenicity (2 case children and 34 control subjects) were excluded. Although we were unable to estimate the effectiveness of the second dose of PRP-OMP because of a limited sample size, the effectiveness of one or more doses was 95% (95% CI 66%, 99%). When the analysis was restricted to case children and control subjects 12 months of age or younger on the date of culture, the effectiveness of a single dose was 91% (95% CI 33%, 99%) and of one or more doses was 94% (95% CI 59%, 99%).

Of 91 control subjects who received at least one Hib conjugate vaccine dose before the case date of culture, 91 (38%) were immunized with PRP-OMP lots 0405T or 0172T, indicating widespread use of the lots of lower-than-expected immunogenicity.[5] To determine the effectiveness of these lots, children who had received either of these lots exclusively (2 case children, 22 control subjects) or no Hib vaccine (34 case children, 89 control subjects) were studied. The effectiveness of a single dose was 89% (95% CI −8%, 99%); the effectiveness of one or more doses was 90% (95% CI 2%, 99%).

Several additional analyses were performed to determine the effect of potential biases on the results of the study. The effectiveness of one or more doses of any conjugate vaccine, 97% (95% CI 73%, 100%), served as the reference analysis. In separate analyses case and control children who had been enrolled in other JHU studies or had a chronic illness, cases whose *H. influenzae* isolates were unavailable for serotyping, and control subjects not among the first four eligible control subjects were excluded. In addition, vaccine effectiveness was determined including breast-feeding and day care attendance in the logistic regression model. The effectiveness was also determined using the first four eligible control subjects, regardless of whether they were enrolled; adjustment for confounders was not possible in this analysis because data on confounding variables were not obtained for nonenrolled control subjects. The resulting estimates of effectiveness ranged from 94% to 97%, not substantially different from the reference estimate.

To investigate further why invasive Hib infection continued to occur despite of excellent vaccine effectiveness, we determined the proportion of control subjects 3 to 17

months of age who had received at least one dose of a Hib conjugate vaccine, which provides an estimate of the coverage rate among Navajo children. Coverage increased from 49% (33 of 68 control subjects) during 1991 to 94% (33 of 35 control subjects) during 1992; no control subjects younger than 18 months of age were enrolled during 1993 (Figure).

DISCUSSION

Like the previous randomized, placebo-controlled PRP-OMP vaccine efficacy trial,[2] this study confirms that PRP-OMP vaccine is highly effective in Navajo children. The finding of a high level of clinical protection of PRP-OMP lots 0405T and 0172T was unexpected because of their strikingly poor immunogenicity. For example, thirteen 12- to 17-month-old children who had received PRP-OMP lot 0405T at 2 and 4 months of age had an anti–PRP geometric mean titer of 0.35.[7] A similar group of children who had received two doses of a lot with expected immunogenicity had a GMT of 1.32. Moreover, five children who had received another poorly immunogenic lot (0498T) at 2, 4, and 6 months of age had GMTs of 0.22, 0.14, 0.15 after the first, second, and third doses, respectively.[8] However, the high point estimates of effectiveness in the analyses of these lots alone and together with all other PRP-OMP lots, in addition to the paucity of reported Hib infection among recipients of these lots,[7] strongly suggests that they provided clinical protection. Our results must be viewed with caution, however, because of the wide confidence intervals surrounding the point estimate of the effectiveness of these lots.

Interestingly, 24% of our case children had received one or more doses of Hib conjugate vaccine despite the evidence of a high level of clinical protection. However, some of these children had not yet completed the infant Hib immunization series and therefore would not necessarily be expected to be protected. In addition, a substantial case vaccination rate is not unexpected even for the highly effective Hib conjugate vaccines, because of the high Hib conjugate vaccine coverage in this population.[17] As an extreme example, relatively few cases of disease would occur with a hypothetical 99% efficacious vaccine with 100% coverage, but all cases would be vaccine failures.

The continued occurrence of *H. influenzae* infection in the several years after licensure appears to be related to the gradual uptake of the vaccine in the population and to infection caused by non–type b serotypes. However, pediatric Hib infection has become very rare, as evidenced by the occurrence of only one case during the first 9 months of 1993. This most likely represents the high effectiveness of the vaccine, a high vaccine coverage rate, and reduced exposure of children to Hib as a result of a vaccine-related decrease in Hib nasopharyngeal colonization.[18-20]

There are several limitations to our study. The data were not collected by individuals unaware of the case-control status of the study subjects. This is unlikely to have biased our effectiveness estimates because we use a standardized data collection form, and equivalent efforts were made to identify medical records from all facilities where the subjects could have received Hib immunization. We had insufficient data to determine the effectiveness of doses given in infancy for cases in the prevention of Hib infection later in childhood.

To our knowledge, this study represents the first instance in which a postlicensure Hib vaccine case-control effectiveness study has been done in the same population as a recent randomized, placebo-controlled efficacy study with the same vaccine. The essentially identical estimates of efficacy in the two studies despite the markedly different study designs validate the case-control method for determining vaccine effectiveness after licensure. This study also underscores the utility of the case-control method for answering questions about vaccine effectiveness after licensure, such as the impact of the use of the PRP-OMP lots of relatively low immunogenicity.

We thank Allyn Schafer, Majel Roanhorse, Roberta Hardy, Maureen O'Connor, Connie Donaldson, Greg Wauneka, Pauline Fields, Pat Brown, Laverna Bitsilly, Lola Riggs, and Genevieve Farrell for their assistance in collecting the data; Alisa Wright for data entry; and Larry Moulton and Neal Halsey for their thoughtful review of the manuscript.

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