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Efficacy of *Haemophilus influenzae* Type b Conjugate Vaccines and Persistence of Disease in Disadvantaged Populations

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ABSTRACT

Objectives. The purpose of this study was to evaluate the effectiveness of *Haemophilus influenzae* type b (Hib) conjugate vaccines among children aged 2 to 18 months and to determine risk factors for invasive Hib disease during a period of declining incidence (1991–1994).

Methods. A prospective population-based case–control study was conducted in a multistate US population of 15.5 million. A laboratory-based active surveillance system was used for case detection.

Results. In a multivariate analysis, having a single-parent mother (odds ratio [OR] = 4.3, 95% confidence interval [CI] = 1.2, 14.8) and household crowding (OR = 3.5, 95% CI = 1.03, 11.7) were risk factors for Hib disease independent of vaccination status. After adjustment for these risk factors, the protective efficacy of 2 or more Hib vaccine doses was 86% (95% CI = 16%, 98%). Among undervaccinated subjects, living with a smoker ($P = .02$) and several indicators of lower socioeconomic status were risk factors for Hib disease.

Conclusions. Hib disease still occurs at low levels in the United States, predominantly in socioeconomically disadvantaged populations. Low immunization coverage may facilitate continuing transmission of Hib. Special efforts to achieve complete and timely immunization in disadvantaged populations are needed. (*Am J Public Health.* 1999;89:364–368)

Before the widespread use of conjugate vaccines, *Haemophilus influenzae* type b (Hib) caused invasive disease in 1 of 200 children younger than 5 years. Hib was the most common cause of bacterial meningitis among children. Among preschool-aged children, two thirds of all Hib meningitis occurred in those younger than 18 months.[1] Between 1987 and late 1990, before Hib conjugate vaccines were first licensed for infants, a substantial decline in Hib disease incidence was noted among children younger than 1 year, who were not at that time being immunized. This decline was attributed to reduction of oropharyngeal carriage among older vaccinated children, leading to reduced transmission in younger age groups.[2,3]

The vaccine efficacy studies leading to licensure for infants were conducted in controlled settings and in homogeneous populations with similar patterns of health care.[4,5] Larger population-based studies can more accurately reflect the effectiveness of vaccine used under conditions outside a study setting and identify factors associated with program failures.[6,7]

Before the introduction of Hib conjugate vaccines, day-care attendance, household crowding, absence of breast-feeding, male sex, and African American race were identified as risk factors associated with invasive disease.[8,9] Despite the striking decline in Hib disease incidence in the United States, the disease persists at low levels several years after the initial decline.[2,10–14] Risk factors for Hib disease in an era of widespread immunization and lower but persistent disease incidence have not been evaluated. Identification of these risk factors is important for focusing disease elimination efforts on populations at risk for disease. Additionally, Hib conjugate vaccines are now being incorporated into the routine immunization programs in nonindustrialized countries. Understanding risk factors for persistent Hib disease will be particularly helpful for countries where uniformly high immunization coverage may not be readily achieved.

We conducted a prospective population-based case–control study in a large population of children aged 2 to 18 months in 5 regions of the United States. The objectives of our study were to evaluate the postlicensure effectiveness of Hib conjugate vaccines and to identify risk factors for invasive Hib disease and undervaccination during a period of declining disease incidence.

Methods

Laboratory-Based Hib Surveillance

This study was conducted in a multistate population with a laboratory-based active surveillance system coordinated by the Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases. The surveillance project included the states of Oklahoma and Maryland; 3 counties in the San Francisco Bay Area, California; 8 counties in metropolitan Atlanta, Ga; and 4 counties in Tennessee. The aggregate population was 15.5 million. In 1990, the

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population of children younger than 5 years in the surveillance areas was more than 1.1 million, of whom 68% were White and 25% were Black. Active surveillance was instituted in 4 of these 5 areas in 1989, and the state of Maryland was added to the project in November 1991.

Surveillance staff maintained biweekly contact with all hospital and clinical laboratories in their area to collect detailed case report forms for all patients with invasive Hib disease. Case information included serotype, clinical syndrome, outcome, patient's date of birth, date of culture, and demographic information. Serotype was determined at the Centers for Disease Control and Prevention for isolates not typed at the hospital or the state health department. In 1991 and 1993, laboratory records in 302 and 399 hospitals (over 90% of all area hospitals), respectively, in the active surveillance areas were reviewed to identify case patients who were missed by routine surveillance during the preceding year. The active surveillance system had identified all but one Hib case among children younger than 18 months that had occurred during the years audited in the surveillance areas.

Case–Control Study

This prospective population-based case–control study was conducted between January 1991 and June 1994. Only confirmed cases of invasive Hib disease (clinically compatible illness with isolation of Hib from a culture from a normally sterile site) were reported and included in the analyses. All case patients with invasive Hib disease who were 2 to 18 months of age were eligible for enrollment. Controls were matched by date and county of birth to patients in a 3:1 ratio. For each case, controls were selected at random from birth certificates in the county of the case patient's birth. Study staff obtained county birth certificate information on the 5 births closest to a randomly chosen time on the patient's day of birth. Extensive efforts were made to enroll as controls the 3 infants whose births were closest to that of the patient. Of all the patients with birth certificate–matched controls, 83% were born within a day of their controls' day of birth; the remaining were born within a median of 4 days (range 2–10 days).

After giving consent, parents of patients and controls were interviewed by telephone by means of a standardized questionnaire. The questionnaire was designed to collect information on risk factors for Hib disease, socioeconomic status, barriers to immunization, and demographic information. To verify and obtain detailed immunization and medical histories, all providers of care to each child that were identified by either parents or study staff were contacted by telephone. Information collected included date, manufacturer, and lot number of all Hib immunizations (HbOC, PRP-OMP, PRP-D, and PRP-T). History was obtained for any medical condition that may predispose a person to invasive Hib disease. Dates of immunization with diphtheria–tetanus–pertussis, measles–mumps–rubella, and oral polio vaccines were also ascertained.

We defined a child as age-appropriately vaccinated with Hib vaccines if he or she had received the primary infant series according to the recommendations of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices.[15,16] Thus, an undervaccinated child was one who was 3 or 4 months of age and who had received no Hib vaccine, one who was 5 or 6 months of age and who had received fewer than 2 vaccine doses, or one who was 7 months of age or older who had received fewer than 3 vaccine doses (unless 2 doses of PRP-OMP had been given). Completion of Hib immunization in a catch-up schedule was not considered age-appropriate vaccination. For both cases and controls, Hib vaccine doses received during the 14-day period before onset of illness were not considered in the analysis.

We defined household crowding as more than 1 person per room in the living quarters. If the guardian (97% were mothers) of the child was divorced, separated, widowed, or never married, we defined the guardian as a "single mother."

Statistical Analysis

Vaccine efficacy (VE) was calculated for 1, 2, 2 or more, 3, and 3 or more doses of Hib conjugate vaccine with the following formula: $VE = (1 - OR) \times 100$, where OR is the odds ratio for Hib vaccination rate for cases compared with controls.[6] The odds ratio and 95% confidence intervals were calculated by conditional logistic regression analysis of matched case–control strata. Exact methods were used to calculate 95% confidence intervals when necessary. Initially, matched univariate and multivariate analyses were undertaken to estimate the effect of potential confounding factors on risk of Hib disease. Independent predictors of Hib disease were then incorporated in the multivariate conditional logistic regression model to adjust for their confounding effects on estimates of vaccine efficacy.

Results

Hib Patients

A total of 57 patients aged 2 to 18 months were identified during the study period. Of these, 42 (74%) were enrolled in the study. Of the remaining 15 patients, 12 could not be contacted, the parents of 2 declined to participate in the study, and for 1, immunization and medical history could not be verified from medical records. The mean age, sex, and race distribution and types of clinical syndrome of patients not enrolled were similar to those of the enrolled patients. Three of the 11 patients for whom vaccination status was known had received a single Hib vaccine dose, and the others had not been vaccinated. Complete sets of case and control information were obtained for 40 of the 57 cases (70%). The mean age of patients in the study was 6.9 months (range, 2–17 months); 58% were 6 months or younger, and 85% were younger than 12 months. A total of 22 (55%) developed Hib meningitis, 12 (30%) had bacteremia, 4 (10%) had cellulitis, and 2 (5%) had pneumonia. Although the incidence of Hib disease among children younger than 5 years in the surveillance areas declined rapidly during the study period, except for 2 quarters in 1993, patients were identified and enrolled during each quarter of the study period (Figure 1).

Of the 93 controls enrolled, 84 (90%) were among the first 5 eligible potential controls identified for the patient. Data were obtained on a mean of 2.3 controls for each patient.

Vaccine Efficacy

Only 4 patients had received 2 or more doses of Hib vaccine, 15 had received 1 dose, and 21 had not been vaccinated. Among the 23 patients 6 months or younger, 11 (48%) were not age-appropriately vaccinated; among the 17 patients 7 months or older, 16 (94%) were not age-appropriately vaccinated. Among the 65 controls 6 months or younger, 18 (28%) were not age-appropriately vaccinated; among the 28 controls 7 months or older, 16 (57%) were not age-appropriately vaccinated. Except for 1 patient and 1 control, all children in the study received HbOC. The only patient who had been vaccinated with more than 2 Hib vaccine doses had received 4 doses of PRP-OMP. This 16-month-old child developed protective levels of anti-PRP antibodies only after receipt of a dose of HbOC given 12 weeks after the onset of disease.

In a univariate regression model, the point estimate for efficacy of a single vac-

cine dose was 55% (95% confidence interval [CI] = –37%, 85%). Three patients had received 2 vaccine doses before illness, resulting in an efficacy estimate of 91% (95% CI = 49%, 98%) for 2 vaccine doses. The protective efficacy of 2 or more doses of Hib conjugate vaccine was 94% (95% CI = 71%, 99%). When adjusted for the 2 risk factors most strongly associated with Hib disease—having a mother who was a single parent and living in a crowded household—the point estimate for efficacy of a single vaccine dose was 56% (95% CI = –63%, 88%). The adjusted efficacy estimate for 2 or more doses was 86% (95% CI = 16%, 98%).

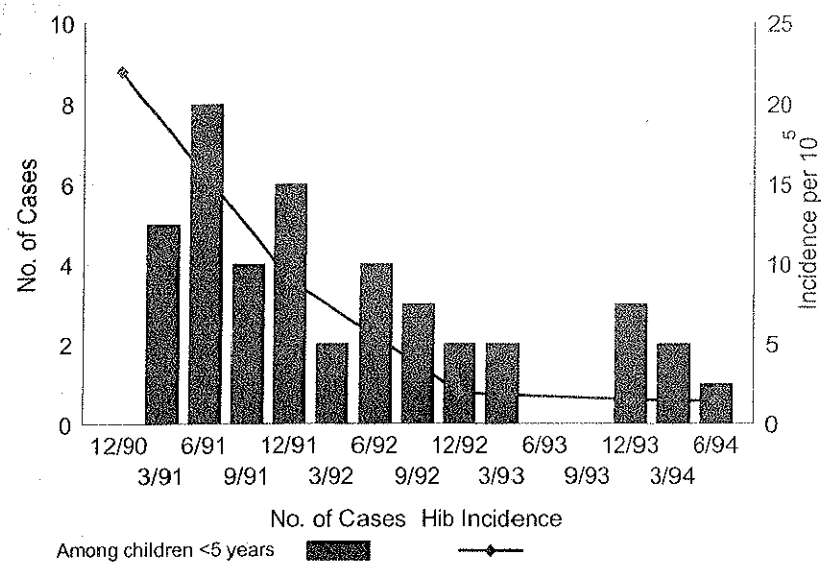
Risk Factors for Hib Disease and Undervaccination

Patients and controls were similar in age, sex, race, and several other characteristics associated with risk of Hib disease (Table 1). Matched univariate analysis identified 7 characteristics as risk factors for Hib disease (Table 1). In a multivariate model, having a mother who was a single parent and living in a crowded household were independently associated with invasive Hib disease. In a separate multivariate model that included vaccination status, having a mother who was a single parent (OR = 4.3, 95% CI = 1.2, 14.8) and living in a crowded household (OR = 3.5, 95% CI = 1.03, 11.7) remained independent risk factors for Hib disease.

Only 9 patients in the study were age-appropriately vaccinated. Of these, 8 were 6 months or younger and thus were too young to have received the complete primary series of Hib vaccine; 6 of these 8 had received 1 vaccine dose, and 2 had received 2 doses. An additional 2 infants were aged 2 months, and one of them had received a single vaccine dose. However, 29 patients in the study (73%) were not age-appropriately vaccinated, and 34 (37%) of the 93 controls were not age-appropriately vaccinated. Since most cases in the study occurred among children who were not age-appropriately vaccinated, and because a considerable proportion of controls were also undervaccinated, we evaluated the risk factors associated with undervaccination separately among patients and controls.

No risk factors for undervaccination were identified among controls. However, an analysis of cases found that having a single-parent mother (OR = 7.7, 95% CI = 1.3, 45), living in a low-income household (OR = 11.3, 95% CI = 1.1, 109), and being the child of a mother who had not finished high school (OR = 11.3, 95% CI = 1.2, 103) were significant risk factors for undervaccination. The proportions of controls in the study who had these risk factors were similar to the proportions among patients who were appropriately vaccinated (19% and 22%, respectively, had a single-parent mother, 23% and 14% lived in a low-income household, and mothers of 17% and 11% had not finished high school).

A matched univariate analysis of all undervaccinated patients and their undervaccinated controls demonstrated associations between disease and a number of indicators of low socioeconomic status, shown in Table 2. A bivariate model controlling for vaccination status demonstrated that the indicators of low socioeconomic status and living with smokers were independently associated with disease.



Note. Figure is based on data from the state of Oklahoma; 3 counties in the San Francisco Bay Area; 8 counties in metropolitan Atlanta; and 4 counties in Tennessee (aggregate population, 10.5 million; data for Maryland were not included because the state did not participate in the whole study period). Data obtained through the multistate laboratory-based surveillance coordinated by the National Center for Infectious Diseases, Centers for Disease Control and Prevention.

FIGURE 1—Onset of illness among patients aged 2 to 18 months enrolled in a US case–control study (1991–1994), by quarter, and annual incidence of invasive *Haemophilus influenzae* type b (Hib) disease among children younger than 5 years from 1990 to 1994.

Discussion

In contrast to controlled, randomized, clinical efficacy trials, population-based postlicensure studies provide information on the effectiveness of vaccines for prevention of disease in the general population.[6,7] Additionally, these studies can identify risk factors associated with continued disease. Inasmuch as several studies had previously confirmed the postlicensure protective efficacy of Hib conjugate vaccines among children older than 18 months, one objective of this study was to evaluate efficacy among infants and younger children. The timing of this study also provided an opportunity to determine risk factors for disease during a period when significant changes occurred in the epidemiology of Hib disease.[2,10–14]

After adjustment for risk factors most strongly associated with Hib disease, the vaccine efficacy estimates obtained for the most frequently used Hib conjugate vaccine (HbOC) in this study are consistent with findings from prospective randomized studies and a case–control efficacy evaluation.[4,5,7] The only patient who had received more than 2 vaccine doses had received 4 doses of 3 different lots of PRP-OMP (none from lots known to be less immunogenic[17]). This 16-month-old child also did not seroconvert following invasive Hib disease, but responded to a dose of HbOC given at 19 months of age. Although a specific immunological defect was not diagnosed, these findings suggest an underlying immune dysfunction.

In our study, patients and controls were similar in several characteristics, such as race, history of breast-feeding, and day-care attendance, which have been identified as risk factors for invasive Hib disease.[8,9] However, univariate analyses suggested several factors that may be associated with increased risk of

TABLE 1—Risk Factors Associated With Invasive Hib Disease Among Children Aged 2 to 18 Months in a US Case–Control Study, 1991–1994

	Patients (n = 40), %	Controls (n = 93), %	Odds Ratio (95% Confidence Interval)
Univariate analysis			
Male sex	53	49	1.4 (0.64, 3.0)
White race	75	78	1.3 (0.5, 3.38)
In day care	13	17	1.5 (0.5, 5.39)
Breast-fed	40	50	1.5 (0.7, 3.4)
Underlying illness	5	2	1.4 (0.4, 5.46)
Single mother[a,b]	55	19	6.4 (2.3, 17.6)*
>1 person per room[b]	45	20	5.3 (1.9, 14.9)*
Family income ≤$15 000/y[b]	54	23	3.8 (1.5, 9.6)*
Maternal education ≤11 grades[b]	45	17	3.8 (1.5, 9.5)*
≥1 smoker at home[b]	55	33	2.2 (1.0, 5.0)*
Immunizations paid through Medicaid or received at public health clinics	69	38	3.0 (1.2, 7.2)*
Mother had difficulty taking time off from work to get child vaccinated	18	6	3.7 (1.1, 13.0)*
Multivariate analysis			
Single mother			7.3 (1.6, 33.0)
>1 person per room			5.5 (1.3, 22.6)

Note. The difference in mean ages (patients, 6.9 months; controls, 6.0 months) was not statistically significant.
[a]Divorced, separated, widowed, or never married.
[b]Variable included in the multivariate analysis.
*$P < .05$.

TABLE 2—Percentages of Undervaccinated Children With Risk Factors Associated With Hib Disease in a US Case–Control Study, 1991–1994

	Patients (n = 29)	Controls (n = 34)	P[a]
Single mother	69	20	<.01
Maternal education ≤11 grades	59	11	<.01
Immunizations paid through Medicaid or received at public health clinics	82	38	.02
≥1 smoker at home	62	34	.02
Family income ≤$15 000/y	65	24	.03

[a]Because the socioeconomic variables listed were highly correlated, 95% confidence intervals could not be estimated for all comparisons.

disease. Some or all of these factors could increase the likelihood of Hib disease by facilitating transmission of infection or by creating obstacles to age-appropriate immunization. Household crowding has been suggested as a risk factor and contributes to the transmission of Hib. Having a mother who is a single parent is associated with lower socioeconomic status and may reflect increased risk of disease owing to lower immunization rates in the surrounding community. Since Hib immunization decreases carriage, areas with low immunization rates may have relatively higher carriage and transmission rates.[3,18–20]

We performed 2 further analyses to investigate the relationship between disease, immunization, and low socioeconomic status. Since most cases occurred among undervaccinated children, we evaluated risk factors for undervaccination separately among patients and controls. Consistent with other studies, having a single-parent mother, low household income, and low maternal education were identified among patients as risk factors for undervaccination.[21–22] Notably, the few patients who were age-appropriately vaccinated appeared to be similar to controls in socioeconomic status. Undervaccination among patients was not restricted to Hib vaccines; patients were also less likely than controls to be age-appropriately vaccinated for diphtheria, tetanus, pertussis, and poliomyelitis (data not shown). Missed opportunities for vaccination by providers have been shown to affect impoverished children more frequently than children from higher socioeconomic backgrounds.[23]

We evaluated factors associated with disease among all undervaccinated children. After adjustment for vaccination status, factors associated with lower socioeconomic status and living with smokers remained predictive of invasive Hib disease. Exposure to cigarette smoke may increase the likelihood of disease by interfering with the defenses of the nasopharyngeal mucosa.

Following an initial precipitous decrease from 1988 to 1992, the rate of decline in incidence of invasive Hib disease among children younger than 5 years has slowed.[13,14] In a population of 10.5 million persons in the active laboratory-based surveillance project areas, the incidence of invasive Hib disease among children younger than 5 years declined from 34 cases per 100 000 in 1989 to 1.9 cases per 100 000 in 1992; the incidence in 1993 and 1994 remained at about 1.5 cases/100 000. An estimated 300 cases of invasive Hib disease occurred annually in the United States during 1993 and 1994 in this age group. This plateau in disease incidence occurred during a period when the overall immunization coverage of children younger than 2 years with 3 Hib vaccine doses was increasing.[24,25] National Immunization Survey data indicate that despite a rapid overall increase in coverage with 3 or more doses of Hib vaccine to 90%, coverage was as low as 71% in a large urban metropolitan area during April 1994 to March 1995.[26] These findings are consistent with the existence of pockets of poorly vaccinated populations.

Other countries, including Canada and Australia, have reported low levels of Hib disease several years after the introduction of infant immunization programs.[27,28] In contrast, in some countries, such as Iceland and Finland, Hib disease has completely disappeared or occurs almost exclusively among immunodeficient children, most likely because of uniformly high immunization coverage with conjugate vaccines.[29,30] Hib conjugate vaccines are becoming part of routine immunization in nonindustrialized countries.[31] Since uniformly high immunization coverage may not be achieved rapidly in many of these countries, invasive Hib disease is likely to persist, especially in underserved populations.

Data from our study suggest that 2 distinct populations of children remain at risk for Hib disease in the United States: undervaccinated children living in socioeconomically disadvantaged conditions and appropriately vaccinated children who are too young to have received a complete primary series of Hib vaccinations or who may have underlying immune defects. This study clearly suggests that lower socioeconomic status is the overwhelming risk factor for the Hib

disease still occurring in the United States. Special efforts to achieve complete and timely immunization in socioeconomically disadvantaged populations are needed. □

Contributors

W. G. Adams developed the study design and questionnaire and initiated data collection. B. D. Plikaytis participated in study design and data analysis. K. A. Robinson participated in questionnaire design and data collection. H. S. Jafari completed data collection, data analysis, and writing of the paper. J. D. Wenger participated in study design, questionnaire design, data analysis, and writing of the paper. All authors guarantee the integrity of the manuscript.

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