Am. J. Trop. Med. Hyg., 60(2), 1999, pp. 263–266

A CASE-CONTROL STUDY OF RISK FACTORS FOR *HAEMOPHILUS INFLUENZAE* TYPE B DISEASE IN NAVAJO CHILDREN

MARK C. WOLFF, LAWRENCE H. MOULTON, WENDY NEWCOMER, RAYMOND REID, AND MATHURAM SANTOSHAM

Departments of International Health and Biostatistics, School of Hygiene and Public Health, and the Department of Pediatrics, School of Medicine, The Johns Hopkins University, Baltimore, Maryland

Abstract. To understand the potential risk factors and protective factors for invasive *Haemophilus influenzae* type b (Hib) disease, we conducted a case-control study among Navajo children less than two years of age resident on the Navajo Nation. We analyzed household interview data for 60 cases that occurred between August 1988 and February 1991, and for 116 controls matched by age, gender, and geographic location. The Hib vaccine recipients were excluded from the analyses. Conditional logistic regression models were fit to examine many variables relating to social and environmental conditions. Risk factors determined to be important were never breast fed (odds ratio [OR] = 3.55, 95% confidence interval [CI] = 1.52, 8.26), shared care with more than one child less than two years of age (OR = 2.32, 95% CI = 0.91, 5.96); wood heating (OR = 2.14, 95% CI = 0.91, 5.05); rodents in the home (OR = 8.18, 95% CI = 0.83, 80.7); and any livestock near the home (OR = 2.18, 95% CI = 0.94, 5.04).

Before the widespread use of conjugate vaccines, incidence rates of invasive *Haemophilus influenzae* type b (Hib) disease among Navajo children were demonstrated to be much higher than in the general U.S. population. During the 1970s, the incidence of Hib meningitis for Navajo children less than five years of age was 152 per 100,000 child-years,[1] compared with 19–60 per 100,000 in various non-Native American communities.[2] The reasons for these elevated rates are not well understood, although environmental factors, genetic predisposition, and delayed maturation of immune functions all may be implicated.

Many factors have been identified in population groups other than the Navajo as being associated with increased risk of Hib disease incidence. These include the use of shared child care facilities,[3–7] large family size or crowding,[5,6,8,9] low socioeconomic status,[8] and smoking.[8] Breast feeding has been shown to be protective.[3,5,6,9,10] In a case-control study of Navajo children, we investigated these and other factors that were unique to the environmental and cultural characteristics of this population, including heating fuels, husbandry practices, and arts and crafts activities.

Although Hib disease has been virtually eliminated in this Navajo population, it is a leading cause of serious childhood illnesses in many countries where Hib vaccines are not routinely administered.[11,12] This case-control study, conducted in a predominantly rural and disadvantaged community just prior to licensure of Hib conjugate vaccines, has relevance to many less industrialized populations.

MATERIALS AND METHODS

Surveillance for Hib disease. From July 1988 through July 1990, active laboratory-based surveillance for Hib disease was carried out on the Navajo Nation in Arizona and New Mexico as part of a trial designed to evaluate the safety and efficacy of a Hib conjugate vaccine (Hib-OMPC: PedvaxHIB®; Merck, Blue Bell, PA).[13] Further surveillance for Hib disease was conducted as part of a study to evaluate the effectiveness of implementation of a Hib vaccine program in all infants immediately after completion of the efficacy trial.

Approximately one-fourth of the Navajo infants born from June 1988 through June 1990 were enrolled in the efficacy trial (n = 5,190). These children were not eligible to be either cases or controls in the case-control study. Cases were children with laboratory-confirmed Hib disease based on an isolate from a normally sterile body fluid. Confirmation was made from reaction to *H. influenzae* antiserum, pattern of growth in the presence of factors X and V, and response to a biochemical panel (Microscan; Baxter Laboratories, West Sacramento, CA).[13] Those who were less than two years of age on the date of culture were eligible to enroll in the case-control study, provided they had not received any Hib vaccine before the date of the positive Hib culture. All cases occurring from August 1988 through February 1991 were included in the case-control study.

Written informed consent was obtained from the parents or guardians of all study participants. The study protocol was approved by the Johns Hopkins University Committee on Human Research, the Navajo Area Indian Health Service, and the Institutional Review Board of the Navajo Nation.

Selection of controls. Two control children were matched to each case by gender, age (within one month), and location of residence. The controls for a given case were identified by examination of the birth logbook kept for each hospital where the index cases were born. The two births of the same sex as the case who were born most closely in time to the case were selected, provided they did not receive any Hib vaccine at an age younger than their case's age at date of culture.

Data collection. At least three attempts were made to contact the parents of all case and control children by conducting home visits scheduled at varying times of day. In addition, attempts were made to locate them at stores and other meeting places. Interviews were conducted with mothers or next of kin between June 1990 and July 1991 by trained Navajo study personnel who were fluent in Navajo and English. Interviews generally took less than 1 hr to complete. Clinic records were abstracted for dates and types of cultures, hospitalizations, and related information.

Statistical techniques. Univariate and multivariate odds ratio analyses were conducted that accounted for the matched design. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using SAS® (SAS Institute,

TABLE 1
Univariate odds ratios (ORs) and 95% confidence intervals (CIs) for invasive *Haemophilus influenzae* type b disease

Dichotomous variable	Cases*	Controls*	Matched OR	95% CI	*P*†
Never breastfed	34/60†	36/116	3.33	(1.59, 7.14)	<0.001
Shared bed	28/60	73/116	0.51	(0.26, 0.99)	0.042
Regular day care	23/60	37/116	1.34	(0.65, 2.75)	0.426
Day care with ≥ 1 other child less than 2 years old	16/60	17/116	2.27	(1.00, 5.15)	0.045
Parent or caretaker smoking	4/60	11/116	0.76	(0.24, 2.42)	0.638
Rural vs urban	38/60	59/116	2.01	(0.96, 4.21)	0.061
>20 miles from hospital	23/60	51/116	0.67	(0.28, 1.58)	0.359
Dirt floor	7/60	8/116	1.83	(0.63, 5.29)	0.257
No electricity	15/60	20/116	1.69	(0.76, 3.85)	0.189
No running water	30/60	44/116	2.08	(1.00, 4.35)	0.046
Wood heating	46/60	69/116	2.53	(1.17, 5.47)	0.016
Coal heating	21/60	36/116	1.25	(0.61, 2.55)	0.540
Any animals in home	25/60	30/116	2.04	(1.05, 3.95)	0.032
Rodents in home	4/60	1/114	8.00	(0.89, 71.6)	0.027
Any livestock near home	46/60	74/116	1.95	(0.93, 4.09)	0.072
Horses near home	15/58	18/111	1.98	(0.90, 4.35)	0.084
Any crafts in house	18/60	35/116	1.02	(0.50, 2.08)	0.952
>3 traditional ceremonies in last year	14/60	25/116	1.16	(0.55, 2.44)	0.699
Parent or primary caretaker speaks fluent English	21/60	52/116	0.59	(0.30, 1.18)	0.131

* Numerator is the number with characteristic; denominator is the total.
† Score test.

Cary, NC) version 6.08 PROC PHREG for conditional logistic regression for matched sets.[14]

RESULTS

Analysis data set. Of the 75 cases determined to be eligible for the study, six (8%) could not be located. Interviews were obtained with relatives of the remaining 69 children. All but two of the interviews were with the mother. Two controls were selected for each of the 75 eligible cases for a total of 150 controls; interviews were obtained for all but 24 (16%). Of the remaining 126 control interviews, 93% were with the child's mother. There were no refusals to be interviewed. One control was excluded due to having received Hib vaccine at an age before that of the matched case's age at date of culture. Three cases who had received a Hib vaccine prior to their date of culture were excluded. Two controls were determined to have birth dates six months and 11 months later than their matched case, and were dropped from the analysis. Following these exclusions, six cases were dropped from analysis because of no remaining matched controls, leaving 56 strata with two controls, and four strata with one control, for a total of 60 cases and 116 controls. Meningitis and bacteremia accounted for 48% and 32%, respectively, of the reported diagnoses of the cases.

Univariate analyses. The controls were born within 32 days of their matched cases; 54% were within 14 days. Cases were an average 1.5 days older than their matched controls, with a median difference of zero days. The results of matched univariate analyses for the main factors under study are shown in Table 1. As anticipated, breast feeding was an important protective variable; invasive Hib disease cases were much more likely to have never breast fed than their matched controls (OR = 3.33, 95% CI = 1.59, 7.14). A protective effect (OR = 0.51, 95% CI = 0.26, 0.99) was associated with the infant sleeping in the same bed with another person, usually with the mother. Shared child care was not an important factor unless it involved the infant being with other infants less than the age of two. This latter condition was associated with a doubling of the odds for being a case (OR = 2.27, 95% CI = 1.00, 5.15). As for sources of indoor air pollution, wood heating was implicated as a possible risk factor (OR = 2.53, 95% CI = 1.17, 5.47), while coal heating and smoking by parents or caretakers were not. The existence of crafts activities in the house, which are potential sources of various airborne irritants, showed no relationship to case/control status. Other indicators of the home environment included lack of running water or electricity in the home, and whether the primary flooring material was dirt. These were all related to some degree with Hib disease, with lack of running water exhibiting the strongest association (OR = 2.08; 95% CI = 1.00, 4.35).

A rural location of the home was associated with a doubling of the OR of Hib disease, as was having any animals in or entering the home, and having any livestock near the home. Mainly responsible for the association with animals in the home was the existence of rodents; the main component of the livestock association was having horses nearby.

Sociocultural characteristics included attendance at traditional ceremonies, and whether the respondent (always a parent or primary caretaker) spoke English fluently. Only the latter had even a mild association (protective, in this case) with Hib disease, and is best interpreted as a proxy for other socioeconomic factors.

Multivariate analyses. Models incorporating several factors simultaneously were constructed from among those determined in the univariate analysis to have an OR of strength at least 1.5 (or less than 1/1.5) or a *P* value for association of less than 0.2. To remain in the model, OR estimates as extreme as 2.0 (or 0.5) and *P* values smaller than 0.15 were required at each stage of model consideration.

We began by incorporating the classic risk factors of breast feeding and day care attendance, as well as the shared bed variable (first model in Table 2). This latter variable may serve as some kind of proxy for breast feeding because mothers traditionally share beds with their infants for other

TABLE 2

Matched odds ratios (and 95% confidence intervals) for variables in the multivariate conditional logistic regression models

	First model	Second model	Third model
Never breast fed	3.21 (1.49, 6.90)	3.23 (1.47, 7.09)	3.55 (1.52, 8.26)
Shared bed	0.61 (0.37, 1.21)		
Shared care with ≥1 child less than 2 years old	2.03 (0.85, 4.82)	2.30 (0.95, 5.56)	2.32 (0.91, 5.96)
Rural vs urban		1.01 (0.35, 2.99)	
No electricity		1.21 (0.46, 3.19)	
No running water		1.66 (0.58, 4.76)	
Wood heating		2.01 (0.82, 4.90)	2.14 (0.91, 5.05)
Rodents in home			8.18 (0.83, 80.7)
Any livestock near home			2.18 (0.94, 5.04)

reasons as well. Although not statistically significant, the OR relating a shared bed to breast feeding was 1.8, and with the breast feeding variable in the model, the shared bed variable did not meet retention criteria for inclusion in subsequent models.

The next block of conceptually related variables contained rural location, electricity, running water, and heating with wood (second model in Table 2). Of these, only wood heating met a criterion for retention in the subsequent model. As for the proximity of animals, the first variables considered were any animals in the home and domestic animals in the home, neither of which met either the odds ratio or significance criteria. Animals generally are kept out of Navajo homes, with cats tolerated for brief periods. The presence of rodents in the home, however, remained important in the multivariate analysis. The livestock near home variable was added, but no specific livestock were related to case status strongly enough for model inclusion. This left the third model in Table 2, which we considered as the overall best model; the speaks English variable was checked for inclusion at this point, but provided virtually no improvement in the model.

It should be noted that while most of the 95% CIs in the third model of Table 2 include the null value of one, the test statistic significance of the associated variables is somewhat greater than these intervals would indicate. In this effectively small sample situation, the score statistic is to be preferred, with size closer to the nominal value than Wald or likelihood ratio test statistics.[15] The score test *P* values were 0.074 for shared care with other children less than two years old, 0.076 for wood heating, 0.040 for rodents in home, and 0.062 for any livestock near the home.

DISCUSSION

Our results confirm the findings of other investigators who reported a strong protective effect of breast feeding.[3,5,6,9,10] Shared child care was associated with a higher risk of Hib disease only where there was at least one other child less than two years old, which occurred in about half of the shared care arrangements. Other studies have found high risks associated with shared care in general,[3–7] but their arrangements may have had much higher proportions of young children. Univariate analyses indicated several variables related to rural life or lower socioeconomic status also to be associated with risk of Hib disease, including living in housing with a dirt floor or lack of running water or electricity. These findings accord with those of a recent case-control study of Hib vaccine effectiveness in Navajo children, which found presence of a household telephone and immunization at private clinics (in urban areas) to be associated with reduced risk of Hib disease.[16] Of the relevant variables identified in our univariate analyses, heating with wood and the existence of rodents in the house or any livestock or husbandry practices near the house were strong predictors in a multivariate regression model. We note, however, that 84% of rural homes reported wood heating, compared with 42% of non-rural homes, and that wood heating may be relevant as a measure of socioeconomic status. Wood heating may also be a significant risk factor in its own right by contributing a significant quantity of suspended particulates. Some investigators have demonstrated the association between wood burning stoves and increased risk for acute respiratory infections.[17–19] On the Navajo Nation, we have determined that infants who present with acute lower respiratory infections are more likely to have severe disease if they come from a home with wood burning stoves.[20] Smoking by parents or caretakers is rare among Navajos (9% in our study), which may explain why it did not appear to be associated with Hib disease.

Unexpected findings included the higher risks associated with rodents in the home or livestock near the home. The rodent association was based on only five reports, and may be due to differential recall between the cases and controls. Both of these variables may be proxies for other socioeconomic factors or for other characteristics of rural housing on which we have no data.

The findings of this study may be relevant to developing regions of the world where poor or rural housing conditions and indoor air pollution are common, and may help justify increased surveillance for and immunization against Hib disease in areas not currently recognized as having a significant problem. Additional studies are needed to determine the epidemiology and risk factors associated with Hib disease in less industrialized countries.

Acknowledgments: We thank Linda Capriati, Deloria Chapo, Janné Croll, Connie Donaldson, and Joe Lacayo for their efforts and dedication to quality data acquisition.

Financial support: Data collection efforts were supported by Merck Research Laboratories (Blue Bell, PA) and The Center for American Indian and Alaskan Native Health (Baltimore, MD).

Disclaimer: The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the Indian Health Service.

Authors' addresses: Mark C. Wolff, The EMMES Corporation, 11325 Seven Locks Road, Suite 214, Potomac, MD 20854. Lawrence H. Moulton and Mathuram Santosham, Department of International Health, The Johns Hopkins University School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, MD 21205. Wendy Newcomer, Department of Psychiatric and Community Health Nursing, University of Maryland, 655 West Lombard Street,

Baltimore, MD 21205-1545. Raymond Reid, PO Box 3000, c/o Northern Navajo Medical Center, Highway 666 North 3, Shiprock, NM 87420.

REFERENCES

1. Coulehan JL, Michaels RH, Hallowell C, Schults R, Welty TK, Kuo JSC, 1984. Epidemiology of *Haemophilus influenzae* type B disease among Navajo Indians. *Public Health Rep 99*: 404–409.
2. Broome CV, 1987. Epidemiology of *Haemophilus influenzae* type b infections in the United States. *Pediatr Infect Dis J 6*: 779–782.
3. Redmond SR, Pichichero ME, 1984. *Haemophilus influenzae* type b disease: an epidemiologic study with special reference to day-care centers. *JAMA 252*: 2581–2584.
4. Istre GR, Conner JS, Broome CV, Hightower A, Hopkins RS, 1985. Risk factors for primary invasive *Haemophilus influenzae* disease: increased risk from day care attendance and school-aged household members. *J Pediatr 106*: 190–195.
5. Cochi SL, Fleming DW, Hightower AW, Limpakarnjanarat K, Facklam RR, Smith JD, Sikes RK, Broome CV, 1986. Primary invasive *Haemophilus influenzae* type b disease: a population-based assessment of risk factors. *J Pediatr 108*: 887–896.
6. Takala AK, Eskola J, Palmgren J, Ronnberg PR, Kela E, Rekola P, Makela PH, 1989. Risk factors of invasive *Haemophilus influenzae* type b disease among children in Finland. *J Pediatr 115*: 694–701.
7. Berg AT, Shapiro ED, Capobianco LA, 1991. Group day care and the risk of serious infectious illnesses. *Am J Epidemiol 133*: 154–163.
8. Vadheim CM, Greenberg DP, Bordenave N, Ziontz L, Christenson P, Waterman SH, Ward JI, 1992. Risk factors for invasive *Haemophilus influenzae* type b in Los Angeles County children 18-60 months of age. *Am J Epidemiol 136*: 221–235.
9. Arnold C, Makintube S, Istre GR, 1993. Day care attendance and other risk factors for invasive *Haemophilus influenzae* type b disease. *Am J Epidemiol 138:* 333–340.
10. Petersen GM, Silimperi DR, Chiu C-Y, Ward JI, 1991. Effects of age, breast feeding, and household structure on *Haemophilus influenzae* type b disease risk and antibody acquisition in Alaskan Eskimos. *Am J Epidemiol 134*: 1212–1221.
11. Cattaneo A, 1994. Current role of vaccination in preventing acute respiratory infections in children in developing countries. *Monaldi Arch Chest Dis 49*: 57–60.
12. Funkhouser A, Steinhoff MC, Ward J, 1991. *Haemophilus influenzae* disease and immunization in developing countries. *Rev Infect Dis 13 (suppl 6)*: S542–S554.
13. Santosham M, Wolff M, Reid R, Hohenboken M, Bateman M, Goepp J, Cotese M, Sack D, Hill J, Newcomer W, Capriotti L, Smith J, Owen M, Gahagan S, Hu D, Kling R, Lukacs L, Ellis RW, Vella PP, Calandra G, Matthews H, Ahonkhai V, 1991. Efficacy of a *Haemophilus influenzae* type b-*Neisseria meningitidis* outer membrane protein conjugate vaccine in Navajo infants. *N Engl J Med 324*: 1767–1772.
14. Breslow NE, Day NE, 1980. *Statistical Methods in Cancer Research.* Volume I. *The Analysis of Case-Control Studies.* IARC Scientific Publications No. 32). Lyon: International Agency for Research on Cancer.
15. Moulton LH, Weissfeld LA, St. Laurent RT, 1993. Bartlett correction factors in logistic regression models. *Comput Stat Data Anal 15*: 1–11.
16. Harrison LH, Tajkowski C, Croll J, Reid R, Hu D, Brenneman G, Weatherholtz RC, Santosham M, 1994. Postlicensure effectiveness of the *Haemophilus influenzae* type b polysaccharide-*Neisseria meningitidis* outer-membrane protein complex conjugate vaccine among Navajo children. *J Pediatr 125*: 571–576.
17. Morris K, Morgenlander M, Coulehan JL, Gahagen S, Arena VC, Morgenlander M, 1990. Wood-burning stoves and lower respiratory tract infection in American Indian children. *Am J Dis Child 144*: 105–108.
18. Henry CJ, Fishbein L, Meggs WJ, Ashford NA, Schulte PA, Anderson H, Osborne JS, Sepkovic DW, 1991. Approaches for assessing health risks from complex mixtures in indoor air: a panel overview. *Environ Health Perspect 95*: 135–143.
19. Johnson AW, Aderele WI, 1992. The association of household pollutants and socio-economic risk factors with the short-term outcome of acute lower respiratory infections in hospitalized pre-school Nigerian children. *Ann Trop Paediatr 12:* 421–432.
20. Robin LF, Lees PSJ, Winget M, Steinhoff M, Moulton LH, Santosham M, Correa A, 1996. Wood-burning stoves and lower respiratory illnesses in Navajo children. *Pediatr Infect Dis J 15*: 859–865.