Immunologic Response to Haemophilus influenzae Type b (Hib) Conjugate Vaccine and Risk Factors for Carriage among Hib Carriers and Noncarriers in Southwestern Alaska

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Continued Haemophilus influenzae type b (Hib) carriage in rural Alaska contributes to the ongoing risk of invasive disease. Community-wide Hib carriage surveys were conducted in three villages in southwestern Alaska. Sixteen carriers and 32 age- and village-matched controls were enrolled and were vaccinated with Hib oligosaccharide-CRM197 conjugate vaccine. Serum immunoglobulin G (IgG) concentration, antibody avidity, and serum bactericidal activity (SBA) were measured prior to Hib vaccination and 2 and 12 months after vaccination. We identified no demographic or behavioral factors associated with Hib colonization. Prior to vaccination, Hib carriers had a higher IgG geometric mean concentration than controls did (8.2 versus 1.6 μg/ml; P < 0.001) and a higher SBA geometric mean titer (7,132 versus 1,235; P = 0.006). Both groups responded to vaccination with increased IgG and SBA. These data illustrate the role of Hib colonization as an immunizing event and show that Hib carriers in communities with ongoing transmission have no evidence of reduced immune responsiveness that may have put them at risk for colonization.

Before 1990, Haemophilus influenzae type b (Hib) was the most common cause of bacterial meningitis in children <5 years of age in the United States (10, 11). During 1990 to 1998, the incidence of invasive Hib disease decreased 99% in the United States following the introduction of the Hib conjugate vaccine (5, 8). In addition to protecting against invasive infection, Hib conjugate vaccine prevents asymptomatic oropharyngeal (OP) Hib colonization or carriage (3, 4, 24, 25, 35). The lower prevalence of Hib carriage in the population decreases the risk of infection even among unvaccinated children through reduced transmission (3, 4, 24, 25, 31, 35).

The mechanism by which Hib conjugate vaccine inhibits oropharyngeal colonization is not well understood. Protection against carriage has been correlated with serum concentrations of immunoglobulin G (IgG) against the Hib polysaccharide polyribosylribitol phosphate (PRP) (13). Anti-PRP IgG concentrations in saliva have been correlated with serum concentrations, suggesting that passive transudation of anti-PRP IgG to mucosal surfaces may be important in blocking colonization (3, 19). In addition to serum concentration, other properties of the anti-PRP antibody response may be important in inhibiting colonization, such as antibody avidity and bactericidal activity (3), but little is known about the relationship of these parameters to carriage.

Prior to the introduction of Hib conjugate vaccines, Alaska Natives in southwestern Alaska experienced the highest known annual incidence of invasive Hib disease worldwide, exceeding 400 cases/100,000 children <5 years of age (37). Disease incidence declined significantly in Alaska after introduction of Hib conjugate vaccine but remained higher than that in other parts of the United States (8, 14). A Hib outbreak occurred in 1996 following a change in the vaccine used, and the resulting investigation revealed that most Hib cases in rural Alaska occurred in children who had at least one dose of Hib conjugate vaccine and that the Hib carriage prevalence was similar to or higher than the overall U.S. prevalence before conjugate vaccine licensure (14, 34). These findings raised questions about why Hib carriage should persist in rural Alaska despite high vaccine coverage.

To determine epidemiologic and immunologic factors contributing to ongoing Hib transmission, we conducted a case-control study to assess risk factors for Hib carriage in southwestern Alaska. We then compared the immunologic response to Hib conjugate vaccine among Hib carriers and noncarriers.

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MATERIALS AND METHODS

Setting. This study was conducted in a region of southwestern Alaska with a population of approximately 25,000 distributed among 52 isolated villages (75 to 1,014 persons/village). The study village populations ranged from 335 to 765 persons and were 90 to 95% Alaska Native. The investigation included two parts: (i) a case-control study to evaluate risk factors for Hib colonization among Hib carriers and controls (noncarriers) and (ii) a longitudinal assessment to compare the immunologic response to Hib conjugate vaccine among Hib carriers and controls. Participants were selected from a community intervention trial conducted in six villages to assess the efficacy of Hib conjugate vaccine in reducing the prevalence of Hib carriage. The current study was conducted in all three villages that received the vaccine intervention.
Carriage surveys. During September 2001, prior to the vaccine intervention, community-wide Hib carriage surveys were conducted, and all village residents were eligible. Over 85% of the residents of each village participated. OP cultures made using Dacron swabs were plated directly onto chocolate-bacitracin agar medium (Remel, Lenexa, KS) and incubated at 35°C for 48 h. Bacterial colonies that appeared morphologically similar to Hib on chocolate agar but failed to grow when plated on sheep blood agar and were unable to utilize delta-aminolevulinic acid were transferred to Mueller-Hinton agar containing Hb antisera (23). Hib isolates grown on the antiserum agar develop a surrounding halo. All halo-positive isolates were confirmed as Hib by growth with X and V factors and by serotyping using Difco latex reagent (Difco Laboratories, Detroit, MI).

Case-control study. A Hib carrier was defined as a person with a positive Hib culture at the initial carriage assessment regardless of carriage status at later assessments. Two age- and village-matched controls were randomly selected for each carrier from the group of Hib noncarriers after the initial carriage survey. The age-matching criteria for eligible controls were ±2 months for carriers aged <24 months, ±1 year for carriers aged 2 to 18 years, and ±5 years for carriers aged over 18 years. Controls were excluded if their OP cultures were positive for Hib at subsequent evaluations.

Two weeks after the initial OP culture surveys, a standard questionnaire was administered in person to evaluate demographic and household characteristics, smoking history, and smokeless tobacco use. Individual medical records were reviewed at the village health clinic to assess antibiotic use during the 30 days before the OP culture, prior receipt of any Hib vaccine or Hib bacterial polysaccharide immunoglobulin, and past medical history for conditions that can predispose to invasive Hib infection, such as renal failure, immunodeficiency, or premature birth. Electronic vaccination records were reviewed to confirm prior receipt of Hib vaccine. For children born after Hib conjugate vaccine was available (1990), adequate vaccination status was defined as receipt of one of the licensed vaccines for persons over 5 years of age, vaccine in this study for persons of any age, four doses of any Hib conjugate vaccine for persons of any age, or ≥1 dose of any Hib conjugate vaccine for children aged ≥15 months.

OP cultures were repeated for case-control participants 2 weeks after the initial carriage survey (simultaneously with vaccine intervention) and 2 and 12 months after the vaccine intervention (Fig. 1). For the 2- and 12-month assessments, OP swabs were plated directly onto Mueller-Hinton agar containing Hib antisera instead of chocolate agar.

Assessment of immunologic parameters. Two weeks after the initial carriage survey, baseline serum specimens were obtained to measure immunologic parameters (Fig. 1), including anti-PRP IgG and IgM concentrations, antibody avidity, and serum bactericidal activity (SBA), a measure of bacterial killing. All parameters (Fig. 1), including anti-PRP IgG and IgM concentrations, antibody concentrations, and SBA titers were log transformed, and the geometric mean concentrations (GMCs) and geometric mean titers (GMTs) were calculated. Dichotomous comparisons of IgG concentrations were performed for values of 0.15, 1.0, and 5.0 μg/ml, which have been correlated with short-term and long-term protection against invasive Hib disease (20) and protection against Hib colonization (13), respectively. We also calculated the proportion of carriers and controls with SBA titers above predefined thresholds (<256, 256 to <4,096, and ≥4,096), based on the SBA titer distribution seen in a previous study (29). Antibody avidities were compared using the geometric mean of the weighted average of NaSCN molar concentration yielding most of the reduction in ELISA IgG absorbance.

Analysis was performed using Stata 8.0 (StataCorp, College Station, TX). Continuous variables were compared by two-sample t test. Binary variables were compared using multiple logistic regression; all models were adjusted for village and a linear age variable. Adjusted odds ratios (OR) and 95% confidence intervals (CI) are presented.

Ethical approval. This study was approved by the Institutional Review Boards of the U.S. Centers for Disease Control and Prevention and the Alaska Area Research and Publications Committee, the Human Subjects Committee at the Yukon-Kuskokwim Regional Health Corporation, and the village or tribal councils in each of the study villages. Written consent was obtained from adult participants and from a parent of all participants under 18 years of age. Written assent was obtained from children aged 7 to 17 years. Because Hib vaccines are not licensed in the United States for persons over 5 years of age, vaccine in this study was administered under the U.S. Food and Drug Administration Investigational New Drug application BB-IND#9862.

FIG. 1. Flow diagram showing timing of study recruitment and data collection, southwestern Alaska, 2001–2002.
### RESULTS

**Carriage surveys.** Among the 1,556 persons with OP cultures, 1,512 (97%) were Alaska Native. Sixteen Hib carriers were identified (Hib carriage prevalence = 1.03%), and 15 (94%) were Alaska Native. All 16 carriers were from two of the three study villages, 12 (2.4%) of 503 participants in one village and 4 (0.56%) of 720 in the other. None of the 333 participants in the third village were colonized with Hib.

**Case-control study.** All 16 Hib carriers and 33 age- and village-matched controls agreed to participate in the case-control study (three controls were matched to one carrier; all others had two matched controls). One control was colonized with Hib at the 2-week follow-up and was therefore excluded from all analysis, leaving 16 carriers and 32 controls in the final study group (Fig. 1). The median age of Hib carriers was 8.8 years (minimum, 4.4 years; maximum, 32.6 years); 69% of carriers and 66% of controls were male (Table 1).

Over 70% of all participants lived in households with >6 persons, and carriers and controls did not differ by the household crowding measures or by the number of children in the home (Table 1). Only two Hib carriers and one control lived in a household with another Hib carrier. Carriers and controls did not differ in terms of tobacco use or vaccine history, including time since last vaccination or type of conjugate vaccine received. Among children born after 1990, all 10 carriers and all 20 controls had been adequately vaccinated. Carriers were more likely than controls to have received antibiotics in the 30 days before OP culture (25% versus 6%, respectively), but the difference was not statistically significant.

**Assessment of immunologic parameters.** Fifteen of the 16 Hib carriers and 30 of 32 controls were available for baseline immunologic testing. Carriers had a higher baseline anti-PRP IgG GMC than controls, and IgG levels for all participants were positively correlated with log IgM concentrations (Fig. 3). Four of the 16 Hib carriers were still colonized with Hib at the time of the baseline serum collection.

## Baseline characteristics of Hib carriers and controls—southwestern Alaska, 2001–2002

| Baseline characteristic | Carriers (n = 16) | Controls (n = 32) | OR (95% CI) |
|-------------------------|------------------|------------------|-------------|
| Demographics           |                  |                  |             |
| Age in yr, median (range) | 8.8 (4.4–32.6)  | 9.6 (3.8–35.6)  | Matched on age |
| Male                    | 11 (69)          | 21 (66)          | 1.2 (0.33 to 4.1) |
| HH characteristics      |                  |                  |             |
| No. of persons in HH, mean (SD) | 6.6 (2.3)       | 6.7 (1.9)       |             |
| ≥2 persons/room         | 4 (25)           | 16 (50)          | 0.32 (0.08 to 1.2) |
| Child aged <5 yr in HH  | 9 (56)           | 20 (62)          | 0.76 (0.21 to 2.8) |
| Undervaccinated child aged <5 yr in HH | 1 (6) | 5 (16) | 0.36 (0.34 to 3.7) |
| ≥3 children in HH aged 5–18 yr | 9 (56) | 16 (50) | 1.3 (0.37 to 4.8) |
| Tobacco use             |                  |                  |             |
| Ever smoked (of those aged >14 yr) | 2/6 (33)         | 8/12 (67)       | 0.21 (0.02 to 1.8) |
| Smoked ≥1 cigarette/day (of those aged >14 yr) | 2/6 (33)         | 6/12 (50)       | 0.44 (0.05 to 3.8) |
| Smokeless tobacco ≥1 time/wk | 5 (31)          | 7 (22)          | 1.8 (0.20 to 8.1) |
| Any current tobacco use | 7 (44)           | 10 (31)         | 2.1 (0.45 to 10) |
| Vaccine history         |                  |                  |             |
| Ever received Hib conjugate vaccine | 10/10 (62) | 20/20 (62) | 0.87 (0.07 to 11) |
| Born after Hib conjugate vaccine available (aged <12 yr) | 10/20 (62) | 20/20 (62) | Matched on age |
| Adequately vaccinated for Hib | 10/10 (100)    | 20/20 (100)     | Undefined |
| ≥82 mo since last vaccination | 5/10 (50)       | 10/20 (50)      | 1.3 (0.11 to 14) |
| Ever received PRP-OMP vaccine | 9/10 (90)     | 19/20 (95)      | 0.49 (0.02 to 10) |
| Ever received HibOC vaccine | 3/10 (30)     | 8/20 (40)       | 0.50 (0.06 to 4.2) |
| Ever received BPIG     | 1/10 (10)       | 2/20 (10)       | 1.2 (0.03 to 42) |
| Medical history        |                  |                  |             |
| Prescribed antibiotics during 30 days before OP culture | 4 (25) | 2 (6) | 5.0 (0.76 to 33) |
| Risk factor(s) for invasive Hib disease | 0 | 0 |  |

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**TABLE 1. Baseline characteristics of Hib carriers and controls—southwestern Alaska, 2001–2002**

*Abbreviations: HH, household; BPIG, bacterial polysaccharide immunoglobulin.*

* Odds ratio and 95% confidence interval adjusted for age and village residence.

* Unless otherwise noted, values are shown as number of subjects with characteristic (percentage) or number of subjects with characteristic/total number of subjects (percentage).

* Includes all rooms in the house. Dichotomized around the median value for controls for comparison.

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ences were not statistically significant; antibody avidity was similar for the two groups.

Immunologic assessment 2 months after vaccination revealed few differences between carriers and controls (Table 2; Fig. 2). Carriers were less likely than controls to have a ≥2-fold increase in anti-PRP IgG concentration (47% versus 93%). SBA titers were higher for carriers than controls, but the difference was not statistically significant. No carriers or controls were colonized with Hib at the 2-month assessment.

Twelve months after Hib vaccination, the anti-PRP IgG GMCs declined to an average of 5.0 μg/ml in carriers and 4.1 μg/ml in controls (P = 0.63), and the proportion with IgG concentrations above the predefined thresholds did not differ between groups (Table 2). Between the baseline and 12-month evaluations, antibody avidity increased in carriers from 0.35 to 0.47 (P = 0.01) and in controls from 0.39 to 0.41 (P = 0.68, Fig. 2). SBA GMTs were 1,351 in carriers and 826 in controls at the 12-month assessment (P = 0.086), and carriers were more likely to have SBA titers above predefined thresholds. No participants were colonized with Hib at the 12-month assessment.

### Table 2. Antibody concentration, avidity, and serum bactericidal activity among Hib carriers and controls before and 2 and 12 months after vaccination with Hib conjugate vaccine (HbOC)—southwestern Alaska, 2001–2002

| Parameter and time after vaccination | Carriers | Controls | OR (95% CI) | P value |
|--------------------------------------|----------|----------|-------------|---------|
| **Baseline (before vaccination)**b |          |          |             |         |
| No. of subjects | 15       | 30       |             |         |
| Anti-PRP IgG GMC, μg/ml (95% CI) | 8.2 (3.7–18.0) | 1.6 (1.1–2.4) | <0.001 |
| No. of subjects (%) with anti-PRP IgG GMC (μg/ml) of: |          |          |             |         |
| ≥0.15 | 15 (100) | 30 (100) | Undefined   |         |
| ≥1.0 | 14 (93) | 22 (73) | 5.6 (0.53–60) | 0.15    |
| ≥5.0 | 10 (67) | 3 (10) | 22 (3.7–133) | 0.001   |
| Anti-PRP IgM GMC, μg/ml (95% CI) | 2.6 (1.8–3.9) | 1.1 (0.74–1.6) |         |
| No. (%) of subjects with anti-PRP IgM GMC of ≥1.0 μg/ml | 14 (93) | 18 (60) | 11 (1.4–85) | 0.024   |
| Avidityc (95% CI) | 0.35 (0.27–0.44)d | 0.39 (0.32–0.47)e | 0.49    |
| SBA, GMT (95% CI) | 7,132 (3,171–16,037) | 1,235 (561–2,705) | 0.006   |
| No. (%) of subjects with SBA titer of: |          |          |             |         |
| <256 | 0 | 5 (17) | 1.0 (referent) | P trend = 0.019 |
| ≥256–4,096 | 4 (27) | 12 (40) | Undefined   |         |
| ≥4,096 | 11 (73) | 13 (43) | Undefined   |         |
| **2 mo after HbOC vaccination** |          |          |             |         |
| No. of subjects | 16       | 31       |             |         |
| Anti-PRP IgG GMC, μg/ml (95% CI) | 17.6 (9.8–31.8) | 19.2 (13.2–28.1) | 0.79    |
| No. (%) of subjects with anti-PRP IgG GMC (μg/ml) of: |          |          |             |         |
| ≥0.15 | 16 (100) | 31 (100) | Undefined   |         |
| ≥1.0 | 16 (100) | 31 (100) | Undefined   |         |
| ≥5.0 | 15 (94) | 28 (90) | 1.7 (0.14–19) | 0.67    |
| No. (%) of subjects with ≥2-fold rise in IgG | 7/15 (47) | 27/29 (93) | 0.05 (0.01–0.34) | 0.002   |
| Avidityc (95% CI) | 0.35 (0.28–0.45) | 0.34 (0.29–0.40) | 0.74    |
| SBA, GMT (95% CI) | 10,173 (5,589–18,516) | 5,990 (3,822–9,388) | 0.15    |
| No. (%) of subjects with SBA titer: |          |          |             |         |
| <256 | 3 (19) | 10 (32) | 1.0 (referent) |         |
| ≥256–4,096 | 13 (81) | 21 (68) | 2.1 (0.49–9.2) | 0.31    |
| ≥4,096 | 2/15 (13) | 16/29 (55) | 0.12 (0.02–0.65) | 0.008   |
| **12 mo after HbOC vaccination** |          |          |             |         |
| No. of subjects | 15       | 29       |             |         |
| Anti-PRP IgG GMC, μg/ml (95% CI) | 5.0 (2.4 to 10.5) | 4.1 (2.9 to 6.0) | 0.63    |
| No. (%) of subjects with anti-PRP IgG GMC (μg/ml) of: |          |          |             |         |
| ≥0.15 | 15 (100) | 29 (100) | Undefined   |         |
| ≥1.0 | 14 (93) | 28 (97) | 0.47 (0.03–8.9) | 0.61    |
| ≥5.0 | 6 (40) | 11 (38) | 1.1 (0.29–3.9) | 0.92    |
| Avidityc (95% CI) | 0.47 (0.39–0.55) | 0.41 (0.35–0.48) | 0.23    |
| SBA, GMT (95% CI) | 1,351 (858–2,128) | 826 (572–1,192) | 0.086   |
| No. (%) of subjects with SBA titer: |          |          |             |         |
| <256 | 0 | 4 (14) | Undefined | P trend = 0.02 |
| 256–<4,096 | 13 (87) | 25 (86) |             |         |
| ≥4,096 | 2 (13) | 0 |             |         |

a Odds ratio and 95% confidence interval adjusted for age and village residence.

b Baseline serum was collected 2 weeks after initial OP culture and prior to Hib vaccination. Carrier versus control status was determined by initial OP culture. No participants were colonized with Hib at the 2- or 12-month assessment.

c Geometric mean of the weighted average of NaSCN molar concentration reducing most of the ELISA IgG absorbance.

d n = 14 (unable to determine avidity for one carrier).

e n = 28 (unable to determine avidity for two controls).
DISCUSSION

Although rates of invasive Hib disease have declined by 95% from the prevaccine era, invasive disease continues to occur in well-vaccinated communities in rural Alaska. This is likely due to continued Hib carriage in these regions and occasional lapses in vaccination of young children. Our case-control study revealed no demographic or behavioral risk factors for Hib colonization. Prior to vaccination with HibOC, Hib carriers had higher anti-PRP IgG and IgM concentrations and higher functional antibody activity (SBA) than the noncarrier controls, suggesting that colonization itself was an immunizing event. Previous studies have also shown that Hib colonization increases serum IgG against Hib capsular antigen (2, 17), but we are not aware of work documenting a similar increase in antibody bactericidal activity. With the use of standard immune markers, Hib carriers in our study had no evidence of impaired immunity to Hib or reduced immune responsiveness to vaccine that may have put them at risk for colonization. These findings support the hypothesis that inadequate immune response is an unlikely cause of ongoing Hib colonization and transmission among Alaska Natives after the widespread use of the conjugate vaccine.

Although not statistically significant, Hib carriers were five times more likely than noncarriers to have recently been prescribed antibiotics. Antibiotic use has been associated with colonization with β-lactamase-producing strains of nontypeable H. influenzae (1). All 16 Hib carriage isolates in our study were resistant to amoxicillin (CDC, unpublished data). Antibiotic susceptibilities among other potentially colonizing bacteria (e.g., nontypeable H. influenzae) would be needed to better understand the possible relationship between antibiotic use and Hib colonization in these communities.

This study is the first to document antibody avidity and serum bactericidal activity in response to Hib colonization or vaccination among Alaska Natives. Serum bactericidal activity is a measure of functional antibody activity or bacterial killing and is normally well correlated with antibody avidity (29). In our investigation, despite similar avidity, carriers had higher bactericidal activity than did controls, even 2 and 12 months after vaccination, when IgG concentrations were no higher in carriers than controls. This difference in bactericidal activity is likely attributable to elevated anti-PRP IgM concentrations among carriers resulting from the immune response to colonization. Unlike colonization, Hib conjugate vaccines do not cause a substantial increase in serum IgM concentrations (22, 28). IgM molecules have five antigenic binding sites and may contribute proportionately more to complement-mediated bactericidal killing than does IgG (16). Log SBA titers were positively correlated with log IgM concentrations. It is worth noting that even the noncarriers in this study had a high SBA GMT among controls resulting from the immune response to colonization. The currently recommended Hib conjugate vaccines have proven effectiveness at preventing invasive disease in Alaska Natives, but continued Hib carriage in well-vaccinated communities raised the question of whether some aspects of the immune response may be inadequate in this population. We found no evidence that Hib carriers differed from controls in their response to Hib conjugate vaccine, suggesting that Hib colonization was likely not attributable to poor quantitative or qualitative humoral immune response to vaccination or colonization. Anti-PRP IgG concentrations were similar among carriers and controls 2 and 12 months after vaccination with no observed differences in the proportion of participants above accepted protective thresholds (0.15, 1.0, and 5.0 μg/ml). Although Hib carriers were less likely than controls to have a ≥2-fold increase in IgG 2 months after vaccination, the higher prevaccine IgG concentrations among carriers make this comparison less meaningful; all five Hib carriers with baseline IgG concentrations of <5.0 μg/ml showed a ≥2-fold increase in concentration (data not shown). Antibody concentrations were also similar to those seen at comparable intervals after vaccination in previous studies in Alaska (7) as well as other parts of the United States (22, 32) and in Europe (18, 36). In addition, antibody avidity, a surrogate for successful immunologic priming (15, 32), increased significantly between baseline and 12 months after vaccination among Hib carriers.

Given the appropriate response to Hib vaccination and the high levels of vaccine coverage among Alaska Native children (96% of those aged 19 to 35 months with ≥3 doses of Hib conjugate vaccine in 2001 [9]), continued Hib carriage in this region is likely related to factors that we did not assess or could...
not measure accurately enough to detect differences between carriers and controls. Low socioeconomic status and crowded housing conditions are common risk factors for infectious diseases, but precise measurement of these factors can be challenging (6). In addition, these conditions are common in rural Alaska and often vary little within communities, which further limits the ability to detect differences between groups.

This study has several limitations. The small sample size limited our ability to exclude potentially important differences between carriers and controls in the case-control study as well as in the immunologic assessment. Our sample size was dependent on the prevalence of Hib carriage in these villages, which was lower than anticipated. In a 1997 carriage study among children aged 1 to 5 years in six communities in southwestern Alaska, 9.3% of participants were colonized with Hib compared to only 0.66% of the same age group in the current study; none of the 86 carriage study participants under age 2 years were colonized. In addition, our study design allowed for the measurement of immunologic parameters only after a participant’s Hib carriage status was known. We had no way to determine immunologic measures for the Hib carriers before they became colonized to know whether they had low anti-PRP antibody concentrations or low functional antibody measures that may have put them at risk for subsequent colonization. However, the high serum bactericidal activity among the carriers at baseline suggests adequate immunologic priming from either previous exposure to Hib or an immunologically cross-reacting microorganism (33) or Hib vaccination. Finally, there may be immunologic parameters important in protection against Hib colonization that we did not measure. For instance, anti-PRP IgA concentrations increase in nasal secretions and in saliva after Hib vaccination (19). However, IgA levels have not been correlated with protection against carriage and the role of IgA in preventing colonization remains unclear (3). Anti-PRP IgG concentrations also increase in saliva after vaccination, but this increase is believed to result from transudation from serum (19). Therefore, serum IgG concentration should be an adequate surrogate for mucosal levels.

From the start of this study in September 2001 through July 2004, only six cases of invasive Hib disease occurred in Alaska (versus 26 cases during 1996 to 1999 [34]). This trend, along with the unexpectedly low carriage prevalence in this study, may mark a true change in the epidemiology of Hib disease in Alaska. However, Hib cases continue to occur in Alaska Native children; during 2001 to 2004, three cases occurred in vaccinated children aged <5 years (5.6/100,000/year), a rate still exceeding the 2003 U.S. rate of 0.2/100,000. Hib also continues to cause significant morbidity and mortality among children in developing countries worldwide (26). Therefore, invasive disease surveillance and further investigation into the ecology and immunology of Hib carriage should continue and public health officials should support policies to ensure universal access to Hib conjugate vaccine in Alaska and around the world.

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