Invasive Haemophilus influenzae Disease in Alaskan Residents Aged 10 Years and Older Before and After Infant Vaccination Programs

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Since 1980 the Centers for Disease Control and Prevention’s (CDCs) Arctic Investigation Program (AIP) in Anchorage, Alaska, has conducted active surveillance for invasive Haemophilus influenzae throughout Alaska. Early studies revealed that Alaska Native children experienced a rate of invasive H influenzae disease 6 to 10 times that of their non-native counterparts.1 Statewide H influenzae type b (Hib) vaccination programs, begun in 1991, have led to a decline in the annual incidence of Hib disease in Alaska Natives from 25 to 40 cases to 1 to 3 cases in children younger than 5 years.2 Of children born in Alaska between 1993 and 1995, 84% received 3 or more doses of Hib conjugate vaccine.3 Immunization rates among Alaska Native children are higher. Between 1994 and 1998, an average of 90% to 95% of urban and 88% to 91% of rural Alaska Native children aged 2 years had received at least 3 doses of Hib conjugate vaccine.3 The impact of Hib vaccine programs on the incidence of H influenzae disease in older Alaskan children and adults has not been evaluated.

Previous studies indicate that adult H influenzae disease is not uncommon in immunocompromised persons or patients with certain underlying conditions (eg, chronic lung disease, sple-
nectomy, leukemia, human immunodeficiency virus infection, and sickle cell disease).\textsuperscript{5,10} Reported rates vary considerably from 0.22 to 5.7 per 100,000 adults per year\textsuperscript{11-15} and are highest in persons with acquired immunodeficiency syndrome (79/100,000 persons).\textsuperscript{16,17} Reported case fatality rates have also been variable, ranging from 2.5\% to 41.6\%.\textsuperscript{7,11-14,16,18} However, most of these rates are derived from case reports and case series. Only a few studies, including 2 from the United States, have used data from population-based surveillance.\textsuperscript{11-13,19,20} One study examined the total disease burden of \textit{H influenzae} in a metropolitan adult population,\textsuperscript{12} and another focused on the emergence of disease caused by serotype f following the introduction of conjugate vaccines.\textsuperscript{18} The population-based study we report here was undertaken to help better understand the trends in incidence and mortality of invasive \textit{H influenzae} in unimmunized Alaskan residents aged 10 years and older before and after the introduction of a statewide Hib vaccination program. Using 17 years of surveillance data, we examined rates of disease in both Alaska Native and non-native populations to answer several questions: Has the incidence of invasive \textit{H influenzae}, its clinical presentations, and mortality changed over time? Have the serotypes responsible for disease in older children and adults changed since the introduction of childhood Hib vaccines? Have certain serotypes or biotypes been more often associated with certain disease states or mortality than others? Are there populations with specific risk factors that could benefit from vaccination with current Hib vaccines or efforts to reduce predisposing risk factors?

**METHODS**

**Case Definition and Population**

Invasive \textit{H influenzae} disease in Alaskans aged 10 years and older from 1980 to 1996 was studied. Invasive \textit{H influenzae} disease was defined as any disease process consistent with bacterial infection in which \textit{H influenzae} organisms were cultured from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, or other aspirate) in any individual aged 10 years and older. Population information was obtained from 1980 and 1990 US census data (Alaska Population Review, 1990 Census and Estimates, Alaska Department of Labor, July 1991) and from population statistics compiled by the Alaska Area Native Health Service of the Indian Health Service.

Eighty-four percent of the Alaska population is nonnative and lives primarily in the urban centers of Anchorage, Fairbanks, and Juneau. The Alaska Native population is quite diverse. For our purposes, the Aleuts, Koniags, Sugcestun, and Chugach were grouped with the Eskimo, while the Athabascans, who inhabit the state’s interior, and the Tlingit, Haida, and Tsimshian peoples of the southeastern seaboard were collectively referred to as Indian. Following Indian Health Service and US census policy, persons of mixed Native- nonnative ancestry were classified as Alaska Native. Of Alaska Natives, 73\% live in rural areas, working mostly as subsistence harvesters, vs 34\% of the Alaska nonnative population.

**Reporting Methods**

Statewide active surveillance for invasive \textit{H influenzae} was implemented by the AIP in 1980. A multistep surveillance protocol that involves 23 Alaska medical laboratories is in place to ensure a high degree of catchment. The laboratories receive transport media, instructions on collection and incubation, data forms, and shipping containers from the AIP and are instructed to submit any isolate they receive that is positive for \textit{H influenzae}. Annually, the AIP returns a list of submitted samples along with serotype and antibiotic susceptibility results back to the participating laboratories for reconciliation. The laboratories are then asked to submit data on any additional isolates that may have failed to have been sent. Personnel from the AIP visit participating facilities to complete case reviews and to identify any unreported cases. Annually, communicable disease surveillance data from the State of Alaska Section of Epidemiology are checked against AIP records as well. In addition, Alaska death certificate data are examined annually for possible missed cases, which are then verified by hospital chart review.

Case reviews for additional demographic, historic, and clinical information are conducted for each patient identified and the information is entered into a surveillance database. Quarterly audits of this database identify incomplete fields. Data are gathered by several means, including direct chart review, the Indian Health Service’s computerized database, and telephone contact with medical records staff, as necessary.

**Laboratory Methods**

All received isolates were verified for serotype by the AIP laboratory in Anchorage. Subcultures of each isolate were reestablished on chocolate agar. \textit{H influenzae} was confirmed by Gram stain and factor V and X requirements (Differentiation Disks; Difco Laboratories, Detroit, Mich), and 2 reference samples of each specimen were stored at −70°C for future testing. Serotyping was conducted by slide agglutination (\textit{H influenzae} a-f typing antisera, Difco Laboratories). Isolates with discrepancies in serotype between the submitting and AIP laboratories were reanalyzed by the CDC Division of Bacterial and Mycotic Diseases in Atlanta, Ga, with the Atlanta results taking precedence for data purposes. Biotyping was conducted on 89 isolates using indole spot (Difco Laboratories) and urease and ornithine decarboxylase tests (BBL Microbiology Systems, Cockeysville, Md).

**Statistical Methods**

We compared the incidence of invasive \textit{H influenzae} between populations using $\chi^2$ tests. The Fisher exact test was used when variable counts were less than 5. The $\chi^2$ test for trend was used to assess the relationship between increasing age and mortality. When controlling for the possible confounding effects of age, the Mantel-Haenszel test was used.
RESULTS

A total of 129 cases of invasive H influenzae were reported in Alaskans aged 10 years and older during the 1980-1996 surveillance period. Isolates were available for 98 patients (76%) and chart review data for 84 patients (65%). Of the 31 isolates that were unavailable for serotyping, 26 (29.2%) of 89 were from 1980-1990 and 5 (12.5%) of 40 from 1991-1996. Of the 84 charts available for review, 58 (65%) and 26 (65%) were from patients presenting in 1980-1990 and 1991-1996, respectively. The Table shows the sex, ethnicity, age, residence, and serotype distribution for these 129 patients who had invasive H influenzae, stratified by period (1980-1990 vs 1991-1996). The cutoff between 1990 and 1991 was chosen to correspond with the introduction of statewide conjugate Hib vaccine use in children. Of 129 cases, 31 were in Alaska Natives (18 Eskimo and 13 Indian) and 98 were in nonnatives. The proportion of Alaska Native patients who had invasive H influenzae decreased significantly from 29% in the first period to 13% in the second (P = .046). The mean age of the patients with invasive H influenzae disease was 46.2 years, which did not vary by period or ethnic group. Patients ranged in age from 10 to 92 years, with 26% of invasive H influenzae disease occurring in persons aged 60 years and older. The age distribution of patients was similar between periods. Approximately 50% of patients were persons living in urban areas.

Of the cases of H influenzae disease in 1980-1990 for which serotype results were obtained, 67% (42/63) were Hib and 24% (15/63) were nontypeable. These proportions changed markedly in 1991-1996 (P < .001). In the latter period Hib accounted for only 14% (5/35) of patients for whom serotyping results were obtained, whereas nontypeable strains were responsible for another 54% (19/35) of patients. Of the non-b serotypes, serotype f was the most common, with 9 patients (5 in the childhood vaccine period), followed by serotype e (4 patients) and serotypes a and c (2 patients each).

Eighty-nine isolates were biotyped (20 [50%] of Alaska Natives and 69 [78%] of nonnatives). Thirty-six percent of isolates were biotype 1, and another 36% were biotype 2. Biotypes 3 and 4 made up 13% and 10% of isolates, respectively. Of the 100 isolates tested, b-lactamase was produced by 35%. Of 90 isolates that were both serotyped and analyzed for b-lactamase production, 38% (15/40) of Hib, 38% (6/16) of other serotypes, and 32% (11/34) of nontypeable isolates were b-lactamase positive. There were no detectable differences in the distribution of biotypes or isolates that were b-lactamase positive between the 2 periods.

The overall incidence of invasive H influenzae in our study population was 1.8 cases per 100 000 persons aged 10 years and older per year (95% confidence interval, 1.50-2.16), with Alaska Natives having a higher rate than nonnatives (2.97 vs 1.62; P = .01). The incidence of invasive H influenzae increased steadily with advancing age from 0.67 cases per 100 000 persons per year in individuals aged 10 to 19 years, to 6.15 cases per 100 000 per year in persons older than 60 years (P < .001). Figure 1 shows a comparison of all H influenzae disease incidence rates in Alaska residents between the study periods for the total population and stratified into Alaska Native and nonnative populations. The total disease burden of H influenzae in those aged 10 years and older was 33% lower in the latter period, when Hib vaccines were administered to children statewide, dropping from 2.1 to 1.4 cases per 100 000 persons per year (P = .03; Figure, A). The largest decrease (71%) was seen in the Alaska Native population in which the rates dropped from 4.2 to 1.2 cases per 100 000 persons per year (P = .005). This decrease was evident in the nonnative population as well, although the decrease in this group from 1.7 to 1.4 cases per 100 000 individuals per year did not reach statistical significance (P = .37).

As seen in Figure 1, B, rates of Hib fell dramatically during the second period. Overall Hib disease in those aged 10 years and older decreased 80% (P < .001). This decrease corresponded to declines in invasive Hib disease observed in Alaska Native and nonnative children younger than 10 years following the introduction of conjugate Hib vaccines in 1991 (Figure 2). Conversely, as seen in Figure 1, C, H influenzae disease attributable to non-b isolates (serotypes a, c, e, f, and nontypeable) increased in the latter pe-


**Figure 1.** Comparison of Incidence of Invasive *Haemophilus influenzae* Disease in Alaska Natives and Nonnative Residents Aged 10 Years and Older Before Childhood *H influenzae* Type b Vaccines (1980-1990) and During Vaccine Use (1991-1996)

<table>
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<th>Nonnative Population</th>
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<tr>
<td>1980-1990</td>
<td>2.1</td>
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<td>1991-1996</td>
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Mean rates are per 100,000 person-years.

**Figure 2.** Comparison of the Incidence of Invasive *Haemophilus influenzae* Disease in Alaska Native and Nonnative Children Younger Than 10 Years Before Childhood *H influenzae* Type b Vaccines (1980-1990) and During Vaccine Use (1991-1996)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Native Population</th>
<th>Nonnative Population</th>
</tr>
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<tbody>
<tr>
<td>1980-1990</td>
<td>75</td>
<td>189</td>
<td>19</td>
</tr>
<tr>
<td>1991-1996</td>
<td>47</td>
<td>4</td>
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Mean rates are per 100,000 person-years.

H influenzae disease rates decreased over time in Alaska Natives and non-natives living in both urban and rural areas of the state. However, this decline is statistically significant (P < .003) only for Alaska Natives living in rural areas.

Pneumonia was the most common presentation overall, accounting for 43% of cases of *H influenzae* disease, followed by sepsis (26%) and meningitis (16%). While the spectrum of disease presentations is similar in both periods, sepsis became a significantly more common presentation in the second period (18% in 1980-1990 vs 43% in 1991-1996; Mantel-Haenszel \( \chi^2 \), \( P = .03 \)).

Sixty-seven cases (80%) had at least 1 underlying medical condition. Alcohol or drug abuse was the most common comorbid state and was noted in 15% (13/84) of available charts. Serotypes of infecting organisms were available for 10 of these 13 patients; 80% of serotypes were Hib. Eleven women (13% of reviewed patients) with invasive *H influenzae* disease were pregnant at the time of their infection. Of these pregnant women, 5 presented with amnionitis and 6 with a sepsis of unknown focus. Isolates from 10 of these pregnant women were serotyped, revealing that 5 cases were caused by nontypeable strains, 4 by Hib, and 1 by serotype c. Other underlying states included chronic obstructive pulmonary disease (12%), diabetes mellitus (12%), malignancy (11%), chronic infection (10%), and trauma (10%). Five patients with an immune deficiency state, 3 with end-stage renal disease, and 2 with a previous splenectomy were also noted. There were no detectable differences between the 2 periods in the number of patients with comorbid conditions.

Mortality data were available for 123 of 129 patients with invasive *H influenzae* disease. Nineteen persons died during the course of their infection (case-fatality ratio [CFR], 15%). The total CFRs for those aged 10 years and older were similar in the earlier and later periods (16% and 14%, respectively; \( P = .92 \)). The CFR among Alaska Natives was 10%, compared with 17% among nonnatives (\( P = .39 \)). Those who died from their infections were older than those who survived (average age 62.4 and 43.3 years, respectively; \( P < .001 \)). The most common clinical presentation associated with mortality was pneumonia (11/19). Only 1 of these patients had chronic obstructive pulmonary disease. Overall, about 20% of *H influenzae* pneumonia and sepsis patients died, compared with less than 10% for other presentations (\( P = .05 \)). However, after adjustment for age this difference was no longer statistically significant (\( P = .15 \)). While nontypeable strains were associated with the highest mortality (21%), there were no significant differences in mortality by serotype (\( P = .61 \)).
COMMENT

Following the widespread introduction in 1991 of Hib vaccines in Alaska infants, the overall incidence of *H influenzae* in unimmunized persons aged 10 years and older decreased 33%, with the rate for Alaska Natives falling 71%. Most of the statewide reduction was caused by the 80% fall in Hib disease, supporting reports of declines in Hib disease in unvaccinated older children and adults in Scandinavia and England. This suggests that the adult disease burden of *H influenzae* may be a function of carriage in children and infants in the community. Studies both in the United States and elsewhere have documented a decline in Hib carriage in vaccinated children following widespread use of Hib conjugate vaccines. Similarly, the diminution of childhood Hib reservoirs in Alaska may explain the decline in Hib disease in older children, adolescents, and adults. However, a study in 1997 found Hib carriage rates of 9.2% in vaccinated Alaska Native children younger than 5 years living in 6 selected villages of rural western Alaska, while a subsequent study in 1998 in similarly aged Alaska Native children living in urban Alaska (Anchorage) showed considerably lower carriage rates (0.9%, R.J.S., unpublished data). These studies show that Hib carriage rates state-wide vary widely and may depend on population and environmental factors, such as household crowding and the presence of adequate sanitation, as well as on vaccination levels.

It has been suggested that lowered oropharyngeal competition from Hib organisms may create an ecological niche in which other *H influenzae* serotypes and nontypeable strains may flourish. Data appear to support this notion because the incidence of invasive *H influenzae* disease from non-b *H influenzae* in those aged 10 years and older increased from 0.5 to 1.1 cases per 100000 individuals per year after childhood Hib vaccines were introduced (P = .01). Enhanced surveillance of *H influenzae* in England, before and after the introduction of Hib vaccine programs in that country, also detected an increase in disease caused by nontypeable *H influenzae*. Thus, Hib vaccines may be indirectly exerting selective pressure that favors an increase in the prevalence of non-b *H influenzae* strain disease among adults. However, several studies in children have shown no difference in the carriage of non-b *H influenzae* strains relative to the vaccination status of the child. In Alaska, among children younger than 10 years, we have observed no increase in invasive disease caused by non-b *H influenzae* strains in the post–conjugate vaccine era. Thus, the reasons for the observed increase in disease caused by non-b *H influenzae* strains in persons aged 10 years and older is unknown. Continued surveillance for invasive disease and further investigation of carriage rates are needed to resolve this question.

Eighty percent of the individuals in our study who presented with an invasive *H influenzae* infection had 1 or more underlying conditions, a proportion similar to those reported in other studies. Alcohol or drug abuse was the most common comorbid state, occurring in 15% of patients. Of isolates from alcoholic individuals, 80% were Hib. We were impressed by the number of patients with invasive *H influenzae* infections who were pregnant (13%), nearly half of whom were infected with Hib. The clinical presentation in these women was divided between amnionitis (5 patients) and sepsis of unknown focus (6 patients). Previous studies have found nontypeable strains, especially biotype 4, to be the major cause of *H influenzae* genital infections. We did not see such an association as only 5 of our cases in pregnant women were caused by nontypeable strains and only 1 was biotype 4.

Mortality due to *H influenzae* was 15% throughout the study period. The apparent increase in nontypeable *H influenzae* as a cause of morbidity parallels the observation that these isolates also were associated with the highest mortality (21%). The potential lethality of nontypeable *H influenzae* species and their propensity to infect patients who have respiratory compromise are well documented.

As with any surveillance system, it is possible that cases were not reported. However, the active, multistep protocol was designed to minimize missed cases. More isolates were unavailable in the first period, probably reflecting an increased awareness by laboratories in the second period after implementation of Hib vaccine programs. However, this would tend to reduce differences in the 2 periods.

The overall rates of invasive *H influenzae* disease have declined in persons aged 10 years and older in Alaska after the introduction of infant vaccination programs, thus giving support for the continued use of the Hib vaccine in the currently recommended age groups. However, the increase of disease caused by non-b *H influenzae* strains calls for continued surveillance of all invasive *H influenzae* disease in Alaska and in other populations where Hib vaccines have proven successful in preventing invasive Hib disease in children.

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Funding/Support: Dr Perdue received fellowship support from the Minority Health Professionals Foundation and the Centers for Disease Control and Prevention.

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Acknowledgment: We thank Debra Parks, BS, Mary Anne Fitzgerald, MPH, and Helen Peters, RN, of the Arctic Investigations Program for their efforts on this project, and Joel Ward, MD, Center for Vaccine Research, Harbor-UCLA Medical Center, and George Brenneman, MD, who were instrumental in the inception of, and providing support for, the Alaska Hib Surveillance Project.

REFERENCES


H INFLUENZAE DISEASE AFTER INFANT VACCINATION PROGRAMS


