Reemergence, in Southwestern Alaska, of Invasive *Haemophilus influenzae* Type b Disease Due to Strains Indistinguishable from Those Isolated from Vaccinated Children

Lynne A. Lucher,1* Michael Reeves,2 Thomas Hennessy,1 Orin S. Levine,2 Tanja Popovic,2 Nancy Rosenstein,2 and Alan J. Parkinson1

*Haemophilus influenzae* type b (Hib) invasive disease and oropharyngeal carriage continue in rural Alaska despite widespread vaccination. This study investigated whether invasive-disease reemergence during 1996–1997 could be attributed to strains distinguishable from strains carried by vaccinated children. Twenty-four invasive and 42 carriage Hib isolates, collected during 1992–1997, were characterized by pulsed-field gel electrophoresis (PFGE), multilocus enzyme electrophoresis, and biotyping. This Hib population was highly clonal, since only 2 strains, electrophoretic type (ET) 55/PFGE 1 and ET 56/PFGE 3, accounted for 62% of all isolates. The ET 55/PFGE 1 and ET 56/PFGE 3 strains were found in 74% of the carriers and caused 80% of the invasive Hib disease that occurred during April 1996–March 1997. Strains causing invasive disease could not be distinguished from strains carried by vaccinated children. Continued monitoring of Hib carriage may provide insights into the epidemiology of continued transmission in an era of widespread vaccination.

*Haemophilus influenzae* type b (Hib) invasive disease and oropharyngeal (OP) carriage rates in young children have dramatically declined where vaccination programs have been implemented [1–3]. Nevertheless, some vaccinated populations with historically high rates of Hib disease and OP carriage, such as American Indians, Alaska Natives, and Australian Aborigines, continue to experience significant OP carriage of Hib [4–6]. Invasive Hib disease among both Alaska Native and non–Alaska Native children and adults declined dramatically after Alaska began a statewide immunization program against Hib in January 1991, using the polysaccharide conjugate vaccine PRP-OMP (PedvaxHib) [7]. In January 1996, the program began using the vaccine HbOC plus DTP (Tetramune) to reduce the number of immunizations that infants received during any 1 visit to a clinic. Unlike PRP-OMP, a single dose of HbOC generally does not elicit protective levels of antibody in infants since only 2 strains, electrophoretic type (ET) 55/PFGE 1 and ET 56/PFGE 3, accounted for 62% of all isolates. The ET 55/PFGE 1 and ET 56/PFGE 3 strains were found in 74% of the carriers and caused 80% of the invasive Hib disease that occurred during April 1996–March 1997. Strains causing invasive disease could not be distinguished from strains carried by vaccinated children. Continued monitoring of Hib carriage may provide insights into the epidemiology of continued transmission in an era of widespread vaccination.

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*Subjects.* Since 1980, the Arctic Investigations Program (AIP) has monitored invasive *H. influenzae* disease in all Alaska residents [10, 11]. Twenty-three microbiology laboratories in hospitals and other medical facilities voluntarily participate by submitting all *H. influenzae* type b (Hib) invasive disease and oropharyngeal carriage isolates, collected by pulsed-field gel electrophoresis (PFGE), multilocus enzyme electrophoresis (MEE), and biotyping, at the time of disease reemergence, 1996–1997.
The identity of all invasive and carriage Hib isolates was determined by plating oropharyngeal swabs onto Hib antiserum agar [15]. The identity of all invasive and carriage Hib isolates was determined by plating oropharyngeal swabs onto Hib antiserum agar [15].

**Table 1.** Age and ethnicity of patients with invasive disease and of carriers from whom *Haemophilus influenzae* type b isolates were collected.

<table>
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<tr>
<th>Age, years</th>
<th>Invasive</th>
<th>Carriage</th>
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<td>Alaska Native</td>
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<tr>
<td>Total</td>
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<td>6 (25)</td>
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*a* Non-Native Alaskans were not sampled for carriage. —, Not sampled for carriage.

**Invasive** isolates to AIP for confirmation of identity, serotyping, and evaluation of antimicrobial susceptibility. To maximize the completeness and sensitivity of case identification, AIP personnel conduct case reviews at the participating facilities, examine State of Alaska Section of Epidemiology disease-surveillance data, and monitor Alaska death-certificate data [12].

This study covers a 5-year surveillance period, April 1992–March 1997. Alaska’s estimated population on 1 July 1997 was 611,300, with an ethnic composition of 74.2% white, 16.7% Alaska Native, 4.6% Asian and Pacific Islanders, and 4.5% black [13]. Seventy-five percent of the population resides in 5 urban centers, while the remaining residents occupy small communities widely dispersed across much of Alaska’s 586,412 square miles.

*Hib isolates.* A total of 66 Hib isolates were available for this study (table 1). Twenty-four isolates were from cases of invasive Hib disease, defined as acute disease yielding Hib from a normally sterile body site (typically, blood or cerebrospinal fluid); these isolates, from laboratories throughout Alaska (figure 1), represented 96% of the 25 known cases of invasive Hib disease during April 1992–March 1997; 14 of these 24 isolates were collected prior to the vaccine change to HibOC in January 1996, whereas the remaining 10 isolates were collected after the vaccine change. Forty-two isolates were cultured from the throats of healthy Alaska Native children who participated in the voluntary Hib carriage survey performed during April–May 1997 in the YKD, in response to the dramatic increase in invasive disease in that region [14]. Hib was isolated by plating oropharyngeal swabs onto Hib antiserum agar [15]. The identity of all invasive and carriage Hib isolates was confirmed by determination of X- and V-factor requirements for growth and by serotyping by slide agglutination [16]. Isolates were stored in 20% skim milk at −80°C.

**PFGE.** Each Hib isolate was grown, from frozen aliquots, on chocolate-agar plates and was subcultured ≥3 times from a single isolated colony prior to creation of plugs. Plugs containing Hib cells were prepared, and the cells were lysed by lysozyme and proteinase K, by means of a bacterial plug kit (Bio-Rad Laboratories), according to the manufacturer’s directions with the following modifications: (1) cells were collected from overnight chocolate-agar plates by cotton swabs and were expressed, at high concentration, into 0.85% NaCl; (2) aliquots were diluted with cell-suspension buffer and were mixed with melted CleanCut agarose (Bio-Rad Laboratories) to contain ~2.5 × 10^8 cfu/mL, on the basis of turbidity determined by an A-just Turbidity Meter (Abbott Laboratories); and (3) plugs were digested overnight at 25°C by SmaI (New England BioLabs) at 120 U/mL, with 100 μg of bovine serum albumin/mL included in the restriction buffer.

PFGE was performed on SmaI-digested plugs by a CHEF-III unit (Bio-Rad Laboratories). Gels of 1% SeaKem ME agarose (FMC Corporation) were prepared and presoaked overnight at 4°C in an excess of running buffer (0.5 × TBE [45 mM Tris, 45 mM borate, and 1 mM EDTA] pH 8.3). After the plugs were loaded, electrophoresis was performed with an initial pulse time of 1 s, final pulse time of 40 s, and a field angle of 120°, at 6 V/cm, for 22 h at 14°C. Plugs containing a mixture of lambda DNA-HindIII fragments and lambda concatemers (New England BioLabs) were included on each gel, as molecular-weight standards. Ethidium bromide–stained gels were visualized on a computer screen by a Gel Doc-1000 unit (Bio-Rad Laboratories), and the images were captured by MultiAnalyst software version 1.1 (Bio-Rad Laboratories). Band-based cluster analysis of the band patterns was performed on the captured images by Molecular Analyst Fingerprinting Plus software version 1.12 (Bio-Rad Laboratories), with the lambda ladder lanes being defined as reference lanes. Pairwise pattern comparisons were made by the Dice coefficient (2 times the number of bands shared, divided by the total number of bands in both lanes), 1.6% band tolerance, alignment optimization, and the UPGMA (unweighted pair-group method using arithmetic averages) clustering method. These settings were determined empirically to maximize 100% similarity scores for several identical samples run on multiple gels. Patterns that differed by either 1 band (93%–96% similarity) or 2 bands (87%–92% similarity) were considered to be potentially epidemiologically related, whereas patterns differing by ≥3 bands (<87% similarity) were considered to be epidemiologically unrelated [17, 18]. Each cluster of similar patterns was assigned an arabic numeral.

**MEE.** Bacterial-cell extracts were prepared, and MEE analysis of 22 enzymes was conducted in 11.5% starch at pH 8.0, as described elsewhere [19]. The genetic relatedness of the electrophoretic types (ETs) was shown as a dendrogram, which was generated by the average-linkage method of clustering [20], by an SAS macro program [21]. Hib strains of ET 1.9, ET 12.5, ET 12.8, and ET 25.6, as previously proposed by Musser [22], were included as reference strains in the analysis. Genetic-distance values >0.3 were considered to be major Hib clusters, whereas ETs with genetic-distance values ≤0.15 were considered to be closely related [22, 23].

**Biotyping of Hib isolates.** Isolates were biotyped by a Minitek system (BioQuest), to detect both the ability of isolates to produce indole and the presence of ornithine decarboxylase and urease activities [24].

**Statistical methods.** Associations between categorical variables were evaluated by the χ^2^ test, by either EpilInfo software version 6.04 [25] or SAS version 6.11. Two-sided P values are reported and represent either the Yates correction for bivariate comparisons or the results of Fisher’s exact test.

**Results**

**Molecular subtyping of Hib isolates.** PFGE typing of all 66 Hib isolates yielded 21 different PFGE patterns produced...
Figure 1. Regional submission of isolates from cases of invasive *Haemophilus influenzae* type b (Hib) disease that occurred during April 1992–March 1997. For each region, the estimated population (as of July 1997), the number of invasive isolates analyzed in the study, and the disease incidence during the 1996–1997 reemergence of Hib invasive disease are provided. The Yukon-Kuskokwim Delta area of southwestern Alaska is enlarged to show the villages that participated in the 1997 Hib-carriage survey.

by *Sma*I. Each pattern contained 10–14 bands that were 10–500 kb in size. Isolates exhibited the same pattern even after multiple subcultures had been characterized. At the 87%-similarity breakpoint, these patterns were categorized into 11 major PFGE clusters (figure 2). Five of the PFGE clusters contained 2–6 related patterns each, whereas the remaining 6 PFGE clusters each contained only 1 pattern. Cluster 1 contained 47% of all Hib isolates and 29% of the PFGE patterns.

The Hib isolates were separated, by MEE, into 18 different ETs (figure 3). The ET distribution among the isolates was highly skewed, with 2 closely related ETs (ET 55 and ET 56) accounting for 68% of all isolates.

Most of the Hib isolates were identified as either biotype I (31/66 [47%]) or biotype IV (32/66 [48%]); the remaining isolates (3/66 [5%]) were biotype II.

*Genetic structure of the Hib isolates.* The Hib strains in this study were highly clonal, as demonstrated by the similarity of ETs (figure 3). Most ETs were found within 2 clusters separated by a genetic distance of <0.15. One cluster contained 54 (82%) of the Hib isolates and 10 (56%) of the ETs, whereas the other contained 5 (7.5%) of the isolates and 4 (22%) of the ETs.

Determining, for each ET, the association between biotype and PFGE pattern put the other typing results into a more defined genetic context (figure 3). Biotyping showed variation in isolates of ET 52 and ET 55, and PFGE typing revealed variation in isolates of ET 52, ET 55, and ET 56. None of the biotypes or the more common PFGE patterns (i.e., those found in ≥4 isolates) was associated exclusively with a single ET. Nevertheless, the following typing characteristics were significantly associated: ET 55 with biotype IV ($\chi^2 = 51$, $P < .001$), ET 55 with PFGE cluster 1 ($\chi^2 = 41$, $P < .001$), and ET 56 with PFGE cluster 3 ($\chi^2 = 41$, $P < .001$). In addition, all ET 55/PFGE 1 isolates were biotype IV, and all ET 56/PFGE 3 isolates were biotype I.

*Temporal distribution of Hib isolates having specific molecular-subtype combinations.* To more fully characterize the reemer-
of invasive Hib disease during 1996–1997, we investigated the distribution, by time of isolate collection, of combinations of Hib molecular subtypes (table 2). Each of the 14 invasive Hib isolates collected during April 1992–March 1996 exhibited a unique ET/PFGE molecular-subtype combination; however, 80% (8/10) of the invasive Hib isolates collected during April 1996–March 1997 were of only 2 molecular-subtype combinations—ET 55/PFGE cluster 1 and ET 56/PFGE cluster 3 (χ² = 8, P < .01)—as were 74% of the carriage isolates collected during April 1997–May 1997.

Distribution, by village, of Hib isolates having specific combinations of molecular subtypes. The YKD was the source of 8 of the invasive isolates and of all of the carriage isolates. In terms of ET or PFGE pattern, the isolates were nonrandomly distributed among the residents of 11 YKD villages (P < .001 for each) (table 3). Isolates with the ET 55/PFGE 1 molecular-subtype combination tended to be associated with village J (χ² = 8, P < .01), where isolates with this molecular-subtype combination were found both in carriers and in patients with invasive disease. Isolates with the ET 56/PFGE 3 molecular-subtype combination were primarily from village F (χ² = 24, P < .001), which was the source of both carriage isolates and invasive isolates with this molecular-subtype combination; 2 other invasive isolates having the ET 56/PFGE 3 molecular-subtype combination were from village D, which has close transportation ties to village F.

Discussion

During the 4 years prior to the January 1996 vaccine change from PRP-OMP to DTP/HbOC, an average of 3.5 cases of invasive Hib disease occurred each year in Alaska. Of the 14 cases that occurred prior to the vaccine change, 3 (21%) occurred in the YKD. In the year following the vaccine change, 10 cases occurred, 5 (50%) of which occurred in patients from the YKD, prompting the carriage survey and analysis of isolates reported in this study.

Our data indicate that the increased incidence of invasive Hib disease in Alaska during April 1996–March 1997 resulted primarily from infection by 2 closely related strains. These strains were first detected among invasive isolates recovered during August (ET 56/PFGE 3) and December (ET 55/PFGE 1) of 1995 and accounted for 80% of the cases during April 1996–March 1997. These findings contrast with the prior 4-year period, during which all cases were caused by strains exhibiting unique molecular-subtype combinations.

Some Hib biotypes, ETs, and outer membrane–protein subtypes can be found among both carriage and invasive isolates, often with little difference in frequencies [22, 26, 27]. Indeed, in the YKD, strains with the ET 55/PFGE 1 and the ET 56/PFGE 3 molecular-subtype combinations were predominant among both carriers and persons with Hib disease. More-frequent carriage surveys during the surveillance period covered by the present study may have helped to clarify transmission patterns.

Previous study of an international collection of 1975 Hib isolates analyzed by MEE, using 17 loci, found the genetic structure of capsulated H. influenzae to be highly clonal [22]. These isolates included 481 from the contiguous 48 states of the United States, as well as 87 collected in Alaska during the early 1980s. In that study, Hib isolates were distributed among 4 genetic lineages: 93% of the Hib isolates were assigned to genetic lineage A, which also contained 78% of the 182 ETs characteristic of Hib. Genetic lineage A also contained 95% of the Alaskan strains included in the present study. The 2 predominant ET clusters within lineage A were designated “A1” and “A2” and included all but 3 lineage-A ETs. We analyzed several Hib strains from the international study and included them, as reference ETs, in the ET dendrogram. The positions of these strains (figure 3) suggest that the strains of the 2 predominant ET clusters that we observed correspond to clusters A1 and A2 within lineage A [22]. Furthermore, 92% of the isolates that we analyzed fell within genetic lineage A (54 in cluster A1 and 7 in cluster A2), a distribution similar to that of the Alaskan isolates included in the international study. Dendrograms generated in both the international study and our study also show that a small number of isolates have ETs that
Figure 3. Multilocus enzyme electrophoretic types (ETs) observed among invasive and carriage Haemophilus influenzae type b (Hib) isolates. The dendrogram illustrates the relationships among the ETs, according to the genetic distance scale (top). Included are the positions of Hib reference strains having ET 1.9, ET 12.5, ET 12.8, and ET 25.6. These strains were assigned the following lineage positions by Musser et al. [22]: cluster A1, ET 1.9; cluster A2, ET 12.5 and ET 12.8; and lineage B, ET 25.6. The dendrogram was constructed with 54 total ETs; only the ETs found among Alaskan isolates and Hib reference-strain ETs are shown. Associations are as follows: ET 55 and biotype IV, \( \chi^2 = 41, P < .001 \); ET 55 and PFGE cluster 1, \( \chi^2 = 51, P < .001 \); and ET 56 and PFGE cluster 3, \( \chi^2 = 41, P < .001 \). N, number of isolates of each ET; BT, biotypes observed within each ET; PFGE, pulsed-field gel electrophoresis (PFGE) pattern cluster numbers observed within each ET.

are separated from the lineage-A ETs by a genetic distance >0.6. The reference ET isolates were collected during the pre–Hib vaccine era and were compared to isolates collected during widespread use of vaccine. Thus, in Alaska, the overall genetic structure of Hib, as analyzed by MEE, does not appear to have been significantly influenced by vaccine-selection pressure.

The genetic structure of Hib has also been demonstrated to be clonal by PFGE alone; in a study of Australian Hib isolates collected during the prevaccine era, SmaI PFGE patterns were clustered into 7 highly divergent genetic groups [28]. Group A contained 47% of the 187 isolates and 55% of the 67 PFGE patterns. Although the size of our sample was smaller, our results were very similar, as reflected by the PFGE pattern distribution that we observed, in which 1 PFGE cluster contained 47% of the Hib isolates and 29% of the PFGE patterns.

Although the overall genetic structure appears to have remained unchanged over time, the biotypes of Alaskan Hib isolates may have changed. Of the 111 invasive isolates collected statewide during 1980–1982, 86% were biotype I, 11% were biotype II, and 4% were biotype IV [10]. In the present study, of 24 invasive isolates collected statewide, 67% were biotype I, 12% were II, and 21% were IV. Biotype IV was not detected among 27 carriage Hib isolates collected from 4 YKD villages during 1982–1983 [29] but accounted for 64% of the YKD carriage isolates in the present study.

Since only 4 biotypes are routinely found for Hib, biotyping has low discriminatory power and is of limited epidemiological value [30]. However, both MEE and PFGE analysis provide a high degree of discriminatory power and typeability for Haemophilus species [31]. Among the Hib isolates in our study, we found some correlations between ET and PFGE pattern, but we also found PFGE patterns 1, 3, and 4 occurring both in genetic lineage A and in the more distant ET 52 and ET 53. Generating PFGE patterns by using 2 or 3 restriction endonucleases per isolate might have increased the ability of PFGE to distinguish between the different Hib genetic backgrounds that were determined by MEE.

The cluster of cases that occurred during April 1996–March 1997 could have been related to the emergence of an Hib strain having increased transmissibility or virulence characteristics. Although associations have been shown between some Hib strains and disease states or carriage [22, 26, 32], we did not detect, among the isolates from the YKD, an association between Hib strain and either disease or carriage. The small size of our sample may have contributed to our inability to detect any such associations. Similarly, among the isolates from the
Table 2. Distribution of *Haemophilus influenzae* type b (Hib) multilocus enzyme electrophoretic type (ET) and pulsed-field gel electrophoresis (PFGE) molecular-subtype combinations, by time of isolation, in Alaska overall and in the Yukon-Kuskokwim Delta (YKD) region.

<table>
<thead>
<tr>
<th>ET cluster</th>
<th>No. of invasive Hib isolates</th>
<th>Year 1 (April 92–March 93)</th>
<th>Year 2 (April 93–March 94)</th>
<th>Year 3 (April 94–March 95)</th>
<th>Year 4 (April 95–March 96)</th>
<th>Year 5 (April 96–March 97)</th>
<th>YKD carriage Hib (April 97–May 97)</th>
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YKD, there were significant village-level differences in strain distribution, as previously had been shown by an analysis of carriage Hib isolates in the YKD [29]. However, we were not able to detect any regional differences in the occurrence of invasive Hib strains across Alaska, because of the small number of isolates from patients from outside the YKD.

In response to the increase in cases of invasive Hib disease after the January 1996 vaccine change from PRP-OMP to DPT/HbOC, a mixed schedule including PRP-OMP for the first dose and HbOC for all subsequent doses was implemented for Alaska Native children during July 1996 [14]. Although the incidence of Hib disease has decreased in Alaska, the rate of Hib disease...
and carriage in the YKD has not decreased to the same extent as it has in non–Alaska Natives and in urban Alaska Natives. This is in contrast to the results found in other Native American groups. Millar et al. [33] found only a single carrier (a 0.3% carriage rate) among 381 Navajo and White Mountain Apache children in a survey during October 1998–June 1999. The carriage rate for Alaska Native children in the YKD was 5%–7% during the prevaccine era [29, 34] and was 9.3% in 1997 [5]. Whether the rate remained the same during the intervening years or was affected in any way by the January 1996 vaccine change to DTP/HbOC is not known.

The observation of higher rates of Hib carriage and disease among children in the YKD highlights the need both to maintain surveillance for invasive Hib disease and to develop more-effective strategies for elimination of Hib colonization in this population. The continued monitoring of Hib carriage, together with the use of molecular-typing methods, may provide insights into the epidemiology of transmission in an era of widespread vaccination.

Acknowledgments

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