Invasive *Haemophilus influenzae* Disease in Utah Children: An 11-Year Population-Based Study in the Era of Conjugate Vaccine

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**Background.** The incidence of invasive *Haemophilus influenzae* infection decreased dramatically since the introduction of the *H. influenzae* serotype b (Hib) conjugate vaccine. *H. influenzae* invasive disease continues to occur and cause significant morbidity and mortality in children aged <5 years. We aimed to report the epidemiology and serotypes of invasive *H. influenzae* disease in children from Utah in the post–Hib vaccine era.

**Methods.** We identified all cases of invasive *H. influenzae* disease, defined as *H. influenzae* isolated from a sterile site, during the period 1998–2008 among children aged <18 years who were living in Utah.

**Results.** We identified 91 cases of invasive *H. influenzae* disease in children. Children aged <5 years accounted for 78 cases (86%). *H. influenzae* serotype a (Hia) was the most common serotype (22 cases), representing 28% of all cases of invasive disease among children aged <5 years. The majority (15 cases [93%]) of Hib disease cases occurred among children aged <5 years and accounted for 18% of all cases of *H. influenzae* invasive disease in this age group. The mean incidence of Hia disease increased from 0.8 cases per 100,000 child-years in 1998 to 2.6 cases per 100,000 child-years in 2008. The incidence of Hib disease among children aged <5 years remained steady at 0.5 cases per 100,000 child-years. Bacteremia accounted for 61% of all cases of invasive disease. One-half (13 of 26) of cases of *H. influenzae* meningitis were due to Hia.

**Conclusions.** *H. influenzae* continues to cause invasive disease in Utah children. Hia is the primary cause of the overall increased incidence of invasive *H. influenzae* disease and leads to disease similar to Hib. Isolated cases of Hib disease demonstrate a continued reservoir. The success of the Hib conjugate vaccine may therefore be vulnerable to vaccine shortages and refusal of vaccination.

*Haemophilus influenzae* capsular serotype b (Hib) causes severe invasive disease in infants and children. Prior to the widespread use of Hib conjugate vaccine in 1990, *H. influenzae* was the most common cause of bacterial meningitis in children in the United States and led to significant morbidity and mortality [1–4]. The incidence and impact of invasive *H. influenzae* disease decreased dramatically with the Hib vaccine [1, 5–8]. The majority of illness now seen in the United States and other developed countries is due to capsular serotypes other than b and to nontypeable strains [5–15]. *H. influenzae* type a (Hia) has been increasingly noted as a cause of severe disease among children [5, 9, 12, 14–17].

Recent clusters of invasive Hib infection among children in Minnesota [18] and Pennsylvania in the midst of Hib vaccine shortages in the United States [19] and increasing vaccine hesitancy in the community highlight the need for ongoing surveillance of invasive disease due to *H. influenzae*. In this article, we describe the epidemiology of invasive *H. influenzae* infection in Utah children during the period 1998–2008.

**PATIENTS AND METHODS**

**Human subjects protection.** Approval for this study was obtained from the Institutional Review Board of the University of Utah, Intermountain Healthcare, and
Utah Department of Health. Informed consent was waived, because all data were de-identified.

**Study design and population.** We conducted a retrospective, population-based study using multiple sources of data, covering the period 1998–2008. We identified all cases of invasive *H. influenzae* disease, a reportable condition, reported to the Utah Department of Health. We further identified cases of laboratory-confirmed invasive *H. influenzae* infection in Utah children aged <18 years using the Intermountain Healthcare computerized microbiology database. More than 75% of pediatric inpatient care in Utah is provided by Intermountain Healthcare hospitals. The identified cases were compared, and the data sets were combined. Finally, we queried the Utah hospital discharge database for the frequency of hospital discharges and deaths coded with the *International Classification of Diseases, 9th Edition*, codes for septicemia due to *H. influenzae* (038.41) and *H. influenzae* meningitis (320.0).

**Case definition.** We defined patients as Utah residents aged <18 years with invasive disease due to *H. influenzae*. Invasive disease was defined according to the Centers for Disease Control and Prevention definition: a clinically compatible case that is confirmed by isolation of *H. influenzae* from a normally sterile site, such as blood, cerebrospinal fluid, joint fluid, pleural fluid, or pericardial fluid [20].

**Clinical and outcome data.** We abstracted demographic and clinical data from the paper and electronic medical records using a standardized data collection tool. Clinical data for cases before 2003 were limited.

**Capsular serotyping.** *H. influenzae* isolated from sterile sites (blood, cerebrospinal fluid, or—less commonly—joint, pleural, or pericardial fluid specimens) was identified on the basis of standardized culture techniques. Laboratories are requested to submit sterile site isolates of *H. influenzae* to the Utah Public Health Laboratory (Salt Lake City) for serotyping. Strains identified in regional laboratories were confirmed at the Utah Public Health Laboratory using monovalent anti-sera. However, not all isolates were confirmed by all laboratories. Strains were classified by capsular type (a–f), as encapsulated non-b (if encapsulated on the basis of colony morphology and microscopic appearance, nonreactive to monovalent anti-sera for type b, but not further characterized), not typed, or nontypeable.

**Molecular characterization of *H. influenzae* type a.** We further characterized 10 of the 12 Hia isolates from 2006–2008 by pulsed-field gel electrophoresis (PFGE). Genomic analysis was performed by standardized pulsed-field gel electrophoresis following restriction digest using *Smal* (ARUP Laboratories). Relatedness was determined on the basis of criteria developed by Tenover et al [21].

**Statistical analysis.** To calculate incidence, we used annual, age-specific population estimates based on the United States 2000 census [22]. Hib vaccine use from 1998 through 2007 was derived from surveys conducted by the Utah Department of Health and the Centers for Disease Control and Prevention [23]. Stata statistical software, version 10.0 (StataCorp) was used for the calculation of the descriptive statistics.

**RESULTS**

**Patient demographics.** We identified 91 cases of invasive *H. influenzae* in children <18 years old in Utah from 1998 through 2008. Thirty seven (41%) of the children were male (P > 0.2); there were no differences in gender distribution by serotype (results not shown). The median age was 11.1 months (interquartile range [IQR], 3.3–12.4 months) (Table 1). Children <5 years old accounted for 78 (86%) of cases.

**Capsular serotype in children aged <5 years.** Of the 78 *H. influenzae* invasive isolates identified in children aged <5 years, 59 (76%) were partially or completely typed (Table 1 and Figure 1). Of these, 5 isolates were encapsulated but not type b and were not further typed.

Hia was the most common serotype among children aged <5 years during the study period. Children with Hia infection were more likely to be <5 years old (P = .03, by the Fisher exact test), compared with children infected with nontypeable *H. influenzae*. The 22 Hia isolates represented 28% of cases of invasive disease in this age group and 41% of fully characterized organisms.

The vast majority (15 cases [93%]) of Hib disease cases occurred in children aged <5 years. Hib accounted for 18% of all *H. influenzae* invasive disease in this age group. We identified 2 cases involving serotype c, 1 case involving serotype d, and 3 involving serotype f. No invasive disease due to serotype e was identified during the study period.

**Temporal trends and incidence.** The mean incidence of *H. influenzae* invasive disease among children aged <5 years was 3.0 cases per 100,000 child-years over the 11-year study period. Taking all encapsulated isolates into account, the mean incidence was 1.8 cases per 100,000 child-years (Figure 2).

The number of children aged <5 years with invasive disease due to Hia increased from 4 over a 5-year period (1998–2002) to 15 in the last 5 years of the study (2004–2008). The overall incidence of Hia among children aged <5 years was 0.8 cases per 100,000 child-years. However, in the final 2 years of the study, the incidence increased to 1.5 and 2.6 cases per 100,000 child-years, respectively.

Invasive disease due to Hib was seen throughout the study period, occurring in 8 of 11 years. The mean incidence of invasive Hib disease among children aged <5 years in our study was 0.5 cases per 100,000 child-years (Figure 2). This rate remained stable over the time period. The reported incidence of invasive Hib disease nationally was estimated to be 0.11 cases per 100,000 child-years in 2007 [19].

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NOTE. Data are no. (%) of patients. CSF, cerebrospinal fluid.

Outcomes. Seventy-five children (82%) required hospitalization (Table 1). These patients spent a median of 7.1 days (interquartile range, 3.3–12.2 days) in the hospital. Children with Hia and Hib infection spent a median of 10 days (interquartile range, 3.9–15.1 days) and 8 days (interquartile range, 4.1–11.0 days) in the hospital, respectively. One-half (13 of 26) of cases of *H. influenzae* meningitis were due to Hia. One 22-month-old boy died in the emergency department; *H. influenzae* was isolated from his blood but was not typed. The estimated Hib vaccine coverage was >90% throughout the study period and was comparable to national estimates (results not shown).

Hia molecular epidemiology. Of the 10 available Hia isolates from the last 3 years of the study, 8 fell into 2 clonal groups. Five of the isolates composed 1 distinct clone.

DISCUSSION

The introduction of Hib conjugate vaccine in 1990 reduced the incidence of invasive *H. influenzae* disease among children from
roughly 41 cases per 100,000 child-years to <2 cases per 100,000 child-years by 1993 and 0.11 cases per 100,000 child-years in 2007 in the United States [1, 19, 24]. We observed that *H. influenzae* still contributes a substantial disease burden in Utah children, predominantly due to Hia. A consistent but low level of Hib disease also remains in the population. Although we are no longer seeing the amount of devastating disease caused by Hib, Hia disease appears to be becoming more common and has similar outcomes to Hib infection.

The majority of invasive disease due to *H. influenzae* in recent studies among children was caused by non-b capsular types [8, 10, 14]. In a study of 5 years of experience at 12 Canadian IMPACT centers, McConnell et al [8] found that 40 (27%) of 147 isolates of invasive *H. influenzae* were non-b encapsulated serotypes, and 47 (32%) were nontypeable. Likewise, in 7 years of surveillance data from Manitoba, Canada, an area with little change in the incidence of *H. influenzae* since the introduction of vaccine, Tsang et al [14] reported that non-b serotypes accounted for the majority of invasive disease in both children and adults.

Much of the increase we observed in invasive *H. influenzae* infections was due to capsular serotype a. With the dramatic reduction in disease due to Hib among young children, Hia has increased in relative importance in many populations [14, 16, 17]. What is less apparent is whether there has been widespread increase in the absolute incidence and whether this represents partial serotype replacement. Hia was noted to cause severe disease among children in the Navajo and White Mountain Apache tribes of the US Southwest in the prevaccine era [2, 17, 25]. Millar et al [17] reported that the overall incidence of invasive Hia disease among Navajo and White Mountain Apache children from 1998 to 2003 was 20.2 cases per 100,000 children aged <5 years, but the rate did not increase significantly after the introduction of the Hib vaccine. The rate of Hia invasive disease remains high among children in the North American Arctic (29 cases per 100,000 child-years among children aged <2 years and 56 cases per 100,000 child-years among indigenous children) [16]. More than one-half of cases of invasive *H. influenzae* disease in these regions are due to Hia. However, without pre–vaccine era Hia surveillance, it is not clear whether the rate is higher than in the prevaccine era. Data from the Active Bacterial Core surveillance program suggest that the incidence of invasive disease due to non-type B *H. influenzae* is stable in the continental United States [26].

Outbreaks of invasive infection due to Hia have been reported in Utah and Alaska [5, 9]. During 1998–1999, we described 5 cases of severe disease in infants [5]. Several strains carried the putative virulence determinant, the IS 1016-bexA deletion. However, no subsequent infections were detected in Utah in the next 3 years. This suggests there was not true strain replacement. In a more recent study from Alaska, a cluster of 5 cases of invasive Hia disease was investigated [9]. The investigators also documented colonization with an indistinguishable strain of Hia in 16% of contacts of 2 cases [9]. Sustained transmission did not occur.

Taken as a whole, the experience with Hia demonstrates that it is capable of causing severe disease among young children, and in most areas, it has become more prevalent than Hib. However, there is no convincing evidence of sustained increases or that earlier concerns about strain replacement have been realized to date. How then do we interpret the incidence data for Hia in the Utah population over recent years? Earlier isolates were not available for molecular typing, but the recent increase appears to be due to 2 distinct clonal types. This is in accordance with...
with the North American Arctic isolates of Hia, which were all found to be closely related based on pulsed-field gel electrophoresis [16]. In contrast, another recent study from Canada demonstrates wide genetic diversity among 4 Hia isolates [27]. It is unclear whether the observations in Utah represent a transient increase, such as the one we observed in 1998–1999 [5], or will instead be a sustained increase.

Invasive disease due to Hib persists at low levels despite almost 2 decades of a successful vaccination program. Recent clusters of invasive Hib disease in Minnesota and Pennsylvania during a period of Hib vaccine recall and shortage suggest that as long as a reservoir of Hib carriage persists, the protection afforded by vaccine may be sensitive to modest changes in coverage.

The incidence of Hib disease in Utah appears to be consistently higher than the average incidence in the United States, despite comparable vaccination rates, suggesting a continued reservoir in Utah. The reasons for this are unclear. Utah has the highest birth rate (21 cases per 1000 total population) and largest household size in the United States [28]. There are some Utah communities with high rates of vaccine hesitancy; however, cases were not clustered geographically in these areas alone. The incidence of Hib disease is higher among persons of Native American and Alaskan Native descent. Although 6 Native American tribes live in Utah, cases were not concentrated among these children either.

A recent study from the United Kingdom demonstrated a point prevalence of Hib carriage of 4.2% (95% confidence interval, 2.5%–5.9%) among children aged 6–16 years in a highly vaccinated population [29]. They concluded that school-aged children who received 3 doses of the Hib vaccine remain a reservoir for Hib. We have not studied the rate of Hib carriage in Utah children, but the consistent number of incident cases suggests that some degree of carriage persists.

The current study has some limitations. Although we used several methods to improve completeness of ascertainment in a passive reporting system, we may under represent the true burden of disease. A recent study from Spain demonstrated 87.8% sensitivity of passive reporting of invasive H. influenzae in children aged <5 years [30]. In 2005, the Utah state passive reporting system was enhanced to improve reporting practices through an educational program. The Intermountain Healthcare data, which was unaffected by the changes in state surveillance, demonstrate the same trends. State discharge and death codes were much less helpful; less than one-half of known cases could be identified, and no additional cases were found using these sources. As in other studies, not all encapsulated non–type b isolates were fully characterized, and 19 isolates were not typed at all. Although the polyvalent slide agglutination assay is an accepted method [31], serotype-specific polymerase chain reaction assays may improve the accuracy of capsular serotyping [13, 32]. Finally, vaccination records were not available for children with Hib.

The striking drop in morbidity and mortality brought about by Hib conjugate vaccine may be less apparent with increases in invasive disease due to other serotypes. We observed an increase in the incidence of invasive disease primarily due to Hia leading to severe disease and outcomes resembling those of Hib. The incidence of Hib in Utah remains low but is 5-fold higher than the national average. These continued cases of Hib disease demonstrate the existence of reservoirs within the community. The success of the Hib conjugate vaccine may therefore be vulnerable to vaccine shortages and immunization refusal.

Acknowledgments

We are indebted to the Primary Children’s Medical Center, Intermountain Healthcare, and all Utah hospitals microbiology laboratories for their continued efforts in H. influenzae isolation. Special thanks also to the H. influenzae capsular serotyping group at the Utah Public Health Laboratory.

Potential conflicts of interest. All authors: no conflicts.

References


