

## Invasive *Haemophilus influenzae* Disease Caused by Non-Type b Strains in Northwestern Ontario, Canada, 2002–2008

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**A high incidence of invasive non-type b *Haemophilus influenzae* disease was found in Northwestern Ontario, Canada; *H. influenzae* type a was the most prevalent serotype (42%). Clinical and demographic analyses indicate that aboriginal children aged <5 years and adults with predisposing medical conditions are the most affected by invasive *H. influenzae* disease in the post-*H. influenzae* vaccine era.**

*Haemophilus influenzae* can cause severe invasive diseases, such as meningitis, epiglottitis, septic arthritis, and septicemia [1]. On the basis of the antigenic properties of *H. influenzae* capsular polysaccharides, 6 serotypes (a, b, c, d, e, and f) have been identified [2]. Before the late 1980s, *H. influenzae* type b (Hib) was the most common cause of bacterial meningitis in children. Introduction of Hib conjugate vaccines in the early 1990s dramatically decreased the incidence of invasive Hib disease among children in many industrialized countries [1]. Since 1991, the Hib conjugate vaccine has been a part of the routine childhood immunization schedule in Canada; after the introduction of the vaccine, the incidence of invasive Hib disease decreased from 1.89 cases per 100,000 persons in 1989 to 0.3 cases per 100,000 persons in 2004 [3].

Although the Hib conjugate vaccines are highly effective in preventing invasive Hib disease, there is concern that *H. in-*

*fluenzae* strains may undergo capsule switching or replacement to fill the ecological niche previously occupied by Hib [4]. The emergence of invasive non-type b *H. influenzae* disease has been reported in several countries [5–8]. Recent reports suggest an increased incidence of invasive *H. influenzae* type a (Hia) disease among indigenous people of North America [9–11]. The objective of this study was to analyze invasive *H. influenzae* disease that occurred during the past 7 years in Northwestern Ontario, a large region of Canada with a substantial aboriginal population.

**Methods.** Cases of invasive *H. influenzae* disease were defined according to the Centers for Disease Control and Prevention criteria [12]: a clinically compatible case that is laboratory confirmed (isolation of *H. influenzae* from a normally sterile site, that is, blood, cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid). Data were collected from Thunder Bay Regional, Sioux Lookout, and Kenora health centers in Northwestern Ontario. Identification of *H. influenzae* was performed using standard methods [7] and confirmed by 16S ribosomal RNA sequencing [13]. All invasive *H. influenzae* isolates were forwarded to reference laboratories, where serotyping was performed using both a bacterial agglutination test and a polymerase chain reaction assay [7]. The hospital charts were retrospectively reviewed for demographic and clinical information.

Incidence rates were calculated by dividing the number of cases of invasive *H. influenzae* disease per year in a specific age group by the total population for this age group in Northwestern Ontario (per 100,000 persons), by means of the most recent census data (2006) [14]. The Public Health Agency of Canada's Notifiable Diseases age groupings were used [3]; for the analysis, some groups were combined because of the small numbers of cases. Statistical analysis was conducted using MA2x2.EXE [15]. This study was approved by the research ethics boards of all involved institutions.

**Results.** From January 2002 to December 2008, 38 cases of invasive *H. influenzae* disease were identified in Northwestern Ontario. The age of patients ranged from 0 (newborn) to 89 years; 19 (50%) of the cases were children (0–9 years old). Nine patients were  $\geq 60$  years old. Among children aged <5 years, male patients were prevalent (10 [62.5%] of 16;  $P < .05$ ; Fisher exact test). For 15 patients, the ethnic background was not recorded, but 20 (52.6%) of the 38 patients were identified as aboriginal, including all infants <1 year old (6 infants) and 8 (61.5%) of the 13 children >1 year old (Table 1).

The majority of *H. influenzae* isolates (34 [89.5%]) were from

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**Table 1. Age, Sex, and Aboriginal Heritage among 38 Patients with Invasive *Haemophilus influenzae* Disease**

Age group, years	No. of patients (% of total)	No. of patients (% of age group)		Aboriginal heritage
		Males	Females	
<1	6 (15.8)	4 (66.7)	2 (33.3)	6 (100)
1–4	10 (26.3)	6 (60.0)	4 (40.0)	6 (60)
5–9	3 (7.9)	1 (33.3)	2 (66.7)	2 (66.7)
10–24	1 (2.6)	0 (0.0)	1 (100)	0 (0.0)
25–59	9 (23.7)	1 (11.1)	8 (88.9)	3 (33.3)
≥60	9 (23.7)	4 (44.4)	5 (55.6)	3 (33.3)
Any	38 (100)	16 (42.1)	22 (57.9)	20 (52.6)

blood, 1 was from pleural fluid, and 3 were from other normally sterile sites. Of the 38 isolates, 31 (81.6%) were serotyped; 13 were *H. influenzae* type a (Hia; 41.9%), 9 were nontypeable (NTHi; 29.0%), 8 were type f (Hif; 25.8%), and 1 was type e (Hie; 3.2%). No cases of invasive Hib disease were observed (Table 2).

Detailed clinical information was available for 28 cases. The most common clinical presentation was sepsis (in 9 cases [32.1%]), followed by pneumonia (in 8 [28.6%]) and epiglottitis (in 3 [10.7%]). Most of the patients fully recovered, but 3 patients died: 2 had severe underlying medical conditions and 1 was an extremely premature newborn baby. The majority of patients had some potentially predisposing factors to invasive *H. influenzae* disease. All of the infants <1 year old either experienced prenatal exposure to toxic substances or had congenital defects. Of the 15 adult patients with available detailed clinical information, 10 (67%) had underlying diseases, such as malignancies, diabetes mellitus, Crohn disease, chronic obstructive pulmonary disease, chronic renal failure, etc (Table 2).

The number of cases of invasive *H. influenzae* disease varied from year to year: 3 in 2002; 4 in 2003; 7 in 2004; 6 in 2005; 7 in 2006; 7 in 2007; and 4 in 2008. Accordingly, the annual incidence rates varied from 1.28 cases per 100,000 persons in 2002 to 2.98 cases per 100,000 persons in 2004, 2006, and 2007 ( $P > .05$ ; meta-analysis test for heterogeneity). For comparison, the incidence of invasive Hib disease for the entire province of Ontario before the introduction of the Hib conjugate vaccine (1989) was 1.42 cases per 100,000 persons; this decreased steadily to 0.07 cases per 100,000 persons in 2004 [3].

The highest incidence rates of invasive *H. influenzae* disease in Northwestern Ontario were found in children aged <5 years, that is, 15.5 cases per 100,000 persons in 2002, 30.9 cases per 100,000 persons in 2004, and 38.7 cases per 100,000 persons in 2006. For the same age group, the incidence of invasive Hia disease reached 7.7 cases per 100,000 persons in 2002, 2003, and 2008; 15.5 cases per 100,000 persons in 2006; and 23.2 cases per 100,000 persons in 2004. In comparison, in Ontario,

the incidence rates of invasive Hib disease for children aged <1 year were 1.55 cases per 100,000 persons in 2002 and 0.78 cases per 100,000 persons in 2004, and for children aged 1–4 years they were 0.18 cases per 100,000 persons in 2002 and 0.37 cases per 100,000 persons in 2004 [3]. Hence, during 2002–2004, the incidence of invasive *H. influenzae* disease, including Hia, among young children in Northwestern Ontario was much higher than the officially recorded incidence of Hib in the whole province.

**Discussion.** To our knowledge, the incidence of invasive *H. influenzae* disease in Northwestern Ontario, a large region with a substantial aboriginal population, has not been previously investigated. Tsang et al [7] identified 122 cases of invasive *H. influenzae* disease in Manitoba, Canada, in 2000–2006, with an increase in non-Hib strains: 69 (57%) were NTHi and 36 (29%) were Hia; the incidence of invasive *H. influenzae* disease nearly matched the rate of invasive Hib disease in the prevaccine era. In the United States, Dworkin et al [16] observed an increase in the incidence of invasive *H. influenzae* disease in adults ≥65 years old during 1996–2004; 283 (54.2%) of 522 isolates were NTHi, and 87 (18.3%) of 475 isolates were Hif. In contrast, we found a greater prevalence of encapsulated strains (71% [22 of 31 cases with determined serotype]), especially Hia (42% [13 of 31 cases with determined serotype]), compared with the prevalence of NTHi. In Ontario, before the introduction of vaccine, the most common strains were NTHi and Hib. Since 2000, the most commonly observed *H. influenzae* isolates are NTHi and Hif (Adam H et al, unpublished data).

Recently, Bruce et al [9] found a high incidence of invasive Hia disease among indigenous people in the North American Arctic, with the highest rate detected among indigenous children <2 years of age, that is, 52.6 cases per 100,000 persons. Compared with other reports of increased incidence rates of Hia disease in regions with a substantial proportion of aboriginal populations [9–11], our report identifies the highest prevalence of Hia disease in an area outside the circumpolar region.

Before the introduction of the Hib conjugate vaccine, the highest incidence of invasive Hib disease in the world was reported among indigenous people in North America and Australia [17–19]. Despite the vaccination, some aboriginal populations remain highly susceptible to Hib [20]. Our study demonstrated an increased prevalence of invasive non-type b *H. influenzae* disease among aboriginal children; that is, 14 (73.7%) of all 19 pediatric cases involved aboriginal children, including all infants <1 year of age. Overall, aboriginal patients accounted for 20 (52.6%) of all 38 cases. Given that the proportion of all people in Northwestern Ontario who are aboriginal is 19.6% [14], our findings imply that this group is disproportionately affected by invasive *H. influenzae* disease. The reason for this is currently unclear and deserves further study. It is possible that some genetic factors determine an increased susceptibility to this

**Table 2. Clinical Characteristics of 38 Patients with Invasive *Haemophilus influenzae* Disease**

Age group, years	No. of patients	Isolation site	Serotype	Clinical presentation	Disease outcome	Underlying conditions <sup>a</sup>
<1	6	Blood 5/6; synovial fluid 1/6 <sup>b</sup> ; placenta 1/6	Hif 2/6; NTHi 2/6; not determined 2/6	Sepsis 3/6; pneumonia 1/6; septic arthritis 1/6; data not available 1/6	Infection cleared 4/6; long-term antibiotic therapy 1/6; death 1/6	Extreme prematurity 1/6; congenital heart defect 1/6; prenatal exposure to toxic substances (alcohol, tobacco, solvents) 4/6
1–4	10	Blood 10/10	Hia 8/10; Hie 1/10; NTHi 1/10	Sepsis 2/10; pneumonia 1/10; urinary tract infection 1/10; pharyngitis 1/10; data not available 5/10	Infection cleared 4/10; transferred to another hospital 1/10; data not available 5/10	Anemia 1/10; systemic lupus erythematosus in mother during pregnancy 1/10; none 3/10; data not available 5/10
5–9	3	Blood 2/3; retro-orbital cavity 1/3	Hia 2/3; not determined 1/3	Tonsillitis 1/3; periocular cellulitis 1/3; data not available 1/3	Infection cleared 2/3; data not available 1/3	Anemia 1/3; none 1/3; data not available 1/3
10–24	1	Blood 1/1	NTHi 1/1	Data not available 1/1	Data not available 1/1	Data not available 1/1
25–59	9	Blood 8/9; abdominal cavity 1/9	Hia 2/9; Hif 2/9; NTHi 2/9; not determined 3/9	Sepsis 2/9; pneumonia 2/9; epiglottitis 2/9; urinary tract infection 1/9; abdominal abscess 1/9; data not available 1/9	Infection cleared 6/9; death 2/9; data not available 1/9	Malignancy <sup>c</sup> 2/9; diabetes mellitus 2/9; cardiomyopathy 1/9; Crohn disease 1/9; alcoholism 1/9; none 3/9; data not available 1/9
≥60	9	Blood 8/9; pleural fluid 1/9	Hia 1/9; Hif 4/9; NTHi 3/9; not determined 1/9	Sepsis 1/9; meningitis 1/9; pneumonia 3/9; empyema 1/9; epiglottitis 1/9; data not available 2/9	Infection cleared 5/9; transferred to another hospital 1/9; data not available 3/9	Malignancy <sup>c</sup> 3/9; tuberculosis 1/9; COPD 2/9; chronic renal failure 1/9; none 2/9; data not available 2/9

**NOTE.** COPD, chronic obstructive pulmonary disease.

<sup>a</sup> Patients with multiple underlying conditions are listed more than once.

<sup>b</sup> *Haemophilus influenzae* was isolated from both blood and synovial fluid.

<sup>c</sup> Cases of malignancy included lymphoma, 1; breast cancer, 1; lung cancer, 1; and multiple myeloma, 2.

disease. An allelic polymorphism in the *V<sub>κ</sub>A2* gene that encodes the predominant antibody to Hib capsular polysaccharide was detected in Navajos [21]. It remains to be determined whether specific genetic factors in indigenous populations may account for insufficient immune defense against non-type b *H. influenzae* disease.

Although no cases of Hib disease were detected in our study, we cannot completely rule out the presence of Hib disease in Northwestern Ontario. Because only 31 (81.5%) of the 38 isolates were serotyped, it is possible that some cases of Hib disease were missed.

Our findings indicate that invasive *H. influenzae* disease in the post-Hib vaccine era affects young children (16 [42%] of 38 patients were <5 years of age), with sepsis and pneumonia being the major clinical presentations. Among adult cases, there was a large prevalence of underlying conditions that could predispose to invasive *H. influenzae* disease by compromising the immune system, such as malignancies, diabetes mellitus, or chronic renal failure.

Despite the widespread use of the Hib conjugate vaccine, invasive *H. influenzae* disease remains an important concern. Aboriginal children and adults with underlying conditions that affect the immune defense may have an increased susceptibility to this infection. Our findings point to the changing epidemiology of invasive *H. influenzae* disease and emphasize the importance of disease surveillance for all serotypes of this pathogen and continued vigilance against invasive *H. influenzae* disease in the post-Hib vaccine era.

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