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Review Article

Global Epidemiology of Invasive *Haemophilus influenzae* Type a Disease: Do We Need a New Vaccine?

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Until recently, the significance of invasive disease caused by *Haemophilus influenzae* serotype a (Hia), in contrast to *H. influenzae* serotype b (Hib), has been largely underestimated. However, during the last decade, Hia was recognized as an important pathogen causing severe infections in young children with a high case-fatality rate comparable to Hib disease before the introduction of pediatric immunization against this infection. Remarkably, the highest incidence rates of invasive Hia disease have been found in some indigenous populations, such as North American Indians and Inuit of Alaska and Northern Canada, reaching the order of magnitude of the incidence rates of Hib in the pre-Hib vaccine era. The reasons for an increased susceptibility to Hia infection among some specific populations groups are unknown. The goal of this paper is to summarize the current knowledge on Hia global epidemiology and to discuss potential prevention of this infection using specific immunization.

1. Introduction

Haemophilus influenzae is an important human-restricted Gram-negative bacterial pathogen, which can cause severe invasive disease, such as meningitis, sepsis, and bacteremic pneumonia in susceptible individuals. Some strains of *H. influenzae* have a polysaccharide capsule representing the major virulence factor and antigen of this bacterial species. On the basis of the antigenic properties, six serotypes of encapsulated *H. influenzae* are distinguished (a, b, c, d, e, and f), and there are also nonencapsulated or nontypeable *H. influenzae* (NTHi). Encapsulated strains exhibit a higher ability to cause invasive disease because the capsule prevents complement-mediated bacteriolysis in the absence of opsonizing antibody [1]. Normal individuals can carry *H. influenzae* in their naso- and oropharynx, and the carriage is considered as the major factor inducing the development of natural immunity against the pathogen, along with exposure to some cross-reactive environmental antigens [2]. The invasive disease mostly affects young children (below 2 years of age), as well as the elderly and immunocompromised individuals. One particular serological variant, *H. influenzae* serotype b (Hib), was the major cause of bacterial meningitis in young children worldwide before the conjugate Hib vaccine became available in the late 1980s. Pediatric vaccination against Hib has resulted in a dramatic decrease in the incidence rates of invasive Hib disease in all countries where the vaccine has been included in the national immunization programs [3]. However, Hib vaccination does not confer protection against other serotypes of *H. influenzae.*

Until recently, the significance of other serotypes of *H. influenzae* in the etiology of invasive bacterial infections has been largely overshadowed by Hib. However, it is obvious that other serological types of *H. influenzae* besides Hib cause significant morbidity and mortality; moreover, their prevalence appears to be increasing in the Hib vaccine era [4]. During the last decade, an increase in the prevalence of infections caused by NTHi has been reported worldwide, suggesting strain replacement following elimination of Hib from populations with high Hib vaccine coverage, as a new ecological niche became available for colonization with non-Hib strains of *H. influenzae* [5–7]. Although an alarming trend towards an increase in the incidence of severe disease caused by NTHi has been now recognized in many countries, less attention is paid to *H. influenzae* serotype a (Hia), which appears to be present in certain geographic regions and among specific populations only. As most of cases of Hia disease are sporadic, the published reports are not always consistent in their findings. While invasive Hia disease has

suffered from inadequate surveillance worldwide, Hia is now recognized as an important pathogen causing serious disease comparable to Hib in severity and case-mortality rates. For example, the case-fatality rate of invasive Hia disease among paediatric cases reported by the Canadian Immunization Monitoring Program ACTive (IMPACT) centers in 1996–2001 reached 16% [8].

Remarkably, the highest incidence rates of invasive Hia disease have been found in some indigenous populations, such as North American Indians and Inuit of Alaska and Northern Canada, reaching the order of magnitude of the incidence rates of Hib in the pre-Hib vaccine era. The reasons for an increased susceptibility to Hia infection among specific populations groups are unknown. The goal of this paper is to summarize the current knowledge on Hia global epidemiology and to discuss potential prevention of this infection using specific immunization.

2. Global Epidemiology of Infections Caused by *H. influenzae* Type a

Only few prospective population-based studies have addressed epidemiology of invasive Hia disease; most of published studies are based on passive laboratory surveillance. The sporadic nature of the disease and the lack of comprehensive reporting make it difficult attaining true estimates of the global incidence. Before the introduction of Hib conjugate vaccines, a very low incidence of invasive Hia disease had been reported in industrialized countries; in the USA and western European countries, 99% of invasive *H. influenzae* disease was caused by Hib (summarized by [9]). However, considerable numbers of invasive Hia disease were reported in specific geographical areas and populations, that is, in Papua New Guinea, The Gambia, Australian Aboriginal populations, and White Mountain Apache Indians in Arizona [10–12]. The same populations had a very high incidence of both overall invasive *H. influenzae* disease and Hib [13, 14]. During 1973–1983, an annual incidence of *H. influenzae* meningitis in White Mountain Apache Indian children younger than 5 years was 254 cases/100,000 that was 8-fold higher than that in the general US population [12]; in 1986, it was 450/100,000 in Australian Aboriginal children [14]. In Central Australia, during 1985–1988, an estimated annual incidence of invasive *H. influenzae* disease among Aboriginal children younger than 5 years old was 991/100,000 [15]. Although in the pre-Hib vaccine era the incidence of invasive Hia disease had not exceeded the incidence of invasive Hib disease, Hia represented a considerable proportion of all invasive *H. influenzae* disease cases in such populations. In Losonsky's report [13], during 15 months of prospective surveillance of invasive *H. influenzae* disease in a White Mountain Apache Indian community, Hia strains were isolated in 3 out of 18 cases (the remaining strains were Hib). In Hansman's report, 2 out of 8 *H. influenzae* isolates from invasive disease in Australian Aboriginal children were reported as Hia [14]. Hanna [15] reported that 8% of all invasive *H. influenzae* infections in preschool Aboriginal children in the northern territory of Australia were caused by Hia. Published data on serotype distribution of invasive *H. influenzae* isolates from developing countries in the pre-Hib vaccine era are incomplete, as many reports do not have information on serotypes other than Hib (reviewed by [16]). Routine immunization against Hib led to a dramatic decrease in the incidence of Hib invasive disease in all countries where it has been implemented, including indigenous populations of Alaska and Australia [17, 18].

Following the introduction of Hib conjugate vaccines, global epidemiology of invasive Hia disease has been characterized by its notable presence in specific areas and populations. In particular, Hia is present in North American Arctic, including Alaska and Northern Canada, Western Canadian provinces, southwestern parts of the USA, especially among indigenous populations living in these areas, and some areas of South America, that is, Brazil. In other parts of the world, invasive Hia disease is rare and only found at very low rates and in certain areas. Systematic review of the literature published since the 1980s identified specific geographic distribution of invasive Hia disease and Hia carriage across different continents (outlined in the next sections and summarized in Table 1).

2.1. Europe. In Europe, invasive Hia disease was very rare in the pre-Hib vaccine era, and there is no evidence of an increase in its incidence since the vaccine has been introduced [5]. The European Union Invasive Bacterial Infection Surveillance (EU-IBIS) reported 10,081 invasive *H. influenzae* isolates from 14 countries (Austria, England, Wales, Finland, Greece, Iceland, Ireland, Italy, Malta, The Netherlands, Norway, Portugal, Scotland, and Slovenia) during 1996–2006; out of them, only 26 Hia isolates were identified, mainly in young children, often in association with meningitis (in comparison, this study has detected 500 Hif isolates). The incidence of invasive Hia disease in children <5 years of age was found to be 0.12/1,000,000 [5]. A prospective active surveillance study of invasive *H. influenzae* disease in children in the UK and Republic of Ireland (from October 1, 1992 to December 31, 1998) found only one invasive Hia isolate out of 147 nontype b isolates in vaccinated children and did not detect any Hia among 84 cases of invasive nontype b *H. influenzae* disease in unvaccinated children [19]. Out of 2,111 cases of invasive *H. influenzae* infections reported in children in England and Wales between 1994 and 2008, including 1,831 isolates with known serotype, only 3 cases of Hia were found [20].

Among other European countries, which have not been included into EU-IBIS, no cases of invasive Hia disease were reported from Sweden before (1987–1992) [58] or after (1997–2009) [59] the introduction of the large-scale anti-Hib vaccination, from Denmark (1997–2006) [60], France (2001–2006) [61], Poland (1996–2001) [62], or Spain (1999-2000) [63]. Single cases of invasive Hia disease were reported from Germany (1998–2005) [64] and Switzerland (1986–1993) [65]. The recent literature indicates that the most important nontype b encapsulated serotype in the post-Hib vaccine era in Europe is Hif, not Hia [5]. Data on Hia carriage in Europe during the last 3 decades have not been reported, except for British studies in the 1960s that identified 12 isolates of Hia among 106 encapsulated strains of *H. influenzae* (11%)

Table 1: Geography of reported cases of invasive Hia disease[#].

(a) U.S.A.[*] (excluding Alaska)

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
White Mountain Apache (east and central Arizona)	Oct 1981–Jan 1983	3 out of 18 cases of invasive *H. influenzae* disease	Not reported	Prospective surveillance	Losonsky et al., 1984 [12]
Metropolitan Atlanta	1983–1985	5 out of 310 invasive *H. influenzae* isolates from all hospitals in the greater Atlanta area	Not reported	2-year survey of invasive *H. influenzae* disease	Elliott et al., 1990 [21]
California, New Jersey, Tennessee, Oklahoma, Missouri, Washington (population 33.5 million)	Jan–Dec 1986	14 out of 1872 invasive *H. influenzae* isolates (0.7%)	0.04	Laboratory-based surveillance during time when Hib polysaccharide vaccines were being introduced	Wenger et al., 1992 [22]
San Francisco county	1989–1991	1 out of 12 invasive *H. influenzae* isolates from adults with HIV infection	Not reported	Population-based, 3-year active surveillance	Steinhart et al., 1992 [23]
Navajo and White Mountain Apache children <5 years (northern and central Arizona, western New Mexico, southern Utah)	1988–2003	76 cases out of 378 invasive *H. influenzae* isolates	20.2 for children <5 years; no increase in rates after Hib vaccination was introduced	Population-based, active laboratory surveillance data	Millar et al., 2005 [24]
4 states (Georgia, Tennessee, Maryland, California); population > 10 million	1994–1995	2 cases of Hia out of 18 *H. influenzae* meningitis	Not reported	Active, population-based surveillance	Schuchat et al., 1997 [25]
Illinois	1996–2004	8 Hia out of 475 *H. influenzae* (4/8 in <5 years old)	Not reported	Retrospective analysis of surveillance data	Dworkin et al., 2007 [7]
Utah children <18 years old	1998–2008	Hia: most prevalent serotype 22 cases/91 invasive *H. influenzae* disease 28% of cases in children <5 years old	In 1998: 0.8 for children In 2008: increased to 2.6	Population-based study In Utah, no Hia in 1991–1998, in 1998-1999: 5 pediatric cases in 10 months, then increased incidence between 1998 and 2008	Bender et al., 2010 [26]
Utah adults	1998–2008	Hia 15/101	0.08 for adults; no annual changes	Population-based study	Rubach et al., 2011 [27]
ABCs (California, Connecticut, Colorado, Georgia, Maryland, Minnesota, New Mexico, Oregon, New York, and Tennessee (11.7% of the US population in 2008)	1999–2008	Hia: 92 (2.2%) of all invasive isolates	Not reported	Active population- and laboratory-based surveillance conducted through Active Bacterial Core surveillance (ABCs) sites Hia: more frequent cause of invasive disease in American Indian and Alaska Native children compared with nonnative children	MacNeil et al., 2011 [28]

(a) Continued.

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
New Mexico	2009-2010	Cluster of 5 cases in 2009; 7 more sporadic cases in 2009-2010	Not reported	ABCs data posted on the website hosted by the Imperial College (UK)	http://haemophilus.mlst.net/ [29]

*Hib conjugate vaccine became available in 1988; in 1991, all infants starting at age of 2 months were recommended to receive the vaccine [30].

(b) Alaska and Canada**

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
Alaska residents aged 10 years and older	1980–1996	2/17 of non-type b serotypeable strains	Not reported	Population-based, descriptive correlational study	Perdue et al., 2000 [31]
IMPACT 12 Canadian pediatric tertiary care centers: nearly 90% of tertiary care pediatric beds in Canada (population 3 million children)	1996–2001	25/166 of invasive *H. influenzae* isolates from children; 76% of patients with Hia: Aboriginal	In the Keewatin Region of Nunavut (2001): 418.8 for Inuit children <5 years; in British Columbia, Alberta, Manitoba, Saskatchewan (1996–2001): 3.7 for Aboriginal children <5 years; 2.3 for Non-Aboriginal children <5 years	Retrospective population-based study	McConnell et al., 2007 [8]
Manitoba	2000–2004	26/52 (50%) of invasive *H. influenzae* isolates	Not reported	Laboratory-based surveillance	Tsang et al., 2006 [32]
Manitoba	2000–2006	36/122 (29%) of invasive *H. influenzae* isolates; 72% of Hia cases: children <2 years	0.26 (2000), 0.69 (2001), 0.51 (2002, 2003), 0.34 (2004), 0.59 (2005), 0.16 (2006)	Laboratory-based surveillance	Tsang et al., 2007 [33]
Alaska and northern Canada	2000–2005	42/88 of typeable *H. influenzae* isolates	0.9 (Alaska: 0.3, northern Canada 3.9); 19.7 for children <2 years (Alaska: 5.7, northern Canada: 79.1); 52.6 for indigenous children <2 years (Alaska: 20.9, northern Canada: 101.9)	Population-based surveillance	Bruce et al., 2008 [34]
Northern Canada (Yukon, northwestern territories, Nunavut, northern Quebec, and Labrador): population 132,956; 59% Aboriginal	2000–2005	31/59 (59%) cases of invasive *H. influenzae* disease with serotype information; 73.3% of these in children < 2 years	Not reported	Population-based surveillance, all Hia cases occurred in Aboriginal persons	Degani et al., 2008 [35]
Ontario	1989–2007	2.1% of 1,455 of invasive *H. influenzae* isolates 8/284 (2.8%) in children < 2 years; 6/160 (3.75%) in children of 2-10 years	Not reported	Population-based surveillance	Adam et al., 2010 [6]
Northwestern Ontario (20% Aboriginal population)	2002–2008	13/31 (41.9%) of invasive *H. influenzae* isolates with serotype information	For children < 5 years: 7.7 (2002, 2003, 2008), 15.5 (2006), 23.2 (2004)	Population-based surveillance	Brown et al., 2009 [36]
Northwestern Ontario (82% Aboriginal population)	2004–2008	7 cases in First Nations communities	7.0	Population-based surveillance	Kelly et al., 2011 [37]

(b) Continued.

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
British Columbia	2008–2009	10% of 98 invasive *H. influenzae* isolates; 80% (8/10) in children <2 years	Not reported	Retrospective laboratory surveillance study	Shuel et al., 2010 [38]
Northern Canada	2000–2010	72 (56% of cases with serotype information) out of 142 invasive *H. influenzae* cases	4.6 (average incidence over 11 years); 87.5 for children <2 years; 6.9 for Aboriginal people	Population-based surveillance	Lourenco et al., 2012 [39]

** In Canada, the first Hib conjugate vaccine became available in 1988 for children older than 18 months of age; the current conjugate vaccine for immunization of infants beginning at 2 months of age was introduced in 1992 [6].

(c) South America

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
Sao Paulo (Brazil)	1977–1991	5 out of 1,094 isolates from CSF (0.5%); in comparison, Hib was isolated in 99.4% of cases of meningitis	Not reported	National surveillance	Landgraf and Vieira, 1993 [40]
Brazil	1990–1999	16 (0.5%) Hia out of 3,204 invasive isolates (prevaccine)	Not reported	Retrospective study; Hib vaccine was introduced in August 1999	Zanella et al., 2002 [41]
The metropolitan region of Salvador (northeast Brazil)	March 1996–September 2000	13/483 (2.7%) isolates from meningitis. Proportion of Hia cases increased from 5/431 (1.2%) to 8/52 (15.4%) after introduction of routine Hib immunization	Prevaccine 0.02; Postvaccine: 0.16 (8-fold increase); In <2 year-old children: increase from 0 to 1.77	Active surveillance for *H. Influenzae* meningitis cases before and after introduction of Hib immunization	Ribeiro et al., 2003 [42]
Metropolitan Salvador, Brazil	August 1996–August 2004	19 out of 25 cases of non-type b *H. influenzae* meningitis (76%): 4 cases in the pre- and 15 in the postvaccination period	Increased from 0.01 to 0.14 in the first year after introduction of vaccine; in children <2 years, increased from 0 to 1.56; during the following 4 years: between 0 and 0.03	Active surveillance for *H. influenzae* meningitis in children	Ribeiro et al., 2007 [43]
Salvador, Brazil	March 1996–September 2007	28/43 (65%) of non-type b *H. influenzae* meningitis	Not reported	Active hospital-based surveillance for meningitis	Lima et al., 2010 [44]
Brazil	1990–2008	In 1990–1999: 24/3,050 of *H. influenzae* meningitis isolates (1%) 2000–2008: 118/860 (14%)	Hia meningitis in infants <1 year: 0.31 in 2000–2002; 0.90 in 2003–2005; 1.48 in 2006–2008	Passive laboratory surveillance; retrospective analysis	Zanella et al., 2011 [45]
Cuba	1993–1995	Hia 0.6% of all *H. influenzae* isolates from meningitis (97% Hib)	Not reported	Nationwide surveillance Hib conjugate vaccine was introduced in 1999 [46]	Martínez et al., 1999 [47]
Colombia	1994–2002	10/683 invasive *H. influenzae* isolates	Not reported	Laboratory-based surveillance Hib conjugate vaccine was introduced in 1998 [46]	Ovalle et al., 2003 [48]

(c) Continued.

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
19 Latin American and 4 Caribbean countries	2000–2005	131/2,159 (6.1%) invasive *H. influenzae* isolates	Not reported	Laboratory-based surveillance Hib vaccine was introduced in Uruguay in 1994, Chile in 1996, Guatemala: 2006, Columbia: 1998 [46]	Gabastou et al., 2008 [49]

(d) Africa

Geographic area/population	Time	Number of reported invasive Hia isolates	Average annual incidence per 100,000 population	Comments	Reference
The Gambia	December 1982–January 1984	4 out of 55 cases of *H. influenzae* meningitis; 3 out of 20 *H. influenzae* pneumonia	Not reported	Detection of IS*1016-bexA* deletion in the encapsulation (*cap*) locus of Hia in isolates from 3 cases	Kroll et al., 1994 [50]
The Gambia	1986 (prevaccine)	2 out of 13 invasive *H. influenzae* isolates; 5 more invasive Hia isolates from the same area	Not reported	Analysis of lung aspirates from 64 patients with acute lobar pneumonia	Wall et al., 1986 [11]
South Africa	Aug 1991–July 1992 (prevaccine)	2 out of 119 invasive *H. influenzae* isolates from children	Not reported	One year prospective study in Cape Town children, one septicaemia, one meningitis	Hussey et al., 1994 [51]
South Africa	July 1999–June 2004 (post-vaccine)	10/712 invasive *H. influenzae* isolates (for comparison: Hif 39/712)	Not reported	National laboratory-based surveillance data, Hib vaccine was introduced in July 1999	Von Gottberg et al., 2006 [52]
East Africa (Kenya, Uganda, Tanzania, Ethiopia)	August 2003–February 2007	16/119 invasive *H. influenzae* isolates from children between 2 months and 5 years of age	Not reported	Paediatric Bacterial Meningitis Surveillance Network in the East African Region. Hib vaccine was introduced in Kenya and Uganda in 2001	Mudhune and Wamae, 2009 [53]

(e) Papua New Guinea and Australia

Geographical area/population	Time	Number of reported cases of Hia disease/isolates	Incidence rate	Comments	Reference
Eastern Highlands of Papua New Guinea children <5 years	1978–1988	6.5% (6/92) of blood *H. influenzae* isolates; 12.3% (9/73) of CSF isolates; 2.9% (1/35) of lung aspirates	Not reported	Laboratory-based surveillance of acute pneumonia and meningitis in children	Gratten and Montgomery, 1991 [54]
Papua New Guinea	March–December 1986	Among 170 adult cases of acute pneumonia, 4/15 of *H. influenzae* isolates from blood culture or/and lung aspirates	Not reported	Prospective study of 170 adult patients with acute pneumonia	Barnes et al., 1987 [55]
Papua New Guinea	March 1980–September 1984	12% of *H. influenzae* isolates from children with meningitis (9 strains)	Not reported	Study of 155 highlands children with bacterial meningitis (2 m–10 y old)	Gratten et al., 1985 [10]
Northern Territory (NT), Australia	mid 1985–mid 1988	5 out of 80 of serotyped *H. influenzae* isolate; all from Aboriginal children; one meningitis	Not reported	Survey of all invasive *H. influenzae* infections over a 3-year period in children under 5 years of age at the NT regional hospitals	Hanna, 1990 [15]

(e) Continued.

Geographical area/population	Time	Number of reported cases of Hia disease/isolates	Incidence rate	Comments	Reference
Central Australia Aboriginal population	June 1985–May 1986	2/8 of serotyped *H. influenzae* from Aboriginal children	Not reported	Population-based surveillance	Hansman et al., 1986 [14]
Central Australia Aboriginal children	May 1989–February 1993	Among 77 children with invasive *H. influenzae* disease <4 years, 7.5% of episodes were caused by Hia (Hib 79% of the isolates)	Not reported	Population-based study on Aboriginal children hospitalized with invasive disease in Alice Springs, Tennant Creek and Katherine	Gratten et al., 1994 [56]
Australia	July 1999–August 2000	4/200 of invasive *H. influenzae* isolates	Not reported	Study of antimicrobial susceptibility of *H. influenzae* isolated from patients with "clinically relevant" conditions, including invasive and noninvasive.	Turnak et al., 2001[57]

[#]Only few prospective population-based studies have been done and most publications present data from convenient samples. Therefore, not all studies report comparable data, such as the incidence rates.

from respiratory specimens of patients with chronic sinusitis and bronchiectasis [66, 67].

2.2. North America. In North America, high incidence rates of invasive Hia disease were found in certain regions and populations, that is, among Navajo and White Mountain Apache in southwestern USA, Alaska, and Utah [12, 24, 26, 27, 31, 34] (Tables 1(a) and 1(b)). According to one recent report, the incidence of invasive Hia disease among children younger than 5 years in Utah is increasing [26]. High incidence rates of invasive Hia disease were reported from northern Canada and western Canadian provinces where a significant proportion of Aboriginal people is present (Manitoba, Saskatchewan, British Columbia) [8, 32, 33, 35, 38] (Table 1(b)). Significant numbers of invasive Hia disease were recently reported from northwestern Ontario, a large sparsely populated area with a substantial proportion of Aboriginal peoples [36, 37]. However, in the whole province of Ontario, during 1989–2007, Hia represented only 2% of all 1,455 invasive *H. influenzae* isolates, and no changes in its prevalence were noted following Hib vaccine introduction in 1991 [6]. North American studies have consistently reported the highest prevalence of Hia as a cause of invasive *H. influenzae* disease in indigenous populations, that is, Alaskan Natives, Inuit, and Canadian First Nations, during both pre- and post-Hib vaccine era [8, 12, 24, 28, 34–37, 39, 68]. Moreover, it appears that the incidence rates of invasive Hia disease in Canadian Arctic are increasing [39].

Current rate of Hia colonization in general North American population is unknown, although early studies found Hia in the nasopharyngeal specimens of healthy children; Hia represented 11% of all encapsulated *H. influenzae* isolates [69]. During an outbreak of invasive Hia disease in Alaska Natives (2003), 5 out of 31 (16%) close contacts of case patients were colonized with Hia [68]. The authors of this paper refer to a 2001 oropharyngeal colonization survey of 720 residents living in one of the villages with this outbreak that did not find Hia carriage. A later study by the same group found a 43% rate of Hia carriage among close contacts of an infant presenting with invasive Hia disease and no carriage in 20 comparison participants [70]. It was recently reported that 0.5% of young children in Mexico City were colonized with Hia; that is, three Hia strains were identified out of 88 *H. influenzae* isolates from nasopharyngeal samples of 573 children 2 months–5 years old [71].

2.3. South America and the Caribbean. In Brazil, before the introduction of Hib vaccine, Hib caused 99% of all invasive *H. influenzae* disease, with only 0.5% prevalence of Hia [40, 41, 72] (Table 1(c)). No Hia carriage was found in a day care center in Sao Paulo in 1997 [73]. However, in the postvaccine time, several studies described an increase in the incidence of invasive Hia disease as well as an emergence of severe cases [42–45, 74] (Table 1(c)). In 2005, 2% of children attending day care, predominantly younger children (4–11 months old), carried Hia in their nasopharynx [75]. A laboratory-based surveillance of *H. influenzae* in three Brazilian states found three Hia among 47 noninvasive *H. influenzae* isolates during 2002-2003, although before Hib vaccine introduction (1990–1999) and during the first 2 postvaccine years (2000-2001) Hia was not detected in nonsterile clinical specimens [74]. An improvement in the surveillance of invasive disease caused by *H. influenzae* in the postvaccine era may potentially account for more frequent detection of Hia in Brazil during the last years.

During 1993–2005, Hia was identified as a cause of invasive disease in other South American and Caribbean countries both before and after Hib vaccine introduction accounting for 0.5–1.5% of all invasive *H. influenzae* isolates in Cuba, Colombia, and Argentina [47, 48, 76] (Table 1(c)). A large laboratory-based surveillance of invasive bacterial disease in 19 Latin American and 4 Caribbean countries (including Brazil) in 2000–2005 identified Hia in 6.1% of all invasive *H. influenzae* isolates [49]. Incidence rates of invasive Hia disease or Hia carriage rates have not been reported in the published literature. In Venezuela, in a prospective epidemiological study of 87 children with acute otitis media, Hia was isolated in 2/35 cases of *H. influenzae* otitis (5.7%) [77].

2.4. Asia. Invasive Hia disease is infrequent in Asia, although several studies reported Hia carriage in both general population and individuals with respiratory infections. During 1993–1997, in a prospective surveillance of infections caused by *H. influenzae* in 6 academic referral Indian hospitals, 125 *H. influenzae* isolates were detected, 97% of which were Hib. In this study, a single case of meningitis caused by Hia was identified [78]. In an earlier study, among 12 invasive *H. influenzae* isolates obtained from patients at Nagpur hospital during one year, one Hia isolate was found [79]. In Korea, in a study conducted in a children's hospital in 1992–1997 (before the introduction of Hib vaccine), no Hia was isolated from invasive infections, although four Hia isolates were detected out of 29 *H. influenzae* isolates from nonsterile body fluids [80]. More recently, in 2002–2004 (after Hib vaccine was introduced), Hia was identified in 2 out of 100 respiratory isolates from private hospitals in Korea [81]. In Nepal, in a study of *H. influenzae* carriage in urban children in 2007 (prior to universal Hib vaccination), three Hia isolates out of 2,195 oropharyngeal swabs were found. In comparison, 5% of the children carried Hib [82]. In one study in China (between September 1998 and September 1999), six Hia isolates were identified out of total of 191 *H. influenzae* isolates obtained from 603 healthy children attending kindergartens [83]. However, a more recent study (2008) that found 31.8% carriage rate of *H. influenzae* in the general population of Shenzhen did not identify a single Hia [84]. A study of 85 children with tuberculosis infection from a closed community in the Far East Russia found three Hia isolates from nasopharynx [85]. Presence of Hia in Japan, Taiwan, Iran, Turkey, or Malaysia has not been reported in the literature.

2.5. Africa. Before the introduction of Hib vaccines, invasive Hia disease was reported in The Gambia and South Africa [11, 51] (Table 1(d)). Later, national-based post-Hib vaccine surveillance in South Africa identified 10 Hia among 712

invasive *H. influenzae* isolates [52]. In the post-Hib vaccine era, invasive Hia isolates were also found in Kenya and some other East African countries [53, 86] (Table 1(d)). Although data from other parts of the continent are incomplete, two large epidemiological studies did not find Hia in Egypt (1977-1978) [87] or Morocco (2004–2009) [88]. For example, the analysis of 276 bacterial isolates from the cerebrospinal fluid of meningitis patients at two Cairo hospitals did not reveal any Hia, although Hib was identified in 12% of the isolates [87]. Incidence rates of invasive Hia disease or Hia carriage rates in African countries have not been reported.

2.6. Australia and Papua New Guinea. A series of studies conducted in Papua New Guinea in the 1980s found high prevalence of Hia in etiology of bacterial meningitis and other invasive disease in young children [10, 54] as well as in adult pneumonia [55] (Table 1(e)). During the same time, Hia carriage was also commonly detected in the upper respiratory tract of children younger than 5 years of age [89] (Table 2). No published data on presence of Hia in this population after 1988 are available.

Similarly, Hia was found in a substantial proportion of Australian Aboriginal children with invasive disease in 1985–1993 [14, 15, 56], and it also represented 2.4% of *H. influenzae* isolates from the nasopharynx of children hospitalized with acute lower respiratory tract infections [90] (Tables 1(e) and 2). In the latter study, 88% of children were colonized with *H. influenzae* [90]. More recently, a large study of antimicrobial susceptibility of *H. influenzae* isolated from patients with "clinically relevant" conditions, including invasive and non-invasive (mostly respiratory) infections in 30 geographically diverse centers of 13 countries during July 1999–August 2000 that found 19 Hia isolates out of 2,676 *H. influenzae* in total, listed four Hia isolates out of 200 *H. influenzae* strains from Australia [57]. A recent study from the Northern Territory in Australia did not find evidence of increasing *H. influenzae* nontype b infection, including Hia, in the population of Australian Aboriginal children [91] (Table 1(e)).

3. Conclusion

The data on global epidemiology of invasive Hia disease are incomplete due to the sporadic nature of the disease and the lack of systematic and comprehensive surveillance programs worldwide. The analysis of published reports on invasive Hia disease and Hia carriage shows presence of this infection in certain geographical areas and populations. At present, the highest incidence rates of invasive Hia disease are found in the North American Arctic, southwestern USA, as well as in northern and western Canada, the areas characterized by relatively high prevalence of indigenous peoples. In the prevaccine time, this infection was found in The Gambia and more recently in South Africa and some East African countries. Hia is also present in Australia and was often found in both Australia and Papua New Guinea in the prevaccine time (more recent data from Papua New Guinea are unavailable). Remarkably, this infection is virtually absent from Europe, Asia, and northern Africa, with only single cases of invasive disease reported from these areas; however, various rates of Hia carriage in healthy children or patients with respiratory conditions have been detected in several countries across Asia and South America. Outbreaks of invasive Hia disease have been described in Alaska (among western Alaska native infants) [68]. Greater incidence rates of invasive Hia disease have been consistently found among Aboriginal than among Non-Aboriginal children, that is, in Australia [15] and North American Arctic [8, 34, 39].

Hence, over the last 30 years, invasive Hia disease has been typically found in young children from either developing countries or indigenous populations of developed countries (USA, Canada, and Australia). The reasons for an increased susceptibility of some specific populations to this infection remain unknown.

4. Do We Need a Vaccine against *H. influenzae* Type a?

Although Hia appears as a significant pathogen only in specific geographic areas and among certain populations, such as indigenous peoples of North America, rather than widespread globally, immunization of susceptible groups would be an important strategy to prevent severe consequences of invasive Hia disease. Indeed, another etiologic agent of bacterial meningitis, *Neisseria meningitides,* causes sporadic disease in North America, yet a vaccine is available due to the severity of the disease and the fact that the disease has been deemed very traumatic for patients with severe sequelae if they survive. It is uncertain whether the emergence of invasive Hia disease is due to the serotype replacement following the wide use of Hib vaccine for pediatric immunization, as a new ecological niche became available following elimination of Hib from heavily immunized populations. Specific reasons behind an increased incidence of invasive Hia disease among some indigenous populations remain unknown and may potentially be related to genetic or environmental factors, or both, especially considering that the same populations experienced the highest incidence rates of invasive Hib disease prior to Hib vaccine introduction.

Immune response to Hia infections has been very little studied, and current knowledge on Hia immunology is based on the assumption that due to chemical similarities between Hia and Hib capsular polysaccharide antigens, the immune response to Hia is analogous to Hib. Some recent studies have found presence of serum bactericidal antibody against Hia in both cord blood and blood from normal donors [92, 93]. However, it remains to be experimentally established whether or not immunology of Hia infection is similar to Hib. Considering the severity of invasive Hia disease, it is important to study specific host factors that may predispose certain populations to this infection, that is, the population genetics, pattern of natural immunity against this pathogen, and prevalence of Hia carriage in populations affected by this disease. Such knowledge will be essential for the development of infection control and prevention measures. Given the successful experience with Hib conjugate vaccines and great similarities between Hia and Hib antigenic characteristics,

Table 2: Reported Hia carriage in Papua New Guinea and Australia.

Geographical area/population	Time	Number of reported noninvasive Hia isolates	Carriage rate	Comments	Reference
Eastern Highlands of Papua New Guinea children <5 years	1978–1988	16 out of 209 (7.6%) *H. influenzae* isolates from nose	Not reported	Laboratory-based surveillance	Gratten and Montgomery, 1991 [54]
Papua New Guinea	March 1980–January 1983	43/505 of *H. influenzae* isolates from the upper respiratory tract of children <5 years	Not reported	Laboratory study of *H. influenzae* isolates from the upper respiratory tract of well children, children with pneumonia, and healthy adults	Gratten et al., 1984 [89]
Central Australia Aboriginal children	May 1990–August 1991	Hia is found in 6 out of 254 (2.4%) *H. influenzae* isolates from nasopharyngeal aspirates of children aged 1 month–12 years	Not reported	Study of carriage in Aboriginal children hospitalized with ALRI in Alice Springs	Gratten et al., 1994 [90]

an approach similar to the one for the existing highly successful Hib-conjugated vaccine can be applied. Hia capsular polysaccharide can be used as a vaccine antigen because it is the major immunogenic component of Hia, and serum antibodies against this antigen are potentially protective against invasive Hia disease [94]. In case of Hib, it has been demonstrated that in immune individuals, IgG and IgM antibodies to capsular polysaccharide antigens effectively protect against invasive disease by triggering complement-mediated bacteriolysis [95].

As bacterial capsular polysaccharides are T-cell-independent antigens, which stimulate a poor immune response in children below the age of 2 years [96], to induce a protective antibody response in young children, conjugation of Hia capsular polysaccharide with a protein carrier, rendering T-cell-dependent properties to the antigen, similar to the Hib conjugated vaccine design, is required. Indeed, immunization with protein-polysaccharide-conjugated vaccines, which are able to recruit T cells providing essential costimulatory signals stimulating antibody production, can successfully overcome low responsiveness of young children to polysaccharide antigens [97]. Because Hib-conjugated vaccines have been highly efficacious, a bivalent Hib-Hia vaccine formulation with similar carriers as those used for Hib vaccines can be used for immunization against both a and b strains of *H. influenzae*.

In addition, one of *H. influenzae* outer membrane proteins can be potentially used as a protein carrier. In particular, protein D is a highly conserved 42 kDa surface lipoprotein of *H. influenzae* and a virulence factor involved in the pathogenesis of respiratory infections [98–100]. Natural serum antibodies to protein D have bactericidal activity against NTHi and can be acquired by children during the first 2-3 years of life [101–103]. Recently, a new 10-valent pneumococcal polysaccharide vaccine conjugated to protein D (Synflorix) has been developed and used to immunize young children against otitis media caused by *Streptococcus pneumoniae* and *H. influenzae* [104, 105]. Protective effect of protein D-based vaccines against invasive disease caused by either NTHi or encapsulated *H. influenzae* has not been addressed, but importantly, this protein was found in all *H. influenzae* strains studied so far, including both encapsulated and nonencapsulated forms [98]. Our recent study found the lack of naturally acquired antibody against protein D in adult individuals immunocompromised as a result of severe organ diseases suggesting this as an underlying reason for an increased susceptibility to invasive NTHi disease among this population [106]. As antibodies to *H. influenzae* protein D exhibit bactericidal activity against nonencapsulated *H. influenzae* [104], conjugation of Hia capsular polysaccharide with protein D may offer additional benefits of protection against other strains of these bacteria, in addition to Hia. A serotype-unspecific vaccine against *H. influenzae*, based on protein D or other common antigens of this pathogen (outer membrane proteins, lipooligosaccharide, etc.), may be a useful approach to induce a broad immunity against infections caused by all types of this microorganism.

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