Socioeconomic Risk Factors for Invasive *Haemophilus influenzae* Type b Disease

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Socioeconomic risk factors for primary invasive *Haemophilus influenzae* type b (Hib) disease include factors that increase exposure to Hib (day care attendance, presence of siblings, and crowded households) and factors that increase an individual's susceptibility to Hib infections (short duration of breast feeding, parental smoking, and frequent infections in general). These factors are consistently found to be associated with risk of Hib disease in studies conducted in populations that differ in their Hib disease epidemiology. However, there are large differences in the prevalence of these risk factors among populations. According to present knowledge, variations in the prevalence of socioeconomic risk factors may explain most of the differences in the epidemiology of Hib disease and may also contribute to the differences in Hib vaccine efficacy in different populations.

Haemophilus influenzae type b (Hib) is a major cause of serious invasive infections in childhood. Spread via droplets followed by oropharyngeal colonization is the most common mode of transmission [1]; mouthing of objects such as toys contaminated with Hib also has been described [2]. Colonization can further give rise to invasive Hib infection. As much as 99% of Hib disease in different populations is endemic [3], and factors associated with primary Hib disease are thus of major public health importance.

The epidemiology of invasive Hib disease varies considerably among populations. Low incidences are found among Caucasian populations in Australia and Europe, whereas up to 10-fold greater rates are found among certain ethnic groups, such as American and Australian native populations [4–9]. In populations with high incidences of Hib disease, the age distribution is shifted toward younger age groups and epiglottitis is infrequently reported [7–9]. Similarly, Hib vaccine efficacy differs considerably between populations [10–13]. Although differences in subtypes of Hib have been demonstrated among populations, they cannot explain these epidemiologic differences [9].

Of all risk factors for invasive Hib disease, young age is the most important [14]. Most studies also show a predominance among males [4–6]. Conditions that impair host defenses as well as several genetic and racial factors have been associated with increased risk [9, 15–18], but evidence to date suggests that these contributions to the overall risk are minor.

Socioeconomic risk factors for invasive Hib disease can be divided into factors that affect an individual's susceptibility (short duration of breast feeding, parental smoking, and frequent infections in general) and that affect an individual's exposure to Hib bacteria (day care attendance, crowded households, and presence of young siblings). These factors may explain most of the differences in Hib disease epidemiology and may also help to explain the variability of Hib vaccine efficacy in different populations [13, 19]. We review the socioeconomic risk factors for invasive Hib disease and compare their impact in different populations. Our sources are recent controlled studies among primarily Caucasian populations in industrialized countries [18, 20–23] conducted using detailed data on cases and population-based controls and multivariate methods to analyze data.

Day Care Attendance

Day care attendance provides an increased exposure to many infectious agents, including Hib [24]. Contact between infants and young children in day care is close; thus it is likely that infectious agents are shared efficiently, leading to increased transmission of pathogens and probably to high infectious doses. In accordance with this expectation, day care attendance has been found to be an important socioeconomic risk factor for invasive Hib disease [20–23, 25] (table 1). The risk is highest for the youngest children and decreases with increasing age, so that there is little increased risk for children >2 years of age [18, 20, 22, 23, 25, 26]. However, one study [21] showed an increased risk with increasing age. That study did not address special day care practices in those settings, which might explain this difference. In a recent study by Wenger et al. [27] the use of towels or handkerchiefs to wipe the children's noses was identified as a specific day care practice that increased the risk of invasive Hib disease.

An increased risk with increasing size of the day care groups and increasing time spent in day care has been demonstrated in several studies [20, 21, 23]. However, such an effect was not detected in Finland, probably reflecting the small group sizes in day care (maximum of 6 infants or 12 1- to 2-year-olds in day care centers and 4–6 in family day care) [22, 28] and also the fact that Finnish children start day care

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Table 1. Estimated risk ratios for socioeconomic risk factors for invasive *Haemophilus influenzae* type b disease in various populations.

Risk factor	USA [21]	USA [20]	Finland [22]	Australia [23]
Day care attendance	1.9* (1.2–3.2)	3.9* (2.3–6.6)	5.0 (2.3–11)	4.3 (2.3–8.3)
Crowding	NS	2.7 (1.3–5.7)	—	4.7 (1.2–18)
Presence of siblings	3.1† (1.6–5.8)	NS	2.6‡ (1.7–4.1)	1.5‡ (0.9–2.7)
Previous hospitalizations	—	—	1.9 (1.0–3.4)	—
Previous otitis media	NS	—	2.2 (1.2–3.9)	—
Breast feeding	0.1§ (0.01–1.0)	0.08§ (0.01–0.6)	0.5‖ (0.3–0.9)	NS

NOTE. Risk ratios (95% confidence intervals) were estimated from multivariate analyses in population-based case-control studies and are for children <5 years of age. NS, not significant; —, not analyzed.

* Risk ratio estimates for 0- to 4-year-olds available only from univariate analysis.

† Elementary school–aged siblings.

‡ Siblings younger than school age.

§ Protective factor for infants <6 months of age.

‖ Protective effect associated with duration of breast feeding of ⩾6 months.

later in childhood than do children in the United States (table 2). Similarly, a recent study by Murphy et al. [25] showed no difference between the risk from attendance at day care centers and day care homes. Thus, a reasonable conclusion is that other characteristics [27] besides group size influence the intensity of exposure and risk of contracting Hib infection.

The start of day care attendance indicates intensive exposure to new infectious agents and could thus be the time when a child is most vulnerable for Hib infection and probably others. Indeed, the risk for invasive Hib disease was significantly higher during the first month of day care than during later months in the study conducted in Finland [22]. This factor has thus far not been studied in other populations. A practical conclusion is that preventive measures are most important just before and during the first month of a child's day care attendance.

Siblings and Crowded Households

Other factors associated with increased exposure to Hib are the presence of siblings [21–23] and crowding [18, 20, 23] (table 1). Crowded large households and especially extended family groups (families with three or more individuals beyond the nuclear family living in the household) have been reported to be a risk factor for Hib disease among Alaska natives (odds ratio [OR], 1.8; 95% confidence interval [CI], 0.9–3.3; $P < .04$) [34, 35] and are probably also an important risk factor among Navajos, who traditionally live in extended family groups.

Presence of siblings of elementary school age [21] or younger than school age [22, 23] has been found to increase the risk for invasive Hib disease. This risk factor is most important among the youngest children, with a doubling of the risk with each additional sibling [22]. The effect of siblings younger than school age was most important in Finland and Victoria, Australia, where day care attendance is uncommon during early childhood (table 2). Possibly in this situation young siblings offer the main source of exposure to Hib, whereas day care attendance plays a bigger role in the United States.

The presence of young siblings may increase the risk of invasive Hib disease in a younger sibling as follows. Children younger than school age have the highest oropharyngeal carriage rates of Hib [36]. Thus, the more siblings of this age a susceptible young child has, the more likely he or she is to acquire Hib and subsequently contract invasive Hib disease. Furthermore, the closer in age the siblings are to the young child, the more intimate the contact and the more likely the transmission of Hib. Close contact may also increase the infectious dose. This hypothesis is supported by results from a Finnish study in which family contacts of patients were studied for oropharyngeal carriage of Hib [37]. The highest carriage rates (86%) were found for a sibling of exactly the same age as the patient, namely a healthy twin, indicating an intimate contact and high rate of transmission between children of the same age. Lower rates were seen among other healthy siblings of twin patients (29%) or among age-

Table 2. Prevalence of day care attendance and breast feeding in various populations in relation to incidence and age distribution of invasive *Haemophilus influenzae* type b meningitis.

	USA [6, 29, 30]	Victoria, Australia [4, 31, 32]	Finland [5, 28, 33]
Day care outside home			
Children <1 year			
Day care center	5	3	0.5
Other	23	3	2
Children <5 years			
Day care center	25	10	13
Other	38	3	14
Duration of breast feeding			
⩾3 months	35	54	90
⩾6 months	27	38	70
⩾9 months	13	13	55
Incidence in children <5 years	60	25	26
% <6 months	19	11	5
% <2 years	81	72	59

NOTE. Prevalences are percentages; incidences are cases/100,000/year.

matched healthy siblings of non-twin patients (54%). The study also found an increased (threefold) risk of primary invasive Hib disease among twins, equally high for mono- and dizygotic twins [37]. This hypothesis is in accordance with the association of increased risk and severity of measles and intensive exposure in large families [38].

Frequent Infections

Previous hospitalization and a history of otitis media were associated with increased risk of Hib disease in a study conducted in Finland [22] (table 1). These have not been previously associated with increased risk for invasive Hib disease [17, 21], although they could have a close connection with increased rate of infection. However, previous hospitalizations (including a variety of diagnoses) increased the risk only moderately; thus it is possible that some socioeconomic factors associated with the probability of the child being hospitalized may have remained unrecognized in the study. A history of otitis media, which more specifically describes the child's history of infectious disease, was more strongly associated with the risk of Hib disease. The risk was highest for children <1 year of age. Although it is common among all US populations, otitis media is 15 times more common among populations with the highest incidence of invasive Hib disease: native Americans and Alaska natives [39].

In the study conducted in Finland, patients and their family members reported symptoms of upper respiratory tract infection (fever, cough, coryza, conjunctivitis, and headache) during 4 weeks before the patient's invasive Hib disease significantly more often than did their age-, sex-, and residence-matched controls and their family members (unpublished data). In the study by Istre et al. [21] such symptoms were not found to be associated with increased risk of Hib disease. A preceding or concurrent viral or *Mycoplasma pneumoniae* respiratory infection has previously been suggested to be associated with development of Hib meningitis [40–42] and is supported by experimental animal studies using influenza A virus, respiratory syncytial virus, and parainfluenza virus types 1 and 2 in the infant rat model [43, 44].

Socioeconomic Status

Previous uncontrolled studies have suggested that low family income and low level of education of the parents increase the risk for invasive Hib disease [45, 46], and this was also found in the univariate analysis in the study by Cochi et al. [20]. However, this effect disappeared when important socioeconomic risk factors such as day care attendance, crowding, presence of siblings, and breast feeding were controlled for [20]. No association between socioeconomic status and risk of Hib disease was found in the studies conducted in Finland and in Victoria, Australia. However, socioeconomic status in these populations is relatively homogeneous, so it was not surprising that statistically significant differences could not be found [22, 23].

Parental Smoking

Parental smoking has been found to be somewhat more common among parents of patients with invasive Hib disease than of controls [20, 22, 23]. Recently Vadheim et al. [18] found the presence of at least two persons in the household who smoked daily to be significantly associated with an increased risk of Hib disease (OR, 5.7; 95% CI, 1.4–23). Parental, especially maternal, smoking has been shown to increase the risk of both upper and lower respiratory tract infections [47, 48] and to impair ventilatory function [49]. It is likely that excessive exposure to tobacco smoke could cause damage to the respiratory mucosa, which could enhance the attachment and invasion of Hib and lead to an increased risk of disease [50]. This mechanism may also play a role among native American populations who traditionally use open fire for heating their homes [51]. This factor is currently being evaluated among Navajo children (Santosham M, personal communication).

Breast Feeding

The only protective factor for invasive Hib disease described so far is breast feeding. In studies conducted in the United States, a protective effect has been demonstrated among infants <6 months of age [20, 21] and among Alaska natives <18 months of age (OR, 0.53; 95% CI, 0.27–0.98) [34, 35]. In Finland, duration of breast feeding for at least 6 months was found to be protective [22] (table 2). The effect of breast feeding among Finnish infants <6 months old could not be analyzed because of the small number of patients in this age group [5, 22] and the fact that the majority of infants are breast fed: 70% of mothers breast feed for at least 6 months and 55% for 9 months [33].

The mechanism of the protective effect is not known. It may involve the presence of Hib anticapsular antibodies in human milk or the enhancement of the immune responses to Hib among breast fed infants [52, 53]; it may also indicate an effect related to the child being breast fed such as the mother staying home with the child.

Discussion

It is remarkable that results from risk factor studies conducted in different populations consistently show the same socioeconomic factors to be associated with risk of invasive Hib disease. The risk is increased by factors that increase exposure to Hib (day care attendance, crowded households, presence of young siblings) and factors that modify the susceptibility (e.g., short duration of breast feeding). Since young age is the most important risk factor for Hib disease, it is reasonable that the socioeconomic risk factors detected in these studies give the most significant risk estimates for the youngest age groups. Furthermore, the estimated risk ratios

for the different risk factors from these studies are comparable: The 95% confidence intervals overlap for each respective risk ratio (table 1).

Thus, the prevalence of these risk factors in different age groups in these populations could be decisive in determining their overall impact. Such variation could actually explain differences in incidence and age distribution between populations. Among 18- to 24-month-old White Mountain Apache children in Arizona an impaired antibody response to Hib capsular polysaccharide was reported, which could theoretically explain the high incidence of Hib disease in that population [54]. However, most of the disease among the Apache children occurs among children <18 months of age, a time when all children, irrespective of genetic background, are unable to respond to polysaccharide antigens [55]. Thus it is likely that genetic factors play a minor role and socioeconomic risk factors such as frequent infections and crowding are of major importance in increasing susceptibility to invasive Hib disease. As discussed by Ward et al. [13], socioeconomic differences that lead to an early and intense exposure to Hib bacteria in the Alaska native population, in addition to the somewhat poorer immunogenicity of the Hib conjugate vaccine among Alaska natives than Finnish children, are important factors in explaining the dissimilar efficacy of the vaccine among Alaska native and Finnish children [12, 13].

We compared the prevalence of day care attendance, the most important risk factor among primarily Caucasian populations in industrialized countries, with the only protective factor, breast feeding (table 2). In the 1980s, infants were ~10 times more likely to be cared for outside the home in the United States [29] than in Finland [28] and 5 times more so than in Victoria, Australia [31]. The same trend was apparent also for children <5 years of age. An increase in the use of day care outside the home has been apparent in all of these countries during the past decade and is continuing.

Prolonged breast feeding has been common in Finland during the past decade, with 70% of mothers breast feeding for at least 6 months [33] compared with 38% in Victoria, Australia [32], and 27% in the United States [30]. Half of Finnish mothers continue breast feeding for >9 months compared with one-tenth of mothers in the United States and Australia. The prolonged breast feeding in Finland is possible because of the entitled maternity leave, which lasts up to 9 months after delivery. Furthermore, ≤8% of mothers start work outside home before the end of the maternity leave [56], so only a minority of infants need to be cared for outside the home (table 2). Both these factors protect Finnish children against invasive Hib disease and shift the age distribution of Hib disease toward older age groups.

In populations with high incidence rates and early onset of Hib disease, such as Alaska natives and native Americans, day care outside the home is not common, and high infection pressure (early and intense exposure to Hib and other pathogens) apparently exists because of the traditional extended families. Furthermore, breast feeding is not very common; 37% of mothers breast feed for at least 6 months and 29% for at least 9 months [34, 35]. In addition, the susceptibility of infants and children may be increased by yet-undefined factors such as inhalation of smoke produced during heating with open fire.

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