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Invasive *Haemophilus influenzae* in the United States, 1999–2008: Epidemiology and Outcomes

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Summary

In a multivariable analysis of cases with invasive *H. influenzae*, prematurity in infants, advanced age and certain chronic diseases in adults were associated with an increased risk of in-hospital death. Nontypeable disease was associated with higher mortality in the elderly.

Keywords

Haemophilus influenzae; United States; multivariable analysis; mortality

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Introduction

Since the introduction of the Hib conjugate vaccine in the United States, there has been a dramatic decrease of Hib among children less than 5 years of age (1, 2). With the decline of Hib, the relative importance of nontypeable *H. influenzae* as a cause of invasive disease has increased. Despite the absence of a capsule, nontypeable strains can still cause invasive disease. The bacterial factors in nontypeable strains that contribute to the pathogenesis of invasive disease are poorly defined, largely due to the genetic and phenotypic diversity of nontypeable strains (3, 4). Additionally, host factors that increase susceptibility to invasive nontypeable disease are not well understood.

Although many epidemiologic studies have reported mortality rates from invasive *H. influenzae*, these rates are often reported by age group, serotype, or clinical presentation. Only one study, to our knowledge, has performed a multivariable analysis to adjust for the relative contributions of such factors (5), and its findings have not been validated in other populations. Understanding risk factors for mortality is important to optimizing prevention strategies, which may someday include use of a non-Hib vaccine.

The goals of the current project are to describe the characteristics and clinical outcomes of pediatric and adult patients with invasive *H. influenzae* (HI) and, through multivariable analysis, identify risk factors for in-hospital mortality. The current report extends the analysis of surveillance data from the Active Bacterial Core surveillance (ABCs) program that was recently published (6).

Patients and Methods

Surveillance

Active, population- and laboratory based surveillance for HI was conducted from January 1, 1999 through December 31, 2008 as part of Active Bacterial Core surveillance (ABCs). ABCs is supported by the U.S. Centers for Disease Control and Prevention (CDC) as part of its Emerging Infections Program (EIP) Network, as described elsewhere (7).

The surveillance area included 5 states and 5 metropolitan areas (6). The population under surveillance was 27,779,979 in 1999 and 35,559,550 in 2008 (representing 10.2% and 11.7% of the US population in 1999 and 2008, respectively).

Definition of variables—A case of HI was defined as isolation of *H. influenzae* from a normally sterile site, which included blood, cerebrospinal fluid (CSF), synovial fluid or other sterile site aspirate; sputum and urine isolates were excluded. All cases were residents of a surveillance area. After case identification, the patient's medical record at the treating facility was reviewed using a standard case report form. Community-acquired cases were defined as isolation in the community setting or within 48 hours of hospital admission, and healthcare-associated cases were defined as isolation more than 2 days after hospitalization. In-hospital mortality, or death with HI, was defined as death due to any cause prior to hospital discharge.

Cases were classified by clinical syndromes in the following manner: a case was designated meningitis if a clinical diagnosis of meningitis had been entered into the patient's medical record or if *H. influenzae* was isolated from the CSF; pneumonia was defined at having a diagnosis of pneumonia entered in the medical record and *H. influenzae* isolated from blood or pleural fluid during the hospital admission. When *H. influenzae* was isolated from blood and no other localized clinical syndrome was described, the case was classified as bacteremia without an identifiable focus.

The following underlying conditions were recorded from abstraction of the medical record: alcohol use, asthma, atherosclerotic heart disease (ASCVD), CSF leak, cirrhosis, cerebral vascular accident (CVA), chronic obstructive pulmonary disease (COPD), diabetes mellitus, dialysis, heart failure, HIV infection, intravenous drug use (IVDU), nephrotic syndrome, smoking, and systemic lupus erythematosus. In addition, a designation of immunocompromised state was utilized if the case patient had asplenia, immunoglobulin deficiency, sickle cell disease, current immunosuppressive therapy or a history of organ transplantation. Hematologic malignancies included lymphoma, leukemia, and multiple myeloma. Non-hematologic malignancies included all other malignancies, excluding basal cell and squamous cell cancer of the skin. Prematurity was defined as birth prior to 37 weeks gestational age. Prematurity was not included on the standard case report form but was determined based on written comments or gestational age less than 37 weeks at birth, if available at chart abstraction.

Chart abstraction for underlying conditions was performed from 1999–2008 at surveillance sites in CA, CT, MN, NY, OR and TN. GA and CO began recording underlying conditions in 2000, MD in 2001, and NM in 2004. NY did not collect information on HIV. Documentation of smoking status was initiated in 2000, and CVA was added in 2001.

Laboratory Methods

In this analysis, *H. influenzae* isolates were classified based on their serotype; serotype b (Hib), nontypeable (non-encapsulated), and non-b (serotypes a, c, d, e, and f). The term "encapsulated" includes Hib and non-b serotypes.

Serotyping of *H. influenzae* was performed at state public health laboratories. Isolates were sent to the CDC, where serotype was confirmed by slide agglutination. Serotyping results were discordant in 6% (256/4191) of the serotyped isolates. In most discordant cases, an isolate was found to be typeable at one laboratory and nontypeable at the other (n=246). In addition, a total of 702 isolates from the Georgia surveillance site were confirmed by capsule gene PCR. For this analysis, the CDC slide agglutination serotype result or the capsule-gene PCR serotype for Georgia isolates was used as the final serotype. If an isolate was non-viable or contaminated on arrival to the CDC, the result from the state laboratory was used.

A molecular analysis of 297 strains classified as nontypeable confirmed that 294 were indeed nontypeable; only 3 were *H. haemolyticus* (S. Satola, personal communication).

Statistical analysis

When medians were calculated, a corresponding interquartile range (IQR) was determined. Categorical variables were compared using the χ^2 test or, if the sample size was small, the Fisher's exact test. Continuous variables were compared with the *t* test. A p-value < 0.05 was considered significant.

A logistic regression model was developed to identify predictors of in-hospital mortality. Separate models were developed for children (<1 and 1–17 years) and adults (≥ 18 years). Cases with incomplete data were excluded from the model. For the adult model, the main predictor variables were serotype and clinical syndrome. Other factors associated with mortality (p-value <0.10) on univariate analysis were also included in the model. Collinearity was assessed with a validated macro (8). All possible two-way interactions were evaluated for the 2 main variables of interest: serotype and clinical syndromes. The likelihood ratio test was used to compare a non-interaction to an interaction model for each series of potential interacting terms. Variables were removed from the model using backward selection, requiring a p-value of less than 0.05 to remain, until the most parsimonious model was achieved. Model aptitude was evaluated with the c-statistic. All statistical analysis was done with SAS version 9.2 (SAS Institute, Cary, North Carolina). This study was approved by Emory University's Institutional Review Board.

Results

A total of 4,839 cases of HI were identified between 1999 and 2008; 93.6% were community-acquired and 6.4% were healthcare-associated. Of the 3,928 community-acquired strains available for serotyping, 68.5% were nontypeable, 27.8% were non-b, and only 3.7% were Hib. Of 263 healthcare-associated infections with known serotype, 85.6% were nontypeable, 12.5% non-b, and 1.9% type b. Among children, healthcare-associated cases occurred a median of 7 days after admission (IQR 3–10), and in adults, healthcare-associated cases occurred a median of 5 days after admission (IQR 4–9).

Children accounted for 828 (17.1%) and adults 4,011 (82.9%) HI cases during the surveillance period. The median age among children was 1.1 years (IQR 83 days-4.4 years), and the median age in adults was 67.7 years (IQR 51.5–80.7).

Demographic characteristics and incidence rates for this surveillance period have been described elsewhere.(6) Tables 1a and 1b show the prevalence of serotypes, clinical syndromes, underlying conditions, and outcomes by age group.

Among the 828 pediatric cases, 174 (21.0%) occurred within 28 days after birth. 161 (92.5%) of these neonatal cases were early-onset (<7 days after birth) and 13 (7.5%) were late-onset (≥7 days after birth). Nearly half of all cases occurring in infants less than 3 months of age were in premature infants. Overall, gestational age was available for 147 infants with HI: 44 (29.9%) were < 28 weeks, 41 (27.9%) were 28–33 weeks, 22 (15.0%) were 34–36 weeks, and 40 (27.2%) were ≥ 37 weeks. Birth weights for these 147 infants were as follows: 36 (24.5%) were < 1000 grams, 31 (21.1%) were 1000–1499 grams, 25 (17.0%) were 1500–2499 grams, and 55 (37.4%) were ≥ 2500 grams. The highest mortality

rates were seen in the infants < 28 weeks gestational age (36.4%) or < 1000 grams at birth (36.1%). Of 35 infants who died, 30 (85.7%) had nontypeable HI disease, 2 (5.7%) had non-b disease, and 3 (8.6%) were infected with strains of unknown serotype.

Underlying conditions were present in 247 of 805 (30.7%) children; 5.2% of children had more than 1 underlying condition. Among children, the most common underlying conditions were prematurity (14.3%), asthma (7.0%), and an immunocompromised state (6.7%).

Underlying conditions were present in 2869 of 3838 (74.8%) adults; 23.0% of adults had 2 underlying conditions, and 24.5% had 3 or more. In adults, the most common underlying conditions were COPD (21.9%), diabetes (19.4%), and ASCVD (18.8%).

As shown in Tables 1a and 1b, hospitalization rates were highest in the ≥ 65 age group (94.9%) and in infants < 3 months (94.1%). Infants < 3 months had the longest hospital stays with a median duration of 11 days (IQR 7–30). In-hospital mortality was highest in cases ≥ 65 years (21.9%), followed by those < 3 months (16.2%) and 40–64 years (12.4%). Mortality rates varied by serotype: type a 7.8% (7/90), type b 10.1% (15/149), type c 27.3% (8/11), type d 42.9% (6/14), type e 12.3% (29/236), type f 9.8% (75/762), nontypeable 17.3% (501/2895), and unknown serotype 16.6% (106/637). Overall in-hospital mortality was 11.0% for infections due to encapsulated strains.

Comparison between nontypeable and encapsulated HI disease

Adults with nontypeable HI were significantly older than adults with encapsulated HI (66.6 vs. 62.8 years, p<0.01). Both adults and children with nontypeable HI had significantly longer lengths of hospital stay than encapsulated cases (children: 17.7 vs. 9.1 days, p<0.01; adults: 10.4 days vs. 8.6 days, p<0.01). Compared to encapsulated HI, nontypeable disease was more likely to cause bacteremia without an identifiable focus, a difference most notable among children (61.2% vs. 28.3%, p<0.01) but also seen in adults (31.1% vs. 26.0%, p<0.01). Nontypeable strains were less likely than encapsulated strains to cause pediatric meningitis (11.0% vs. 33.5%, p<0.01). Nontypeable HI was associated with higher mortality rates than encapsulated HI in infants <1 year of age and in adults (infants <1 yr 14.6% vs. 5.7%%, p=0.01; adults 18.8% vs. 12.2%, p<0.01).

Children with nontypeable HI were more likely to be premature infants than those with encapsulated disease (21.6% vs. 1.9%, p<0.01). Several underlying conditions were significantly more common in adults with nontypeable HI than those with encapsulated HI, including ASCVD (21.0% vs. 16.1%, p<0.01), CSF leak (0.5% vs 0, p=0.04), dialysis (8.2% vs. 4.5%, p<0.01), heart failure (19.8% vs. 9.7%, p<0.01), hematologic malignancy (7.2% vs. 4.8%, p<0.01), and non-hematologic malignancies (11.3% vs. 7.3%, p<0. 01). Compared to cases with nontypeable HI, adult cases of encapsulated HI were more likely to use alcohol (8.3% vs. 5.9%, p=0.01), smoke (21.8% vs. 4.7%, p<0.01), have asthma (10.0% vs. 7.1%, p<0.01), HIV (7.1% vs. 3.3%, p<0.01), or IVDU (3.3% vs. 1.3%, p<0.01).

Predictors of in-hospital death

Characteristics associated with in-hospital mortality on univariate analysis are shown in Table 2. There were 648 cases of unknown serotype, all of which were excluded from this

analysis. No significant differences were noted in length of hospitalization or rates of death between cases of known and unknown serotype. Cases of unknown serotype, however, were significantly older (56.8 vs. 54.2 years, p=0.04).

Two pediatric models were constructed using variables that had a p-value <0.10 on univariate analysis. The first model for children < 1 year of age had 360 cases and included the following variables: age < 3 months, race, prematurity (<28 weeks, and 28–36 weeks), and serotype. After backward selection, only prematurity was associated with in-hospital death: <28 weeks (OR 7.1, 95% CI 3.2–15.6), 28–36 weeks (OR 2.1, 95% CI 0.9–4.8). The model for children aged 1–17 years had 372 cases and included the following variables: bacteremia without identifiable focus, dialysis, hematologic malignancy and healthcare-associated HI. After backward selection, healthcare-associated HI (OR 5.66, 95% CI 1.84–17.39) and dialysis (OR 18.11, 95% CI 2.77–118.65) were associated with in-hospital death.

In adults, 18 variables with a p-value <0.10 on univariate analysis were included in the logistic regression model (Table 2). No collinearity was present. Interaction was detected between age and serotype (nontypeable vs. encapsulated) using the likelihood ratio test (p=0.02). Among cases with nontypeable HI, patients ≥ 40 years had greater in-hospital mortality than cases 18–39 years (40–64 years: OR 1.97, 95% CI 1.05–3.67; ≥ 65 years: OR 4.01, 95% CI 2.20–7.32). However, increasing age did not significantly increase the risk of death in cases of encapsulated disease. The presence of HI due to nontypeable strains was significantly associated with increased in-hospital death in those 65 years of age and older (OR 1.81, 95% CI 1.31–2.52). Other factors associated with in-hospital death in multivariable analysis, as shown in Table 3, were healthcare-associated HI (OR 2.42, 95% CI 1.66–3.53), bacteremia without identifiable focus (OR 2.74, 95% CI 1.70–4.42), bacteremic pneumonia (OR 2.11, 95% CI 1.32–3.36) and the presence of the following underlying conditions: cirrhosis (OR 3.74, 95% CI 2.24–6.25), CVA (OR 2.10, 95% CI 1.45–3.06) dialysis (OR 1.74, 95% CI 1.24–2.45), heart failure (OR 1.53, 95% CI 1.19–1.97), and non-hematologic malignancies (OR 1.81, 95% CI 1.34–2.46). Patients with asthma were less likely to die with HI (OR 0.60, 95% CI 0.38–0.95). The area under the Receiver Operating Characteristic (ROC) curve for the final model indicated good discrimination (c=0.712).

Discussion

With the dramatic decline of Hib disease, the relative importance of nontypeable HI has increased. The overall incidence of invasive nontypeable HI remains low in countries like the United States (1 per 100,000 persons), but rates of nontypeable disease are higher at the extremes of age (6, 9, 10). In addition, nontypeable strains now account for over half of all cases of invasive *H. influenzae* disease in the US and other parts of the world (11–14). Despite their diminished virulence, nontypeable strains can result in serious disease. In the current study, nontypeable HI was associated with longer hospital stays and higher mortality rates than encapsulated disease in both children and adults. The health status of the patient is likely to be a factor in susceptibility to nontypeable HI disease and to less favorable clinical outcomes.

The current study reiterates the importance of nontypeable HI as a neonatal pathogen (15). In infants < 3 months of age with invasive HI, 82% of disease was due to nontypeable strains and 86% of all in-hospital deaths were associated with nontypeable strains. Many of the infections in neonates occurred within one week of birth, suggesting acquisition during labor and delivery or in utero.

Prematurity was common among infants with HI, as has been seen in other studies (16, 17). More than a quarter of all children with HI had underlying conditions. Others have reported a higher prevalence (41–70%) of underlying conditions in children with HI (4, 18), but one of these studies reflected the experience of a single tertiary care center (4) and the other represented a smaller population than the current project (18).

Prematurity was the lone factor predictive of death with HI in children < 1 year of age, and the risk was higher among babies <28 weeks. Since documentation of prematurity was not uniformly recorded on the case report form during the 1999–2008 study period, it is possible that the prevalence was under-reported and thus, the association between prematurity and death may be underestimated.

The prevalence of underlying conditions among adults in this cohort (74.8%) was similar to other reports (19–21). With the decline of encapsulated disease, the traditional risk factors for HI (e.g. defects in humoral immunity, asplenia) may be changing. In the current study, certain co-morbidities in adults were more likely to be associated with nontypeable rather than encapsulated HI, including ASCVD, heart failure, dialysis, and malignancy. None of these conditions confers a specific immune defect, suggesting that predisposition to nontypeable disease is multifactorial. The high prevalence of cardiovascular disease among cases of nontypeable HI has been previously described (10).

In the current project, the relationship between nontypeable HI and in-hospital death among those ≥ 65 years of age persisted even after adjusting for other predictors of death. Although prior studies have identified a high case-fatality rate for nontypeable strains, particularly in the elderly, these studies have not used a multivariable analysis to define the relative contribution of nontypeable disease (6, 9, 10). The current analysis also determined that increasing age, a common risk factor for worse outcomes, was only associated with higher mortality rates in nontypeable infections but not in encapsulated infections. Since nontypeable strains have been considered less likely to cause invasive disease than encapsulated strains (22), this association may reflect the relative importance of the host's susceptibility rather than virulence of the nontypeable pathogen. Adults who developed nontypeable infections may have been more debilitated with significant underlying illnesses than those who developed encapsulated infections. The current project, however, did not document the functional status of case patients or severity of underlying diseases.

Several underlying conditions were associated with in-hospital death in adults, including cirrhosis, CVA, dialysis, heart failure, and non-hematologic malignancies. Dialysis was also associated with in-hospital death in children 1–17 years of age. A better understanding of those at risk for poor outcomes with HI may become particularly relevant if a nontypeable or universal HI vaccine is developed. Older adults may be candidates for a nontypeable

vaccine, although vaccine responsiveness would be a concern (23). A vaccine that used *H. influenzae*-derived protein D as a carrier protein for pneumococcal polysaccharides showed a decrease in otitis media due to both *S. pneumoniae* and nontypeable *H. influenzae* among children (24), but it has yet to be shown whether a similar approach would work for other nontypeable HI infections.

The current study has several strengths. Using active, population-based surveillance, the characteristics of HI in a large cohort were closely monitored over 10 years. Isolates were collected for serotype verification and clinical and demographic information was recorded from the medical records. Few studies have achieved the power to assess the association of comorbidities, clinical and isolate characteristics with outcomes of HI, as has been done in the current project.

The study has several limitations. First, the multivariable analysis reflects only in-hospital mortality, which is not a complete measure of overall clinical outcome and does not determine whether in-hospital deaths were attributable to HI. In addition, although data were carefully collected on the presence of underlying conditions, the severity of these conditions was not quantified. Controlling for the overall debilitation of the patient may provide a better understanding of the association between nontypeable HI and death. Finally, the sample size for the pediatric models was relatively small, which resulted in less precise estimations.

In conclusion, invasive *H.influenzae* is now primarily an infection associated with nontypeable strains in adults with chronic diseases. On multivariable analysis, in-hospital death was associated with prematurity in infants, dialysis and healthcare-associated onset in older children, and a number of chronic diseases in adults. Nontypeable HI was associated with increased mortality in the elderly. Further investigation is needed to better understand the host factors that predispose to serious infection and poor outcomes associated with nontypeable HI and to help identify those who would benefit from future HI vaccines.

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Table 1

a. Characteristics of children with invasive *H. influenzae*, 1999–2008

	Age <3 mos (n=216) %	Age 3–11 mos (n=186) %	Age 1–4 yrs (n=230) %	Age 5–17 yrs (n=196) %	Total (n=828) %
Serotypes					
Nontypeable	82.2	37.3	50.0	64.3	59.0
Non-b	6.4	43.2	34.4	20.4	25.7
Type b	3.2	11.9	7.4	5.1	6.7
Unknown	8.2	7.6	8.3	10.2	8.6
Syndromes					
Bacteremia w/o focus	83.6	33.0	34.8	46.9	50.1
Pneumonia	7.3	20.0	29.6	19.4	19.2
Meningitis	5.9	33.5	19.1	14.3	17.7
Other	3.2	13.5	16.5	19.4	13.0
Underlying conditions[1]					
Any condition	51.2	10.6	23.2	35.3	27.3
Asthma	0	3.9	11.4	12.6	6.2
Dialysis	0	0	0.5	2.1	0.5
Heart failure	0	0.6	1.4	0	0.4
Hematologic malig	0	0	3.6	7.9	2.5
HIV/AIDS	0	0.6	0	4.6	1.2
Immunocompromised	0.5	2.2	10.0	14.2	6.0
Nephrotic syndrome	0	0	0.5	2.6	0.7
Non-hematologic malig	0	0	2.3	2.6	1.1
Prematurity	49.8	2.8	1.4	0	12.7
Hospitalization	94.1	80.5	78.3	74.0	81.9
Healthcare-associated HI	4.6	6.5	8.7	6.6	6.6
Length of stay in days, median (IQR)	11 (7–30)	8 (4–14)	6 (3–11)	4 (3–9)	8 (3–15)
In-hospital Mortality	16.2	6.5	4.4	5.6	8.3

b. Characteristics of adults with invasive *H. influenzae*, 1999–2008

	Age 18–39 yrs (n=485) %	Age 40–64 yrs (n=1341) %	Age ≥ 65 yrs (n=2185) %	Total (n=4011) %
Serotypes				
Nontypeable	60.8	53.3	64.8	60.5
Non-b	19.0	28.2	20.3	22.8
Type b	2.3	3.4	1.7	2.3
Unknown	17.9	15.2	13.1	14.4
Syndromes				
Bacteremia w/o focus	37.7	32.1	26.5	29.7
Pneumonia	31.3	51.2	66.2	56.9
Meningitis	9.7	6.9	2.8	5.0
Other	21.2	9.9	4.6	8.4
Underlying conditions[2]				
Any condition	51.3	75.2	79.6	74.8
Alcohol	5.9	12.5	2.8	6.4
Asthma	9.0	10.7	6.0	7.9
ASCVD	0.4	9.1	28.7	18.8
Cirrhosis	2.0	4.7	1.3	2.5
COPD	2.2	16.4	29.6	21.9
CSF leak	0.9	0.6	0.1	0.4
CVA[3]	0.3	3.0	7.7	4.6
Diabetes	6.1	19.2	22.4	19.4
Dialysis	4.4	7.3	7.9	7.3
Heart failure	1.5	7.5	25.7	16.8
Hematologic malig	2.2	7.2	6.8	6.4
HIV/AIDS	13.3	7.7	0.1	4.2
Immunocompromised	9.0	14.9	11.3	12.2
IVDU	4.6	3.7	0	1.8
Lupus	1.8	0.8	0.4	0.7
Nephrotic syndrome	0.4	0.3	1.2	0.8

b. Characteristics of adults with invasive *H. influenzae*, 1999–2008

	Age 18–39 yrs (n=485) %	Age 40–64 yrs (n=1341) %	Age ≥ 65 yrs (n=2185) %	Total (n=4011) %
Non-hematologic malig	2.6	10.0	12.3	10.4
Smoker[3]	21.9	27.9	8.3	16.5
Hospitalization	85.6	91.0	94.9	92.5
Healthcare-associated HI	7.8	7.5	5.2	6.3
Length of stay in days, median (IQR)	4 (3–9)	7 (4–13)	6 (4–11)	6 (4–11)
In-hospital Mortality	7.1	12.4	21.9	17.0

[1] Information on underlying conditions was available for 215 cases <3 mos, 180 cases 3–11 mos, 220 cases 1–4 yrs, and 190 cases 5–17 yrs. HIV status was not collected in New York State.

[2] Information on underlying conditions was available for 456 cases 18–39 yrs, 1276 cases 40–64 yrs, and 2106 cases ≥65 yrs. HIV status was not recorded in New York State.

[3] Surveillance for smoking status began in 2000 and for CVA in 2001.

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Table 2

Association between clinical characteristics and in-hospital mortality among 754 pediatric and 3407 adult cases of invasive *H. influenzae* disease, 1999–2008

Characteristic	Children < 1 year			Children 1–17 years			Adults		
	Deaths (n=43) %	Survived (n=325) %	p-value	Deaths (n=20) %	Survived (n=366) %	p-value	Deaths (n=574) %	Survived (n=2833) %	p-value
Age < 3 mos	74	51	<0.01	--	--	--	--	--	--
Age > 65 years	--	--	--	--	--	--	4	13	<0.01
Male gender	49	42	0.44	60	45	0.18	45	44	0.70
White race	65	68	0.70	50	53	0.79	73	70	0.13
Black race	33	20	0.07	25	25	0.99	12	16	0.03
Healthcare-associated	5	6	1.00	25	7	0.02	11	5	<0.01
NT v. encapsulated	84	65	0.01	65	62	0.79	79	69	<0.01
Bacteremia	65	59	0.45	60	38	0.05	34	29	0.01
Pneumonia	16	12	0.39	20	27	0.50	62	57	0.06
Meningitis	12	21	0.14	15	18	1.00	2	6	<0.01
Other syndromes	0	1	1.00	0	2	1.00	2	7	<0.01
Underlying conditions	**(n=40)**	**(n=320)**	**p-value**	**(n=19)**	**(n=353)**	**p-value**	**(n=558)**	**(n=2714)**	**p-value**
Alcohol	--	--	--	--	--	--	9	6	0.01
Asthma	3	2	0.51	0	13	0.15	5	9	0.01
ASCVD	--	--	--	--	--	--	27	18	<0.01
Cirrhosis	--	--	--	5	1	0.15	5	2	<0.01
CSF leak	--	--	--	0	<1	1.00	0	<1	0.23
CVA	--	--	--	0	<1	1.00	10 (n=471)	4 (n=2406)	<0.01
COPD	--	--	--	--	--	--	24	22	0.40
Diabetes	0	<1	1.00	0	<1	1.00	22	19	0.05
Dialysis	--	--	--	11	1	0.02	13	6	<0.01
Heart failure	--	--	--	5	1	0.15	27	15	<0.01

Characteristic	Children < 1 year			Children 1–17 years			Adults		
	Deaths (n=43) %	Survived (n=325) %	p-value	Deaths (n=20) %	Survived (n=366) %	p-value	Deaths (n=574) %	Survived (n=2833) %	p-value
Hematologic malig	--	--	--	16	5	0.08	8	6	0.30
HIV	0	<1	1.00	0	2	1.00	3 (n=490)	5 (n=2486)	0.18
Immunocompromised	0	2	1.00	16	12	0.71	16	12	0.01
IVDU	--	--	--	--	--	--	3	2	0.22
Non-heme malig	--	--	--	0	3	1.00	16	9	<0.01
Prematurity	55	26	<0.01	0	1	1.00	--	--	--
Smoker	--	--	--	--	--	--	26 (n=253)	18 (n=2578)	0.01
Any malignancy	--	--	--	16	8	1.00	22	15	<0.01
Any non-cancerous underlying condition	60	29	<0.01	21	24	1.00	75	63	<0.01

[*] For pediatric cases, the Fisher's exact test was used to compare rates for all underlying conditions and selected other variables when the cell counts were small. The χ^2 test was used to compare all remaining categorical variables.

Table 3

Predictors of in-hospital mortality in 2877 adult cases of invasive *H. influenzae* determined by logistic regression

Variable	Odds ratio (95% CI)
Age: 40–64 vs. 18–39 yrs	
nontypeable	1.97 (1.05–3.67)
encapsulated	1.29 (0.51–3.23)
Age: ≥ 65 vs. 18–39 yrs	
nontypeable	4.01 (2.20–7.32)
encapsulated	1.47 (0.59–3.67)
Nontypeable vs. encapsulated	
18–39 yrs	0.82 (0.48–1.40)
40–64 yrs	1.02 (0.65–1.60)
≥ 65 yrs	1.81 (1.31–2.52)
Healthcare-associated HI	2.42 (1.66–3.53)
Bacteremia without identifiable focus	2.74 (1.70–4.42)
Bacteremic pneumonia	2.11 (1.32–3.36)
Asthma	0.60 (0.38–0.95)
Cirrhosis	3.74 (2.24–6.25)
CVA	2.10 (1.45–3.06)
Dialysis	1.74 (1.24–2.45)
Heart failure	1.53 (1.19–1.97)
Non-hematologic malignancy	1.81 (1.34–2.46)