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**The Changing Epidemiology of Invasive *Haemophilus influenzae* Disease in Metropolitan Atlanta during the Hib Vaccine Era, 1989-2008**

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# The Changing Epidemiology of Invasive *Haemophilus influenzae* Disease in Metropolitan Atlanta during the Hib Vaccine Era, 1989-2008

**By**

**Daniel Livorsi, MD**

**Advisor: Monica M. Farley, MD**

**An abstract of**
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**Abstract:**

**The Changing Epidemiology of Invasive *Haemophilus influenzae* Disease in Metropolitan Atlanta during the Hib Vaccine Era, 1989-2008**

**By Daniel Livorsi, MD**

**Background:** An effective *Haemophilus influenzae* type b (Hib) conjugate vaccine was licensed in the U.S. for use in young children in 1987 and infants in 1990. We describe changes in the epidemiology of invasive *H. influenzae* (HI) disease after Hib vaccine introduction and evaluate predictors of mortality.

**Methods:** Population-based, active surveillance was conducted for HI in metropolitan Atlanta, GA between 1/1/89 and 12/31/08.

**Results:** A total of 1207 cases of HI were identified during 1989-2008. The incidence of HI decreased significantly between 1989 and 2008 (5.1 to 1.1 cases per 100K, $\chi 2$ trend $p<0.001$). Rates of HI decreased significantly in all age groups except those ≥ 65 yrs. The largest absolute decline of HI was in infants < 2 yrs (90.9 to 6.4 cases per 100K, $\chi 2$ trend $p<0.001$). Rates of Hib disease decreased in children (99% decrease, $\chi 2$ trend $p<0.001$) and adults (96% decrease, $\chi 2$ trend $p<0.001$). Rates of capsule type f increased in adults (205% increase, $\chi 2$ trend $p=0.04$).

The median age for HI cases was 10 months in children and 60 years in adults. Seventy-one percent of adults and 23% of children had underlying conditions. The relative risk of HI was higher in blacks than whites: 1.5 (95% CI 1.3-1.7). Children accounted for 73% of cases in 1989-1990 but only 24% in 2000-2008. In 1989-1990, Hib caused 85% of HI disease in children and 56% in adults. During 2000-2008, the most common isolates were either nontypeable (66%) and type f (24%).

Overall in-hospital mortality rate was 12% (7% in children, 16% in adults). On multivariate analysis of cases from 2000-2008, risk factors for in-hospital death included age < 2 years, age ≥ 40 years, bacteremia without an identified focus, and nontypeable disease.

**Conclusion:** Since introduction of the Hib conjugate vaccine, the incidence of HI disease has significantly decreased in all age groups except ≥ 65 years. Hib disease has declined in children and non-immunized adults. HI is now primarily a disease of adults with chronic diseases due to nontypeable and type f strains. In-hospital death with invasive HI infection was associated with the extremes of age and infection with nontypeable strains.

# The Changing Epidemiology of Invasive *Haemophilus influenzae* Disease in Metropolitan Atlanta during the Hib Vaccine Era, 1989-2008

**By**

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**A thesis submitted to the Faculty of the**
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## Introduction:

*Haemophilus influenzae* is a gram-negative bacterium responsible for a variety of infections. *H. influenzae* has 6 serotypes (a-f), which are based on the antigenic properties of the capsular polysaccharide. Non-encapsulated strains are classified as nontypeable *H. influenzae*.

*H. influenzae* is a normal commensal within the upper respiratory tract of humans. Secretions or droplets from the nose or throat of a colonized person can spread the bacteria to others. Rates of colonization with nontypeable *H. influenzae* are high and exceed 50% by the age of 5 years (1). Before widespread use of the Hib conjugate vaccine, 2-4% of children were colonized with *H. influenzae* serotype b (Hib). These children served as a natural reservoir of Hib, facilitating transmission to other children or adults.

Due to a variety of host and bacterial factors, colonization with *H. influenzae* can sometimes result in local respiratory or invasive disease. Nontypeable strains are commonly associated with non-invasive respiratory infections such as sinusitis, otitis media, or pneumonia. In contrast, Hib is often associated with serious invasive infections, such as bacteremia, septic arthritis, and meningitis.

Hib is the most virulent of all serotypes, a property attributed to its distinctive polysaccharide capsule: a linear polymer of ribosyl-ribitol phosphate (PRP). Animal models have repeatedly demonstrated the heightened virulence of Hib compared to other serotypes (2, 3). Epidemiologic studies have also highlighted the unique role of Hib, particularly as a cause of serious pediatric disease. In the pre-vaccine era, approximately

1/200 children developed an invasive infection with Hib by the age of 5, which far exceeded the incidence of any other serotype, as well as nontypeable disease. The highest incidence of Hib meningitis was seen around 18-24 months of age, or the period when maternally-acquired serum antibodies to PRP reach their nadir.

The Hib conjugate vaccine induces antibodies to the PRP capsule, substantially reducing both Hib colonization and invasive disease. In December 1987 the first Hib conjugate vaccine was licensed in the United States for children at least 18 months of age. Licensure of the vaccine was expanded to include infants at least 2 months of age in October 1990, and a 3-dose primary series with a booster dose was subsequently recommended for all infants in the U.S.

In 1989, the Georgia Emerging Infections Program began active, population-based surveillance for cases of invasive *H. influenzae* (HI) disease in metropolitan Atlanta. The timing of the project provided a unique opportunity to monitor the ecological effects of the introduction of the Hib conjugate vaccine. Between 1989 and 2008, over 1200 cases of HI disease were identified, and over 75% of the corresponding isolates have been collected. The specific aims of the current study were to:

1. Describe changes in the incidence of HI disease between 1989 and 2008 in children and adults to assess the long-term impact of the introduction of the Hib vaccine for infant use in 1990,
2. Describe changes in the serotype distribution of *H. influenzae* invasive disease over this same time span,
3. Evaluate predictors of mortality in patients with HI disease.

**Background:**

Since the introduction of the Hib vaccine, there has been a dramatic decrease of Hib among children less than 5 years of age (4-6). With the decline of Hib, the relative importance of other forms of *H. influenzae*, particularly nontypeable disease, has increased. Despite the absence of a capsule, nontypeable strains can still cause invasive disease. The bacterial factors in nontypeable strains that predispose to invasive disease are poorly defined. Identifying these factors is complicated by the genetic and phenotypic diversity found among nontypeable disease (7, 8). Additionally, host factors likely contribute to susceptibility to invasive nontypeable HI in some cases. To begin addressing these questions, large epidemiologic studies, like this current project, are needed.

A few studies have reported that the incidence of HI disease is again slowly rising, particularly among adults (9-12) but also among children (9, 13). A rising incidence of type a, type f, and nontypeable strains have been reported in certain geographic regions (13-15).

The apparent rise of non-vaccine serotypes has been well described for invasive pneumococcal disease after the introduction of the heptavalent pneumococcal conjugate vaccine (16, 17). It remains unclear whether this same phenomenon, known as serotype replacement, has occurred after the introduction of the Hib conjugate vaccine (18, 19). Analyzing data over a longer time span, as done in this study, may help better define these epidemiologic trends.

Finally, although many epidemiologic studies have reported mortality rates from HI, these rates are often reported by age group, serotype, or clinical presentation. Only one study, to our knowledge, has performed a multivariate analysis to adjust for the relative contributions of these different factors (20). This study collected data through active, population-based surveillance in parts of Canada, Denmark, and Australia between 2000 and 2008. All patients with a blood culture positive for *H. influenzae* were included, and the primary outcome was 30-day fatality. A logistic regression model identified the following factors as predictive of death: male gender, hospital onset, age ≥ 50 years, lower respiratory tract infection, bacteremia without focus, or central nervous system infection.

The findings of this analysis have not been validated in other populations. Using similar covariates, the current project will analyze predictors of death from invasive HI disease in metropolitan Atlanta.

## Methods:

*Hypotheses:*

1. A heavily Hib-vaccinated population of infants will lead to significant indirect effects in unimmunized adults: the serotype distribution will be substantially altered in adult disease.
2. Pneumonia will be a significant predictor of mortality for HI after adjusting for other covariates.

*Case ascertainment and case definitions:* Patients to be included in the study have been identified through the Active Bacterial Core Surveillance (ABCs) program of the Georgia Emerging Infections Program (GA EIP). Beginning in 1989, the GA EIP has performed prospective population and laboratory-based surveillance for all HI cases in the 8-county Health District 3 of metropolitan Atlanta. Surveillance was expanded to the 20-county metropolitan Atlanta statistical area (MSA) in 1997.

To identify cases, ABCs personnel contacted all clinical microbiology laboratories within the surveillance area twice weekly and performed audits at least every 6 months. A case of invasive *H. influenzae* infection was defined as isolation of *H. influenzae* from a normally sterile site, which included blood, cerebrospinal fluid, joint, or other normally sterile site aspirate; sputum and urine isolates were excluded. Serotyping of isolates was performed by slide agglutination and confirmed by capsule-gene polymerase chain reaction. After case identification, the patient's medical record at the treating hospital was reviewed using a standard case report form to collect data on demographics, clinical characteristics, and outcomes.

Cases that were not residents of the surveillance area were excluded.

The population-based *H. influenzae* surveillance study was approved by the institutional review boards of Emory University and the Georgia Department of Human Resources.

*Descriptive analysis:* Descriptive epidemiologic analysis was performed for all cases of HI from January 1, 1989 through December 31, 2008. Using US Census bureau data, the annual incidence of HI disease was calculated. The numerator was the total number of cases, and the denominator was the total number of people living in metropolitan Atlanta at that time. Incidence calculations were also performed within serotypes, 5 age categories (<2, 2-4, 5-17, 18-39, 40-64, and ≥ 65 years), gender groups, and certain racial categories.

To evaluate annual trends over time, the Mantel-Haenszel chi-square test was calculated after ensuring no deviation from linearity. Annual incidence rates for all 20 years of the study were used to calculate the $\chi 2$ test statistic. Percentage change was used to compare the incidence rates from the first year of the study with the last year of the study. Percentage change was calculated using the following formula: [(later rate – baseline rate)/baseline rate] x 100. When the sample size was too small for the chi-square test, only percentage change was reported.

*Statistical analysis*

*Definition of predictor and outcome variables:* The outcome measure of interest was in-hospital mortality, defined as death prior to hospital discharge. The primary

exposure variable of interest was clinical syndrome. Other variables included age, gender, race, serotype, and underlying condition.

Age was treated as a categorical variable (age groups: <2, 2-4, 5-17, 18-39, 40-64, and ≥65). Race was categorized as white, black, American Indian, Asian, Pacific Islander, or unknown. Serotypes were divided into 4 categories: type b, non-b encapsulated, nontypeable, and unknown, or non-classified.

Any of the following diseases were considered to be underlying conditions: multiple myeloma, sickle cell disease, asplenia, immunoglobulin deficiency, immunosuppressive therapy, leukemia, Hodgkin's disease, asthma, emphysema, systemic lupus erythematosus, diabetes mellitus, nephrotic syndrome, renal failure, HIV infection, acquired immunodeficiency syndrome, cirrhosis, cerebral vascular accident, atherosclerotic heart disease, heart failure, cerebrospinal fluid leak, intravenous drug use, solid organ malignancy, organ transplant, and other illnesses.

Clinical syndromes were classified into one of the following categories: bacteremia without focus, meningitis, otitis media, pneumonia, cellulitis, epiglottitis, peritonitis, pericarditis, septic abortion, chorioamnionitis, septic arthritis, osteomyelitis, endometritis, and unclassified. Cases could have more than one clinical syndrome.

Since chart reviews for underlying conditions and clinical syndromes were initiated in 2000-2008, only those years were included in the univariate and multivariate analysis.

*Univariate analysis:* The Chi-Square test was used to compare the occurrence of certain variables among cases who died and who survived. Odds ratios (OR) and

corresponding 95% confidence intervals were calculated to look for associations between predictor variables and the outcome of in-hospital mortality.

*Multivariate analysis:* An unconditional logistic regression was performed to determine predictors of in-hospital mortality. Dummy variables were constructed for all covariates that were neither continuous nor dichotomous, which included race and serotype. Dummy variables were also constructed for age using 2-39 years as the reference group.

The Hosmer-Lemeshow goodness of fit test determined how well the likelihood procedure fit the observed data to the logistic function. Collinearity was assessed using a macro developed by Dan Rosen, PhD. Collinearity was deemed present if the conditional index was greater than 23.0 and $\geq 2$ variables had variance decomposition proportions exceeding 0.5. The likelihood ratio test was used to compare a non-interaction to an interaction model for a series of potentially interacting variables.

*Sample size:* All power calculations were performed with the assistance of Kirk Easley, M.S., the Associate Director of Emory's Biostatistics Consulting Center.

A prior study reported a mortality rate of 20% in *H. influenzae* pneumonia and 11% for all other HI infections (21). In the current study's database, 33% of cases had *H. influenzae* pneumonia, and the overall in-hospital mortality rate was known to be 13%. Using these assumptions, a logistic regression analysis showed that a sample size of 1000 patients will provide 96% statistical power to detect a difference in hospital mortality between pneumonia and non-pneumonia cases. This difference in hospital mortality

corresponds to an odds ratio of 2.0. Based on the above calculations, the study's database of 1207 cases will be adequately powered to test our hypotheses.

**Results:**

A total of 1207 invasive HI cases were collected from 1989 through 2008; 408 (34%) in children less than 18 years of age and 799 (66%) in adults. Demographic characteristics of children and adults are shown in Table 1.

*Children:* The median age of children with invasive HI disease was 10 months (IQR 4 months-2 years). The overall in-hospital mortality rate was 7%. An underlying condition was present in 27 of 120 children (23%). The most common underlying conditions were asthma (10%), sickle cell disease (5%), and immunosuppressive therapy (4%).

During 2000-2008, the most common clinical syndrome among children was bacteremia without an identified focus (57%) followed by pneumonia (19%), meningitis (11%), and otitis media (6%). There were 3 cases of peritonitis, 1 of septic arthritis, and no cases of epiglottitis.

*Adults:* The median age of adults was 60 years (IQR 43-76). The overall in-hospital mortality rate was 16%. An underlying condition was present in 289 of 405 adults (71%). The most common underlying conditions were solid organ malignancy (30%), COPD (22%), diabetes (21%), heart failure (18%), and atherosclerotic cardiovascular disease (15%).

During 2000-2008, pneumonia was the most common clinical syndrome among adults, accounting for 59% of cases. Bacteremia without an identified focus comprised 27% of adult cases and meningitis 4%. There were 4 cases of septic arthritis, 3 of epligottitis (1 type b, 2 type f), 3 of peritonitis, 3 of septic abortion, and 1 of pericarditis.

*Burden of disease:* In 1989, 61% of all HI cases were in children < 2 years of age. Overall, 77% of cases in 1989 were in children less than 18 years of age, and 23% were in adults. In comparison, only 15% of cases in 2008 were in children < 2 years. In 2008, adults accounted for 81% of all invasive HI disease (Figure 1).

*Risks:* Male children were at higher risk of invasive HI disease than female children: RR 1.45 (1.03-2.04). No gender differences were noted in adults: RR 0.87 (0.73-1.05). Blacks were at higher risk of acquiring HI compared to whites: RR 1.46 (1.28-1.65). In 1989-90, children were at higher risk of disease compared with adults: RR 7.93 (5.94-10.58). By 2000-2008, the risk of HI was lower in children compared to adults: RR 0.77 (0.63-0.95).

*Epidemiologic trends:* Table 2 and Figure 2 show the epidemiologic trends by serotype for the overall population between 1989-1990 and 2007-2008. Total HI decreased from 5.10 cases per 100,000 person-years to 1.09 cases per 100,000 person-years (79% decrease, $\chi^2$ trend $p<0.0001$). This overall decline was driven by the decrease in type b disease, which decreased from 2.51 to 0.02 cases per 100,000 (99% decrease, $\chi^2$ trend $p<0.0001$). As shown in Table 3, type b disease decreased significantly in both children (99.6% decrease, $\chi^2$ trend $p<0.0001$) and adults (98% decrease, $\chi^2$ trend $p<0.0001$).

Rates of disease due to nontypeable strains decreased in children (63% decrease, $p=0.047$) but did not change significantly in adults. Rates of types a and e disease remained relatively stable over the course of the study. Rates of types c and d disease were negligible throughout the study period. There was a strong trend for an increase in

type f disease rates: 0.09 to 0.23 cases per 100,000 (170% increase, $\chi^2$ trend p=0.056). The rise of type f was most prominent among adults; adult rates increased from 0.09 cases to 0.26 cases per 100,000 (205% increase, $\chi^2$ trend p=0.035).

For the overall population, the number of unknown serotypes also decreased from 1.85 to 0.18 cases per 100,000 (90% decrease, $\chi^2$ trend p<0.0001). During the first year of surveillance, unknowns accounted for 47% of all isolates. By 2008, 20% of all identified cases were classified as unknown. Of note, the distribution of unknown isolates among the different age groups reflected the distribution of the age groups in the general population.

The youngest age group (those <2 years of age) saw the largest absolute decrease in HI: 90.91 cases to 6.37 cases per 100,000 (93% decrease, $\chi^2$ trend p<0.0001). Significant decreases were also seen in the 2-17, 18-39 and 40-64 age groups (Table 4). In the ≥ 65 age group, however, no significant decrease of invasive HI disease was noted (6.91 to 5.35 cases per 100,000 [22% decrease, $\chi^2$ trend p=0.456]).

*Serotype distribution:* During 1989-1990, 85% of all HI cases among children were type b and 14% were nontypeable (Figure 3). In comparison, during 2000-2008, only 6% of pediatric HI cases were type b. The most prevalent causes of invasive HI disease in children during 2000-2008 were nontypeable (67%) and type f (21%) strains. One-third of all nontypeable cases in children occurred within the first 2 months of life.

Among adults in 1989-1990, 56% of HI disease was type b, 29% was nontypeable, and 7% was type f. During 2000-2008, 66% of adult cases were due to nontypeable isolates, 25% type f, and 6% type e.

Of 285 nontypeable cases during 2000-2008, including both adults and children, 38% were bacteremia without an identified focus, 52% pneumonia, and 4% meningitis (Table 5a). During 2000-2008, there were 131 non-b encapsulated cases: 24% were bacteremia without focus, 57% were pneumonia, and 9% were meningitis. There were 13 cases of type b disease during 2000-2008: 15% bacteremia without focus, 23% pneumonia, and 31% meningitis.

During 2000-2008, the mortality rates for different serotypes were as follows: type b 0/13 (0%), non-b encapsulated 11/131 (8%), nontypeable 52/285 (18%) and unknown 11/96 (12%).

*Changes in the incidence of positive CSF cultures:* The incidence of cases with positive CSF cultures decreased from 1.93 per 100,000 in 1989-1990 to 0.03 per 100,000 in 2007-2008 (98% decrease, $\chi^2$ trend $p<0.0001$).

Type b caused 95% of cases with CSF-positive cultures in 1989-1990. In contrast, only 13% of CSF-positive cultures in 2000-2008 were due to type b. Other isolates from CSF cultures in 2000-2008 included nontypeable (44%), type f (19%), type e (19%), and type a (6%).

*Changes in the incidence of positive blood cultures:* The incidence of cases with positive blood cultures decreased from 4.34 per 100,000 in 1989-1990 to 1.00 per 100,000 in 2007-2008 (77% decrease, $\chi^2$ trend $p<0.0001$).

74% of positive blood cultures in 1989-1990 were identified as type b and 21% were nontypeable. In contrast, only 3% of positive blood cultures in 2000-2008 were due

to type b. Other isolates from blood cultures in 2000-2008 included nontypeable (67%), type f (24%), and type e (5%).

*Univariate analysis for predictors of in-hospital mortality:* Exploratory analysis for predictors of death (Tables 5a-5c) revealed high mortality rates in nontypeable strains, cases with bacteremia without focus, and persons ≥ 65 years.

As shown in Tables 6, $\chi^2$ test revealed an association with in-hospital death for both serotype and bacteremia without focus. As shown in Table 7, bacteremia without focus carried a higher odds of death, OR 1.83 (1.11-3.01). In comparison to encapsulated strains, nontypeable strains also had a higher odds of death, OR 2.70 (1.36-5.35).

*Multivariate analysis for predictors of in-hospital mortality:* An unconditional logistic regression model was developed to assess risk factors of in-hospital mortality. Based on a causal diagram (Figure 4), age, race, gender, underlying condition, and serotype were all deemed potential confounders. These variables were all associated with the exposure, potential risk factors for the outcome, and outside the causal pathway. The exposure variables of interest were the 3 clinical syndromes: bacteremia, pneumonia, and meningitis.

There were 525 cases of HI identified between 1/1/2000 and 12/31/2008. Three of these cases were excluded from the model due to incomplete outcome data. Since there were no deaths among the 13 Hib cases, Hib was excluded from the model.

As shown in Table 8, the model revealed an association with death for the following exposure variables: nontypeable strains, bacteremia without focus, age < 2

years, age 40-64 years, and age ≥ 65 years. Neither pneumonia nor meningitis was associated with in-hospital death.

The goodness of fit test was not significant ($\chi^2$=7.23, p=0.51), indicating that the observed data adequately fit the model. Collinearity was not detected between exposure variables (Table 9). Using the likelihood ratio test, no interaction was detected between the exposure variables (i.e. pneumonia and bacteremia) and the covariates (Table 10). Meningitis was excluded from tests of interaction, because there was only 1 death among meningitis cases. Interaction was not tested for race, because the dummy variables were unstable in the interaction calculations.

Using stepwise regression, a final restrained model was constructed (Table 11). The goodness of fit test was not significant ($\chi^2$=5.00, p=0.66). In comparison to persons between the ages of 2 and 39 years, the following age groups carried a higher odds of death: <2, 40-64, and ≥ 65. Compared to non-b encapsulated strains, nontypeable strains had a higher odds of death: OR of 2.42 (1.20-4.89). Bacteremia without focus was also predictive of mortality with an OR of 2.10 (1.22-3.63).

**Discussion:**

Since the introduction of the Hib conjugate vaccine, the burden of HI disease has shifted from children to adults. Adults are now at a slightly higher risk of disease than children, and adults account for almost three-quarters of all invasive HI cases. The overall incidence rate of invasive HI disease in adults, however, has decreased.

The impact of the Hib conjugate vaccine has been dramatic. Children have seen a direct benefit from the vaccine with decreased HI rates in all age groups, especially children < 2 years. Adults have benefited indirectly from the vaccine, presumably due to herd immunity. Vaccinated children are no longer nasopharyngeal carriers of Hib, and thus the potential for transmission of Hib to adults has been substantially reduced.

The risk of invasive HI disease is now highest at the extremes of age. Although HI disease in children < 2 years has significantly declined, the risk of disease is still highest in infants less than 2 years of age. The higher risk of HI disease among infants may reflect relative immunodeficiencies in this age group that predispose to HI disease. The next highest risk is seen among persons ≥ 65 years, which may reflect immunosenescence and/or the impact of underlying conditions in this age group.

Rates of invasive HI disease are higher among male children than female children, a finding reported in several other studies (9, 22, 23).

The risk for HI was higher among blacks than whites (24, 25). Compared to whites, blacks have also been shown to be at higher risk of bacteremic pneumonia in general (26) and invasive pneumococcal disease (27, 28). Socioeconomic factors may

explain some of this disparity (29, 30), and in fact, prior studies that have controlled for socioeconomic factors found no increased risk for HI disease among blacks (31).

Type a was not a major cause of HI in our cohort, which contrasts with other surveys (32-34). Type a was prevalent in other reports (14), particularly among indigenous populations (32-35). This geographic and ethnic specificity to serotype predominance is not well understood.

Our surveillance revealed a significant increase of type f, which has also been reported in other studies (15, 36). In one study, the increase in type f was only seen in children (13). In contrast, the present study found an increase in type f among adults. The risk of type f in metropolitan Atlanta remains small (<1 case/100,000 persons) but warrants continued monitoring. Non-b *H. influenzae* may be the target for future vaccine development. Interestingly, 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* (37).

With the dramatic decline of Hib disease, the relative importance of nontypeable disease has increased. Nontypeable strains now account for two-thirds of all invasive HI disease. The decrease in the incidence of nontypeable disease observed in children is unlikely to be related to the vaccine itself. Given the high prevalence of type b disease during 1989-1990, some of these nontypeable strains may have actually been unrecognized type b strains. Such a misclassification would have falsely increased the incidence of nontypeable disease during the pre-vaccine years, thereby creating a pseudo-decline in nontypeable disease.

In the multivariate analysis of non-Hib cases, age, bacteremia without focus, and nontypeable strains were associated with in-hospital mortality. Higher rates of death at the extremes of age is a well-documented phenomenon among invasive bacterial infections and was seen in the only other multivariate analysis that looked at risk factors for HI case-fatality (20). In the current study, even after controlling for potential confounders, an association between age and death was seen. These particular age groups are probably more prone to severe manifestations of HI disease.

Patients who had bacteremia without an identified focus may have had a delay in recognition of HI disease leading to a delay in antibiotic therapy and worse clinical outcomes. Even though pneumonia conferred a 14% mortality rate, it was not associated with worse in-hospital death on multivariate analysis. Of note, there was only 1 death among cases of meningitis, so it too was not significantly associated with worse outcomes on multivariate analysis.

It's unclear what factors contributed to the increased case-fatality associated with nontypeable HI disease compared with disease due to non-b encapsulated strains. Since nontypeable strains are thought to be less virulent than encapsulated strains, it's tempting to speculate that nontypeable disease may be a marker for impaired host defenses and severe debilitation. This may be especially true among children. Although only 25% of children with nontypeable disease had an underlying condition, 1/3 of all pediatric nontypeable cases occurred within the first 2 months of life. Other unidentified factors in these infants may have predisposed them to poor outcomes.

This report has several strengths. Using active, population-based surveillance, the study monitored the effects of HI in a large metropolitan Atlanta population for 20 years. The study also provides a full microbiological and clinical description of the cohort.

The study also has some limitations. First, the serotype classification was unknown for a moderate number of HI cases. This was more of a problem in the early years of surveillance and largely reflects difficulty in collecting isolates from all participating microbiology laboratories. Although our surveillance revealed several strong epidemiologic trends, it's possible that some of these trends would have appeared even stronger if more unknowns were serotyped. Second, our data is not nationally representative but reflects the experience of a single metropolitan area. Third, our multivariate analysis reflects only in-hospital mortality, which is a sub-optimal indicator of overall clinical outcomes. Finally, even though data was collected on the presence of underlying conditions, the severity of these conditions was not quantified. Controlling for the overall debilitation of the host may have reduced the association between nontypeable disease and in-hospital mortality.

Further research is needed to better understand the host factors that predispose to infection with and mortality from invasive nontypeable disease. In addition, future studies should focus on identifying bacterial factors that determine whether exposure to nontypeable HI strains results in invasive disease or asymptomatic colonization. These factors, if identified, could be the target for future vaccine development.

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**Tables and Figures:**

Table 1. Characteristics of 1207 cases of invasive *H. influenzae*

| **Characteristic** | **Children (n=408)** | **Adults (n=799)** |
|---|---|---|
| **Age, median (IQR)** | 10 months<br>(4 months-2 years) | 60 years<br>(43-76 years) |
| **Gender: Male**<br>**Female** | 57%<br>43% | 43%<br>57% |
| **Race: White**<br>**Black** | 48%<br>50% | 62%<br>36% |
| **Underlying condition:** | 23% | 71% |
| **Hospitalization rate** | 82% | 93% |
| **Nosocomial invasive *H.influenzae*** | 4% | 7% |
| **In-hospital mortality** | 7%<br>**<2 yrs***:* 9%<br>**2-4 yrs***:* 2%<br>**5-17 yrs:** 2% | 16%<br>**18-39 yrs:** 6%<br>**40-65 yrs:** 13%<br>**≥ 65 years:** 22% |

Table 2. Changes in the incidence of invasive *H. influenzae* disease by serotype for the overall population (n=1207)

| Serotype | 1989-1990 incidence | 2007-2008 incidence | % change | $\chi^2$ trend p-value |
|---|---|---|---|---|
| **a** | 0.02 | 0.02 | -9% | * |
| **b** | 2.51 | 0.02 | -99% | <0.0001 |
| **c and d** | 0 | 0 | 0 | -- |
| **e** | 0.04 | 0.06 | +36% | * |
| **f** | 0.09 | 0.23 | +170% | 0.056 |
| **NT** | 0.58 | 0.58 | 0 | 0.970 |
| **Unknown** | 1.85 | 0.18 | -90% | <0.0001 |
| **Total** | 5.10 | 1.09 | -79% | <0.0001 |

* Chi-square for trend results were invalid due to small cell counts

Table 3. Changes in the incidence of type b, non-b, and type f isolates among children less than 18 years of age and adults

| Age group | 1989-1990 incidence | 2007-2008 incidence | % change | $\chi^2$ trend p-value |
|---|---|---|---|---|
| **Children: Total** | 14.25 | 0.82 | -94% | <0.0001 |
| **type b** | 7.71 | 0.03 | -99.6% | <0.0001 |
| **nontypeable** | 1.24 | 0.46 | -63% | 0.047 |
| **type f** | 0.08 | 0.16 | +98% | * |
| **Adults: Total** | 1.80 | 1.21 | -33% | 0.0017 |
| **type b** | 0.66 | 0.01 | -98% | <0.0001 |
| **nontypeable** | 0.34 | 0.63 | +84% | 0.246 |
| **type f** | 0.09 | 0.26 | +205% | 0.035 |

* Chi-square for trend results invalid due to small cell counts

Table 4. Changes in the incidence of invasive *H. influenzae* disease based on age groups

| **Age Group** | **1989-1990 incidence** | **2007-2008 incidence** | **% change** | **$\chi^2$ trend p-value** |
|---|---|---|---|---|
| **< 2 years** | 90.91 | 6.37 | -93% | <0.0001 |
| **2-17 years** | 3.04 | 0.15 | -95% | <0.0001 |
| **18-39 years** | 0.83 | 0.26 | -68% | <0.0001 |
| **40-64 years** | 1.82 | 1.02 | -44% | 0.031 |
| **≥ 65 years** | 6.91 | 5.35 | -23% | 0.456 |

Descriptive analysis of factors associated with in-hospital mortality

Table 5a. Characteristics of HI cases based on infecting serotype, 2000-2008 (n=525)

| | **Type b (n=13)** | **Non-b encapsulated (n=131)** | **Nontypeable (n=285)** | **Unknown (n=96)** |
|---|---|---|---|---|
| Adults cases | 54% | 79% | 76% | 81% |
| Median age (IQR) | 68 yrs (44-76) | 59 yrs (48-72) | 67 yrs (48-81) | 60 yrs (44-75) |
| Underlying condition | 71% | 72% | 74% | 64% |
| Child cases | 46% | 21% | 24% | 19% |
| Median age (IQR) | 19 mos (8 mos-8 yr) | 8 mos (5-14 mos) | 13 mos (1 wk-4 yrs) | 10 mos (1 wk-5 yrs) |
| Underlying condition | 33% | 18% | 25% | 17% |
| | | | | |
| | **Type b (n=13)** | **Non-b encapsulated (n=131)** | **Nontypeable (n=285)** | **Unknown (n=96)** |
| **Syndromes** | | | | |
| Bacteremia without focus | 15% | 24% | 38% | 39% |
| Pneumonia | 23% | 57% | 52% | 37% |
| Meningitis | 31% | 9% | 4% | 4% |
| **Mortality** | | | | |
| Children | 0% | 4% | 16% | 6% |
| Adults | 0% | 10% | 19% | 13% |
| Total | 0% | 8% | 18% | 12% |

**Most common underlying syndromes by serotype, 2000-2008**

**Nontypeable:** COPD 18%, Heart failure 18%, diabetes 15%, other malignancy 13%

**Non-b:** COPD 21%, diabetes 14%, HIV, 11%, atherosclerotic CV disease 8%, immunosuppressive therapy 8%

**Type b:** COPD 31%, immunosuppresive therapy 23%, leukemia 23%, other malignancy 15%

Table 5b. In-hospital mortality from invasive *H. influenzae* by clinical syndrome, 2000-2008 (n=522)

| Clinical syndrome | Mortality (%) |
|---|---|
| **Bacteremia without focus (n=175)** | 34/175 (19%) |
| **Pneumonia (n=262)** | 37/262 (14%) |
| **Meningitis (n=31)** | 1/31 (3%) |
| **Other (n=25)** | 0/25 (0%) |
| **Unclassified (n=39)** | 3/42 (7%) |

*Outcome data was missing on 3 cases

Table 5c. In-hospital mortality from invasive *H. influenzae* by age group, 2000-2008 (n=522)

| Age group (# of cases) | Mortality rates |
|---|---|
| **<2 years (79)** | 15% |
| **2-4 years (17)** | 0% |
| **5-17 years (23)** | 4% |
| **18-39 years (54)** | 6% |
| **40-64 years (164)** | 15% |
| **≥ 65 years (185)** | 18% |

*Outcome data was missing on 3 cases

Table 6. The occurrence of potential risk factors for in-hospital mortality among cases of invasive *H. influenzae* disease, 2000-2008

| Variable | Deaths (n=74) | % of deaths | Survived (n=451) | % of survivors | $\chi 2$ | p-value |
|---|---|---|---|---|---|---|
| **Age ≥ 65** | 33 | 45% | 154 | 34% | 3.03 | 0.082 |
| **Gender (male)** | 35 | 47% | 216 | 48% | 0.01 | 0.911 |
| **White race** | 47 | 64% | 274 | 61% | 0.20 | 0.652 |
| **Black race** | 25 | 34% | 143 | 32% | 0.13 | 0.723 |
| **Underlying condition** | 52 | 70% | 264 | 59% | 3.65 | 0.056 |
| **Serotype (NT vs encapsulated)** | 52/63 | 83% | 233/366 | 64% | 8.59 | **0.003** |
| **Pneumonia** | 37 | 50% | 225 | 50% | <0.01 | 0.986 |
| **Bacteremia without focus** | 34 | 46% | 143 | 32% | 5.77 | **0.016** |
| **Meningitis** | 1 | 1% | 30 | 7% | * | 0.105 |

* Fisher's exact test used due to small cell counts

Table 7. Odds ratios of potential risk factors for in-hospital mortality in cases of invasive *H. influenzae* disease, 2000-2008

| Variable | OR | 95% confidence interval |
|---|---|---|
| **Age ≥ 65 years** | 1.57 | 0.95-2.58 |
| **Gender (males to females)** | 0.97 | 0.59-1.59 |
| **White race** | 1.12 | 0.68-1.87 |
| **Black race** | 1.10 | 0.65-1.85 |
| **Underlying condition** | 1.67 | 0.98-2.85 |
| **Serotype (nontypeable vs encapsulated)** | **2.70** | **1.36-5.35** |
| **Pneumonia** | 1.00 | 0.61-1.64 |
| **Bacteremia without focus** | **1.83** | **1.11-3.01** |
| **Meningitis** | 0.19 | 0.03-1.43 |

Table 8. Multivariate analysis for predictors of in-hospital mortality in 509 cases of HI, 2000-2008 (all ages)

| Variable | Estimated parameter | Standard Error | Odds Ratio | 95% CI |
|---|---|---|---|---|
| **<2 years** | 1.42 | 0.62 | **4.14** | **1.23-13.96** |
| **40-64 years** | 1.48 | 0.58 | **4.41** | **1.42-13.70** |
| **≥ 65 years** | 1.60 | 0.59 | **4.96** | **1.56-15.74** |
| **Non-black, non-white vs. white race** | 0.15 | 1.16 | 1.16 | 0.12-11.27 |
| **Black vs. white race** | 0.27 | 0.29 | 1.31 | 0.74-2.31 |
| **Male vs. female** | -0.06 | 0.27 | 0.94 | 0.56-1.58 |
| **Underlying condition** | 0.36 | 0.33 | 1.43 | 0.75-2.72 |
| **NT vs. encapsulated** | 0.81 | 0.36 | **2.24** | **1.10-4.56** |
| **Unknown vs. encapsulated** | 0.40 | 0.46 | 1.49 | 0.60-3.68 |
| **Bacteremia without focus** | 1.45 | 0.73 | **4.28** | **1.02-17.96** |
| **Pneumonia** | 0.84 | 0.73 | 2.31 | 0.55-9.71 |
| **Meningitis** | -0.17 | 1.20 | 0.84 | 0.08-8.86 |

*Type b excluded, because it could not be coded as a separate variable. There were only 13 cases, and none died.

Table 9. Collinearity diagnostics for the logistic regression model of in-hospital death due to invasive *H. influenzae* disease

Collinearity diagnostics for nonlinear models using the information matrix: Eigenvalues, condition indexes, and variance decomposition proportions (VDP's)

| Variable | VDP1 | VDP2 | VDP3 | VDP4 | VDP5 | VDP6 | VDP7 |
|---|---|---|---|---|---|---|---|
| Eigenval | 0.0137 | 0.0454 | 0.12617 | 0.19313 | 0.42540 | 0.53745 | 0.66628 |
| CondIndx | 19.8980 | 10.9496 | 6.56479 | 5.30610 | 3.57525 | 3.18077 | 2.85676 |
| | . | . | . | . | . | . | . |
| Intercept | 0.9704 | 0.0177 | 0.00875 | 0.00097 | 0.00144 | 0.00002 | 0.00000 |
| a1 | 0.1447 | 0.5002 | 0.01197 | 0.07270 | 0.03949 | 0.05738 | 0.07550 |
| a2 | 0.1928 | 0.6088 | 0.07179 | 0.00939 | 0.03165 | 0.00555 | 0.00192 |
| a3 | 0.1751 | 0.6526 | 0.10874 | 0.00611 | 0.00081 | 0.01037 | 0.00433 |
| r1 | 0.0001 | 0.0003 | 0.00046 | 0.00527 | 0.00011 | 0.01658 | 0.07652 |
| r2 | 0.0232 | 0.0113 | 0.00247 | 0.00220 | 0.17829 | 0.54185 | 0.15969 |
| h1 | 0.0376 | 0.0356 | 0.68068 | 0.19422 | 0.01516 | 0.00019 | 0.00154 |
| h2 | 0.0652 | 0.0067 | 0.41197 | 0.09118 | 0.00000 | 0.00073 | 0.00865 |
| GENDER | 0.0095 | 0.0042 | 0.00408 | 0.00983 | 0.71558 | 0.22635 | 0.01084 |
| BACTEREM | 0.6502 | 0.2668 | 0.03104 | 0.00083 | 0.00347 | 0.00456 | 0.02825 |
| MENING | 0.2154 | 0.0545 | 0.00101 | 0.00001 | 0.00002 | 0.00221 | 0.01995 |
| PNEU | 0.6189 | 0.3235 | 0.01870 | 0.00240 | 0.00288 | 0.00495 | 0.01909 |
| UNDRLY | 0.0029 | 0.0000 | 0.18331 | 0.78579 | 0.00205 | 0.00039 | 0.01115 |

| Variable | VDP8 | VDP9 | VDP10 | VDP11 | VDP12 | VDP13 |
|---|---|---|---|---|---|---|
| Eigenval | 0.94899 | 0.96937 | 1.02540 | 1.10838 | 1.50274 | 5.43759 |
| CondIndx | 2.39372 | 2.36841 | 2.30280 | 2.21492 | 1.90223 | 1.00000 |
| | . | . | . | . | . | . |
| Intercept | 0.00007 | 0.00002 | 0.00000 | 0.00001 | 0.00000 | 0.00064 |
| a1 | 0.00986 | 0.00011 | 0.00395 | 0.02554 | 0.05731 | 0.00128 |
| a2 | 0.03121 | 0.00049 | 0.00039 | 0.04413 | 0.00012 | 0.00182 |
| a3 | 0.01523 | 0.00158 | 0.00001 | 0.01181 | 0.01175 | 0.00157 |
| r1 | 0.00341 | 0.32147 | 0.57153 | 0.00196 | 0.00170 | 0.00064 |
| r2 | 0.02190 | 0.00025 | 0.01835 | 0.00920 | 0.02314 | 0.00817 |
| h1 | 0.00265 | 0.01207 | 0.00572 | 0.00976 | 0.00028 | 0.00458 |
| h2 | 0.08513 | 0.18863 | 0.08208 | 0.05184 | 0.00536 | 0.00250 |
| GENDER | 0.00341 | 0.00349 | 0.00050 | 0.00000 | 0.00250 | 0.00971 |
| BACTEREM | 0.00009 | 0.00017 | 0.00187 | 0.00223 | 0.00955 | 0.00102 |
| MENING | 0.31592 | 0.16702 | 0.07498 | 0.14367 | 0.00506 | 0.00031 |
| PNEU | 0.00001 | 0.00012 | 0.00092 | 0.00009 | 0.00736 | 0.00105 |
| UNDRLY | 0.00030 | 0.00042 | 0.00003 | 0.00070 | 0.00713 | 0.00582 |

r1 = non-black, non-white race / white race
r2 = black race / white race
h1 = nontypeable / non-b encapsulated
h2 = unknown isolates / non-b encapsulated

Table 10. Wald Chi-Square Test for Interaction between Predictor Variables and Clinical Syndromes

| Variable | Wald $\chi 2$ statistic | p-value |
|---|---|---|
| Age | 5.08 | 0.079 |
| Gender | 0.67 | 0.71 |
| Underlying | 0.37 | 0.83 |
| Serotype | | |
| h1*bacteremia | 0.46 | 0.50 |
| h1*pneumonia | 0.04 | 0.84 |
| h2*bacteremia | 0.28 | 0.60 |
| h2*pneumonia | 0.36 | 0.55 |

h1 = nontypeable / non-b encapsulated
h2 = unknown serotype / non-b encapsulated

Table 11. Final restrained logistic regression model for predictors of in-hospital mortality in 509 cases of HI, 2000-2008 (all ages, excluding type b)

| Variable | Estimated parameter | Standard Error | Odds Ratio | 95% CI |
|---|---|---|---|---|
| **Age (reference: 2-39 yrs)** | | | | |
| **< 2 years** | 1.37 | 0.61 | **3.94** | **1.20-12.98** |
| **40-64 years** | 1.66 | 0.57 | **5.27** | **1.74-15.98** |
| **≥ 65 years** | 1.81 | 0.56 | **6.12** | **2.05-18.27** |
| **Serotype (reference: non-b encap)** | | | | |
| **Nontypeable** | 0.88 | 0.36 | **2.42** | **1.20-4.89** |
| **Unknown** | 0.36 | 0.46 | 1.43 | 0.58-3.49 |
| **Bacteremia without focus** | 0.74 | 0.28 | **2.10** | **1.22-3.63** |

**Figure 1. Contribution of different age groups to the overall annual burden of invasive *H. influenzae* disease**

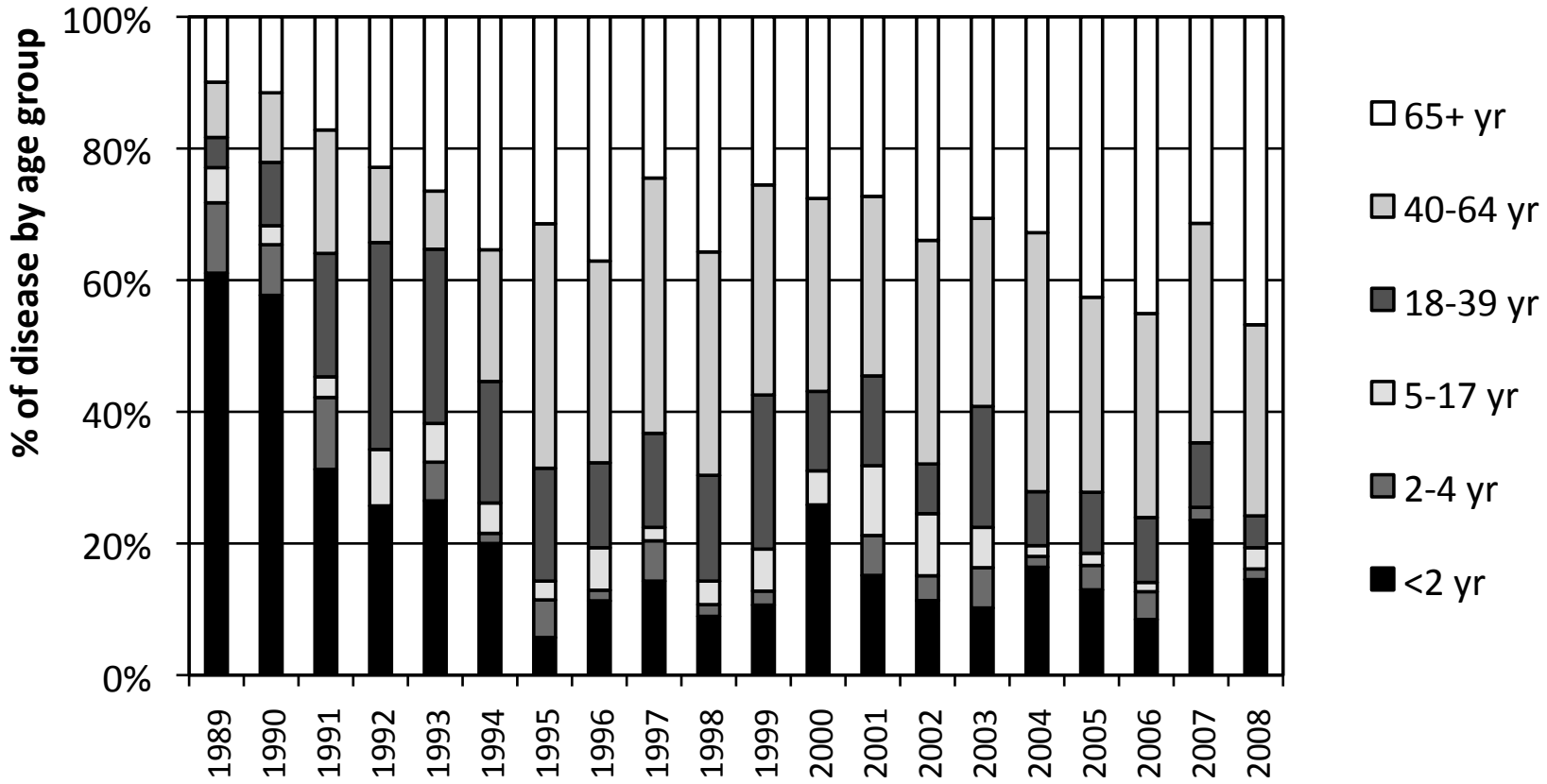

**Figure 2. Incidence of invasive *H. influenzae* by serotype**

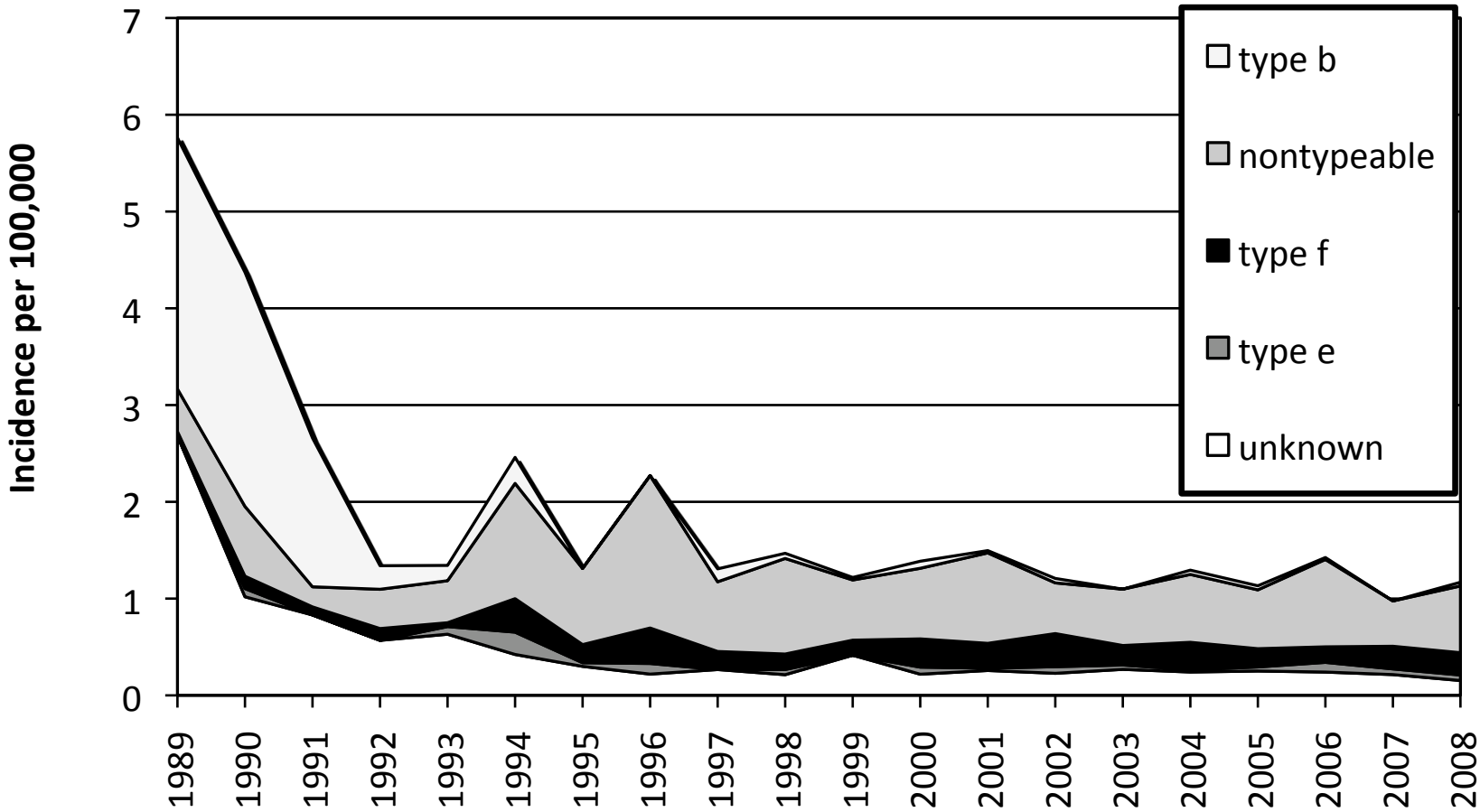

**Figure 3. Proportion of invasive *H. influenzae* disease caused by each serotype among children and adults**

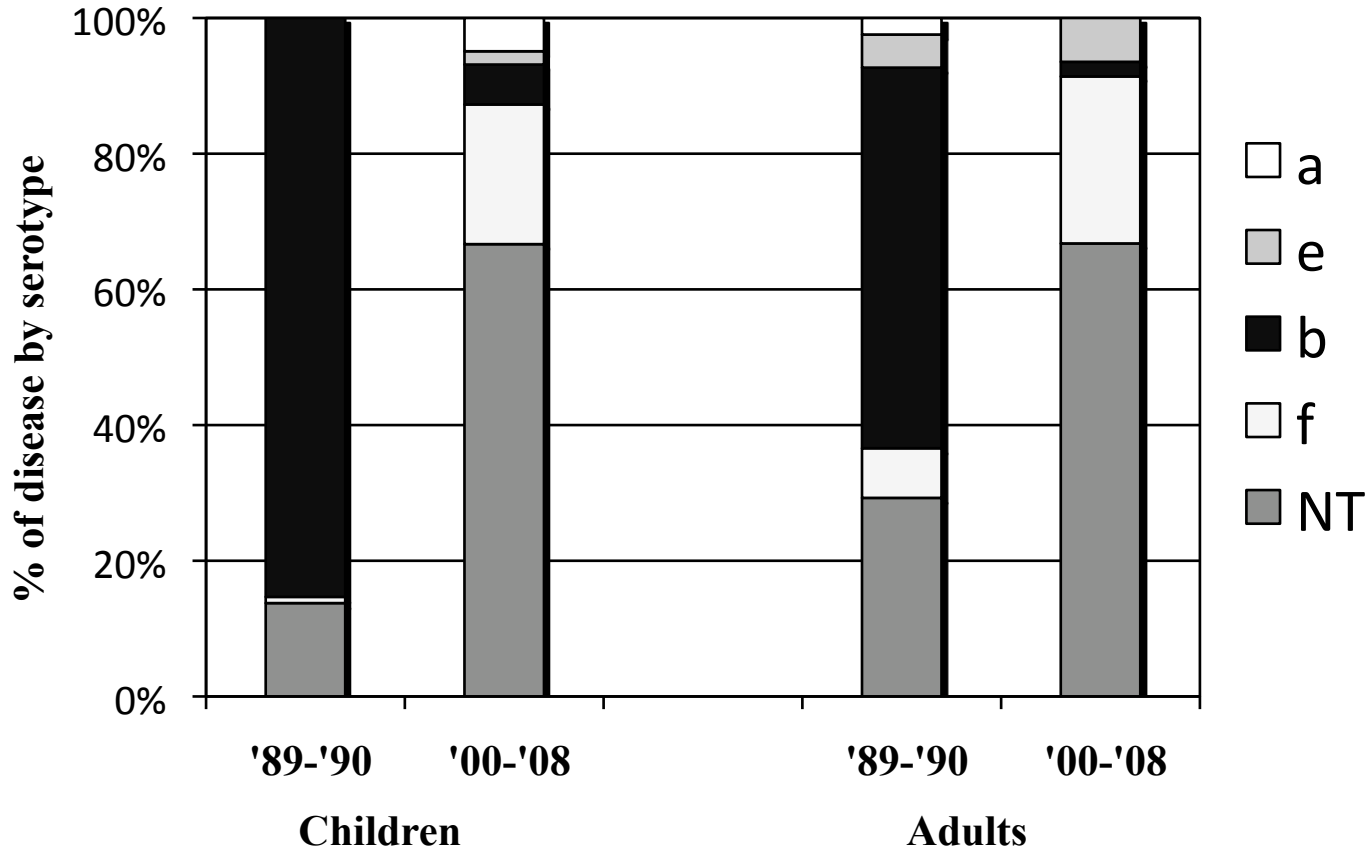

**Figure 4. Causal diagram for potential contributors to in-hospital mortality from invasive *H. influenzae***