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# Invasive *Haemophilus influenzae* in the United States, 1999—2008: Epidemiology and outcomes

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**Summary** *Objectives:* Introduction of the *Haemophilus influenzae* type b (Hib) conjugate vaccine has resulted in a dramatic reduction of Hib disease in the U.S. and an increase in the relative importance of infections caused by nontypeable strains. The current project describes the characteristics and clinical outcomes of pediatric and adult patients with invasive *H. influenzae* (HI) and, through multivariable analysis, identifies risk factors for in-hospital mortality.
*Methods:* HI cases were identified during 1999—2008 through active surveillance as part of Active Bacterial Core surveillance (ABCs). Multivariable analysis was performed with logistic regression to identify factors predictive of in-hospital death.

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*Results:* 4839 cases of HI were identified from 1999–2008. Children accounted for 17.1% of cases and adults 82.9%. Underlying conditions were present in 20.7% of children and 74.8% of adults. In-hospital mortality was highest in cases ≥65 years (21.9%) and <3 months (16.2%).

The risk of in-hospital death in children <1 year was higher among those who were prematurely-born (<28 weeks, OR 7.1, 95% CI 3.2–15.6; 28–36 weeks OR 2.1, 95% CI 0.9–4.8) and, among children aged 1–17 years, higher in those with healthcare-associated onset and dialysis (OR 5.66, 95% CI 1.84–17.39; OR 18.11, 95% CI 2.77–118.65). In adults, age ≥40 was associated with death in nontypeable, but not encapsulated, infections. Infections with nontypeable strains increased the risk of death in cases ≥65 years (OR 1.81, 95% CI 1.31–2.52). Healthcare-associated HI, bacteremia without identifiable focus, bacteremic pneumonia, associated cirrhosis, cerebrovascular accident, dialysis, heart failure, and non-hematologic malignancy also increased the risk of death in adults.

*Conclusion:* Prematurity in infants, advanced age and certain chronic diseases in adults were associated with an increased risk of in-hospital death. Nontypeable HI was associated with higher mortality in the elderly.



## 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 *Haemophilus 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 h 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