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Epidemiology of invasive nontypeable *Haemophilus influenzae* disease—United States, 2008–2019

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Abstract

Background: Nontypeable *Haemophilus influenzae* (NTHi) is the most common cause of invasive *H. influenzae* disease in the United States. We evaluated the epidemiology of invasive NTHi disease in the United States, including among pregnant women, infants, and people with HIV (PWH).

Methods: We used data from population- and laboratory-based surveillance for invasive *H. influenzae* disease conducted in 10 sites to estimate national incidence of NTHi, and to describe epidemiology in women of childbearing age, infants aged ≤30 days (neonates), and PWH living in the surveillance catchment areas. *H. influenzae* isolates were sent to the Centers for Disease Control and Prevention for species confirmation, serotyping, and whole genome sequencing of select isolates.

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Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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Results: During 2008–2019, average annual NTHi incidence in the United States was 1.3/100,000 population overall, 5.8/100,000 among children aged <1 year and 10.2/100,000 among adults aged ≥80 years. Among 225 reported neonates with NTHi, 92% had a positive culture within the first week of life and 72% were preterm. NTHi risk was 23 times higher among preterm compared to term neonates, and 5.6 times higher in pregnant/postpartum compared to non-pregnant women. Over half of pregnant women with invasive NTHi had loss of pregnancy post-infection. Incidence among PWH aged ≥13 years was 9.5 cases per 100,000, compared to 1.1 cases per 100,000 for non-PWH (RR=8.3; 95% CI=7.1–9.7; p<0.0001).

Conclusion: NTHi causes substantial invasive disease, especially among older adults, pregnant/postpartum women, and neonates. Enhanced surveillance and evaluation of targeted interventions to prevent perinatal NTHi infections may be warranted.

Summary:

The incidence of invasive nontypeable *H. influenzae* (NTHi) disease in the United States increased from 2008 to 2019, particularly impacting pregnant women, neonates, and older adults. A vaccine against invasive NTHi infections could prevent substantial morbidity and mortality.

Keywords

Haemophilus influenzae ; nontypeable *Haemophilus influenzae*; epidemiology; *Haemophilus influenzae* vaccines

Introduction

Infection with *Haemophilus influenzae* (Hi) can cause life-threatening invasive disease in vulnerable populations such as children, older adults, and persons with chronic medical conditions [1]. Hi can have a polysaccharide capsule; unencapsulated strains are termed nontypeable. Because encapsulation was thought to be associated with virulence, nontypeable Hi (NTHi) was previously assumed to cause less severe invasive disease or non-invasive mucosal infections [2, 3]. However, since the introduction of Hi serotype b (Hib) vaccines in the 1980s, NTHi has become the most common cause of invasive Hi infections in the United States [1]. Invasive NTHi has been increasing in other countries, including Canada, Portugal, Slovenia, Sweden, and the Netherlands, representing 43–91% of all invasive Hi isolates [4]. Across 12 countries in Europe, NTHi caused 78% of all reported invasive Hi cases and increased 7.4% annually from 2007–2014 [5].

In addition to increases in incidence overall, NTHi infection has been noted as a particular concern in certain sub-populations. In the United Kingdom during 2009–2012, invasive NTHi incidence was 17 times higher in pregnant compared to non-pregnant women [6]; importantly, in all but two cases of NTHi among these pregnant women, infection resulted in the end of pregnancy: either miscarriage, stillbirth, or birth of the infant at the time of infection. Among U.K. neonates, 97% of invasive Hi disease was caused by NTHi, and the incidence of invasive NTHi was substantially higher among preterm neonates; infants born <28 weeks gestation were 365 times more likely to develop invasive NTHi disease compared to term neonates [7]. In nearly all cases, NTHi was isolated within 48 hours of birth.

Increases in invasive NTHi infection (often presenting as septic arthritis) have also been reported among HIV-infected men who have sex with men in metropolitan Atlanta, Georgia [8]. Two unique clonal NTHi strains (sequence type (ST) 1714 and 164) were identified and associated with NTHi septic arthritis among people with HIV (PWH) in Atlanta.

The objective of this analysis was to assess the epidemiology of invasive NTHi disease in the United States. Additionally, we described risk of invasive NTHi in pregnant women, neonates, and PWH.

Methods

Active Bacterial Core Surveillance and Laboratory Methods

Active population- and laboratory-based surveillance for invasive Hi disease was conducted as a part of Active Bacterial Core surveillance (ABCs). ABCs is supported by the Centers for Disease Control and Prevention (CDC) as a part of the Emerging Infections Program Network [9]. The surveillance area includes California (3 San Francisco Bay-area counties), Colorado (5 Denver-area counties), Connecticut (statewide), Georgia (20 Atlanta-area counties, 2008–2009; statewide, 2010–2019), Maryland (statewide), Minnesota (statewide), New Mexico (statewide), New York (15 Rochester- and Albany-area counties), Oregon (statewide), and Tennessee (11 counties, 2008–2009, 20 counties, 2010–2019). The population under surveillance ranged from 36,322,812 in 2008 to 45,041,453 in 2019, representing 11.9% of the U.S. population in 2008 and 13.7% in 2019 [10].

A case was defined as isolation of NTHi from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF]) in an ABCs surveillance-area resident. Epidemiologic and clinical information, including HIV status, was abstracted from medical records. Outcome was based on patient status at hospital discharge. Infants with gestational age <22 weeks were excluded from ABCs because that is below the age of fetal viability. Hi isolates were serotyped at state public health laboratories and sent to CDC for species confirmation and serotyping. Whole genome sequencing of select isolates was performed at CDC using methods previously described [1, 11–13].

Statistical Analysis

Data from 1 January 2008 through 31 December 2019 were included in this analysis. Cases of invasive NTHi disease were classified into mutually exclusive syndrome categories. Cases were classified as meningitis if a clinical diagnosis of meningitis was recorded in the medical record or NTHi was isolated from CSF; bacteremic pneumonia if pneumonia was recorded in the medical record and NTHi was isolated from blood or pleural fluid; and bacteremia if NTHi was isolated from blood and the medical record did not note meningitis or bacteremic pneumonia. Race was categorized as White, Black, American Indian and Alaska Native (AI/AN), or Asian/Pacific Islander (Asian/PI). Ethnicity was categorized as Hispanic/Latino or Non- Hispanic/Latino. A neonate was defined as an infant aged ≤30 days, and preterm was defined as birth at <37 weeks gestation. Women of childbearing age were defined as women aged 15–44 years; pregnancy status at the time of NTHi isolate collection was ascertained through medical record review. Women with a NTHi isolate

collected ≤30 days following a delivery or miscarriage were classified as postpartum. Adults aged ≥18 years with documented HIV infection were classified as PWH and compared to adults without documented HIV infection.

Incidence rates were reported as cases per 100,000 population and calculated using National Center for Health Statistics'(NCHS) bridged-race postcensal population estimates [10] for ABCs sites; nationwide estimates were calculated by directly standardizing to the age and race distribution of the U.S. population. For race-stratified nationwide incidence estimates, missing race was multiply imputed using sequential regression multiple imputation [14] via IVEware software (Institute for Social Research, University of Michigan, Ann Arbor). Variance estimates were calculated using standard combining rules for multiply imputed data. Incidence rates were compared using incidence rate ratios (IRR). The 95% confidence intervals (CIs) around the directly standardized rates were calculated using a method derived from the relationship between the Poisson distribution and the gamma distribution, whereas estimated age and race-specific 95% CIs were calculated using exact CI for a Poisson random variable [15]. A negative binomial model with 95% CIs was used to estimate average annual percentage change in incidence from 2008–2019.

We were unable to estimate national incidence for neonates and pregnant women due to unavailability of national counts for these populations. To assess incidence in the ABCs surveillance area in infants aged <1 year by month of life, monthly population denominators were calculated by dividing the ABCs catchment population aged <1 year by 12. Denominators for pregnant women were calculated using live birth estimates. We used state vital records and national vital statistics reports to obtain ABCs site-specific live birth data. The population of preterm infants was calculated using the proportion of births in the United States that were preterm in 2019 [16].

Incidence rates for PWH were calculated using the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention AtlasPlus database [17]. HIV prevalence data from AtlasPlus was used to determine the PWH population size for each ABCs site. The non-PWH population denominator was calculated by subtracting the PWH population denominator from the NCHS population estimates. Denominator data was available for individuals aged ≥13 years in AtlasPlus, so incidence calculations for PWH were restricted to individuals aged ≥13 years.

Case-fatality ratios were calculated using the proportion of cases with known outcomes as the denominator. Wilcoxon rank-sum tests were used to compare continuous variables and Pearson's χ^2 test was used for categorical variables. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[§] At each ABCs site, it was deemed either a public health assessment or human subjects research, for which approval was granted by local institutional review boards.

Results

Invasive NTHi epidemiology in the United States

A total of 5,991 cases of invasive NTHi disease were reported to ABCs sites from 2008–2019, representing 72% of all invasive Hi cases with known serotyping results. Overall, 47.3% of patients were male; 70.7% were White, 16.4% were Black, 1.1% were AI/AN, 3.2% were Asian/PI, and 8.6% had unknown race (Supplemental Table 1). Case fatality was 15.5% overall and was highest among those aged ≥80 years (25.2%; Table 1). Nearly all patients were hospitalized (93.3%); children aged <1 year had the longest median duration of hospitalization (14 days) and the highest proportion admitted to an intensive care unit (61.4%). Most patients aged ≥15 years (84.3%) had at least one underlying condition. Among all patients, 24.9% of individuals had an immunocompromising condition, with the highest proportion among those aged 45–64 years (31.1%). The most common immunocompromising conditions were receiving immunosuppressive therapy and solid organ malignancy.

Overall, the estimated national average annual incidence of invasive NTHi disease was 1.3/100,000 (Table 2), representing an average annual increase of 3.9%, from 1.1/100,000 in 2008 to 1.6/100,000 in 2019 (Figure 1). The estimated national annual number of cases ranged from 3,264 in 2008 to 5,113 in 2019 (estimated average annual cases, 4244). Incidence rose more sharply after 2014, with an average annual increase of 4.8% (95% CI: 4.1–5.5) from 2014–2019, compared to 2.6% (95% CI: 1.8–3.4) in 2008–2013. Average annual incidence differed by age and was highest among children aged <1 year (5.8/100,000) and adults aged ≥80 years (10.2/100,000). By age group, the largest average annual percent increase in incidence was noted among people aged 15–44 years (6.7%; Table 2). Incidence was significantly lower in Asian/PI persons compared to all other racial groups (Figure 3). Among women of childbearing age, invasive NTHi disease incidence among Black women (0.7/100,000) was over twice that of White or AI/AN women (0.3/100,000).

Invasive NTHi among pregnant women and infants in ABCs sites

Among 400 women of childbearing age with invasive NTHi, 105 (27.0%) were either pregnant (n=59) or postpartum (n=46) at the time of infection (Table 3). Pregnant/postpartum women with invasive NTHi disease were younger and healthier than their non-pregnant counterparts; nearly all had bacteremia, and none died (Table 3). Pregnancy outcome was known for 95 (90.4%) of the 105 pregnant/postpartum women with NTHi. Of those, 33 (34.7%) delivered a live, illness-free neonate, 52 (54.7%) had either spontaneous abortion or stillbirth, 2 (2.1%) had an induced abortion, 1 (1.1%) had a live birth but neonatal death, and 7 (7.4%) had a neonate with clinical infection around the time of birth. A significantly higher proportion of women who were postpartum at the time of infection had a pregnancy outcome of a live, illness-free infant compared to women who were pregnant at the time of infection (54.8% vs. 18.9%, p=.0003). Among the seven neonates with clinical infection who were born to women with pregnant/postpartum infections, 5 (71%) had confirmed NTHi infection within the first day of life and cause of infection was not provided for the remaining 2 neonates. Three of the five with confirmed NTHi were born

extremely premature (23–25 weeks gestation). Four had bacteremia, one had bacteremic pneumonia, and all survived. Isolates from all five mother/infant pairs were sequenced. Each infant had an identical ST to the paired maternal isolate; however, the five paired isolates had different STs (46, 84, 139, 266, and 2317). Invasive NTHi incidence among pregnant/postpartum women within ABCs jurisdictions was 5.6 times higher (95% CI: 4.4–7.0) compared to non-pregnant women of childbearing age (1.7/100,000 vs. 0.3/100,000).

A total of 225 neonates and 122 infants aged 1–11 months with invasive NTHi infection were reported. Compared to older infants with NTHi, more neonates had bacteremia (85% vs. 52%, p<0.0001) and required ICU care (70% vs. 46%, p<0.0001). Most neonates (n=163, 72.4%) were born premature. Among those born premature, 61 (37.4%) were born at 22–28 weeks gestation, 52 (31.9%) at 29–32 weeks, 48 (29.4%) at 33–36 weeks, and 2 (1.2%) were missing gestational age. Case fatality among neonates was 12.0% overall and varied by gestational age. The highest case fatality was among neonates born 22–28 weeks (36.1%); no term neonates died. Nearly all neonates (207, 92.0%) had a positive culture within the first 7 days of life, with 183 (81.3%) positive cultures from the day of birth. Neonatal invasive NTHi incidence in the ABCs sites was 43.0/100,000 overall, and higher among AI/AN and Black compared to White neonates (76.7 and 49.9/100,000 respectively, vs 37.5/100,000). NTHi incidence was 20 times higher in neonates compared to older infants aged 1–11 months (43.0/100,000 vs. 2.1/100,000). Among neonates, NTHi incidence was 23 times higher (95% CI: 17.1–31.4) among preterm compared to term neonates (304.3/100,000 vs. 13.2/100,000).

Invasive NTHi among PWH in ABCs sites

Of the 5,297 cases of invasive NTHi infection among adults aged ≥18 years in the ABCs sites, 167 (3.2%) were among PWH. When compared to those without HIV, PWH were more likely to be male (79.6% vs. 45.0%, p<0.0001), younger (median age 42.0 vs. 71.0 years, p<0.0001), and Black (77.8% vs. 13.4%, p<0.0001) (Supplemental Table 2). While PWH were more likely to have septic arthritis (7.2% vs. 0.9%, p<0.0001) than HIV-uninfected persons, 83% (10 of 12) of patients with NTHi septic arthritis were residents of the metropolitan Atlanta area described previously [8]. In addition, the proportion of NTHi cases among PWH did not increase in any ABCs sites other than Atlanta. Incidence among PWH aged ≥13 years was 9.5 cases per 100,000, compared to 1.1 cases per 100,000 for non-PWH aged ≥13 years (RR=8.3; 95% CI=7.1–9.7; p<0.0001). No additional cases among PWH were reported in people aged 13-<18 years in the ABCs sites.

Discussion

NTHi represented over 70% of all invasive Hi disease in the United States during 2008–2019, consistent with previous studies showing that NTHi is responsible for the majority of invasive Hi disease since introduction of the Hib vaccine [1]. The present study further demonstrates that like other countries, NTHi incidence has been increasing in the United States, with the sharpest increases seen in more recent years. The largest annual rate increases were noted in adolescents and younger adults (15–44 years). Additionally,

racial disparities exist among persons with invasive NTHi, particularly among neonates and women of reproductive age.

We showed that NTHi causes substantial invasive disease among pregnant women and neonates. While no pregnant women or term neonates died, NTHi infection among pregnant women often resulted in fetal loss or preterm delivery, consistent with a recent study that suggested intra-uterine perinatal transmission as the mechanism for these negative pregnancy outcomes [18]. Our findings were also consistent with previous U.K. studies among pregnant women and neonates, but with some notable differences. While we found a lower relative risk of disease in preterm vs. term neonates compared to the United Kingdom, estimated incidence among all neonates in our study was 10-fold higher than reported in the United Kingdom [7,19]. Likewise, incidence among non-pregnant women of childbearing age was higher in the present analysis (0.3/100,000) compared to the reported U.K. incidence (0.17/100,000). These differences likely reflect the different epidemiology of NTHi in the ABCs catchment areas compared to U.K. national estimates but could also be due to an under-recognition of pregnant females in our surveillance data. For this analysis, a female was only noted to be pregnant/postpartum if the information was available upon chart review at the time of infection; some pregnant women were likely misclassified.

In the United States, group B streptococcal (GBS) infection is the most common cause of early-onset neonatal sepsis. However, in the era of GBS screening and intrapartum antibiotics, the incidence of early-onset GBS sepsis has declined [20]. Studies evaluating causes of early-onset sepsis in the United States have noted that gram-negative infections, including Hi, can be more common than GBS among preterm neonates [20, 21]. There are no prevention strategies such as prenatal screening, intrapartum antibiotics, or vaccination in place for neonatal sepsis caused by any gram-negative organisms.

Given the distinct clinical presentations of NTHi infections among pregnant women, neonates, and PWH, existence of specific NTHi strains associated with genitourinary colonization or transmission has been theorized. Early evaluations suggested a possible association of specific strains with cases in neonates and pregnant women [22, 23]; however, more recent studies have identified diverse STs and high genetic diversity among NTHi specimens from infant cases [24]. This is consistent with the results from our study where we identified 5 different STs among the 5 mother/baby isolate pairs. In addition, while a previously described clonal NTHi strain has caused an increase in infections among PWH in Atlanta, to date this strain has only been detected in two cases in one other ABCs site outside of Atlanta. However, surveillance is ongoing, and we will continue to monitor this strain and the unique predominance of septic arthritis among the cases it causes. In-depth genome sequencing analysis of invasive NTHi isolates, including isolates from pregnant women, neonates and PWH, could provide additional insight into bacterial genetic factors that are associated with transmission or colonization.

Currently Hib is the only serotype of Hi preventable by vaccination, and no prevention measures are available for NTHi. While vaccines against NTHi could prevent substantial invasive disease in populations at increased risk of the disease, biological aspects of the NTHi bacterium such as the lack of a polysaccharide capsule, antigenic variation, and

high genetic diversity make vaccine development more challenging than for encapsulated Hi [25, 26]. Protein D, a highly conserved surface lipoprotein, has been proposed as a possible NTHi vaccine target [27]. A 10-valent pneumococcal vaccine has been developed that uses NTHi Protein D as a carrier protein [28]. However, estimates of the efficacy of this vaccine for reducing NTHi nasopharyngeal carriage and otitis media have varied widely from −35.0% to 41.4% [29], and the 10-valent pneumococcal vaccine is currently not licensed in the United States. A NTHi-specific vaccine that includes Protein D and two other NTHi proteins has been developed and is currently beginning clinical trials [30, 31]. To date, the endpoints for all NTHi vaccine clinical trials have primarily focused on the prevention of mucosal infections such as otitis media or chronic obstructive pulmonary disease exacerbations; further research will be needed to assess the ability of NTHi vaccines to prevent invasive infections.

In the decades since Hib vaccine introduction, NTHi has replaced Hib as the predominant Hi pathogen. The highest incidence of NTHi occurs at the extremes of ages. Pregnant women and neonates are at particular risk for invasive NTHi infection, and the possibility of intra-uterine perinatal transmission warrants further investigation. CDC is conducting enhanced laboratory-based and molecular surveillance for maternal and neonatal infections caused by Hi, including NTHi, to better understand this perinatal pathogen and inform the development of public health prevention measures. Finally, these data indicate that a NTHi vaccine effective against invasive infections could prevent substantial morbidity and mortality.

§ See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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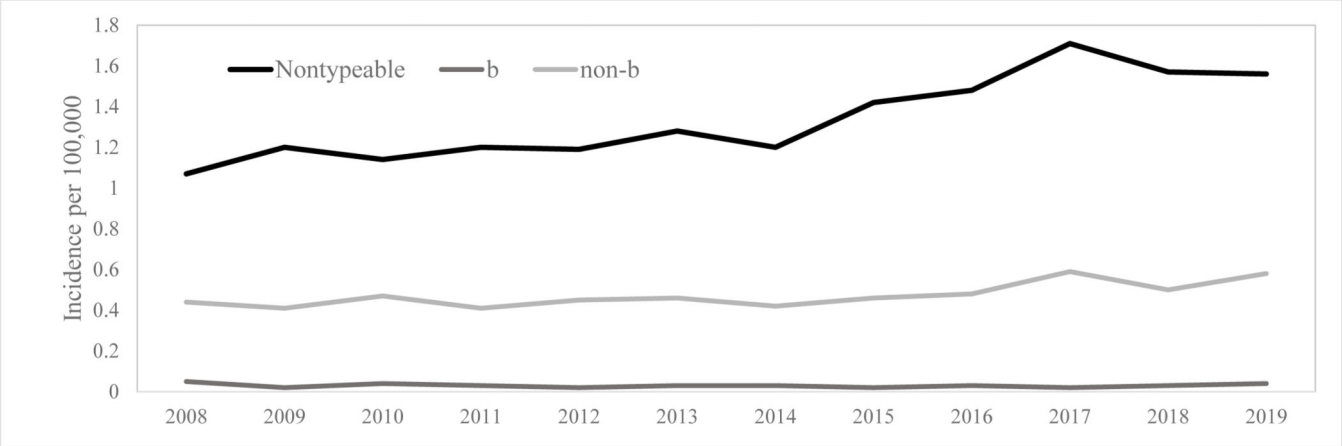

Figure 1.
Trends in estimated incidence of invasive *H. influenzae* disease—United States, 2008–2019

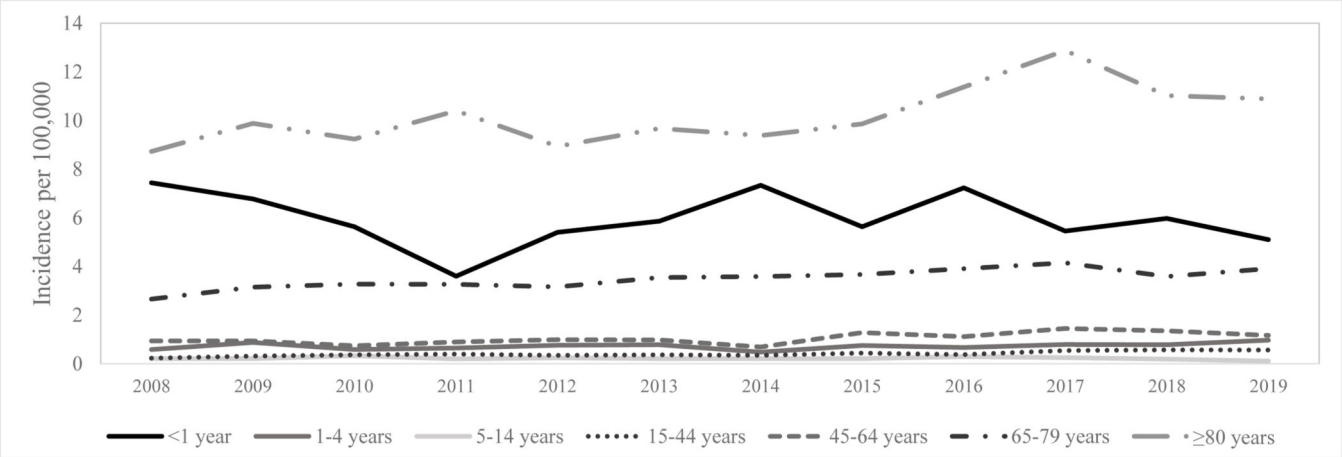

Figure 2.

Trends in estimated incidence of invasive nontypeable *H. influenzae* disease, by age group—United States, 2008–2019

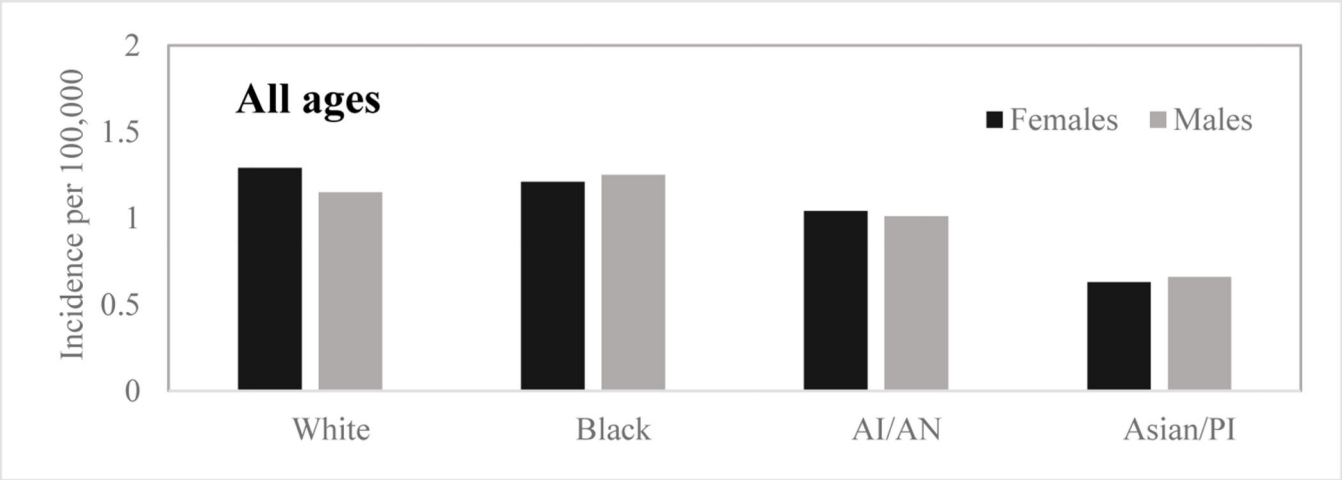

Figure 3.

Annual estimated incidence of invasive nontypeable *H. influenzae* disease by race and sex —United States, 2008–2019

AI/AN, American Indian/Alaska Native; PI, Pacific Islander

Table 1.

Clinical characteristics of patients with invasive nontypeable *H. influenzae* disease, by age group—Active Bacterial Core Surveillance, United States, 2008–2019

	<1 year	1–4 years	5–14 years	15–44 years	45–64 years	65–79 years	≥80 years	Overall
N	347	174	136	768	1285	1639	1642	5991
Clinical syndrome								
Bacteremic pneumonia	63 (18.2%)	66 (37.9%)	32 (23.5%)	200 (26.0%)	726 (56.5%)	1118 (68.2%)	1264 (77.0%)	3469 (57.9%)
Bacteremia	254 (73.2%)	82 (47.1%)	82 (60.3%)	481 (62.6%)	432 (33.6%)	418 (25.5%)	351 (21.4%)	2100 (35.1%)
Meningitis	30 (8.7%)	18 (10.3%)	13 (9.6%)	54 (7.0%)	92 (7.2%)	78 (4.8%)	18 (1.1%)	303 (5.1%)
Other/Unknown	0	8 (4.6%)	9 (6.6%)	33 (4.3%)	35 (2.7%)	25 (1.5%)	9 (0.6%)	119 (2.0%)
Hospitalized	335 (96.5%)	151 (86.8%)	99 (72.8%)	669 (87.1%)	1190 (92.6%)	1563 (95.4%)	1581 (96.3%)	5588 (93.3%)
Duration in days, median (Interquartile Range)	14 (9–35)	5 (4–11)	5 (2–10)	5 (3–9)	7 (4–11)	7 (4–11)	6 (3–9)	6 (4–11)
Admitted to ICU	213 (61.4%)	44 (25.3%)	25 (18.4%)	207 (27.0%)	501 (39.0%)	668 (40.8%)	598 (36.4%)	2256 (37.7%)
1 or more underlying condition	165 (47.6%)*	72 (41.4%)	61 (44.9%)	483 (62.9%)	1103 (85.8%)	1459 (89.0%)	1452 (88.4%)	4795 (80.0%)
Case fatality	32 (9.3%)	4 (2.3%)	7 (5.2%)	58 (7.6%)	154 (12.0%)	260 (15.9%)	412 (25.2%)	927 (15.5%)

Abbreviations: ICU, intensive care unit.

* In 157 (95%) of 165 patients aged <1 year the underlying condition is prematurity

Table 2.

Annual estimated incidence of invasive nontypeable *H. influenzae* disease and average annual percent change in incidence, by age group and sex—United States, 2008–2019

	Incidence[a] (95% CI)	Average Annual Percent Change, 2008–2019
Age (years)		
<1 year	5.8 (5.3–6.5)	−1.1 (−2.1–0.0)
1–4 years	0.7 (0.6–0.8)	2.2 (0.7–3.8)
5–14 years	0.2 (0.2–0.3)	−2.4 (−4.0– −0.7)
15–44 years	0.4 (0.4–0.5)	6.7 (5.8–7.6)
45–64 years	1.1 (1.0–1.1)	4.5 (3.9–5.0)
65–79 years	3.5 (3.4–3.7)	2.8 (2.3–3.3)
≥80 years	10.2 (9.7–10.7)	2.3 (1.9–2.8)
Sex		
Females	1.4 (1.4–1.4)	3.8 (3.5–4.2)
Males	1.3 (1.3–1.3)	4.4 (4.0–4.8)
Total	**1.3 (1.3–1.4)**	**3.9 (3.7–4.2)**

Abbreviations: CI, confidence interval.

[a]Cases per 100,000 persons per year

Table 3.

Epidemiologic and clinical characteristics of women of childbearing age (aged 15–44 years) with invasive nontypeable *H. influenzae* disease, by pregnancy status—Active Bacterial Core Surveillance, 2008–2019

Characteristic	Pregnant/Postpartum	Not Pregnant	p-value
N	105	295	
Age, median	25.0 years	35.0 years	**<0.0001**
Race:			0.9
White	48 (45.7%)	147 (49.8%)	
Black	33 (31.4%)	90 (30.5%)	
AI/AN	1 (1.0%)	3 (1.0%)	
Asian/PI	5 (4.8%)	13 (4.4%)	
Unknown	18 (17.1%)	42 (14.2%)	
Ethnicity:			0.7
Hispanic/Latino	15 (14.3%)	34 (11.5%)	
Non-Hispanic/Latino	65 (61.9%)	192 (65.1%)	
Unknown	25 (23.8%)	69 (23.4%)	
Clinical syndrome:			**<0.0001**
Bacteremic pneumonia	4 (3.8%)	85 (28.8%)	
Bacteremia	101 (96.2%)	166 (56.3%)	
Meningitis	0	23 (7.8%)	
Other/Unknown	0	21 (7.1%)	
Hospitalized	94 (89.5%)	256 (86.8%)	.7
ICU	11 (10.5%)	72 (24.4%)	**0.01**
1 or more underlying condition	31 (29.5%)	195 (66.1%)	**<0.0001**
Case fatality	0	17 (5.8%)	**0.01**

Abbreviations: AI/AN, American Indian and Alaska Natives; PI, Pacific Islander