

# Current Epidemiology and Trends in Invasive *Haemophilus influenzae* Disease—United States, 1989–2008

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**Background.** With the introduction of *Haemophilus influenzae* serotype b (Hib) conjugate vaccines, there has been a dramatic reduction of Hib disease in young children and the epidemiological trends of invasive *H. influenzae* have shifted.

**Methods.** Data were collected from active surveillance for invasive *H. influenzae* disease conducted through Active Bacterial Core surveillance sites during 1989–2008.

**Results.** During 1999–2008, the estimated mean annual incidence of *H. influenzae* infection was 1.62 cases per 100 000 population; 15.3% of cases were fatal. Incidence was higher among adults aged  $\geq 65$  years, compared with other age groups. The largest burden of disease among children aged  $< 5$  years was in infants aged  $< 1$  year; many of these cases occurred during the first month of life in preterm or low-birth weight infants. An estimated 10% of the total burden of disease among children aged  $< 5$  years occurred in American Indian and Alaska Native children. During 1989–2008, 7559 cases of *H. influenzae* disease were reported from Active Bacterial Core surveillance sites. Small increases in the incidence of serotypes a, e, and f were observed during 1989–2008. The largest of these increases was in serotype f and was primarily among adults aged  $\geq 18$  years.

**Conclusions.** Since the introduction of Hib conjugate vaccines, the incidence of invasive disease caused by *H. influenzae* in the United States has decreased dramatically; however, a considerable burden of non-Hib disease is still present in the oldest and youngest age groups. There is no evidence of substantial replacement disease with non-b serotypes in young children in the United States.

Invasive *Haemophilus influenzae* and *Haemophilus influenzae* serotype b (Hib) have been described as important causes of disease and death in children, immunocompromised persons, and adults with certain underlying medical conditions [1–6]. Hib was once the

most common cause of bacterial meningitis in children aged  $\leq 5$  years in the United States [5, 6]. After the introduction of Hib polysaccharide vaccine in 1985 and Hib conjugate vaccines during 1987–1990, the incidence of invasive *H. influenzae* disease among children aged  $< 5$  years decreased by  $> 99\%$  [5, 7–9]. However, rates of invasive *H. influenzae* and Hib remain higher among American Indian and Alaska Native children [10, 11].

With the dramatic reduction of Hib disease in young children because of universal vaccination, the epidemiological trends of *H. influenzae* have shifted, and recent reports describe an increase of disease in adults aged  $> 65$  years [12] and an increase of *H. influenzae* disease caused by non-b encapsulated serotypes [13–15].

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Surveillance for *H. influenzae* disease is essential to monitor for shifts in disease incidence, to understand the burden of invasive *H. influenzae* disease, and to develop public health prevention strategies. The greatest burden of disease occurs at both ends of the life spectrum—in the youngest infants and in older adults. We analyzed data from 20 years of active, population- and laboratory-based surveillance for invasive *H. influenzae* infection in a large, multistate catchment area to describe the epidemiology and characterize trends in the incidence of *H. influenzae* infection in the United States.

## METHODS

### Surveillance

Active, population- and laboratory-based surveillance for invasive *H. influenzae* disease was conducted from 1 January 1989 through 31 December 2008 as part of Active Bacterial Core surveillance (ABCs). ABCs is supported by the United States Centers for Disease Control and Prevention (CDC) as part of its Emerging Infections Program Network, as described elsewhere [16].

The surveillance areas included California (3 San Francisco Bay area counties, 1989–2008), Connecticut (statewide, 1995–2008), Colorado (5 Denver area counties, 2000–2008), Georgia (8 Atlanta area counties, 1989–1996; 20 Atlanta area counties, 1997–1999, 2004–2008; statewide, 2000–2003), Maryland (statewide, 1991–2008), Minnesota (statewide, 1995–2008), New Mexico (statewide, 2004–2008), Oregon (statewide, 1995–2008), New York (7 Rochester area counties, 1997–1998; 15 Rochester and Albany area counties, 1999–2008), Tennessee (5 urban counties, 1989–1998; 11 urban counties, 1999–2008). The population under surveillance ranged from 7 055 880 in 1989 to 35 559 550 in 2008 (representing 2.9% of the US population in 1989 and 11.7% in 2008).

A case of invasive *H. influenzae* was defined as isolation of *H. influenzae* from a normally sterile site (eg, blood or cerebrospinal fluid [CSF]) in a surveillance area resident. Epidemiologic and clinical information was abstracted from medical records. Outcome of illness was based on patient status at the time of hospital discharge; no information was collected on whether the death was attributed to *H. influenzae* infection. Regular laboratory audits were conducted to identify cases missed during routine surveillance.

The following hierarchical definition was used to assign a single syndrome for cases: a patient was defined as having meningitis if a clinical diagnosis of meningitis had been reported in the patient's medical record or if *H. influenzae* was isolated from a CSF sample and as having pneumonia if pneumonia was reported in the patient's medical record and *H. influenzae* was isolated from a blood or pleural fluid sample. A patient was defined as having septic arthritis if *H. influenzae* was isolated

from a joint fluid sample and as having isolated bacteremia if *H. influenzae* was isolated from a blood sample and no localized clinical syndrome was described.

### Laboratory Methods

Serotyping of *H. influenzae* was done at state public health laboratories, after which the isolates were sent to the CDC, where serotype was confirmed by slide agglutination. The CDC result was used as the final serotype. If an isolate was nonviable or contaminated on arrival at CDC after sending 2 times, the result from the state laboratory was used. In this analysis, *H. influenzae* isolates were classified on the basis of their serotype; serotype b (Hib), nontypeable (nonencapsulated), and non-b (serotypes a, c, d, e, and f).

### Statistical Analyses

Incidence rates were calculated using US Census data for the ABCs sites, and estimates of the number of cases and deaths in the 50 states were calculated standardizing for race and age group. Rates calculated for 1989 used 1990 population estimates as denominators, because appropriate race stratifications were not available in 1989 census data. For rate calculations, an ABCs site was included only if data were collected for the complete year. The 95% confidence interval (CI) around the standardized rate was calculated using a method derived from the relationship between Poisson distribution and the gamma distribution [17]. Incidence rates are reported as cases per 100 000 population. Trends over time were assessed using the Cochran-Armitage test for trend; when data were not linear, we reported the percentage change in incidence.

Race was classified as white, black, American Indian and Alaska Native, or Asian/Pacific Islander. Patients with unknown race were distributed based on the known racial distribution in each ABCs site and age group. The case-fatality ratio was calculated using the proportion of cases with known outcomes as the denominator.

## RESULTS

### Current Epidemiology: 1999–2008

During 1999–2008, 4838 cases of *H. influenzae* disease were reported from ABCs sites, resulting in an estimated mean annual incidence of 1.62 cases per 100 000 population; 15.3% of cases were fatal. An estimated 4725 cases of *H. influenzae* disease occurred annually in the United States during this period, with an estimated 3625 cases in 1999 and 4700 cases in 2008. The mean annual incidence of *H. influenzae* disease ranged from 1.26 to 2.00 cases per 100,000 population (median, 1.59 cases per 100,000 population) among surveillance sites.

Table 1 shows the standardized incidence and case-fatality ratio associated with *H. influenzae* disease by age group and

**Table 1. Annual Estimated Incidence and Case-Fatality Ratio Associated With *Haemophilus influenzae*, by Age Group and Serotype—United States, 1999–2008**

Age (years)	Serotype b		Non-b		Nontypeable		Total <sup>a</sup>	
	Incidence (95% CI)	CFR	Incidence (95% CI)	CFR	Incidence (95% CI)	CFR	Incidence (95% CI)	CFR
<1	0.71 (.47–1.02)	7.3	2.23 (1.80–2.74)	5.3	5.87 (5.15–6.65)	14.4	9.54 (8.63–10.54)	11.6
1–4	0.11 (.06–.17)	0	0.47 (.37–.59)	2.6	0.68 (.56–.81)	5.7	1.37 (1.20–1.56)	4.0
5–17	0.02 (.01–.03)	0	0.07 (.05–.10)	13.0	0.23 (.19–.27)	4.8	0.35 (.31–.41)	5.8
18–34	0.01 (.00–.02)	0	0.07 (.05–.09)	5.2	0.29 (.25–.33)	4.3	0.44 (.39–.49)	4.7
35–49	0.03 (.02–.05)	22.1	0.21 (.18–.25)	9.7	0.43 (.39–.48)	7.1	0.82 (.76–.89)	9.5
50–64	0.05 (.03–.07)	4.1	0.50 (.44–.56)	9.5	0.92 (.83–1.00)	14.9	1.70 (1.59–1.81)	13.0
≥65	0.11 (.08–.15)	16.3	1.29 (1.18–1.42)	14.1	4.09 (3.88–4.31)	23.6	6.31 (6.05–6.58)	21.3
Total	0.05 (.04–.06)	9.7	0.38 (.35–.40)	10.7	0.99 (.95–1.02)	17.1	1.63 (1.58–1.67)	15.3

Abbreviations: CFR, case fatality ratio; CI, confidence interval.

<sup>a</sup> Includes cases with unknown serotype.

serotype during 1999–2008. Incidence was highest among children aged <1 year and adults aged ≥65 years. Table 2 shows the epidemiologic characteristics of patients with nontypeable and non-b *H. influenzae* disease by age group.

*H. influenzae* was isolated from blood in 4414 cases (91.2%), CSF in 259 cases (5.4%), joint fluid in 54 cases (1.1%), pleural fluid in 84 cases (1.7%), and peritoneal fluid in 71 cases (1.5%). In 72 cases (1.5%), *H. influenzae* was isolated from both blood and CSF samples. Information on syndrome was available for 4584 cases (94.7%). Pneumonia was the most frequent clinical syndrome (53.3%), followed by

bacteremia (34.7%) and meningitis (7.6%). The median age of patients with pneumonia was 70 years (range, 0–110 years), whereas the median age of patients with bacteremia was 52 years (range, 0–105 years) and with meningitis was 29.5 years (range, 0–96 years). The majority of patients were hospitalized (90.7%); the median duration of hospitalization was 6 days (range, 0–609 days). Patients with bacteremia were hospitalized a median of 6 days (range, 0–609 days), patients with pneumonia were hospitalized a median of 7 days (range, 0–309 days), and patients with meningitis were hospitalized a median of 9 days (range, 0–98 days).

**Table 2. Epidemiologic Characteristics of Patients With Invasive Nontypeable or Non-b *Haemophilus influenzae* Disease, by Age Group, Active Bacterial Core Surveillance, 1999–2008**

	Nontypeable					Non-b				
	<1 year (n = 247)	1–4 years (n = 116)	5–17 years (n = 126)	18–64 years (n = 1010)	≥65 years (n = 1415)	<1 year (n = 93)	1–4 years (n = 79)	5–17 years (n = 40)	18–64 years (n = 470)	≥65 years (n = 444)
Sex:										
Male	54.3%	54.3%	54.0%	51.5%	42.8%	62.4%	60.8%	42.5%	39.8%	39.2%
Race:										
White	66.8%	50.0%	56.4%	56.6%	79.7%	67.7%	44.3%	65.0%	57.5%	81.3%
Black	25.1%	31.9%	22.2%	23.4%	7.3%	16.1%	26.6%	20.0%	28.3%	6.8%
AI/AN	0.8%	0.9%	0.0%	0.9%	0.4%	9.7%	17.7%	5.0%	1.1%	0.2%
Asian/PI	2.4%	4.3%	4.0%	2.1%	2.5%	0.0%	2.5%	0.0%	0.9%	0.2%
Other/Unknown	4.9%	12.9%	17.5%	17.0%	10.2%	6.5%	8.9%	10.0%	12.3%	11.5%
Syndrome <sup>a</sup> :										
Meningitis	6.2%	18.2%	16.8%	10.3%	2.8%	46.1%	27.4%	13.5%	5.7%	3.4%
Bacteremia	77.0%	42.7%	54.9%	40.3%	26.7%	30.8%	31.5%	46.0%	27.1%	27.3%
Pneumonia	14.4%	33.6%	20.4%	44.9%	69.4%	8.8%	30.1%	32.4%	62.2%	66.2%
Other	2.4%	5.5%	8.0%	4.5%	1.2%	14.3%	11.0%	8.1%	5.1%	3.1%
Serotype a						24.7%	39.2%	7.5%	4.9%	2.7%
Serotype e						11.8%	3.8%	15.0%	21.1%	26.8%
Serotype f						59.1%	54.4%	72.5%	71.5%	68.5%
Serotype c or d						3.2%	2.5%	2.5%	2.5%	1.6%

<sup>a</sup> The number of cases with syndrome available: nontypeable (243 for <1 year, 110 for 1–4 years, 113 for 5–17 years, 949 for 18–64 years, and 1394 for ≥65 years), non-b (91 for <1 year, 73 for 1–4 years, 37 for 5–17 years, 436 for 18–64 years, and 414 for ≥65 years).

**Table 3. Annual Estimated Incidence of *Haemophilus influenzae* Disease, by Serotype and Race, Among Children Aged <5 Years—United States, 1999–2008**

	Serotype b			Non-b <sup>b</sup>			Nontypeable			Total <sup>a</sup>		
	White	Black	AI/AN	White	Black	AI/AN	White	Black	AI/AN	White	Black	AI/AN
<1 year	0.66 (0.40–1.01)	0.36 (0.07–1.06)	10.07 (3.27–23.50)	2.17 (1.68–2.76)	1.81 (1.01–2.99)	20.14 (9.66–37.05)	5.72 (4.90–6.63)	7.61 (5.85–9.74)	4.03 (0.49–14.55)	9.07 (8.03–10.20)	11.12 (8.96–13.63)	42.30 (26.19–64.66)
1 year	0.07 (0.01–0.24)	0.12 (0.00–0.68)	0.00 (0.00–7.32)	0.53 (0.30–0.86)	1.34 (0.67–2.40)	11.91 (4.37–25.92)	0.69 (0.43–1.06)	2.07 (1.21–3.32)	1.98 (0.05–11.06)	1.52 (1.11–2.03)	3.78 (2.57–5.36)	15.88 (6.86–31.29)
2–4 years	0.11 (0.05–0.20)	0.00 (0.00–0.16)	2.60 (0.71–6.67)	0.25 (0.15–0.37)	0.51 (0.26–0.88)	6.51 (3.12–11.97)	0.52 (0.38–0.70)	0.97 (0.61–1.45)	0.00 (0.00–2.40)	0.93 (0.74–1.15)	1.52 (1.06–2.10)	10.41 (5.95–16.91)

<sup>a</sup> Includes cases with unknown serotype.

<sup>b</sup> Estimated incidence and annual number of serotype a cases in AI/AN children: <1 year (17.96 per 100 000); 1 year (9.85 per 100 000); 2–4 years (6.51 per 100 000).

Isolates were available for serotyping at the CDC or state health departments for 4190 cases (86.6%). Of the 3576 tested at both the state laboratory and CDC, 263 (7.4%) had discrepant results between the 2 laboratories, and 58 (22.1%) were type b at the state laboratory but determined to be nontypeable at CDC. Nontypeable cases accounted for 2914 (69.5%), type a for 92 (2.2%), type b for 150 (3.6%), type c for 11 (0.3%), type d for 14 (0.3%), type e for 238 (5.7%), and type f for 767 (18.3%).

### Epidemiology in Children Aged <5 Years

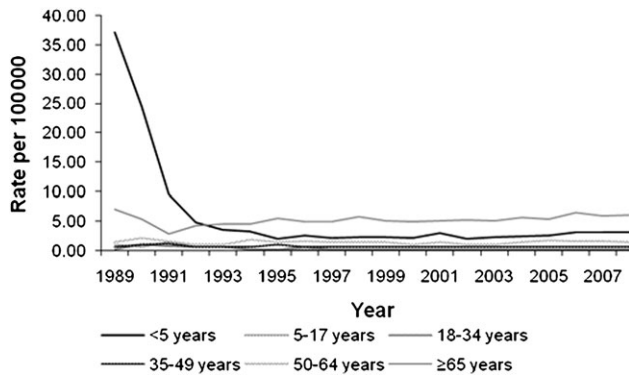
During 1999–2008, 632 cases were reported in children aged <5 years. The largest burden of disease among children aged <5 years was in infants aged <1 year (401 [63.5%]); 175 cases (27.7%) were in infants aged <1 month. The estimated national incidence of *H. influenzae* disease was 9.54 cases per 100,000 population among infants aged <1 year, 2.03 cases per 100,000 population among infants aged 1 year, and 1.14 cases per 100,000 population among children aged 2–4 years. Among infants aged <1 month, gestational age was known for 144 cases; 83 (57.6%) were <34 weeks, and 104 (72.2%) were <37 weeks (range, 23–43 weeks). Birth weight was available for 150 infants; 68 (45.3%) were <1500 g, and 94 (62.7%) were <2500 g (range, 482–4189 g). One hundred sixty-one (92%) of cases in infants aged <1 month occurred during the first week of life (<7 days), and 95% of disease was caused by nontypeable organisms.

The burden of *H. influenzae* disease among American Indian and Alaska Native children is much greater than that in the general US population. Incidence by race and serotype among children aged <5 years is shown in Table 3. Serotypes a and b are more frequent causes of invasive disease in American Indian and Alaska Native children, compared with non-Native children, whereas nontypeable cases are more common in non-Native children, compared with American Indian and Alaska Native children (Table 3).

With the successful use of Hib vaccine in children aged <5 years, the incidence of Hib disease has decreased to 0.23 cases per 100,000 population. Nontypeable *H. influenzae* has become an important cause of invasive disease among children aged <5 years, with an estimated incidence of 1.73 cases per 100,000 population; 62.5% of cases in this age group were caused by nontypeable *H. influenzae*. Among infants aged <1 year, 66.9% of cases were caused by nontypeable *H. influenzae*. Compared with children with Hib disease, children with nontypeable *H. influenzae* are significantly more likely to present with bacteremia than with meningitis (data not shown).

### Epidemiology in Adults Aged ≥65 Years

The incidence of invasive *H. influenzae* is higher among adults aged ≥65 years than among other age groups (Table 1). The risk of disease continues to increase with increasing age; among adults aged 65–69 years, incidence was 3.55 cases per 100 000



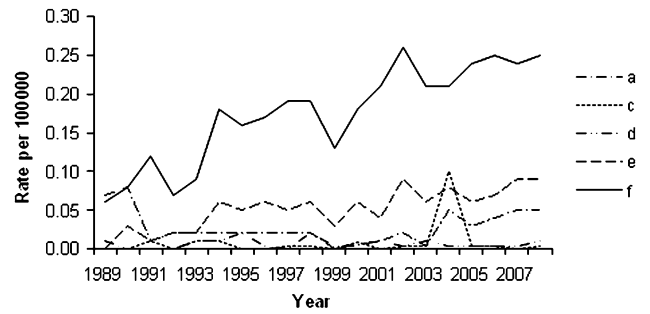
**Figure 1.** Trends in incidence of invasive *Haemophilus influenzae* disease, by age group—United States, 1989–2008.

population; among persons aged 70–74 years, incidence was 4.62 cases per 100 000 population; among persons aged 75–79 years, incidence was 5.92 cases per 100 000 population; among persons aged 80–85 years, incidence was 7.81 cases per 100 000 population; and among persons aged  $\geq 85$  years, incidence was 13.48 cases per 100 000 population. The proportion of disease that occurs in black persons aged  $\geq 65$  years is substantially lower than that in other age groups (Table 2). A higher proportion of patients aged  $\geq 65$  years were hospitalized (data not shown), and patients in this age group had a higher case-fatality ratio (Table 1).

Among persons aged  $\geq 65$  years, 19.5% were residents of nursing homes; 22.8% and 7.3% of patients infected with nontypeable and non-b *H. influenzae*, respectively, were nursing home residents. Among persons aged  $\geq 85$  years, 38.1% were residents of nursing homes; 40.2% and 18.1% of patients infected with nontypeable and non-b *H. influenzae*, respectively, were nursing home residents. In the United States, 4% of the population aged  $\geq 65$  years and 14% of the population aged  $\geq 85$  years are residents of nursing homes [18].

#### Trends in Disease Incidence: 1989–2008

During 1989–2008, 7559 cases of *H. influenzae* disease were reported from ABCs sites. During 1989–1998, 76% of isolates were available for serotyping, and during 1999–2008, 87% of isolates were available for serotyping. In 1989, 79.7% of invasive disease was caused by Hib and 16.8% by nontypeable strains. By 2008, only 3.0% of invasive disease was caused by Hib and 68.4% by nontypeable strains. The estimated mean annual incidence of *H. influenzae* infection decreased by 65%, from 4.39 cases per 100 000 population in 1989 to 1.55 cases per 100 000 population in 2008. *H. influenzae* infection incidence among children aged  $< 5$  years decreased from 37.18 cases per 100 000 population in 1989 to 3.09 cases per 100 000 population in 2008 (92% decrease) (Figure 1), mostly because of decreases in the incidence of Hib infection. Among adults  $\geq 65$  years, *H. influenzae* infection incidence remained largely stable



**Figure 2.** Trends in incidence of invasive *Haemophilus influenzae* disease caused by non-b encapsulated serotypes—United States, 1989–2008.

(12% decrease); however, large increases in the incidence of infection caused by non-b types and nontypeable strains were observed. Figure 2 shows trends in the incidence of invasive *H. influenzae* disease caused by non-b encapsulated serotypes; the largest increase in incidence was observed for serotype f (0.06 cases per 100 000 population in 1989 to 0.25 cases per 100 000 population in 2008; 317% increase). Serotype f was observed primarily among adults, with 83% of cases reported in adults aged  $\geq 18$  years.

During the study period, the median age of patients increased significantly. In 1989, the median patient age for patients with non-b and nontypeable cases was 28 years (range, 0–96 years), and 31.9% of patients were aged  $< 5$  years, whereas in 2008, the median patient age had increased to 63 years (range, 0–100 years), and 48.2% of patients were  $\geq 65$  years of age.

## DISCUSSION

The epidemiology of invasive *H. influenzae* infection has shifted dramatically in the post-Hib vaccination era, with the majority of the disease now caused by nontypeable *H. influenzae* in all age groups. Overall decreases in *H. influenzae* infection incidence among children aged  $< 5$  years have persisted, but rates of *H. influenzae* disease among adults aged  $\geq 65$  years have remained largely stable. The largest burden of *H. influenzae* disease continues to occur in the youngest and oldest age groups. Many cases in children aged  $< 5$  years occur during the first month of life, in preterm or low-birth weight infants. An estimated 10% of the total burden of disease among children aged  $< 5$  years occurs in American Indian and Alaska Native children, who account for 1% of the total population of children aged  $< 5$  years in the United States. Historically, American Indian and Alaska Native children have been at increased risk of Hib disease. This may be attributable to continued transmission in adverse living conditions (eg, household crowding, poverty, and poor indoor air quality) disproportionately experienced by many American Indian and Alaska Native children [11]. Invasive *H. influenzae*

disease is associated with severe outcomes, and among persons aged  $\geq 65$  years, nearly 25% of cases result in death. Risk factors for disease and whether clinical outcomes in older persons are directly to the result of invasive *H. influenzae* disease or of complications of other underlying medical conditions remain unclear.

The epidemiology of *H. influenzae* at the national level is similar to reports from local areas [12, 15] and other countries post-Hib implementation [19, 20]. However, it is difficult to assess whether observed increases in rates of *H. influenzae* disease are true increases in disease or a result of improved surveillance over the past 20 years. ABCs methods have not changed significantly, but there have likely been improvements in clinical practice, laboratory testing, and recognition of *H. influenzae* disease over time, particularly in the older age groups.

The non-Hib invasive disease burden might be an opportunity for prevention through development of new vaccines. The epidemiology of invasive disease suggests these vaccines should not target capsular antigens, because most disease is caused by nontypeable *H. influenzae* and a high level of genetic diversity has been found among nontypeable *H. influenzae* isolates [21, 22]. A pneumococcal vaccine licensed in Europe is conjugated to protein D, a protein found on the outer membrane of *H. influenzae* organisms, which may have broad coverage against *H. influenzae* [23]. Protein-based vaccines are being developed for broad coverage against pneumococcal organisms, which could serve as a model for future *H. influenzae* vaccines. Moreover, *H. influenzae* vaccines with broad coverage may have a substantial impact on noninvasive disease, such as otitis media, pneumonia, and sinusitis [24].

Understanding how *H. influenzae* is being transmitted, especially to neonates and older persons, may help to determine for which age groups vaccination should be targeted for the greatest disease prevention. To be most effective, *H. influenzae* vaccines should have an impact on nasopharyngeal carriage, because the populations at greatest risk are the most difficult to protect through primary vaccination. A vaccine that is able to reduce acquisition of *H. influenzae* colonization in the nasopharynx can interrupt transmission, leading to protection of vulnerable populations through herd immunity.

Hib disease remains a major cause of childhood mortality in developing countries [25], but the number of countries including Hib on their primary immunization schedule is rapidly expanding [26]. Long-term disease trends in the United States are encouraging for these countries, because there is no evidence of substantial replacement disease with non-b serotypes in young children. Nevertheless, in some countries, rates of Hib disease are similar to or greater than rates observed in American Indian and Alaska Native children [25]; those countries might also continue to see a substantial burden of non-Hib disease. In addition, countries that implement a 3-dose primary series and no booster

vaccine dose after age 12 months might not sustain low rates of Hib disease. Several years after implementing a 3-dose series, Hib disease rates increased in the United Kingdom, leading the country to move the third dose to after 12 months of age [27, 28].

Since the introduction of Hib conjugate vaccines, the incidence of disease due to *H. influenzae* in the United States has decreased dramatically; however, there is still a substantial burden of non-Hib disease in the oldest and youngest age groups. Mortality associated with non-Hib disease in these age groups is similar to that seen with Hib disease. Studies are needed to identify risk factors for disease to determine how to maximize benefits from interventions designed to decrease incidence and severity in these age groups. In addition, although lower than in the pre-Hib vaccine era, American Indian and Alaska Native children aged  $< 5$  years continue to be at significantly higher risk for invasive *H. influenzae* disease than other populations, and an early focus of interventions in this population should be a key consideration of *H. influenzae* disease prevention strategies in the United States.

## Notes

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