

Chapter 2: *Haemophilus influenzae* serotype b (Hib)

Elizabeth C. Briere, MD, MPH; Xin Wang, PhD

I. Disease Description

Haemophilus influenzae invasive disease is caused by the bacterium *Haemophilus influenzae*. *H. influenzae* may be either encapsulated (typeable) or unencapsulated (nontypeable). Six antigenically distinct capsular types of *H. influenzae* (types a–f) that can cause invasive disease in persons of any age have been identified. Nontypeable strains can also cause invasive disease but more commonly cause mucosal infections.

Invasive *H. influenzae* diseases include clinical syndromes of meningitis, bacteremia or sepsis, epiglottitis, pneumonia, septic arthritis, osteomyelitis, pericarditis, and cellulitis. In contrast, syndromes of mucosal infections such as bronchitis, sinusitis, and otitis media are considered noninvasive disease. The noninvasive syndromes are not nationally notifiable.

Before the introduction of effective vaccines, *H. influenzae* serotype b (Hib) was the cause of more than 95% of invasive *H. influenzae* diseases among children younger than 5 years of age. Hib was the leading cause of bacterial meningitis in the United States among children younger than 5 years of age and a major cause of other life-threatening invasive bacterial diseases in this age group. Meningitis occurred in approximately two-thirds of children with invasive Hib disease, resulting in hearing impairment or severe permanent neurologic sequelae, such as mental retardation, seizure disorder, cognitive and developmental delay, and paralysis in 15%–30% of survivors. Approximately 4% of all cases were fatal.¹

II. Background

Since the introduction of the Hib polysaccharide and conjugate vaccines in 1985 and 1990, the incidence of invasive Hib disease in children less than 5 years of age has decreased by 99%, to less than 1 case per 100,000 children younger than 5 years of age.^{2–5} Continued monitoring of invasive *H. influenzae* disease through the Active Bacterial Core surveillance (ABCs) system, which includes serotype information on all invasive *H. influenzae* isolates, has demonstrated low rates of invasive Hib in children younger than 5 years of age; between 2010–2013, the average incidence was 0.14 cases per 100,000, which is below the Healthy People 2020 goal of 0.27/100,000.^{6–10}

In the post-Hib vaccine era, the epidemiology of invasive *H. influenzae* disease in the United States has changed. Studies suggest that the majority of invasive *H. influenzae* disease in all age groups is now caused by nontypeable *H. influenzae*.¹¹

III. Importance of Rapid Case Identification

Rapid identification of cases is important to allow for early administration of chemoprophylaxis and Hib vaccine, if needed, to household and childcare classroom contacts of case-patients.¹² Early notification of *H. influenzae* invasive disease cases in children younger than 5 years is also important to ensure isolates are saved for serotyping. State health departments with questions about serotyping should contact the CDC Meningitis and Vaccine-Preventable Diseases Branch laboratory at 404-639-3158.

IV. Importance of Surveillance

H. influenzae surveillance information is used to monitor the effectiveness of Hib immunization programs and vaccines, to assess progress toward Hib disease elimination, and to describe the epidemiology of non-b invasive *H. influenzae* disease.



V. Disease Reduction Goals

Hib disease has declined rapidly because of widespread immunization of infants and young children with conjugate vaccines and because humans are the only known reservoir for Hib.

VI. Case Definition

The following case definition for invasive *H. influenzae* disease has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 2014.¹³

Clinical case description

Invasive disease caused by *H. influenzae* can produce any of several clinical syndromes, including meningitis, bacteremia, epiglottitis, pneumonia, septic arthritis, cellulitis, or purulent pericarditis; endocarditis and osteomyelitis occur less commonly.

Laboratory criteria for diagnosis

- Detection of *Haemophilus influenzae* type b antigen in cerebrospinal fluid [CSF]
- Detection of *Haemophilus influenzae*-specific nucleic acid in a specimen obtained from a normally sterile body site (e.g., blood or CSF), using a validated polymerase chain reaction (PCR) assay; or
- Isolation of *Haemophilus influenzae* from a normally sterile body site (e.g., CSF, blood, joint fluid, pleural fluid, pericardial fluid)

Case classification

Probable:

Meningitis with detection of *Haemophilus influenzae* type b antigen in cerebrospinal fluid [CSF]

Confirmed:

- Isolation of *Haemophilus influenzae* from a normally sterile body site (e.g., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid)

OR

- Detection of *Haemophilus influenzae* -specific nucleic acid in a specimen obtained from a normally sterile body site (e.g., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid), using a validated polymerase chain reaction (PCR) assay

Case Classification Comments:

Positive antigen detection test results from urine or serum samples are unreliable for diagnosis of *H. influenzae* disease.

Isolates of *Haemophilus influenzae* are important for antimicrobial susceptibility testing.

Note: The positive antigen test results can occur from circulation of Hib antigen in urine or serum; this circulation can be caused by asymptomatic Hib carriage, recent vaccination, or fecal contamination of urine specimens. Cases identified exclusively by these methods should be considered suspect cases only

VII. Laboratory Testing

Culture

Confirming a case of Hib disease requires culturing and isolating the bacteria from a normally sterile body site. Most hospital and commercial microbiologic laboratories have the ability to isolate *H. influenzae* from cultured specimens. Normally sterile-site specimens for isolation of invasive *H. influenzae* include CSF, blood, joint fluid, pleural effusion, pericardial effusion, peritoneal fluid, subcutaneous tissue fluid, placenta, and amniotic fluid. All *H. influenzae* isolates should be tested for antimicrobial susceptibility to ampicillin, one of the third-generation cephalosporins, chloramphenicol, and meropenem. Further antimicrobial susceptibility testing should be considered for isolates obtained from cases in which a failure in treatment or chemoprophylaxis is suspected or in an outbreak setting.

Serotype testing (serotyping)

Serotyping distinguishes encapsulated strains, including Hib, from unencapsulated strains, which cannot be serotyped. The six encapsulated serotypes (designated a–f) have distinct capsular polysaccharides that can be differentiated by slide agglutination with type-specific antisera.

To make public health decisions about chemoprophylaxis, microbiology laboratories should perform serotype testing of *H. influenzae* isolates.¹³ Even though Hib disease has declined, laboratories should continue routine serotyping. If serotyping is not available at a laboratory, laboratory personnel should contact the state health department. State health departments with questions about serotyping should contact the CDC Meningitis and Vaccine Preventable Diseases Branch laboratory at 404-639-3158.

Antigen detection

Because the type b capsular antigen can be detected in body fluids, including urine, blood, and CSF of patients, clinicians often request a rapid antigen detection test for diagnosis of Hib disease. Antigen detection may be used as an adjunct to culture, particularly in the diagnosis of patients who have received antimicrobial agents before specimens are obtained for culture. The method for antigen detection is latex agglutination (LA). LA is a rapid and sensitive method used to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid but false negative and false positive reactions can occur.

If the Hib antigen is detected in CSF but a positive result is not obtained from culture of sterile site, the patient should be considered as having a probable case of Hib disease and reported as such. Because antigen detection tests can be positive in urine and serum of persons without invasive Hib disease, persons who are identified exclusively by positive antigen tests in urine or serum should not be reported as cases.

PCR

Although culture is the gold standard for confirming *Haemophilus influenzae*, real-time PCR is an accepted alternative. In recent years, significant improvements have been made in both the sensitivity and specificity of PCR assays used for the detection of *Haemophilus influenzae*. Real-time PCR assays are available to detect DNA of all six *Haemophilus influenzae* serotypes in blood, CSF, or other clinical specimens. A major advantage of PCR is that it allows for detection of *H. influenzae* from clinical samples in which the organism could not be detected by culture methods, such as when a patient has been treated with antibiotics before a clinical specimen is obtained for culture. Even when the organisms are nonviable following antimicrobial treatment, PCR can still detect *H. influenzae* DNA.¹⁴ Isolation of the bacterium is needed to test for antimicrobial susceptibility.

Subtyping

Although not widely available, subtyping the Hib bacterium by pulsed field gel electrophoresis (PFGE),^{15, 16} and multilocus sequence typing (MLST) can be performed for epidemiologic purposes. Some subtyping methods such as outer membrane proteins, lipopolysaccharides, and enzyme electrophoresis are no longer recommended or performed because they were unreliable or too labor intensive. The state health department may direct questions about subtyping to the CDC Meningitis and Vaccine Preventable Diseases Branch laboratory at 404-639-3158.

For additional information see Chapter 22, “Laboratory Support for Surveillance of Vaccine-Preventable Diseases.”

VIII. Reporting

Invasive *H. influenzae* disease became nationally notifiable in 1991. Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.¹⁷ These regulations and laws list the diseases to be reported and describe those responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, child care facilities, or other institutions. Vaccine failure information should be collected for case-patients who received all required doses of vaccines but still contracted Hib. CDC has a form for reporting vaccine failures, or a state form can be used if available. Persons reporting should contact their state health department for state-specific reporting requirements. The Meningitis and Vaccine-Preventable Diseases Branch, NCIRD, can be contacted during office hours, 8:00 a.m.–4:30 p.m. Eastern time, at 404-639-3158.

Reporting to CDC

A provisional report of probable and confirmed cases should be sent to the National Notifiable Disease Surveillance System by the state health department via the National Electronic Telecommunications System for Surveillance (NETSS) or the National Electronic Disease Surveillance System (NEDSS), when available, within 14 days of the initial report to the state or local health department ([Appendix 4, *Haemophilus influenzae* Disease Surveillance Worksheet \[159KB, 1 page\]](#)). Reporting should not be delayed because of incomplete information or lack of confirmation. Cases of disease should be reported by the state in which the patient resides at the time of diagnosis.

The [Expanded *Haemophilus influenzae* serotype b Surveillance Worksheet \(Appendix 4\)](#) can be used to collect information on each case. Many state health departments have the technology available to send this detailed case report information to CDC through NETSS by using supplemental data entry screens. States that do not have access to supplemental data entry screens should contact CDC. The highest priority for completion of supplemental information forms should be given to cases of *H. influenzae* invasive disease in children younger than 5 years of age. The second highest priority for completion of forms should be cases of *H. influenzae* invasive disease in children 5–14 years of age.

Information to collect

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may be collected at the direction of the state health department.

- Demographic information
 - Name
 - Address
 - Date of birth
 - Age
 - Sex
 - Ethnicity
 - Race
- Reporting Source
 - County
 - Earliest date reported
 - Case ID
- Clinical
 - Date of illness onset
 - Type of disease syndrome (meningitis, bacteremia, epiglottitis, pneumonia, arthritis, osteomyelitis, pericarditis, cellulitis)
- Outcome (patient survived or died)
 - Date of death
- Laboratory
 - Serotype of isolate
 - Specimen source from which organism was isolated (blood, CSF, pleural fluid, peritoneal fluid, pericardial fluid, joint fluid, amniotic fluid, or other normally sterile site)
 - Date first positive culture identified as *H. influenzae*
 - Date of specimen collection
- Antibiotic susceptibility
- Vaccination status (for serotype b or unknown serotype infections only)
 - Dates of Hib immunization
 - Manufacturer name
 - Vaccine lot number
 - If not vaccinated, reason

- Epidemiologic
 - Attendance in child care

IX. Vaccination

Table 1 and Table 2 list the Hib monovalent and combination conjugate vaccines that are currently available and the recommended vaccination regimens for each vaccine. The combination vaccines include the Hib monovalent vaccine and vaccines for other vaccine-preventable diseases in one vial, thus decreasing the number of injections needed for protection. Based on the recommended vaccination schedule, infants should receive three primary doses of Hib conjugate vaccine with PRP-T (monovalent or combination) at ages 2, 4, and 6 months, or two primary doses of PRP-OMP (monovalent or combination) at 2 and 4 months. A booster dose should be administered at age 12–15 months with any of the Hib vaccines. Any type of licensed Hib vaccine may be used interchangeably to complete the series. However, the PRP-T Hiberix vaccine is only licensed for use as a booster dose and should not be used for the primary series. The number of doses needed to complete the primary series is determined by the type of vaccine used; if a PRP-OMP vaccine is not administered as both doses in the primary series, a third dose of Hib vaccine is needed to complete the series.^{18–21} The recommended schedule for Hib vaccination of previously unvaccinated children is shown in Table 3.

Table 1. Hib monovalent conjugate vaccines currently available and recommended regimens for routine vaccination of children in the United States

Licensed vaccine (Manufacturer)	Trade name	Primary series	Booster (final) dose
PRP-T (Sanofi Pasteur)	ActHIB	2, 4, 6 months	12–15 months
PRP-OMP (Merck & Co., Inc)	PedvaxHIB	2, 4 months	12–15 months
PRP-T (GlaxoSmithKline)	Hiberix	Not licensed for primary series	12–15* months

*The recommended age for Hiberix is 15 months but to facilitate timely vaccination, vaccine can be given as early as 12 months of age

Table 2. Combination vaccines currently available and recommended regimens for routine vaccination of children in the United States

Licensed vaccine (Manufacturer)	Trade name	Primary series	Booster (final) dose
PRP-OMP + HepB (Merck & Co., Inc)	COMVAX	2, 4 months	12–15 months
PRP-T + DTaP+IPV (Sanofi Pasteur)	Pentacel	2, 4, 6 months	12–15* months
MenCY/PRP-T (GlaxoSmithKline)	MenHibRix	2, 4, 6 months	12–15* months

*The recommended age for the fourth dose of Pentacel is 15–18 months, but can be given as early as 12 months, provided at least 6 months have elapsed since the third dose; the recommended age for the fourth dose of Hib-MenCY is 12–18 months.

Table 3. Recommended schedule for Hib conjugate vaccine administration among previously unvaccinated children*

Age at first dose	Primary doses	Booster (final) dose**
2–6 months	2–3 [§] doses, 4 weeks apart	At 12–15 months [†]
7–11 months	2 doses, 4 weeks apart	At 12–15 months
12–14 months	1 dose	8 weeks later
15–59 months	1 dose	NR
>59 months	NR	NR

* Detailed catch-up schedule available at <http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html>

** Hiberix brand PRP-T vaccine is approved only for the last dose of the Hib series; The recommended age for Hiberix is 15 months but to facilitate timely vaccination, vaccine can be given as early as 12 months of age; The recommended age for the fourth dose of Pentacel is 15–18 months, but can be given as early as 12 months, provided at least 6 months have elapsed since the third dose; The recommended age for the fourth dose of Hib-MenCY is 12–18 months.

[§] Note: 2–3 doses depending on whether PRP-T or PRP-OMP vaccine was used

[†] Only necessary if 2 or 3 primary doses (depending on whether PRP-T or PRP-OMP vaccine was used) were received before age 12 months.

X. Enhancing Surveillance

Elimination of childhood Hib disease requires participation by all levels of the healthcare system so that all cases are identified and assessed rapidly and reported promptly, and data on reported cases are used in an optimal manner to prevent disease among unvaccinated or undervaccinated populations. The activities listed here can improve the detection and reporting of cases as well as the completeness and quality of reporting. See Chapter 19, “Enhancing Surveillance,” for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

Ensuring that all isolates from children are serotyped

Because of the need to make rapid decisions about chemoprophylaxis, serotype should be determined and reported for all *H. influenzae* isolates. It is particularly important that serotype be reported for cases in children younger than 5 years of age; the second highest priority is for cases among children 5–14 years of age. This information is also used to determine whether a case indicates a vaccine failure (i.e., a vaccinated person who gets the disease) or a failure to vaccinate. The state public health laboratory or another reference laboratory should be able to provide serotype testing of *H. influenzae* isolates. Hospital laboratories unable to perform serotype testing should forward all *H. influenzae* isolates for serotyping to one of these laboratories, or should contact the state health department for advice, if necessary.

Monitoring surveillance indicators

Regular monitoring of surveillance indicators, including reporting dates, time intervals between diagnosis and reporting, and completeness of reporting may identify specific areas of the surveillance system that need improvement. Important indicators to evaluate the completeness and overall quality of the surveillance system include the following:

- The proportion of *H. influenzae* cases reported to NNDSS with complete information (clinical case definition–species, specimen type; vaccine history; and serotype testing)
- Proportion of Hib cases among children younger than 5 years of age with complete vaccination history
- Proportion of Hib cases among children younger than 5 years of age with serotyped isolate

Monitoring the incidence of invasive disease due to non-b *H. influenzae*

The epidemiology of invasive *H. influenzae* disease in the United States has shifted in the postvaccination era. Nontypable *H. influenzae* now causes the majority of invasive *H. influenzae* disease in all age groups. Using data from active surveillance sites from 2004 through 2013, the estimated annual incidence of invasive nontypable and non-b *H. influenzae* disease in children younger than 5 years of age was 1.66/100,000 and 0.93/100,000, respectively (unpublished data). These rates may be used as a surveillance indicator for monitoring the completeness of invasive *H. influenzae* case reporting. Although limited data

are available on temporal and geographic variability in incidence of nontypable and non–type-b invasive disease, use of these surveillance indicators is encouraged.

XI. Case Investigation

Laboratory, hospital, and clinic records should be reviewed during case investigations by health department personnel in order to collect important information such as serotype, immunization status, dates of vaccination, vaccine lot numbers, and clinical illness description and outcome. The Expanded *Haemophilus influenzae* serotype b Surveillance Worksheet may be used as a guide for collecting demographic and epidemiologic information in a case investigation (see Appendix 4).

Investigating contacts

Identification of young children who are household or childcare contacts of patients with Hib invasive disease and assessment of their vaccination status may help identify persons that should receive antimicrobial prophylaxis or who need to be immunized.

The Advisory Committee on Immunization Practices recommends that because children who attend child care are at increased risk for Hib disease, efforts should be made to ensure that all child care attendees younger than 5 years of age are fully vaccinated.¹² Children < 24 months of age who develop invasive Hib disease should repeat the Hib vaccine series because they can remain at risk of a second episode of disease; children >24 months of age who develop invasive Hib disease usually develop a protective immune response and do not need immunization. For household contacts of a person with invasive Hib disease, no rifampin chemoprophylaxis is indicated if all persons are 48 months of age or older, or if children younger than 48 months of age are fully vaccinated according to the schedule in Table 3. Rifampin chemoprophylaxis is recommended for index case patients (unless treated with cefotaxime or ceftriaxone) and all household contacts in households with members aged <4 years who are not fully vaccinated or members aged <18 years who are immunocompromised, regardless of their vaccination status. The recommended rifampin dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. A dose of 10 mg/kg once daily for 4 days is recommended for neonates (less than 1 month of age).¹²

The risk of Hib invasive disease for child care center contacts of a patient with Hib invasive disease case is thought to be lower than that for a susceptible household contact. Public health officials should refer to the American Academy of Pediatrics (AAP) Red Book 2012 for information on chemoprophylaxis of child care center contacts.¹²

There are no guidelines for control measures around cases of invasive nontypable or non-b *H. influenzae* disease. Chemoprophylaxis is not recommended for contacts of persons with invasive disease caused by nontypable or non-b *H. influenzae* because cases of secondary transmission of disease have not been documented.^{22, 23}

References

1. Broome CV. Epidemiology of *Haemophilus influenzae* type b infections in the United States. *Pediatr Infect Dis J* 1987;6:779–82.
2. Bisgard KM, Kao A, Leake J, Strebel PM, Perkins BA, Wharton M. *Haemophilus influenzae* invasive disease in the United States, 1994–1995: near disappearance of a vaccine-preventable childhood disease. *Emerg Infect Dis* 1998;4:229–37.
3. CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United States, 1987–1995. *MMWR* 1996;45:901–6.
4. CDC. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children—United States, 1987–1997. *MMWR* 1998;47:993–8.
5. CDC. Progress toward elimination of *Haemophilus influenzae* type b invasive disease among infants and children—United States, 1998–2000. *MMWR* 2002;51:234–7.
6. CDC. Active Bacterial Core Surveillance (ABCs) Report. Emerging Infections Program Network, *Haemophilus influenzae*, 2010.
7. CDC. Active Bacterial Core Surveillance (ABCs) Report. Emerging Infections Program Network, *Haemophilus influenzae*, 2011.

8. CDC. Active Bacterial Core Surveillance (ABCs) Report. Emerging Infections Program Network, *Haemophilus influenzae*, 2012.
9. CDC. Active Bacterial Core Surveillance (ABCs) Report. Emerging Infections Program Network, *Haemophilus influenzae*, 2013.
10. Healthy People 2020 Topics and Objectives. (Accessed October 23, 2014, at <http://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives>)
11. MacNeil JR, Cohn AC, Farley M, et al. Current epidemiology and trends in invasive *Haemophilus influenzae* disease—United States, 1989–2008. *Clin Infect Dis* 2011;53:1230–6.
12. American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Pickering LK, ed. Red Book: 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012; 345–52.
13. Council of State and Territorial Epidemiologists. Revision of the National Surveillance Case Definition for Invasive *Haemophilus influenzae* Disease [137KB, 7 pages]. Position Statement 14-ID-05.
14. Granoff DM, Feavers IM, Borrow R. Meningococcal vaccines. In: Plotkin SA, Orenstein WA, Offit PA. Vaccines. 4th ed. Saunders; 2003:959–87.
15. Lucher LA, Reeves M, Hennessy T, Levine OS, Popovic T, Rosenstein N, et al. Reemergence, in southwestern Alaska, of invasive *Haemophilus influenzae* type b disease due to strains indistinguishable from those isolated from vaccinated children. *J Infect Dis* 2002;186:958–65.
16. Fry AM, Lurie P, Gidley M, Schmink S, Lingappa J, Fischer M, et al. *Haemophilus influenzae* type b disease among Amish children in Pennsylvania: reasons for persistent disease. *Pediatrics* 2001;108(4):E60.
17. Roush S, Birkhead G, Koo D, Cobb A, Fleming D. Mandatory reporting of diseases and conditions by health care professionals and laboratories. *JAMA* 1999;282:164–70.
18. Greenberg DP, Lieberman JM, Marcy SM, Wong VK, Partridge S, Chang SJ, et al. Enhanced antibody responses in infants given different sequences of heterogeneous *Haemophilus influenzae* type b conjugate vaccines. *J Pediatr* 1995;126:206–11.
19. Anderson EL, Decker MD, England JA, Edwards KM, Anderson P, McInnes P, et al. Interchangeability of conjugated *Haemophilus influenzae* type b vaccines in infants. *JAMA* 1995;273:888–9.
20. Bewley KM, Schwab JG, Ballanco JA, Daum RS. Interchangeability of *Haemophilus influenzae* type b vaccines in the primary series: evaluation of a two-dose mixed regimen. *Pediatrics* 1996;98:898–904.
21. Briere EC, Rubin L, Moro PL, Cohn A, Clark T, Messonnier N. Prevention and control of *Haemophilus influenzae* type b disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2014;63(RR01);1–14.
22. Bruce MG, Zulz T, DeByle AP, et al. *Haemophilus influenzae* serotype a invasive disease, Alaska, USA, 1983–2011. *Emerging Infectious Diseases* 2013;19:932–7.
23. Hammitt LL, Block S, Hennessy TW, et al. Outbreak of invasive *Haemophilus influenzae* serotype a disease. *The Pediatr Infect Dis J* 2005;24:453–6.