Chapter 2: *Haemophilus influenzae* type b Invasive Disease

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I. Disease description

Haemophilus influenzae (Hi) invasive disease is caused by the bacterium *Haemophilus influenzae*. Hi may be either encapsulated (typeable) or unencapsulated (nontypeable). Six antigenically distinct capsular types of Hi (types a-f) have been identified that can cause invasive disease in persons of any age. Nontypeable strains may also cause invasive disease but are less virulent than encapsulated strains and are rare causes of serious infection among children.

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, *Haemophilus influenzae* serotype b (Hib) was the cause of > 95% of invasive Hi diseases among children < 5 years of age. Hib was the leading cause of bacterial meningitis in the United States among children < 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 neurological 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

Before the introduction of Hib conjugate vaccines for infants in late 1990, an estimated 20,000 children < 5 years of age developed invasive Hib disease annually in the United States. Approximately 1 of 200 children developed invasive Hib disease before the age of 5 years, and nearly two-thirds of all cases occurred among children < 18 months of age. By 2000, the incidence of all Hi invasive disease among children < 5 years of age reported to the CDC declined by 96%—from 41 cases per 100,000 in 1987 to 1.6 cases per 100,000 in 2000.[2-5] Laboratory-based surveillance data from the Active Bacterial Core surveillance (ABCs) system, which included serotype information on all invasive Hi isolates, provided direct evidence of a decline in Hib disease. From 1989 to 2000, there was a 99% reduction in Hib invasive disease among children < 5 years of age, which coincided with the introduction and use of Hib conjugate vaccines among infants and children.[2-5]

Because Hib has become a rare cause of invasive disease in the U.S., there is an increased need to correctly identify the serotype of the causative Hi isolate. Serotyping by slide agglutination can sometimes be inaccurate, especially since it is not performed frequently in most laboratories. One study found that 28 (70%) of 40 Hi isolates from ABCs sites that had been reported as "Hib" to CDC were actually nontypeable Hi isolates.[6] Accurate serotype data on all Hi isolates from children < 5 years of age is critical variable for monitoring the Hib vaccine program effectiveness.

III. Importance of rapid case identification

Rapid case identification is important for early administration of Hib vaccine and, if needed, for chemoprophylaxis to household and childcare classroom contacts of cases.[7] In addition, early notification of Hi invasive disease cases in children aged < 5 years is needed to obtain the Hi isolate before it is discarded so that it can be serotyped and forwarded to the CDC Meningitis and Special Pathogens Laboratory.[5,6]

IV. Importance of surveillance

Surveillance information is used to monitor the effectiveness of immunization programs and vaccines and to assess progress towards disease elimination.

V. Disease reduction goals

Because of the rapid decline of Hib due to widespread immunization of infants and young children with conjugate vaccines, the elimination of Hib disease among children < 5 years of age in the United States has been proposed as an objective for the year 2010.[8]

VI. Case definition

The following case definition for *H. influenzae* (invasive disease) has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in May 1997.[9]

Clinical case definition

Invasive disease caused by *H. influenzae* can produce any of several clinical syndromes, including meningitis, bacteremia, epiglottitis, or pneumonia.

Laboratory criteria for diagnosis

Isolation of *H. influenzae* from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF] or, less commonly, joint, pleural, or pericardial fluid).

Case classification

Probable: A clinically compatible case with detection of *H. influenzae* type b antigen in cerebrospinal fluid (CSF).

Confirmed: A clinically compatible case that is laboratory-confirmed.

Comment: Positive antigen detection test results from urine or serum samples are unreliable for diagnosis of Hib invasive disease. The positive antigen test results can occur from circulation of Hib antigen in the 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 not be reported.

Microbiology laboratories should perform serotype testing of all *H. influenzae* isolates, particularly those obtained from children < 15 years of age.

VII. Laboratory testing

Culture

Confirming a case of Hib requires culturing and isolating the bacterium 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 cerebrospinal fluid (CSF), blood, joint fluid, pleural effusion, pericardial effusion, peritoneal fluid, subcutaneous tissue fluid, placenta, and amniotic fluid. All Hi isolates should be also tested for antimicrobial susceptibility.

Serotype testing (serotyping)

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

To monitor the occurrence of invasive Hib disease, microbiology laboratories should perform serotype testing of all *H. influenzae* isolates,[6,10] particularly those obtained from children < 5 years of age. To monitor the disease burden and long-term vaccine effectiveness, Hi isolates from children 5–14 years should also be serotyped and reported. Even though Hib disease has declined, laboratories need to continue routine serotype testing. Contact your state health department if serotyping is not available at your laboratory. In addition, because of inconsistencies in serotype results of Hi isolates, the CDC Meningitis and Special Pathogens Laboratory will serotype (or retest to confirm the reported serotype) all *H. influenzae* isolates from invasive disease cases among children aged < 15 years.[5,6] Contact the laboratory at 404-639-3158 for more information.

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. Methods for

antigen detection include latex agglutination (LA) and counterimmunoeletrophoresis. Latex agglutination is a rapid and sensitive method used to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid; Counterimmunoelectrophoresis is a more specific but less sensitive test than LA; this test takes longer and is more difficult to perform.

If the Hib antigen is detected in the CSF and there is no positive result from culture or sterile site, the patient should be considered 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. Polymerase chain reaction (PCR) assays for Hib in clinical specimens are available for research purposes only.[11] Isolation of the bacterium is needed to confirm Hi invasive disease and to test for antimicrobial susceptibility.

Subtyping

Although not widely available, subtyping the Hib bacterium on the basis of outer membrane proteins, lipopolysaccharides, enzyme electrophoresis, or pulsed-gel electrophoresis on DNA[12] can be performed for epidemiologic purposes. The state health department may direct questions about subtyping to the CDC Meningitis and Special Pathogens Laboratory at 404-639-3158.

For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 19, "Laboratory Support for the Surveillance of Vaccine-preventable Diseases."

VIII. Reporting

Invasive Hi 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.[13] These regulations and laws list the diseases to be reported and describe those responsible for reporting, such as health-care providers, hospitals, laboratories, schools, childcare facilities, and other institutions. Contact your state health department for reporting requirements in your state or for questions about reporting. During office hours, 8:00 a.m.– 4:30 p.m. Eastern Time, contact staff at the Bacterial Vaccine-Preventable Diseases Branch, NIP, at 404-639-8257.

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 National Electronic Disease Surveillance System (NEDSS), when available, within 14 days of the initial report to the state or local health department. Reporting should not be delayed because of incomplete information or lack of confirmation.

The National Bacterial Meningitis and Bacteremia Case Report form (see **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. The highest priority for completion of supplemental information forms is cases of Hi invasive disease in children < 5 years of age. The second highest priority for completion of forms is cases of Hi 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

- Clinical
  - Date of illness onset
  - Type of disease syndrome (meningitis, bacteremia, epiglottis, pneumonia, arthritis, osteomyelitis, pericarditis, cellulitis)
  - Date of first positive culture obtained

- Outcome (case 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)

- Antibiotic susceptibility

- Vaccination status (for type b or unknown serotype infections only)
  - Dates of Hib immunization
  - Manufacturer name
  - Vaccine lot number
  - If not vaccinated, reason

- Epidemiological

– Attendance in childcare

IX. Vaccination

Table 1 lists the Hib conjugate vaccines that are currently available. Two combination vaccines that include the Hib conjugate vaccine have been licensed by the FDA following immunogenicity and safety studies (**Table 2**). These combination vaccines decrease the number of injections needed for protection against vaccine-preventable diseases.

The recommended schedule for Hib conjugate vaccine administration among previously unvaccinated children is given in **Table 3**.[7] Based on the recommended schedule, infants should receive three primary doses of Hib conjugate vaccine with HbOC or PRP-T at ages 2, 4, and 6 months, or two primary doses PRP-OMP at 2 and 4 months. A booster dose should be administered at age 12–15 months with any of the conjugate vaccines. Any type of licensed Hib vaccine may be used interchangeably to complete the series, and the number of doses needed to complete the series is determined by the type of vaccine used (e.g., 4 doses if either HbOC or PRP-T is used at least once).[13]

X. Enhancing surveillance

Elimination of childhood Hib disease requires participation by all levels of the health-care system in rapid identification, assessment, and prompt reporting of all cases and optimal use of these data to prevent disease among un- or under-vaccinated populations. The activities listed here can improve the detection and reporting of cases and improve the comprehensiveness and quality of reporting. See Chapter 16, "Enhancing Surveillance," for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

Assuring that all isolates from children are serotyped

Because Hib vaccines protect against serotype b organisms only, serotype should be determined and reported for all *Haemophilus influenzae* isolates. It is particularly important that serotype be reported for cases among children < 5 years of age; the second highest priority is for cases among children 5–14 years of age. This information is 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 available for serotype testing of *H. influenzae* isolates. Hospital laboratories unable to perform serotype testing should forward all Hi isolates for serotyping to such a laboratory. Contact your state health department if serotyping is not available.

Because of the need to obtain serotype information on all cases of Hi invasive disease among children < 15 years of age, the CDC Meningitis and Special Pathogens Laboratory will serotype (or retest to confirm the reported serotype) the *H. influenzae* isolates.[5,6]

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:

- Proportion of Hi cases with known serotype among children < 5 and among children 5–14 years of age
- Proportion of Hib cases with complete vaccination information (date, manufacturer, lot number)

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

Data from active surveillance sites suggest an expected rate of invasive disease due to non-type b *H. influenzae* to be ≥ 1.0 per 100,000 children aged < 5 years.[14] This rate may be used as a surveillance indicator for monitoring the quality or for reporting *H. influenzae* type b invasive disease cases. Although limited data are available on temporal and geographic variability in incidence of non-type b invasive diseases, use of this surveillance indicator is encouraged.

XI. Case investigation

Laboratory, hospital, and clinic records should be reviewed during case investigation 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 National Bacterial Meningitis and Bacteremia Case Report form 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 Hib invasive disease cases and assessment of their vaccination status may help identify persons who should receive antimicrobial prophylaxis and who need to be immunized.

The Advisory Committee on Immunization Practices recommends that because children who attend childcare are at increased risk for Hib disease, efforts should be made to ensure that all childcare attendees < 5 years of age are fully vaccinated.[7,15] A child who has recovered from invasive Hib disease should receive Hib conjugate vaccine because natural infection does not always result in the development of antibodies protective against the *H. influenzae* capsular polysaccharide (PRP). For household contacts of a person with invasive Hib disease, no rifampin chemoprophylaxis is indicated if all persons are ≥ 48 months of age or if children < 48 months of age are fully vaccinated according to **Table 3**.

In households with one or more infants < 12 months of age, with a child 1–3 years of age who is inadequately vaccinated, or with an immunocompromised child, all household contacts, including the index case-patient, should receive rifampin prophylaxis. The recommended dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. Neonates (< 1 month of age) should receive 10 mg/kg once daily for 4 days.[7] The risk of Hib invasive disease for childcare center contacts of a 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 2000* for information on chemoprophylaxis of childcare center contacts.[15]

Table 1. Hib conjugate vaccines currently available

Licensed vaccine	Trade name	Manufacturer/Distributor
HbOC	HibTITER®	Wyeth (formerly Lederle-Praxis Laboratories)
PRP-T	ActHIB® OmniHIB®	Aventis Pasteur GlaxoSmithKline
PRP-OMP	PedvaxHIB®	Merck & Company

Table 2. Combination vaccines containing Hib conjugate vaccines

Licensed vaccine	Trade name	Manufacturer/Distributor
PRP-T + DTaP[¶]	TriHIBit®	Aventis Pasteur
PRP-OMP + HepB	COMVAX™	Merck & Company

[¶] On July 15, 1997, TriHIBit® was licensed for use only for the fourth dose of the DTaP and Hib vaccination series among children 15–18 months of age, to be administered at least 6 months following the third DTP or DTaP dose.

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

Vaccine	Age (months) at first vaccination	Primary series	Booster
HbOC/PRP-T	2–6	3 doses, 2 months apart	12–15 months
	7–11	2 doses, 2 months apart	12–18 months
	12–14	1 dose	2 months later
	15–59	1 dose	NR
PRP-OMP	2–6	2 doses, 2 months apart	12–15 months
	7–11	2 doses, 2 months apart	12–18 months
	12–14	1 dose	2 months later
	15–59	1 dose	NR

NR = Not required

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