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) that can cause invasive disease in persons of any age have been identified. Nontypeable strains may also cause invasive disease but are less virulent than encapsulated strains and cause only infrequently serious infection in 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.

Because Hib has become a rare cause of invasive disease in the United States, the need to correctly identify the serotype of Hi isolate from any invasive disease has increased.

Before the introduction of effective vaccines, *H. influenzae* serotype b (Hib) was the cause of more than 95% of invasive Hi 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

Before the introduction of Hib conjugate vaccines for infants in late 1990, an estimated 20,000 children younger than 5 years of age (approximately 1 in 200 children) developed invasive Hib disease each year in the United States; nearly two-thirds of all cases occurred among children younger than 18 months. By 2000, the incidence of all Hi invasive disease among children younger than 5 years of age reported to 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 younger than 5 years of age, which coincided with the introduction and use of Hib conjugate vaccines among infants and children.[2–5] Continued monitoring of Hi invasive disease through ABCs demonstrated a decrease in invasive Hib rates in children younger than 5 years of age, with the average incidence from 2000 to 2004 being 0.14 cases per 100,000.[6–10]

Because Hib has become a rare cause of invasive disease in the United States, the need to correctly identify the serotype of Hi isolate from any invasive disease has increased. Serotyping by slide agglutination can sometimes be inaccurate, especially since it is not performed routinely 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.[11] Another study found discrepancies between the results of slide agglutination subtyping performed at state health departments and those of polymerase chain reaction (PCR) capsule typing performed at CDC for 56 (40%) of 141 isolates.[12] Accurate serotype data on all Hi isolates from children younger than 5 years of age is critical for monitoring Hib vaccine effectiveness. These studies emphasize the importance of quality control and quality assurance in laboratory serotyping.

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 case-patients.[13] In addition, early notification of Hi invasive disease cases in children younger than 5 years is needed to obtain the Hi isolate before it is discarded so that it can be serotyped. 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

Surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data about a health-related event for use in public health action to reduce morbidity and mortality and to improve health. Surveillance serves at least eight public health functions. These include supporting case detection and public health interventions, estimating the impact of a disease or injury, portraying the natural history of a health condition, determining the distribution and spread of illness, generating hypotheses and stimulating research, evaluating prevention and control measures, and facilitating planning.[14]

Hib surveillance information is used to monitor the effectiveness of immunization programs and vaccines and to assess progress toward disease elimination. It is important that states report data in a timely manner so that national trends of disease can be determined.

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. The elimination of Hib disease among children younger than 5 years of age in the United States has been proposed as an objective for the year 2010.[15]

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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.[16]

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)

[Detection of H. influenzae type b–specific antigen in CSF by latex agglutination, counterimmunoelectrophoresis, or other methods can only be used as evidence of a probable case.]

Case classification

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

Confirmed: A clinically compatible case that is laboratory confirmed by isolation of *H. influenzae* type b from a normally sterile site.

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

[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 Hi isolates should be tested for antimicrobial susceptibility according to guidelines in M2-A9 Performance Standards for Antimicrobial Disk Susceptibility Tests (January 2006) from the Clinical Laboratory Standards Institute.[17]

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 monitor the occurrence of invasive Hib disease, microbiology laboratories should perform serotype testing of all *H. influenzae* isolates,[11, 18] particularly those obtained from children younger than 5 years of age. To monitor disease burden and long-term vaccine effectiveness, Hi isolates from children ages 5–14 years should also be serotyped and reported. 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. Methods for antigen detection include latex agglutination (LA) and counterimmunoeletrophoresis. LA is a rapid and sensitive method used to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid. Counterimmunoelectrophoresis is more specific but less sensitive than LA; this test takes longer and is more difficult to perform.

If the Hib antigen is detected in CSF and no bacteria are isolated from culture of a sterile site, the patient should be considered to have a probable case of Hib disease and be reported as such. Because antigen detection tests can be positive in urine and serum of persons without invasive Hib disease, a case that is identified exclusively by positive antigen tests in urine or serum should not be reported as a true case. Polymerase chain reaction (PCR) assays for Hib in clinical specimens are available for research purposes only.[19–21] Isolation of the bacterium is needed to confirm Hi invasive disease, determine the serotype, and test for antimicrobial susceptibility.

Subtyping

Although not widely available, subtyping the Hib bacterium by pulsed field gel electrophoresis (PFGE),[22, 23] multilocus sequence typing (MLST), and 16S rRNA gene sequence typing 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 on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 22.

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.[24] 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 infants 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). 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* type b Surveillance Worksheet (Appendix 5) 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 Hi invasive disease in children younger than 5 years of age. The second highest priority for completion of forms should be 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
  - 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 Hi
  - Date of specimen collection
- 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
- Epidemiologic
  - Attendance in child care

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.

Table 1. Hib conjugate vaccines currently available*

Licensed vaccine	Trade name	Manufacturer/Distributor
PRP-T	ActHIB®	sanofi pasteur
PRP-OMP	PedvaxHIB®	Merck & Co., Inc

* *In April 2007, Wyeth discontinued production of HibTITER® (HbOC).*

Table 2. Combination vaccines containing Hib conjugate vaccines

Licensed vaccine	Trade name	Manufacturer/Distributor
PRP-T + DTaP*	TriHIBit®	sanofi pasteur
PRP-OMP + HepB	COMVAX™	Merck & Co., Inc
PRP-T + DTaP+IPV	Pentacel®	sanofi pasteur

* *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 at 1st dose (months)	Primary series	Booster
PRP-T (ActHIB®)	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 (PedvaxHIB)	2–6	2 doses, 2 months apart	12–15 months
	7–11	2 doses, 2 months apart	12–15 months
	12–14	1 dose	2 months later
	15–59	1 dose	NR

* *In April 2007, Wyeth discontinued production of HibTITER® (HbOC).*
NR = Not required

The recommended schedule for Hib conjugate vaccine administration to previously unvaccinated children is shown in Table 3.[13] Based on the recommended schedule, infants should receive three primary doses of Hib conjugate vaccine with PRP-T at ages 2, 4, and 6 months, or two primary doses of 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: four doses are required if either HbOC or PRP-T was administered to a child at least once.[25–27]

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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 Hib vaccines protect against serotype b organisms only, 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 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 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 Hi 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–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 0.9 per 100,000 children younger than 5 years of age.[28] This rate 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 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 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* type b Surveillance Worksheet may be used as a guide for collecting demographic and epidemiologic information in a case investigation (see Appendix 5).

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 who 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.[13, 29] 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. 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. In households with one or more infants younger than 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 (less than 1 month of age) should receive 10 mg/kg once daily for 4 days.[13] 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 2006 for information on chemoprophylaxis of child care center contacts.[29]

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