

Chapter 2: Haemophilus influenzae invasive disease

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I. Disease Description

Haemophilus influenzae (Hi) 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 cases of invasive *H. influenzae* disease 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 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 in children younger than 5 years of age.^{2–5} Continued monitoring of invasive *H. influenzae* disease through Active Bacterial Core surveillance (ABCs), 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 2010–2017, the average incidence was 0.15 cases per 100,000, which is below the Healthy People 2020 goal of 0.27/100,000.^{6–11}

In the post-Hib vaccine era, the epidemiology of invasive *H. influenzae* disease in the United States has changed. The majority of invasive *H. influenzae* disease in all age groups is now caused by nontypeable *H. influenzae*.^{6–10, 12}

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.¹³ Early notification of *H. influenzae* invasive disease cases in children younger than 5 years of age is also important to ensure isolates are saved for serotyping. For questions related to *H. influenzae* serotyping, please contact CDC-INFO at <https://www.cdc.gov/cdc-info/> or by telephone Monday–Friday from 8:00 am–8:00 pm Eastern Time at 800-232-4636.



IV. Importance of Surveillance

H. influenzae surveillance information is used to describe the epidemiology of invasive *H. influenzae* disease, to detect outbreaks of Hib disease, to assess progress toward Hib disease elimination, and to determine appropriate verification and validation criteria for current and potential serotyping methods.

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 2014.¹⁴

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 *H. influenzae* type b antigen in cerebrospinal fluid (CSF)
- Detection of *H. 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 *H. influenzae* from a normally sterile body site (e.g., CSF, blood, joint fluid, pleural fluid, or pericardial fluid)

Case classification

Probable:

Meningitis with detection of *H. influenzae* type b antigen in CSF

Confirmed:

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

OR

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

Comment:

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

Note: 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

Rapid and reliable laboratory results are critical for prompt diagnosis and implementation of appropriate prevention and control measures. Refer to Chapter 22, “Laboratory Support for Surveillance of Vaccine-preventable Diseases.” (<http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html>) for specific information on specimen collection, identifying *H. influenzae*, determining *H. influenzae* serotypes, and antimicrobial susceptibility testing. Isolates of *H. influenzae* are important for antimicrobial susceptibility testing.

Specimen collection

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or disease confirmation. Guidelines have been published for specimen collection and handling of microbiologic agents (<https://stacks.cdc.gov/view/cdc/7590>). Information is also available on using CDC laboratories as support for reference and disease surveillance (<https://www.cdc.gov/ncezid/dsr/specimen-management-branch.html>); this includes

- a central website for requesting lab testing (<https://www.cdc.gov/laboratory/specimen-submission/index.html>);
- the form required for submitting specimens to CDC (see <https://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf> CDC Form 50.34);
- information on general requirements for shipment of etiologic agents (Appendix 24; <https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix24-etiological-agent.pdf>)—although written to guide specimen submission to CDC, this information may be applicable to submission of specimens to other laboratories; and
- the CDC Infectious Diseases Laboratories Test Directory (<https://www.cdc.gov/laboratory/specimen-submission/list.html>), which not only contains a list of orderable tests for that institution, but also detailed information on appropriate specimen types, collection methods, specimen volume, and points of contact.

VIII. Reporting and Case Notification

Case reporting within a jurisdiction

Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance.¹⁵ These regulations and laws list the diseases to be reported and describe those responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, childcare facilities, or other institutions. Reporting of *H. influenzae* varies by state; while some states report all known cases of invasive *H. influenzae* regardless of age or serotype, other states limit reporting to only cases of Hib or cases among patients <5 years of age. Persons reporting should contact their state health department for state-specific reporting requirements. Detailed information on reportable conditions in each state is available through CSTE.

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; a state form can be used if available. For questions related to *H. influenzae* surveillance and reporting, please contact CDC-INFO at <https://www.cdc.gov/cdc-info/> or by telephone Monday–Friday from 8:00 am–8:00 pm EST at 800-232-4636.

Case notification to CDC

Provisional notification of probable and confirmed cases of *H. influenzae* disease should be sent to CDC using the eventcode 10590 in the National Notifiable Diseases Surveillance System (NNDSS), when available, within 14 days of the initial report to the state or local health department. The *H. influenzae* surveillance worksheets are included as Appendix 4 to serve as guides for data collection to be included in case investigations and case notification to CDC.

Case notifications should not be delayed because of incomplete information or lack of confirmation; data can be updated electronically as more information becomes available. The state in which the patient resides at the time of diagnosis should submit the case notification to CDC.

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 type b or unknown serotype infections only)
 - Dates of Hib immunization
 - Manufacturer name
 - Vaccine lot number
 - If not vaccinated, reason
- Epidemiologic
 - Attendance in childcare

IX. Vaccination

For specific information about Hib vaccination, refer to The Pink Book [<https://www.cdc.gov/vaccines/pubs/pinkbook/index.html>], which provides general recommendations, including vaccine use and scheduling, immunization strategies for providers, vaccine content, adverse events and reactions, vaccine storage and handling, and contraindications and precautions.

X. Enhancing Surveillance

Elimination of childhood Hib disease requires participation by all levels of the healthcare system so that all cases are identified, assessed, 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, (<http://www.cdc.gov/vaccines/pubs/surv-manual/chpt19-enhancing-surv.html>) 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 through 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, CDC Bacterial Meningitis Laboratory (<https://www.cdc.gov/meningococcal/laboratory.html>) or one of the Association of Public Health Laboratories (APHL) Vaccine Preventable Diseases Reference Laboratories (http://www.aphl.org/programs/infectious_disease/Pages/VPD.aspx) should be able to provide serotype testing of *H. influenzae* isolates. Hospital laboratories unable to perform serotype testing should forward all *H. influenzae* isolates (or clinical specimens if culture isolate is not available) 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 invasive *H. influenzae* cases reported to NNDSS with complete information (clinical case definition—species, specimen type, vaccine history, and serotype testing)
- The proportion of invasive *H. influenzae* cases among children younger than 5 years of age with complete vaccination history
- The proportion of invasive *H. influenzae* 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. Nontypeable *H. influenzae* now causes the majority of invasive *H. influenzae* disease in all age groups. Using data from active surveillance sites from 2010 through 2017, the estimated annual incidence of invasive nontypeable and non-b *H. influenzae* disease in children younger than 5 years of age was 1.63/100,000 and 1.19/100,000, respectively (unpublished data). Since invasive disease due to nontypeable and non-b *H. influenzae* strains are not prevented by vaccination in any age group and Hib cases continue to occur among adults, rates of nontypeable and non-b invasive *H. influenzae* disease in a jurisdiction serve as surveillance indicators with the presence of reported cases suggesting that surveillance is adequate. Although limited data are available on temporal and geographic variability in incidence of nontypeable and non-b invasive diseases, 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, clinical illness description, and outcome. The Expanded *Haemophilus influenzae* serotype b Surveillance Worksheet (see Appendix 4) may be used as a guide for collecting demographic and epidemiologic information in a case investigation.

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 childcare facilities are at increased risk for Hib disease, efforts should be made to ensure that all childcare attendees younger than 5 years of age are fully vaccinated.¹³ 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. (<https://www.cdc.gov/vaccines/pubs/pinkbook/hib.html>) Rifampin chemoprophylaxis is recommended for index case-patients (unless treated with cefotaxime or ceftriaxone) and all household contacts in households with members less than 4 years of age who are not fully vaccinated or members less than 18 years of age 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).¹³

The risk of Hib invasive disease for childcare 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 Red Book 2018 for information on chemoprophylaxis of childcare center contacts.¹³

There are no guidelines for control measures around cases of invasive nontypeable or non-b *H. influenzae* disease. Chemoprophylaxis is not recommended for contacts of persons with invasive disease caused by nontypeable or non-b *H. influenzae* because cases of secondary transmission of disease have not been documented.^{16,17} However, the American Academy of Pediatrics Red Book 2018 states that clinicians may consider prophylaxis of contacts of index cases of invasive *H. influenzae* type a disease.¹³

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