

**Submission Date:** 4/17/14

**Committee:** Infectious Disease

**Title:** Revision of the National Surveillance Case Definition for Invasive *Haemophilus influenzae* Disease

## I. Statement of the Problem

Invasive *Haemophilus influenzae* disease is nationally notifiable and the case definition does not include PCR as an acceptable diagnostic test for case classification. (CDC. Case definitions for infectious conditions under public health surveillance. MMWR 1997; 46[No.RR-10]:15; Public Health Reporting and National Notification for Invasive *Haemophilus influenzae* type b (Hib) infection, 09-ID-33). Although culture is the gold standard for confirming invasive *Haemophilus influenzae*, polymerase chain reaction (PCR) is an accepted alternative. In recent years, significant improvements have been made in both the quality of PCR and the assays used for the detection of *Haemophilus influenzae* (Wang, 2011 & 2012). Reflex PCR assays are available to detect DNA of all six *Haemophilus influenzae* serotypes in blood, CSF, or other clinical specimens (WHO Meningitis Manual, Chapter 10: PCR for Detection and Characterization of Bacterial Meningitis Pathogens: *N. meningitidis*, *H. influenzae*, *S. pneumoniae*). A major advantage of PCR is that it allows for detection of *Haemophilus 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.

## II. Background and Justification

### Background

*Haemophilus influenzae* is a bacterium that has encapsulated (typable) or unencapsulated (nontypable) strains. Encapsulated strains express 1 of 6 antigenically distinct capsular polysaccharides (type a, b, c, d, e or f). *Haemophilus influenzae* non-type b strains can cause invasive disease clinically similar to type b (Hib) disease (pneumonia, bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, or purulent pericarditis). Nontypable strains can also cause invasive disease but more commonly cause mucosal infections such as otitis media, conjunctivitis, and sinusitis.

Hib was once the most common cause of bacterial meningitis in children aged  $\leq 5$  years in the United States. Since the introduction of Hib conjugate vaccines in the United States, the incidence of invasive Hib disease in children aged  $< 5$  years decreased by 99%, to less than 1 case per 100,000. During 2000-2012, the average annual incidence rate of invasive Hib disease in children younger than 5 years of age in the United States remained below the Healthy People 2020 goal of 0.27/100,000.

The epidemiology of invasive *Haemophilus influenzae* disease in the United States has shifted in the post-Hib vaccination era. Nontypable *Haemophilus influenzae* now causes the majority of invasive disease in all age groups, with the greatest burden of disease among the youngest and oldest age groups. From 1999 through 2008, the annual incidence of invasive nontypable *Haemophilus influenzae* disease was 1.73/100,000 in children younger than 5 years of age and 4.08/100,000 in adults  $\geq 65$  years of age. Rates of invasive *Haemophilus influenzae* and Hib remain higher among Native American and Alaska Native (AI/AN) children than non-Native children. During 1998–2009, the average annual incidence of Hib disease in children aged  $< 5$  years in the United States was 8–10 times higher (1.3/100,000) among AI/AN children than it was among white (0.16/100,000) and black (0.12/100,000) children, respectively. Invasive *Haemophilus influenzae* is associated with severe outcomes, especially in older adults; among  $\geq 65$  year-olds the overall case fatality ratio (CFR) is estimated to be 19.5% and increases with age, ranging from 10.2% to 27.5%.

Justification

In the clinical setting the diagnosis of invasive *Haemophilus influenzae* disease is based on clinical presentation, as well as a variety of laboratory tests (culture, PCR, etc.). Culture remains the gold standard laboratory test for identification of *Haemophilus influenzae* with virtually 100% specificity. However, *Haemophilus influenzae* has fastidious growth requirements and culture has poor sensitivity in specimens from person who have received antibiotics.

PCR is a rapid test and has high sensitivity. Although the specificity can vary, considerable improvements have been made in the quality of PCR testing performed in many public health and commercial laboratories during the last decade as a result of both improvements in the assays and communication and training efforts from CDC. Availability of PCR in public health laboratories has also expanded over the last several years as a result of these efforts. The recently developed and validated *Haemophilus influenzae* species-specific PCR assay is capable of detecting all six serotypes (a-f) and nontypable *Haemophilus influenzae* with high sensitivity and specificity.

As the epidemiology of invasive *Haemophilus influenzae* disease in the United States has shifted, it is important to monitor specimens for both b and non-b serotypes so that cases of invasive *Haemophilus influenzae* disease are appropriately identified and classified in national burden estimates. With the increased reliability of PCR and its ability to detect not only *Haemophilus influenzae* but its serotypes, classifying PCR positive cases as “confirmed” accurately describes public health confidence in PCR as a reliable diagnostic test.

**III. Statement of the desired action(s) to be taken**

The invasive *Haemophilus influenzae* case definition should be updated by including PCR as an acceptable laboratory test and classifying PCR positive *Haemophilus influenzae* cases as confirmed.

1. Utilize standard sources (e.g. reporting\*) for case ascertainment for invasive *Haemophilus influenzae* disease. Surveillance for *Haemophilus influenzae* disease should use the following recommended sources of data to the extent of coverage presented in Table III.

**Table III. Recommended sources of data and extent of coverage for ascertainment of cases of *Haemophilus influenzae* disease.**

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	X	
Laboratory reporting	X	
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers)	X	
Death certificates	X	
Hospital discharge or outpatient records	X	
Extracts from electronic medical records	X	
Telephone survey		
School-based survey		
Other _____		

2. Utilize standardized criteria for case identification and classification (Sections VI and VII) for *Haemophilus influenzae* disease and add *Haemophilus influenzae* disease to the *Nationally Notifiable Condition List*.

- 2a. Immediately notifiable, extremely urgent (within 4 hours)
- 2b. Immediately notifiable, urgent (within 24 hours)
- 2c. Routinely notifiable

CSTE recommends that all States and Territories enact laws (statute or rule/regulation as appropriate) to make this disease or condition reportable in their jurisdiction. Jurisdictions (e.g. States and Territories) conducting surveillance (according to these methods) should submit case notifications\*\* to CDC.

3. CDC should publish data on *Haemophilus influenzae* disease as appropriate in *MMWR* and other venues (see Section IX).

CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined above.

Terminology:

\* Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance TO local or state public health.

\*\*Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Condition List TO CDC.

#### IV. Goals of Surveillance

To provide information regarding the epidemiology of *Haemophilus influenzae* disease to facilitate prevention and control efforts.

**V. Methods for Surveillance: Surveillance for *Haemophilus influenzae* disease should use the recommended sources of data and the extent of coverage listed in Table III.**

#### VI. Criteria for case identification

**A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.**

Report any illness to public health authorities that meets any of the following criteria:

1. Isolation of *Haemophilus influenzae* (any type) from any normally sterile body site (e.g., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid)
2. Detection of *Haemophilus influenzae*-specific nucleic acid in 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
3. Meningitis with *Haemophilus influenzae* type b (Hib) antigen detected in CSF
4. Any case of epiglottitis
5. The healthcare record indicates a diagnosis of disease caused by *Haemophilus influenzae*
6. The death certificate indicates disease caused by *Haemophilus influenzae* as a cause of death or a significant condition contributing to death.

Other recommended reporting procedures

- All cases of *Haemophilus influenzae* infection, regardless of serotype, should be reported.
- Reporting should be on-going and routine.
- Frequency of reporting should follow the state health department's routine schedule.

**B. Table of criteria to determine whether a case should be reported to public health authorities**

Table VI-B. Table of criteria to determine whether a case should be reported to public health authorities.

Criterion	Reporting	
<i>Clinical Evidence</i>		
Meningitis	N	
Epiglottitis		S
Healthcare record indicates a diagnosis of disease caused by <i>Haemophilus influenzae</i>		S
Death certificate indicates disease caused by <i>Haemophilus influenzae</i> as a cause of death or a significant condition contributing to death.		S
<i>Laboratory Evidence</i>		
Isolation of <i>Haemophilus influenzae</i> (any type) from a normally sterile site		S
Detection of <i>Haemophilus influenzae</i> -specific nucleic acid in a normally sterile body site using a validated polymerase chain reaction (PCR) assay		S
Detection of <i>Haemophilus influenzae</i> type b (Hib) antigen in CSF	N	

Notes:

S = This criterion alone is sufficient to identify a case for reporting.

N = All “N” criteria in the same column are necessary to identify a case for reporting.

O = At least one of these “O” (Optional) criteria in each category (i.e., clinical evidence and laboratory evidence) in the same column – in conjunction with all “N” criteria in the same column – is required to identify a case for reporting. (These optional criteria are alternatives, which means that a single column will have either no O criteria; no column should have only one O.)

**C. Disease-specific data elements**

Disease-specific data elements to be included in the initial report are listed below.

*Epidemiological Risk Factors*

Immunization History

Number of doses of Hib-containing vaccine and type of vaccine (PRP-OMP vs PRP-T) received

Date of last dose of Hib-containing vaccine

Daycare center attendance

Contact with a confirmed case of *Haemophilus influenzae* disease

**VII. Case Definition for Case Classification**

**A. Narrative: Description of criteria to determine how a case should be classified.**

*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

*Comment(s)*

Positive antigen test results from urine or serum samples are unreliable for diagnosis of *Haemophilus influenzae* disease and should not be used as a basis for case classification.

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

**Clinical Criteria**

Invasive disease may manifest as pneumonia, bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, or purulent pericarditis; less common infections include endocarditis and osteomyelitis.

**Laboratory Criteria**

- 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., cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid, pericardial fluid)

**Epidemiologic Linkage**

Not applicable for case classification.

**Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance**

**B. Classification Tables**

Criterion	Case Definition	
	Probable	Confirmed
<i>Clinical Evidence</i>		
Meningitis	N	
<i>Laboratory Evidence</i>		
Isolation of <i>Haemophilus influenzae</i> (any type) from a normally sterile site		S
Detection of <i>Haemophilus influenzae</i> -specific nucleic acid in a normally sterile body site using a validated polymerase chain reaction (PCR) assay		S
Detection of <i>Haemophilus influenzae</i> type b (Hib) antigen in CSF	N	

Notes:

S = This criterion alone is sufficient to classify a case

N = All "N" criteria in the same column are necessary to classify a case

**VIII. Period of Surveillance**

Surveillance should be on-going.

## IX. Data sharing/release and print criteria

Notification to CDC for confirmed and probable cases and all cases prior to classification is recommended.

- Data on reported Hib cases in children <5 years are summarized monthly for NCIRD staff and distributed internally via the NCIRD monthly surveillance report for vaccine preventable diseases. Cases of invasive *Haemophilus influenzae* in all ages and in children <5 years reported electronically through NNDSS are summarized weekly in the MMWR Notifiable Diseases Tables and yearly in the MMWR Surveillance Summaries. Aggregate data will be published in reports, the MMWR, and peer-reviewed journals as the public health need arises.
- State-specific compiled data will continue to be published in the weekly reports and annual MMWR Surveillance Summaries. Aggregate data are included in PAHO and WHO annual reports. The frequency of additional publication of this data, in the MMWR and peer-reviewed journals, is dependent on disease epidemiology and public health need.
- Currently aggregate data on *Haemophilus influenzae* cases reported to NNDSS are summarized in yearly reports to PAHO. No personal identifying or state specific information is re-released to PAHO, WHO, or other parties.

## X. References

Centers for Disease Control and Prevention. Prevention and Control of *Haemophilus influenzae* Type b Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2014; 63 (No. RR-1): 1-14.

Council of State and Territorial Epidemiologists (CSTE). Public Health Reporting and National Notification for invasive *Haemophilus influenzae* type b (Hib) Infection. 09-ID-33 Atlanta: CSTE; June 2010. Available from: <http://www.cste.org>

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Wang X, Mair R, Hatcher C, Theodore MJ, Edmond K, et al. Detection of bacterial pathogens in Mongolia meningitis surveillance with a new real-time PCR assay to detect *Haemophilus influenzae*. Int J Med Microbiol. 2011 Apr; 301(4):303-9.

Wang X, Theodore MJ, Mair R, Trujillo-Lopez E, du Plessis M, et al. Clinical Validation of Multiplex Real-Time PCR Assays for Detection of Bacterial Meningitis Pathogens. Journal of Clinical Microbiology. March 2012; 50(3): 702-708.

WHO Meningitis Manual. 2011. Available at: <http://www.cdc.gov/meningitis/lab-manual/index.html>. Accessed June 25, 2014.

## XI. Coordination

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