Invasive Disease caused by *Haemophilus influenzae*

Investigative Guidelines

June 2021

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To identify preschool-age children who may have been significantly exposed to *Haemophilus influenzae* type b (Hib) cases.
2. To establish close observation of such exposed children for signs of illness.
3. To recommend antibiotic prophylaxis, immunization, or both to appropriate contacts of Hib cases.
4. To identify additional cases and establish risk factors for non-Hib cases.

1.2 Laboratory and Physician Reporting Requirements

Physicians are required to report suspected or confirmed cases of *Haemophilus influenzae*-related invasive disease, including bacteremia, meningitis, pneumonia, and epiglottitis, within 24 hours — **regardless of serotype**. Laboratories must report isolation of *H. influenzae* from normally sterile sites within one working day; by law, such isolates must be forwarded to the Oregon State Public Health Laboratory (OSPHL).

Confirmed primary specimens from sterile sites tested using culture-independent diagnostic tests (CIDTs) should be sent to OSPHL for serotyping at CDC, upon approval from the Oregon Public Health Division (OPHD).

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report all confirmed and presumptive (but *not* suspect) cases to OPHD (see definitions below) by the end of the calendar week of initial physician or lab report. Submit case data electronically. **Note that all cases of *H. influenzae* are reportable, <u>regardless of serotype, and require a case interview</u>;** we just get more excited about type b cases.
2. Begin follow-up investigation within 24 hours.
3. Identify significant contacts and recommend prophylaxis within 24 hours for Hib cases.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Haemophilus influenzae (Hi) is a small, Gram-negative bacillus. There are at least six serotypes of *H. influenzae* (designated a–f) distinguished by their capsular antigens, as well as unencapsulated (nontypeable) strains. Despite its name, this bacterium has nothing to do with influenza. (Note also that it is spelled differently, too.)

2.2 Description of Illness

Disease can take many forms, including meningitis, bacteremia, periorbital or other cellulitis, septic arthritis, osteomyelitis, pericarditis, epiglottitis, or pneumonia. Onset of symptoms is usually abrupt, and may include fever, headache, lethargy, anorexia, nausea, vomiting, and irritability. Progressive stupor or coma is common with meningitis.

Infections spread via the bloodstream after penetration of the mucous membranes of the nasopharynx. The exact mechanism allowing the penetration is unknown, but a recent upper respiratory tract infection may facilitate invasion. People with cochlear implants are at increased risk for bacterial meningitis.

Prior to routine vaccination, *H. influenzae* type b was the most common cause of bacterial meningitis and is a major cause of other invasive disease (including epiglottitis) in young American children. Before the introduction of conjugate vaccines in 1990, one child in 200 developed *Haemophilus* disease by the age of five.

Asymptomatic carriage of Hib is not uncommon; in the pre-vaccine era the organism was recovered from the upper respiratory tract of 2%–5% of healthy children. Thus, isolates from sputum or other not normally sterile sites are *not* indicative of invasive disease.

Neonatal sepsis and noninvasive upper respiratory tract disease, including otitis media, sinusitis, and bronchitis are often caused by nontypeable strains of *H. influenzae*. These organisms can be recovered from the nasopharynx of 40% to 80% of healthy children.

Most *H. influenzae* cases in Oregon are nontypeable. From 2017–2019 there were 300 cases of invasive *H. influenzae*; 74% were nontypeable, 0.3% were type b, 8% were type f, and 17.7% were of another serotype or unknown. No cases of Hib were reported in 2019. Since 1995 there have been 58 cases of serotype b infection, 13 of which occurred in children under age 4. No cases have been reported in this young age group since 2012.

2.3 Reservoirs

Human cases and carriers.

2.4 Modes of Transmission

Hib bacteria are transmitted by direct contact with respiratory droplets and discharges from the nose and throat of infected or colonized persons. With Hib, children <4 years of age who have had prolonged household, children's facility, or other close contact with a case are at increased risk of disease. The risk of secondary disease among household contacts is age-dependent and estimated to be 4% for children <2 years of age, 2% for children 2–3 years of age, 0.1% for children 4–5 years of age, and 0% among immunocompetent contacts over the age of 6. The overall risk of secondary disease in children's facilities seems to be less than in households and is estimated at 1%–2% for children <2 years of age and less than 1% in children age 2 or older.

2.5 Incubation Period

The incubation period is hard to define, because most persons who acquire Hi infections are asymptomatically colonized. Those who become ill following exposure to a case usually do so within 10 days, although the risk may be slightly elevated for up to 60 days.

2.6 Period of Communicability

As long as the organism is present in discharges from the nose or throat. Communicability ends within 24 hours of initiation of appropriate chemoprophylaxis. Note, however, that some antibiotics used to treat invasive disease do not eradicate the organism from the nasopharynx (see §5.3 below). Those exposed ≥7 days before onset of illness in the case are not at significantly increased risk. Hib cases are probably most infectious during the 3 days prior to onset of symptoms.

2.7 Treatment

Initial therapy for children with Hi meningitis is cefotaxime or ceftriaxone. Ampicillin may be substituted if the isolate is susceptible. Beta-lactamase-negative, ampicillin-resistant strains of Hi have been described, and some experts recommend caution in using ampicillin when minimum inhibitory concentrations of 1–2 µg/mL are found. Treatment of other invasive Hi infections is similar. Intravenous therapy is continued for 7–10 days and longer in complicated infections.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

- 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, using a validated polymerase chain reaction (PCR) assay

3.2 Presumptive Case Definition

- Meningitis with detection of *Haemophilus influenzae* type b antigen in cerebrospinal fluid (CSF)
- Patients with compatible illness who are epi-linked to a confirmed case, and from whom small, pleomorphic Gram-negative bacilli are detected in a specimen from a normally sterile site (e.g., blood, CSF, or synovial fluid)

3.3 Suspect Case (*not* reportable to OPHD)

Non-epi-linked patients with compatible illness and the laboratory findings listed for presumptive cases.

3.4 Services Available at the Oregon State Public Health Laboratory (OSPHL)

OSPHL will confirm the identification of *H. influenzae* and serotype isolates from sterile sites. Isolates should be sent on media that support the growth of the organism (e.g., chocolate agar). Complete specimen acceptance criteria for isolate submission are available on OSPHL's Lab Test Menu at www.healthoregon.org/labtests under "*Haemophilus influenzae* Serotype."

Primary specimens from sterile sites confirmed using culture-independent diagnostic tests (CIDTs) should be sent to OSPHL for serotyping at CDC, upon approval from OPHD. Submission criteria for primary specimens to be forwarded and tested at CDC should follow the acceptance criteria available at the CDC Test Directory; scroll down to "*Haemophilus influenzae* Identification and Serotyping" at www.cdc.gov/laboratory/specimen-submission/list.html.

All specimens must be properly packaged in double containers with absorbent material around them and be accompanied by a completed General Microbiology Test Request Form. Please indicate on the Test Request Form if the specimen was confirmed using CIDT methods to allow for proper forwarding of specimen to the CDC.

4. ROUTINE CASE INVESTIGATION

All cases of *H. influenzae* are reportable and require a case interview, regardless of serotype. If there is at least one incompletely immunized child <4 years of age in the case's household, do not wait for serotype confirmation; begin prophylaxis of all household members within 24 hours.

4.1 Identify Source of Infection

Usually, this is not possible because the organism is carried asymptomatically by a high percentage of people. Follow-up for all serotypes includes completion demographic, risk, follow-up, clinical and laboratory modules in Orpheus. Although a long shot, with Hib cases it is worth checking if any household or children's facility contacts have had any illness suggestive of *H. influenzae*-caused invasive disease within the previous 60 days.

4.2 Identify Potentially Exposed Persons

While awaiting serotype report:

1. Determine whether any other members of the immediate household are <4 years of age, and if so, assess their Hib immunization status. If there is at least one unimmunized or incompletely immunized child <4 years of age, begin prophylaxis of all household members within 24 hours.[1] If no household members <4 years of age are identified, no further action is recommended until the case has received a confirmation of serotype b.
2. Determine whether the case had prolonged contact (4 or more hours in a day) with other children under age 2 in a children's facility in the week prior to onset of illness. If so, refer to §6. **We do NOT recommend taking further action in a children's facility unless a case of serotype b has been confirmed**.[2]
3. Culturing of exposed persons to identify carriers is not useful.

4.3 Environmental Evaluation

None

5. CONTROLLING FURTHER SPREAD

5.1 Education

Parents or guardians of potentially exposed children <4 years of age (to type b cases) should be instructed to monitor these contacts for 14 days for fever, lethargy, irritability, loss of appetite, vomiting, or other signs of illness, and to seek medical care immediately should any illness occur. If the exposed child is a children's facility contact, this observation should continue for 60 days. (See §6.)

5.2 Isolation

Droplet precautions should be implemented until 24 hours have passed following initiation of antibiotic therapy.

5.3 Follow-up of Hib Cases

Therapy for invasive Hib disease might not eradicate respiratory carriage of the organism. Therefore, convalescing children—especially those having contact with children <4 years of age in households or <2 years of age in children's facilities—should receive appropriate chemoprophylaxis for at least 24 hours before resuming contact with any unimmunized or incompletely immunized children. Treatment of Hib disease with ceftriaxone or cefotaxime will eradicate nasal carriage. No other antibiotics used for treatment eradicate carriage, so a child treated with anything other than ceftriaxone or cefotaxime will require rifampin prophylaxis.

5.4 Immunization and Prophylaxis

1. Passive Immunization

None.

2. Active Immunization

Hib conjugate vaccines are available for use in children 6 weeks through 59 months of age (see ACIP guidelines). Because of the length of time necessary to develop antibodies, vaccination does not play a major role in the management of patients with Hib disease or their contacts. The effects of Hib vaccination on asymptomatic carriage of Hib are uncertain. Thus, although immunized children may be protected from invasive disease, they may acquire and pass the organism to other, susceptible children. Children developing Hib invasive disease before the age of two are at high risk of recurrent Hib disease; they should be immunized according to the age-appropriate schedule ASAP during convalescence. Any earlier doses of Hib vaccine received by such children should be discounted.

3. Antibiotic Prophylaxis

Appropriate chemoprophylaxis should be recommended for *all household contacts* of Hib cases in the following circumstances:

- Household with at least 1 child <4 years of age who is unimmunized or incompletely immunized*
- Household with a child <12 months of age who has not received the primary series
- Household with an immunocompromised child, regardless of that child's Hib immunization status

(In general, further action is NOT recommended until a case has received a confirmation of serotype b. However, if there is at least one incompletely immunized child <4 years of age in the case's household, do not wait for serotype confirmation; begin appropriate chemoprophylaxis of all household members within 24 hours.)

Chemoprophylaxis should be instituted as rapidly as possible. If more than 14 days have passed since the last contact with the index patient, the benefit of chemoprophylaxis is likely to be decreased.

Chemoprophylaxis should also be considered for children's facility contacts when 2 or more cases of Hib invasive disease have occurred within 60 days and unimmunized or incompletely immunized children attend the facility. Recommendations for prophylaxis should be communicated to the case's physician and at least one responsible adult in the household.

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* Complete immunization is defined as having had at least 1 dose of conjugate vaccine at ≥15 months of age; 2 doses between 12 and 14 months of age; or a 2- or 3-dose primary series at <12 months with a booster dose at ≥12 months of age.

The rifampin dosage is 20 mg/kg (maximum 600 mg) once daily for 4 days. For neonates (<1 month of age) the dose is 10 mg/kg once daily for 4 days. Rifampin is available in 150-mg and 300-mg capsules. It can be mixed with several teaspoons of applesauce or jelly, or suspended in a simple syrup (Syrup NF, Wild Cherry Syrup, etc.), following the manufacturer's instructions. Rifampin chemoprophylaxis is not recommended for pregnant women. Those taking rifampin should be informed that it can cause gastrointestinal upset, orange discoloration of urine, discoloration of soft contact lenses, and decreased effectiveness of oral contraceptives. Note that the 4-day rifampin schedule for eradication of *H. influenzae* carriage is reliably effective against *N. meningitidis* carriage as well, but not vice versa.

If contacts meeting prophylaxis guidelines have been advised by the local public health authority (LPHA) to take rifampin but are unable to obtain rifampin by any other means due to financial circumstances, the LPHA may dispense rifampin out of its TB stock. After dispensing, the LPHA must then email the state TB program describing the circumstances and the amount of rifampin dispensed.

6. WHEN THE CASE IS IN A CHILDREN'S FACILITY (HIB ONLY)

Ascertain whether the case was in any children's facility or baby-sitting situation for least 4 hours in at least one day of the week prior to onset. If so, determine whether any children <2 years of age were in the same room. If so:

1. The operator of the facility should be asked about other cases of meningitis or other suspect invasive disease among other children during the past 2 months.
2. The parents of children in the same classroom as the case should be notified (preferably in writing) of the occurrence of Hib disease in the facility. The notice should advise parents:
   - to monitor their children carefully for a 60-day period for signs of illness such as fever, irritability, lethargy, and loss of appetite; and
   - to seek medical care immediately should such symptoms occur.
3. Instruct the children's facility administrator to notify the LPHA immediately if another child becomes ill within the next 60 days. When 2 or more cases of Hib have occurred within 60 days and unimmunized or incompletely immunized children attend the children's facility, rifampin prophylaxis for workers and attendees should be considered. The LPHA should consult with OPHD if this circumstance arises.

7. STERILE SITES

Table: Defined Sterile Sites

Sterile site category	Sterile Sites	Sites that require clarification	Non-Sterile Sites
Blood	• Blood • Blood from an indwelling line	• Blood clot	• Blood from a recently removed line • Catheter site • Catheter tip • Cord blood
CSF	• Cerebral spinal fluid • Cranial fluid • Spinal fluid • VP Shunt fluid/infection		
Pleural Fluid	• Chest fluid • Chest fluid from chest tube • Empyema or Empyema fluid • Fluid unspecified from Pleura • Pleural fluid • Pleural peel • Pleural abscess • Pleural tissue • Parietal pleura • Thoracentesis fluid		• Chest wall abscess
Peritoneal Fluid/abdominal cavity	• Abdominal fluid • Ascites (fluid) • Intraperitoneal fluid or abscess • Paracentesis fluid • Pericolic space • Peritoneal abscess • Peritoneal dialysate • Peritoneal dialysate effluent • Peritoneal fluid, whether or not there is a perforated • Peritoneum • Retroperitoneal abscess	• Pelvic abscess • Pelvic fluid	• Appendix rupture • Bowel (intact or perforated) • Hemodialysis dialysate • Hemodialysis effluent • Unspecified dialysate or effluent
Pericardial Fluid	• Pericardial fluid		
Joint/Synovial Fluid	• Bursa • Disc space • Fluid unspecified from joint or synovial • Glenohumeral joint • Hip capsule • Hip-internal abscess • Hip tissue/Biopsy • Joint or synovial fluid • Knee prepatella • Knee tissue or biopsy • Meniscus • Needle aspirate of any specific joint	• Ganglion cyst • Humeral head • Olecranon (bone vs joint) • Surgical tissue • Wrist specimens	

Sterile site category	Sterile Sites	Sites that require clarification	Non-Sterile Sites

	• Popliteal fossa
	• Popliteal space abscess
	• Prepatellar bursa
	• Prosthetic hardware or Swab
	  ○ Hip prosthesis
	  ○ Knee arthroplasty
	  ○ Metatarsal implant
	• Subacromial space abscess
	• Synovium		

Bone	• Bone • Bone abscess • Bone marrow • Bone surgically obtained • Clavicle tissue • Cranial bone flap • Disc abscess • Disc fluid • Humerus abscess • Intraspinal abscess • Mastoid • Mastoid bone • Medullary canal tissue • Paraspinal abscess • Periosteum • Spinal or lumbar abscess or Phlegmon • Spinal or lumbar surgical specimen • Spinal or lumbar tissue spinal swab • Transmetatarsal tissue • Vertebral disk	• Bone exposed to wound • Olecranon (Bone vs joint) • Prosthesis fluid • Surgical Tissue • Thoracic tissue • Wrist specimens	

Internal body site	Sterilely Obtained Biopsy, Tissue, Abscess, Aspirate, Fluid, or
	Swab from:
	• Brain
	  ○ Brain abscess fluid
	  ○ Epidural abscess
	  ○ Epidural fluid
	  ○ Intradural fluid
	  ○ Meninges
	  ○ Sagittal tissue
	• Heart
	  ○ Bypass graft
	  ○ Mitral valve
	• Kidney
	  ○ Renal
	  ○ Perinephric/perirenal
	  ○ Subphrenic
	• Liver
	  ○ Perihepatic
		• Breast
		• Deep neck abscess
		• Surgical tissue
			• Bartholin glad (abscess)
			• Bronchoalveolar lavage
			• Bronchoalveolar specimen
			• Bronchogenic cyst
			• Lung
			• Vein tissue that recently had a line removed

Sterile site category	Sterile Sites	Sites that require clarification	Non-Sterile Sites

	• Lymph node
	  ○ Intraparotid abscess
	  ○ Lymph node abscess
	• Ovary
	  ○ Ovarian abscess
	  ○ Tubo-ovarian abscess
	• Pancreas
	• Spleen
	• Vascular tissue (blood-bearing vasculature)
	  ○ Artery
	  ○ Aortic sac
	  ○ AV fistula or graft
	  ○ Iliac artery wall
	  ○ Popliteal artery
	  ○ Popliteal tissue artery
	• Vitreous fluid		

Other sterile site*	Sterilely Obtained Biopsy, Tissue, Abscess, Aspirate, Fluid, or Swab **<u>Deep Tissue</u>** • Arytenoid tissue • Bladder • Corpus cavernosum • Deep foot tissue • Endometrium • Inguinal sac • Mediastinum • Omentum • Parotid gland • Peritoneum • Prostate • Rectus Sheath • Sarcoma Mass • Scalp-internal • Scleral Buckle • Scrotal Abscess • Scrotal Sac • Thyroid **<u>Fluid (Sterile)</u>** • Deep Pelvic Abscess • Lymphocele • Pacer Pocket Fluid • Subgaleal Fluid	• Allograft • Axilla • Breast • Groin abscess • Mastoid cavity • Mesh • Scrotum • Stenson's Duct • Surgical tissue • Surgical swab • Abdominal seroma • Abdomen or Chest wall abscess • Deep abscess • Deep neck abscess • Groin abscess • Hematoma seroma • Intra-abdominal abscess • Seroma, in general • Subcutaneous implant pocket • Umbilical hernia sac	• Amniotic fluid • Aqueous fluid • Bartholin gland (abscess) • Bile or biliary fluid • Boils • Bowel • Bronchoalveolar lavage • Catheter tip or site • Cholecystectomy fluid • Cord blood • Cornea • Ear • Furuncles • Gallbladder • Gland or Cyst – Any type • Glandular abscess • Hemodialysis Dialysate • Hidradinitis suppurativa • Incision fluid drainage • Jackson-Pratt drain fluid • Lacrimal sac • Lung • Middle Ear • Oral cavity • Pacemaker • Paranasal sinus • Peritonsilar Abscess • Placenta • Rheumatoid Nodule

Sterile site category	Sterile Sites	Sites that require clarification	Non-Sterile Sites
			• Sebaceous Gland • Skin • Skin abscess • Sphenoid Sinus • Sputum • Subcutaneous Fat • Superficial abscess • Superficial Skin Abscesses • Superficial Skin Infections • Throat • Thyroglossal duct cyst • Urine • Urinary Catheter • Wound • Wound Vac Fluid

*General sterile site note: Ambiguous and non-specific sources should never be recorded as sterile sites. Examples of ambiguous sources include the following: fluid (sterile), abscess, tissue, surgical specimen (sterile), aspirate, etc. To be considered a sterile site, additional information on the actual location within the body needs to accompany the reported source. Examples of these should be reported as (but are not limited to): abdominal abscess, deep leg tissue, groin aspirate, etc.

8. REFERENCES

1. Osterholm MT, Pierson LM, White KE, Libby TA, Kuritsky JN, McCullough JG. The risk of subsequent transmission of *Haemophilus influenzae* type b disease among children in day care: results of a two-year statewide prospective surveillance and contact survey. N Engl J Med 1987; 316:1–5.
2. Broome CV, Mortimer EA, Katz SL, Fleming DW, Hightower AW. Special Report—Use of chemoprophylaxis to prevent the spread of *Haemophilus influenzae* b in day-care facilities. N Engl J Med 1987; 316:1226–8.

UPDATE LOG

June 2021. Clarified timeliness of antibiotic prophylaxis. (Martin).

January 2020. Updated serotype data, clarified follow-up requirements for all cases (regardless of serotype), sundry edits. (Poissant)

May 2018. Added sterile site table. (Poissant)

September 2017. Updated laboratory submission instructions. (Poissant)

March 2017. Put in new template. (Byster)

February 2015. Updated case definitions to be in line with CSTE case definitions. Added PCR as acceptable test for a confirmed case. (Poissant)

January 2015. Section 2.2: Updated serotype distribution with 2014 data. (Poissant)

December 2010. Clarified recommendations for prophylaxis while awaiting serotype report. Updated epidemiological data. (Jamie Thompson).

January 2007. Updated chemoprophylaxis regimens and practices associated with the daycare settings. Addressed the use of cetotaxime and ceftriaxone in treatment of invasive disease and eradication of nasal carriage.