

The background of the top half of the page features a green watercolor-style background with white line drawings of various Haemophilus influenzae bacteria. These include several large, roughly spherical cells with concentric internal structures, and a prominent, larger spherical cell on the right side covered in numerous small, hair-like projections (pili).

Haemophilus influenzae

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DISEASE AND VACCINE CHARACTERISTICS

The bacteria *Haemophilus influenzae* type b (Hib) was the leading cause of non-epidemic bacterial meningitis worldwide in children prior to the introduction of Hib vaccine. *H. influenzae* can be unencapsulated or capsulated (six capsular types or serotypes), although 95% of severe disease is caused by capsular type b (Hib). *H. influenzae* can asymptomatically colonize the human nasopharynx, particularly in children. The bacteria can spread contiguously to cause otitis media and sinusitis or be aspirated to cause pneumonia. More rarely, it can cause invasive disease, predominantly meningitis and pneumonia but also epiglottitis, septic arthritis and others. Over 90% of invasive *H. influenzae* disease occurs in children < 5 years of age, the majority in infants; children in less developed settings tend to be infected earlier in infancy. Case fatality rates can be high for *H. influenzae* meningitis, ranging from 5% with proper treatment to as high as 60% without. Among survivors, 20–40% suffer sequelae such as deafness and blindness. It is estimated that in 2008, 199 000 HIV-negative children < 5 years of age died from *H. influenzae* disease (1). HIV-infected infants are at a several-fold increased risk of invasive *H. influenzae* disease.

Current Hib vaccines conjugate the Hib polysaccharide capsule to one of several carrier proteins that can be used effectively (2). Hib vaccines are available in monovalent formulations or combined with other antigens: diphtheria-tetanus-pertussis (DTP) vaccine, hepatitis B vaccine and inactivated polio vaccine (IPV). Hib vaccines are given as a three- or four-dose schedule in the primary series starting as early as six weeks of age; some countries give a booster dose at 12–18 months of age. Recommended schedules include three primary doses without a booster (3p+0), two primary doses plus a booster (2p+1) or three primary doses with a booster (3p+1). Countries that have high coverage of Hib vaccine with any of these schedules have observed a > 90% decline in invasive Hib disease. Some countries have identified an increase in Hib disease in countries without a booster dose, but this has been small and not sustained (3).



RATIONALE AND OBJECTIVES OF SURVEILLANCE

The objectives of surveillance *H. influenzae* are to:

- quantify disease burden and epidemiology to inform vaccine introduction decisions (such as dosing schedule and product choice)
- evaluate vaccine impact and monitor serotype distribution
- identify immunization programme implementation gaps and provide data to determine if changes in vaccine policy are needed (such as booster doses).



TYPES OF SURVEILLANCE RECOMMENDED

MINIMAL SURVEILLANCE

The minimal surveillance standard for *H. influenzae* disease is sentinel hospital surveillance for meningitis, previously referred to as Tier 1 Invasive Bacterial Vaccine Preventable Disease (IB-VPD) surveillance (4).

- Surveillance can be implemented in one or multiple hospitals that admit children with meningitis and other severe diseases. Surveillance should be active in enrolling suspected cases and implementing appropriate laboratory testing to confirm *H. influenzae*.
- Sentinel surveillance is case-based and prospective. It should be undertaken only in hospitals with sufficient numbers of cases identified to make the surveillance useful (100 cases per site per year of suspected meningitis). Surveillance in smaller hospitals is not worth the resource investment and can also lead to erroneous conclusions due to small numbers of cases.
- Sentinel site surveillance may not be sufficient to meet all objectives. Addition of other surveillance or research methods, such as case-control studies to assess vaccine effectiveness, might be needed.

ENHANCED SURVEILLANCE

Two types of enhanced surveillance for *H. influenzae* are possible.

1. Expanded sentinel hospital surveillance

Meningitis sentinel surveillance can be expanded to include pneumonia and sepsis (previously referred to as Tier 2 IB-VPD surveillance). The characteristics of this surveillance are the same as meningitis sentinel surveillance: case-based, active and prospective. Pneumonia and sepsis surveillance should only be undertaken in hospitals of sufficient size to have a meaningful number of cases (500 cases per site per year for meningitis + pneumonia/sepsis). While it is difficult to identify the etiology of pneumonia, radiography can be used to identify WHO-defined endpoint pneumonia, which is more specific for bacterial pneumonia such as that caused by *H. influenzae* (6).

2. Population-based surveillance for invasive *H. influenzae* disease

- » A defined catchment population is required in order to calculate incidence.

- » Population-based surveillance can be done around one sentinel hospital or at a regional level with multiple hospitals. Previously, this had been called Tier 3 IB-VPD surveillance.
- » If done in multiple hospitals in a defined region (district, province, etc.), most hospitals in the catchment area should collect sterile site specimens on most suspected cases as part of routine clinical practice, and these specimens should be tested for *H. influenzae*. This approach is often laboratory-based, where the entry point into the surveillance system is a laboratory detection of an invasive pneumococcal disease (IPD) case. These cases can then be followed up to gather more epidemiologic information. An example of this type of surveillance is the GERMS network in South Africa (3).
- » Population-based surveillance achieves the same objectives as sentinel site surveillance, with the addition of assessing incidence to monitor burden by age group and increases in non-b *H. influenzae* serotypes, because serotype-specific incidence rates are preferable to case counts for following temporal trends.

TARGET POPULATION

The target population is children aged 0–59 months for all types of surveillance. Primary disease affects infants, while vaccine failures tend to occur in children > 1 year of age (7). Hib disease is rare in older children and adults. In practice, however, older children and adults may be included in enhanced surveillance systems for bacterial meningitis, since pneumococcus and meningococcus do occur in older age groups.

LINKAGES TO OTHER SURVEILLANCE

Where possible, surveillance for *H. influenzae* should be integrated with that for other causes of bacterial meningitis and pneumonia, such as pneumococcus and meningococcus. When conducting sentinel surveillance for meningitis, pneumonia or sepsis, all three pathogens should be routinely tested for. Laboratory testing for antimicrobial resistance can be integrated with surveillance for other bacteria (such as typhoid).



CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED MENINGITIS FOR CASE FINDING

- Any child aged 0–59 months admitted to hospital with sudden onset fever ($> 38.5^{\circ}\text{C}$ rectal or 38°C axillary) and one of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal signs.

OR

- Any patient aged 0–59 months hospitalized with a clinical diagnosis of meningitis.

PROBABLE BACTERIAL MENINGITIS

A suspected meningitis case with cerebrospinal fluid (CSF) examination showing at least one of the following:

- Turbid appearance
- Leucocytosis (> 100 cells/ mm^3)
- Leucocytosis ($10\text{--}100$ cells/ mm^3) AND either an elevated protein (> 100 mg/dL) or decreased glucose (< 40 mg/dL). Note: If protein and glucose results are not available, diagnose using the first two conditions (turbid appearance or leucocytosis > 100 cells/ mm^3).

CONFIRMED *H. INFLUENZAE* MENINGITIS

A suspected or probable meningitis case that is laboratory-confirmed by culture or identification of *H. influenzae* (by antigen detection, immunochromatography, polymerase chain reaction (PCR) or other methods) in the CSF or blood from a child with a clinical syndrome consistent with meningitis.

SUSPECTED PNEUMONIA FOR CASE FINDING

Any child aged 0–59 months demonstrating cough or difficulty breathing and displaying fast breathing when calm, as defined by age:

- Age 0 to < 2 months: 60 breaths/minute or more
- Age 2 to < 12 months: 50 breaths/minute or more
- Age 12 to ≤ 59 months: 40 breaths/minute or more

SUSPECTED SEVERE PNEUMONIA FOR CASE FINDING

Any child aged 0–59 months with a cough or difficulty breathing and displaying one or more of the following:

- inability to drink or breastfeed
- vomiting everything
- convulsions
- prostration/lethargy
- chest in-drawing
- stridor when calm.

WHO-DEFINED ENDPOINT PNEUMONIA

Pneumonia in a patient with a chest radiograph showing an infiltrate consistent with pneumonia: dense, fluffy alveolar consolidation or pleural effusion (or both).

CONFIRMED *H. INFLUENZAE* PNEUMONIA

Any person meeting the definition of pneumonia or severe pneumonia who has a positive culture of *H. influenzae* from blood or pleural fluid.

SUSPECTED SEPSIS FOR CASE FINDING

Any child aged 0–59 months admitted to hospital with the presence of at least two of the following danger signs and without meningitis nor pneumonia clinical syndrome:

- inability to drink or breastfeed
- vomiting everything
- convulsions (except in malaria endemic areas)
- prostration/lethargy
- severe malnutrition
- hypothermia ($\leq 36^{\circ}\text{C}$).

CONFIRMED *H. INFLUENZAE* SEPSIS

A person who meets the definition of sepsis and has a positive culture of *H. influenzae* from a normally sterile site.

CONFIRMED INVASIVE *H. INFLUENZAE* DISEASE

- *H. influenzae* identified via culture from any normally sterile site (e.g., blood, CSF, pleural fluid, joint fluid) in a symptomatic person
- *H. influenzae* identified in the CSF or pleural fluid by antigen detection, immunochromatography or PCR.

Note that for blood, only culture confirms invasive Hib disease, as these other detection methods have not been shown to have enough specificity to diagnosis Hib, particularly in children.



CASE INVESTIGATION

In sentinel hospital surveillance, all children aged 0–59 months with suspected meningitis meeting the suspected case definition should have a lumbar puncture to collect CSF unless the procedure is clinically contraindicated. CSF should be collected before antibiotic administration, otherwise the laboratory may be unable to culture the pathogen and therefore unable to provide information on antimicrobial susceptibility. However, a specimen should be obtained in all suspect cases as bacterial pathogens can still be detected even after antimicrobial therapy has begun. For expanded

surveillance approaches, patients with suspected pneumonia and sepsis should also have appropriate clinical specimens taken. Treatment of patients should not be delayed while awaiting collection of specimens or results from the laboratory. In sentinel surveillance and population-based surveillance, case report forms should be filled out on all suspected cases. In laboratory-based IPD surveillance, cases will be reported retrospectively, and likely will already have been treated. Medical record follow-up should be done to gather key data elements.



SPECIMEN COLLECTION

Care should be taken to minimize any risk of cross-contamination during manipulation or aliquotting. For example, use sterile dispensing technique with appropriate pipettes, tips and tubes. The types of specimen that may be collected include CSF (meningitis cases), blood samples (meningitis, pneumonia and sepsis) and pleural fluid (pneumonia cases).

VOLUME OF SPECIMENS TO COLLECT

➤ CSF

- » 3 mL in total, 1 mL into each of three test tubes.
 - **Tube 1:** Chemical analysis: protein and glucose tests
 - **Tube 2:** Microbiological tests
 - **Tube 3:** Record overall appearance; perform white blood cell count
- » If only one tube of CSF is available, it should be given to the microbiological laboratory for culture/PCR/antigen testing. However, an aliquot of 50–100 µL should be spared from that tube for molecular testing.

- » The presence of blood in the CSF can affect cultures, since antibiotics in blood can inhibit bacterial growth. If more than one tube is being collected, the first tube may contain contaminated blood from lumbar puncture and should not be the tube sent to the microbiology laboratory.

➤ Blood

- » 1–3 mL is considered adequate for a child, and 5–10 mL for an adult.
- » Collected blood should be diluted in blood culture broth in order to obtain blood cultures. It is important to use appropriate ratios of blood to culture broth for optimal bacterial growth. The recommendations of the culture broth manufacturer should be closely followed.
 - Add 1–3 mL of blood from a child to 20 mL of blood culture broth.
 - Add 5–10 mL of blood from an adult to 50 mL of blood culture broth.

► Pleural fluid

Approximately 20–40 mL of aspirated fluid should be immediately placed into tubes coated with appropriate anticoagulant (EDTA or heparin) for biochemistry (5 mL), microbiology (5–10 mL), cytology (10–25 mL), and PCR testing (200 µL–1 mL). Use a heparin-coated syringe for the pH measurement.

TIMING OF COLLECTION

► CSF

- » Collect CSF as soon as possible after admission, preferably before antibiotic therapy is started.
- » Inform the laboratory that a lumbar puncture is to be performed so the technician can be ready to process the sample as soon as possible.

► Blood and pleural fluid

- » Collect prior to administration of antibiotics, whenever possible.

STORAGE AND TRANSPORT

► CSF

- » Refer CSF to the laboratory immediately.
- » If specimen cannot be processed in one or two hours, inoculate 0.5–1.0 mL into trans-isolate (T-I) medium and incubate vented at 35–37°C with 5% CO₂ overnight, or until transport is possible (up to four days). If transport is delayed beyond four days, store at room temperature (unvented) until referral.
- » CSF specimen should not be refrigerated – keep at room temperature.

- » CSF should be processed in a microbiology laboratory within two hours of collection. If there is not access to a microbiology laboratory, inoculated T-I media should be sent from the health facility to the district or reference laboratory as soon as possible. Districts should send the inoculated T-I media to the reference laboratory at least twice a week.

► Blood and pleural fluid

- » Blood and pleural fluid should be immediately inoculated (within one minute) into a blood culture bottle and transported to a microbiology laboratory as soon as possible for overnight incubation and growth of bacteria. All inoculated blood culture media should be protected from temperature extremes (< 18°C or > 37°C) with a transport carrier and thermal insulator (such as extruded polystyrene foam).
- » Inoculated blood culture bottles should not be placed in the refrigerator.
- » Blood cannot be transported before being placed in a blood culture bottle because the syringes do not contain any anticoagulant and the blood will coagulate within a few minutes.

LONG-TERM STORAGE

► CSF, blood, and pleural fluid

- » Store isolates frozen at -20°C to allow further testing (serotyping and antimicrobial susceptibility testing) in the future, or if culture capacity does not exist in local hospitals and processing needs to occur at reference laboratory.
- » If available, storing isolates in a -70°C freezer is preferable.



LABORATORY TESTING

CSF

Meningitis syndrome may be caused by various pathogens; therefore, clinical syndromic surveillance must be complemented by a strong laboratory component. Laboratory confirmation of *H. influenzae* meningitis is done by culture, PCR or antigen detection (8). Bacterial culture is the first priority for confirmation and isolation of the pathogen. Culture is considered as a gold standard but has low sensitivity due to potential antibiotic use by the patient before sample collection.

Many local hospitals will not have adequate capacity for culture, and frozen samples will need to be sent to reference laboratories in the region.

CSF samples should be cultured on blood agar plates (BAP) and supplemented chocolate agar plates (CAP) that are prepared with 5–10% sheep or horse blood. The optimal medium for growth for *H. influenzae* is CAP with X and V factors, whereas pneumococcus grows best on BAP.

PCR is recommended on all suspected cases because bacterial culture might be inhibited if the case has already received antibiotics. As PCR capacities are not always available at district or hospital level, the remaining volume of original non-manipulated CSF can be frozen and sent to either a national or regional reference laboratory for further testing.

Rapid diagnostic test kits (RDTs) can be used since they increase yield and provide results quickly for clinical care and outbreak identification. In general, RDTs only identify the species and not the serotype or serogroup. There are two commonly used types of RDTs. Results should be interpreted according to manufacturer's instructions.

- **Immunochromatography:** BinaxNOW® kit can be used on CSF and pleural fluid for detection and lower-level characterization of pneumococcus. While it identifies only *S. pneumoniae* and not *H. influenzae*, it is recommended for use in cases of suspected meningitis to identify bacterial etiology.
- **Latex agglutination testing (LAT):** Commercial latex kits often have a short shelf life and can be expensive.

Gram stain should not be used to confirm cases, but it is reliable and relatively inexpensive if staff are well trained and reagents are quality controlled. On Gram stain, *H. influenzae* are small, pleomorphic gram-negative rods or coccobacilli with random arrangements.

Report all RDT results to clinical staff within one to two hours of testing. Report CSF and blood culture reports to the clinicians daily if cultures are done in hospital laboratory.

BLOOD

Blood culture can be used to diagnosis *H. influenzae* meningitis, pneumonia and sepsis. The laboratory methods for blood culture are the same for all syndromes. However, the sensitivity of blood culture for *H. influenzae* pneumonia is lower than for the other syndromes because only approximately 10–15% of *H. influenzae* pneumonia cases are bacteremic.

- For blood culture with maximum yield of isolates, subculture all negative cultures after five days of incubation before they are discarded.
- PCR and RDTs are not used routinely on blood to diagnose *H. influenzae* due to low sensitivity and specificity.

Report all RDT results to clinical staff within one to two hours of testing. Report CSF and blood culture results to the clinicians daily if cultures are done in hospital laboratory.

ANTIMICROBIAL RESISTANCE (AMR) TESTING

- To the greatest extent possible, sites should perform antimicrobial sensitivity testing for all *H. influenzae* isolates and evaluate these data by the following: antibiotic type and route, time of antibiotic administration before culture, volume of fluid cultured, geographic area and serotype (8).
- Recommended methods are disk diffusion (modification of the Kirby-Bauer technique) and antimicrobial gradient strip diffusion (9).

QUALITY ASSURANCE SYSTEMS

All of the above laboratory standards should be complemented by good quality assurance and quality control systems to ensure that laboratory data generated for surveillance are of good quality. WHO recommends that laboratories participate in external quality assessment (EQA) programmes and send out a selection of specimens and isolates for confirmatory testing to another level of laboratory (national, regional or global) for quality control (QC).

Most sentinel site laboratories will not have the necessary equipment to carry out higher level characterization (serotyping, antimicrobial susceptibility or PCR), and thus should refer isolates and specimens from suspected, probable and confirmed cases to national or regional reference laboratories that are able to provide quality assurance and higher level testing of CSF specimens. Each laboratory should be enrolled in an appropriate EQA/proficiency testing programme. While not an explicit objective of surveillance for pneumococcus (or other IB-VPDs), such surveillance systems can be used to build laboratory capacity globally as well as identify gaps in laboratory capacity.

LABORATORY NETWORKS

The Global Invasive Bacterial Vaccine-Preventable Diseases (IB-VPD) Laboratory Network is a global network of > 100 laboratories that support invasive bacterial disease surveillance (10). It is coordinated by WHO and Public Health England. IB-VPD has developed standardized laboratory procedures and guidelines for data collection, and has implemented quality assurance and quality control systems.



DATA COLLECTION, REPORTING AND USE

RECOMMENDED DATA ELEMENTS

► Minimal data elements for sentinel hospital meningitis surveillance

- » Sentinel site information – site name or code
- » Demographics
 - Name (if confidentiality is a concern the name can be omitted if a unique identifier exists)
 - Unique case identifier
 - Date of birth (or age if date of birth not available)
 - Sex
 - Place of residence (city, district, and province)
- » Clinical data
 - Signs and symptoms of illness (including those in case definitions)
 - Date of symptom onset
 - Date of admission
 - Treatment
 - Patient outcome (survived without sequelae, survived with sequelae, died)
 - Discharge diagnosis
- » Vaccination history
 - Source of information [vaccination card, Expanded Programme on Immunisation (EPI) registry, verbal report]
 - Hib vaccine received. If yes:
 - Number of doses received
 - Date(s) received
 - Type of Hib vaccine
 - Pneumococcal vaccine received. If yes:
 - Number of doses received
 - Date(s) received
 - Type and formulation of pneumococcal vaccine
 - Meningococcal vaccine received. If yes:
 - Number of doses received
 - Date(s) received
 - Type of meningococcal vaccine
- » Laboratory methods and results
 - CSF collected
 - Unique ID for linkage to clinical data
 - Local laboratory ID
 - Date and time of collection
 - Specimen collected before antibiotic provision?
 - Appearance of CSF
 - Date specimens sent to laboratory
 - Date and time of CSF specimen received at laboratory
 - Condition of specimen
 - Upstream test results if referred from a lower tiered laboratory (Gram stain, WBC, protein, glucose, culture, RDT)
 - Results
 - CSF
 - * Whole cell count
 - * Glucose level
 - * Protein level
 - * Culture done
 - ~ Culture results
 - * Gram stain done
 - ~ Gram stain result
 - * BinaxNOW® done
 - ~ BinaxNOW® result
 - * LAT done
 - ~ LAT result
 - * PCR done
 - ~ PCR results
 - * Serotyping/serogrouping
 - ~ *H. influenzae*
 - ~ *S. pneumoniae*
 - ~ *N. meningitidis*
 - Final case classification

► **Additional minimal data elements for pneumonia/ sepsis and IPD surveillance**

- » Laboratory
 - Blood collection
 - Blood specimen ID
 - Date and time of collection
 - Specimen collected before antibiotic treatment
 - Date specimens sent to laboratory
 - * Date and time of blood specimen received at laboratory
 - * Culture done
 - ~ Culture result
 - * Gram stain done
 - ~ Gram stain result
 - Pleural fluid (PF) collected
 - Pleural fluid specimen ID
 - Date and time of collection
 - Specimen collected before antibiotic treatment
 - Date specimens sent to laboratory
 - Date and time of pleural fluid specimen received at laboratory
 - Culture done
 - * Culture result
 - Gram stain done
 - * Gram stain result
 - BinaxNOW® done
 - * BinaxNOW® result
 - PCR done
 - * PCR results
 - Biochemistry results

► **Additional data elements for population-based invasive *H. influenzae* disease surveillance**

- » Catchment area population by age groups (0–5 months, 6–11 months, 12–23 months, and 24–59 months)

REPORTING REQUIREMENTS AND RECOMMENDATIONS

Report confirmed Hib cases to the Ministry of Health monthly. Zero reporting (no cases) should be done in sentinel surveillance sites. Aggregate reporting is sufficient for routine reporting, even if case-based surveillance is conducted. There are no global reporting requirements for Hib.

RECOMMENDED DATA ANALYSES

Sentinel hospital meningitis surveillance

- Confirmed *H. influenzae* and Hib meningitis case counts, stratified by onset date (week, month, year), age group and sex.
- Probable and suspected meningitis case counts, stratified by the same groupings as confirmed cases.
- Confirmed *H. influenzae* and Hib meningitis death counts and case-fatality ratios.
- Probable and suspected meningitis death counts and case-fatality ratios.
- Median and range of duration of hospital stay for all suspected meningitis hospitalizations and for meningitis due to *H. influenzae* and Hib.
- Note: If IB-VPD surveillance is ongoing for other bacterial causes of meningitis (meningococcus and pneumococcus), then a similar reporting structure should be used for laboratory-confirmed cases of those etiologies.

Sentinel hospital invasive *H. influenzae* disease surveillance (meningitis, pneumonia and sepsis)

- Confirmed invasive *H. influenzae* and Hib disease case counts, stratified by onset date (week, month, year), age group, sex and syndrome.
- Suspected meningitis, pneumonia and sepsis case counts, stratified by the same groupings as confirmed cases.
- Confirmed invasive *H. influenzae* and Hib disease death counts and case-fatality ratios.
- Suspected meningitis, pneumonia and sepsis death counts and case-fatality ratios

Population-based invasive *H. influenzae* disease surveillance

- Incidence of confirmed invasive *H. influenzae* and Hib disease, stratified by onset date (week, month, year), age group, sex and syndrome.

USING DATA FOR DECISION-MAKING

- Determine the local disease burden (cases, deaths, disability).
- Monitor trends in disease epidemiology.

- Prioritize *H. influenzae* disease among other diseases of public health importance.
- Advocate for and implement proper control strategies such as immunization.
- Evaluate the impact of immunization services and identify areas with weak performance.
- Evaluate vaccine impact and effectiveness.



SURVEILLANCE PERFORMANCE INDICATORS

TABLE
1

Surveillance performance indicators for *H. influenzae*

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)	COMMENTS
COMPLETENESS OF REPORTING	Consistent reporting throughout year	At least 10 months with reporting (including zero reporting)	Number months reporting per year	Ideal is 12 months and confirmed zero reporting if no cases
CASE ASCERTAINMENT	Minimum number of cases reported annually	≥ 80 suspected meningitis cases per year; ≥ 400 suspected cases of meningitis plus pneumonia or sepsis, per year	Number of cases reported per year	Ideal is ≥ 100 suspected meningitis cases per year; ≥ 500 suspected cases of meningitis plus pneumonia or sepsis, per year
SPECIMEN COLLECTION	Proportion of suspected cases with specimens collected	≥ 80%	# of suspected cases with specimen collected / # of suspected cases x 100	Specimen is CSF for meningitis surveillance and CSF, blood or pleural fluid in pneumonia and sepsis surveillance; ideal is ≥ 90%
LABORATORY CONFIRMATION WITH SEROTYPE DETERMINATION	Proportion of laboratory-confirmed cases classified as Hib vs. non-Hib	> 60%	# of laboratory-confirmed cases classified as Hib vs. non-Hib / # of laboratory-confirmed cases x 100	For sentinel hospitals that do serotyping or send isolates for serotyping; ideal is ≥ 80%

LABORATORY

- EQA and QC of the laboratory should be completed annually.
- There is no minimum number of cases that should test positive for *H. influenzae* since it varies widely among countries and depends on Hib conjugate vaccine use.



CLINICAL CASE MANAGEMENT

All cases of invasive *H. influenzae* disease should be hospitalized and promptly treated with intravenous (or intramuscular) antibiotics to which the bacteria are susceptible. Supportive care including fluids, oxygen and

possibly mechanical ventilation might be necessary. Take CSF and blood samples before antibiotic treatment, if possible. Treat patient with presumptive antibiotics without waiting for laboratory results.



CONTACT TRACING AND MANAGEMENT

Contact tracing is not routinely done for *H. influenzae* surveillance.



SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

Although most Hib disease is sporadic, Hib can cause outbreaks in setting such as daycare centers. Sentinel site surveillance is not designed to identify all outbreaks since they will be geographically limited, so other types of surveillance with greater geographic coverage will be needed to identify outbreaks.

DEFINITION OF AN OUTBREAK

There is no accepted definition of a *H. influenzae* or Hib cluster or outbreak. Some have considered a cluster of serious pneumococcal disease to be two or more temporally linked cases that occurred in a closed setting (11), and this could also be applied to *H.*

influenzae disease. If the serotype is the same among *H. influenzae* cases, this strengthens the evidence for an epidemiologically linked cluster.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK

No change to surveillance is generally needed during an outbreak.

PUBLIC HEALTH RESPONSE

Reactive vaccination is not an established strategy for *H. influenzae* outbreaks. Prompt recognition of cases and timely treatment with antibiotics is important.



SPECIAL CONSIDERATIONS FOR *H. INFLUENZAE* SURVEILLANCE

- ▶ Some countries in the African meningitis belt, which have significant meningococcal disease burden and limited confirmation capacity, perform syndromic meningitis surveillance. Typically, this is part of the Integrated Disease Surveillance and Response (IDSR). Meningitis surveillance is not pathogen-specific and covers the three vaccine preventable disease pathogens associated with bacterial meningitis: *N. meningitidis*, *S. pneumoniae* and *H. influenzae*. These require laboratory capacity to identify and distinguish. This surveillance can be nationwide or regional, and is typically aggregate passive surveillance. The objective of this surveillance is to detect outbreaks for a rapid public health response. For meningococcus, the public health response includes reactive vaccination; for *H. influenzae* and pneumococcal outbreaks, reactive vaccination is not an accepted strategy.
- ▶ IB-VPD surveillance can be leveraged to monitor other VPDs and non-VPDs such as typhoid, diphtheria and pertussis, and can help to build global bacteriology capacity, especially in a time where antimicrobial resistance is a high public health priority.
- ▶ Measuring the impact of Hib conjugate vaccine can be challenging. The impact of Hib conjugate vaccines can be measured using surveillance data and observational studies, such as case-control studies and time series analysis of secondary data sources (12). The most appropriate method for measuring vaccine impact should be chosen based on the setting, and multiple methods and outcomes may need to be used to accurately measure impact.



REFERENCES

REFERENCES CITED

1. World Health Organization. *Estimated Hib and pneumococcal deaths for children under 5 years of age, 2008*. In: *Immunization, vaccines and biologicals [website]*. Geneva: World Health Organization; 2013 (http://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en/).
2. World Health Organization. *Haemophilus influenzae type b (Hib) vaccination position paper – September 2013*. *Wkly Epidemiol Rec*. 2013;88(39):413–28 (<http://www.who.int/wer/2013/wer8839.pdf?ua=1>).
3. von Gottberg A, Cohen C, Whitelaw A, Chhagan M, Flannery B, Cohen AL, et al. *Invasive disease due to Haemophilus influenzae serotype b ten years after routine vaccination, South Africa, 2003–2009*. *Vaccine*. 2012;30(3):565–71. doi: 10.1016/j.vaccine.2011.11.066.
4. World Health Organization. *WHO-coordinated Sentinel Hospital VPD Surveillance Networks*. In: *Immunization, vaccines and biologicals [website]*. Geneva: World Health Organization; 2018 (http://www.who.int/immunization/monitoring_surveillance/burden/vpd/sentinel_surveillance/en/).
5. World Health Organization. *Surveillance tools for meningitis sentinel hospital surveillance: field guide to rapidly estimate the hospital catchment population (denominator) and the annual rate of hospitalisations*. Geneva: World Health Organization; 2015 (http://www.who.int/immunization/documents/monitoring/WHO_IVB_15.02/en/).
6. World Health Organization. *Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children*. Geneva: World Health Organization; 2001 (http://apps.who.int/iris/bitstream/10665/66956/1/WHO_V_and_B_01.35.pdf).
7. Ladhani S, Heath PT, Slack MP, McIntyre PB, Diez-Domingo J, Campos J, et al. *Haemophilus influenzae serotype b conjugate vaccine failure in twelve countries with established national childhood immunization programmes*. *Clin Microbiol Infect*. 2010;16(7):948–54. doi: 10.1111/j.1469-0691.2009.02945.x.
8. European Society of Clinical Microbiology and Infectious Diseases. *EUCAST guidance documents in susceptibility testing*. In: *European Committee on Antimicrobial Susceptibility Testing [website]*. Basel, Switzerland: European Society of Clinical Microbiology and Infectious Diseases; 2016 (http://www.eucast.org/guidance_documents/).
9. Centers for Disease Control and Prevention & World Health Organization. *Laboratory methods for the diagnosis of meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae, 2nd edition*. Geneva: World Health Organization; 2011 (http://www.who.int/immunization/research/development/WHO_IVB_11.09_eng.pdf?ua=1).
10. World Health Organization. *Invasive Bacterial Vaccine Preventable Diseases Laboratory Network*. In: *Immunization, vaccines and biologicals [website]*. Geneva: World Health Organization; 2017 (http://www.who.int/immunization/monitoring_surveillance/burden/laboratory/IBVPD/en/).
11. Basarab M, Ihekweazu C, George R, Pebody R. *Effective management in clusters of pneumococcal disease: a systematic review*. *Lancet Infect Dis*. 2011;11(2):119–30. doi: 10.1016/S1473-3099(10)70281-4.
12. World Health Organization. *Measuring impact of Streptococcus pneumoniae and Haemophilus influenzae type b conjugate vaccination*. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/75835/1/WHO_IVB_12.08_eng.pdf).