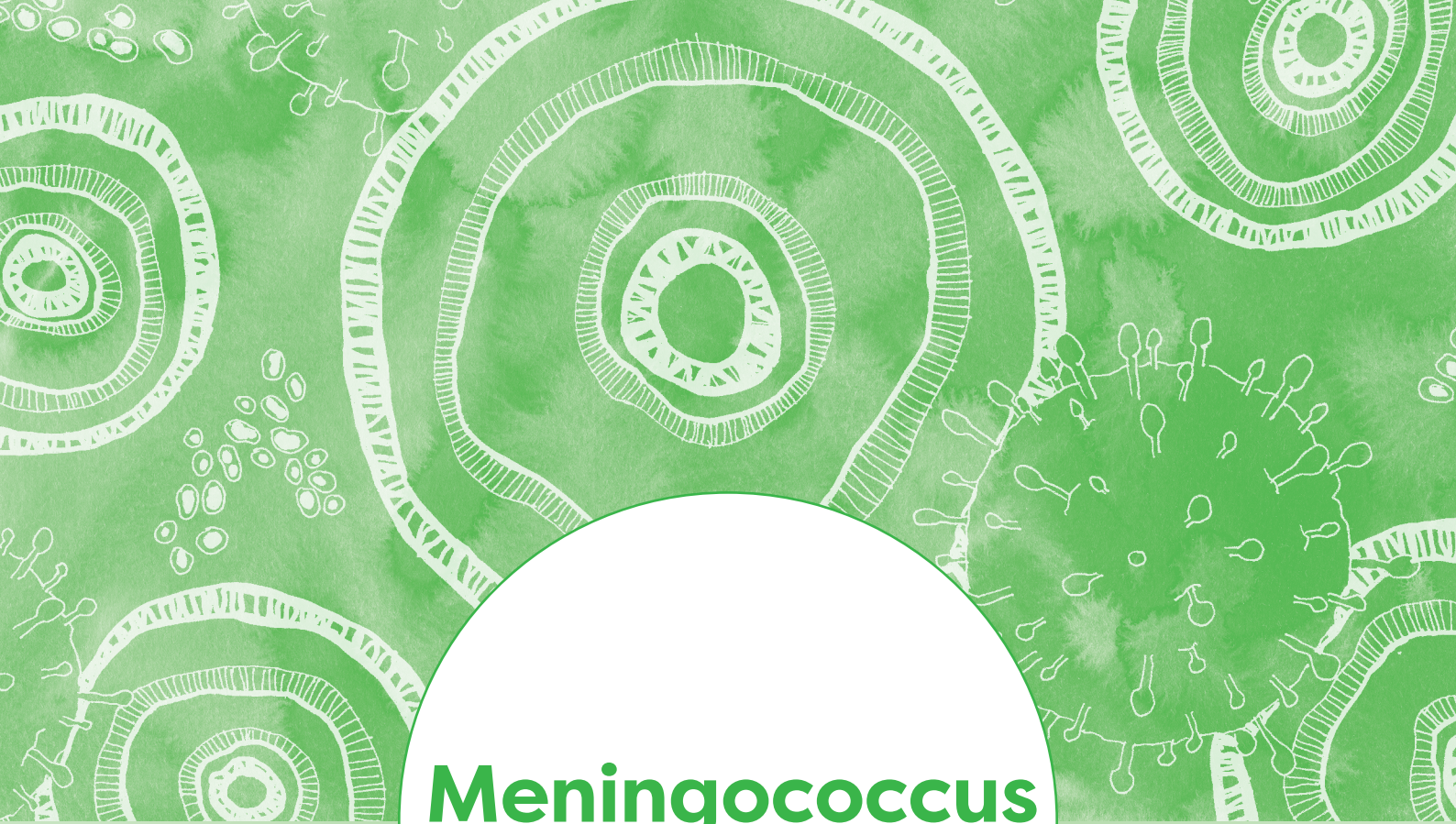




Meningococcus

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DISEASE AND VACCINE CHARACTERISTICS

Neisseria meningitidis (Nm) is a gram-negative bacterium that usually resides harmlessly in the human pharynx. Under certain conditions, asymptomatic carriage can progress to invasive meningococcal disease (IMD), resulting in meningitis, fulminant septicemia or both. The majority of invasive infections are caused by meningococci of serogroups A, B, C, X, W or Y capsular polysaccharides. These serogroups can cause both endemic disease and outbreaks, but their relative prevalence varies considerably with time and geographic location. In the African meningitis belt (from Senegal in the west to Ethiopia in the east), serogroup A has historically been the most important serogroup causing large epidemics. The recent epidemiology of meningococcal disease in Africa is changing, particularly in the wake of the introduction of the conjugate serogroup A vaccine over the last decade; in addition, outbreaks caused by serogroups C, W and X have occurred more frequently in recent years. In Europe, North America and Latin America, serogroups B, C and W currently cause the majority of disease, while in Asia, though surveillance data are limited, serogroups A and C appear to cause most disease.

IMD includes meningitis and septicemia, but *Neisseria meningitidis* can also rarely cause arthritis, myocarditis, pericarditis, invasive pneumonia, necrotizing fasciitis and endophthalmitis. Clinical disease occurs 2–10 days after infection, and commonly within 3–4 days. Signs of meningitis in older children and adults include fever, nausea/vomiting, neck stiffness, headache, photophobia and altered mental status, whereas infants have non-specific presentation with common symptoms that include fever, poor feeding, vomiting and lethargy. Meningococcal septicemia often initially presents with systemic symptoms and signs of meningitis, and progresses to often include a non-blanching haemorrhagic (petechial or purpuric) rash. Untreated IMD is often fatal. Even with antibiotic treatment case-fatality rates can exceed 10%, and 10–20% of survivors are left with permanent sequelae such as deafness, intellectual disability and amputations due to necrosis of the extremities.

Both plain polysaccharide and protein-polysaccharide conjugate vaccines are available against meningococci of serogroups A, C, W and Y. Plain polysaccharide vaccines can be 2-to-4-valent, and are mostly

BOX 1

Surveillance for IMD vs. bacterial meningitis

All countries should aim to undertake IMD surveillance, which focuses on cases of IMD based on laboratory confirmation or strict clinical grounds (meningitis or septicemia with characteristic hemorrhagic rash). Effective IMD surveillance depends on laboratory capacity to detect *N. meningitidis*. These updated surveillance standards focus primarily on surveillance for IMD due to *N. meningitidis*, which is a change from the 2003 surveillance standards that described syndromic bacterial meningitis surveillance. The change reflects increasing global laboratory capacity and changing meningococcal epidemiology. However, meningitis surveillance should still be implemented in countries with an historically significant burden of bacterial meningitis or limited laboratory confirmation capacity (such as countries of the African Meningitis Belt). Meningitis surveillance should not be targeted at a single pathogen, but should rather include testing for the three main vaccine-preventable bacterial causes of meningitis: *N. meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. It should also include other bacterial causes of meningitis, if the lab capacity exists. See Annex A, Bacterial meningitis surveillance.

administered in campaigns in response to outbreaks as a single dose to persons ≥ 2 years of age. Compared to plain polysaccharide vaccines, protein-polysaccharide conjugate vaccines (hereafter referred to as conjugated vaccines) are more immunogenic, elicit immunologic memory and are effective in infants as young as 2 months of age. In addition, repeat doses of conjugated vaccine boost immune responses in contrast to repeat plain polysaccharide vaccination, which may lead to hyporesponsiveness or reduced responses. Most importantly, conjugate vaccines prevent acquisition of carriage. Conjugate vaccines can be monovalent

or multivalent. The dosing age and schedule depends on the serogroup of the vaccine and setting. Mass campaigns with monovalent serogroup A conjugate vaccine among people aged 1–29 years old in the African meningitis belt have resulted in a substantial decrease in meningococcal A disease. A single dose of this vaccine is now being introduced into the routine immunization schedule in these countries. Serogroup B vaccines are based on recombinant or purified proteins.



RATIONALE AND OBJECTIVES OF SURVEILLANCE

The surveillance system aims to provide reliable and timely data to:

- detect and confirm cases, which should lead to appropriate public health response
- detect and confirm outbreaks
- describe the epidemiology of *N. meningitidis* disease
 - » assess the case burden and incidence trends
 - » monitor the circulation and distribution of specific strains
- » monitor changes in circulating serogroups
- » monitor antibiotic susceptibility.
- measure the impact of control measures, including vaccine effectiveness and failure
- identify geographical areas and populations at risk in order to implement and adapt adequate control measures.



TYPES OF SURVEILLANCE RECOMMENDED

Minimum surveillance in all countries should be nationwide and case-based, and should include all ages. The site of case detection should include both of the following:

- **Laboratory-based:** Laboratories should report confirmed and probable cases based on their findings.
- **Facility-based.** Clinicians should also report probable cases of meningitis or septicemia, as defined below. It is important to train clinicians on IMD clinical syndrome, including specific recognition of purpuric skin lesions.



CASE DEFINITIONS AND FINAL CLASSIFICATION

CONFIRMED IMD CASE

N. meningitidis is identified via culture or polymerase chain reaction (PCR) from a purpuric skin lesion or any normally sterile site (blood, cerebrospinal fluid [CSF] or other fluids such as synovial fluid).

PROBABLE IMD CASE

Clinical diagnosis of meningitis or septicemia **and** at least one of the following:

- purpuric rash where IMD is considered the most likely cause (linked to confirmed cases with other causes of haemorrhagic rash excluded or considered less likely)

- gram-negative diplococci identified from any normally sterile site (blood, CSF) or from a purpuric skin lesion
- *N. meningitidis* antigen detection (for example, by latex agglutination testing) from any normally sterile site or from a purpuric skin lesion.

Note that because IMD surveillance is based on laboratory findings or a characteristic haemorrhagic rash, there is no suspected case definition.



CASE INVESTIGATION

All probable and confirmed IMD cases should undergo thorough epidemiological and laboratory investigation, ideally within 24 hours of notification. The goals of case investigation in this setting are to make sure patients have received or been referred for proper

treatment, search for other cases and identify close contacts for control measures such as vaccination or chemoprophylaxis.



SPECIMEN COLLECTION

Specimens to diagnose IMD are collected from any normally sterile site according to the clinical presentation, such as blood or CSF for meningitis or sepsis and aspirate or biopsy of haemorrhagic rash for purpuric skin lesions (1). In some settings, meningococcus can be isolated from other specimen types such as synovial fluid, but such specimens are generally not part of routine surveillance for IMD. 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.

VOLUME OF SPECIMENS

➤ 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

► Blood

- » 5–10 mL for an adult. As it may be difficult to collect more than 3 mL of blood from a child, 1–3 mL is considered adequate.
- » 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 1–2 mL of blood from a child to 20 mL of blood culture broth. For adults, add 5–10 mL of blood from an adult to 50 mL of blood culture broth.

TIMING OF COLLECTION

- Specimens should be collected as soon as possible, preferably before antibiotic therapy. However, collection of specimens should never delay administration of antibiotics.
- Inform the laboratory so the technician can be ready to process the specimen as soon as possible.

STORAGE AND TRANSPORT

► CSF

- » Refer CSF to the lab immediately.
- » If specimen cannot be processed in 1–2 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 4 days). If transport is delayed beyond 4 days, store at room temperature (unvented) until referral.
- » CSF should be processed in a microbiology laboratory within two hours of collection. *N. meningitidis* is a fragile bacterium and requires

rapid culturing. If there is no access to a microbiology laboratory, inoculated T-I media should be sent from the health facility to the district or reference laboratory within 24 hours. Districts should send the inoculated T-I media to the national or regional reference laboratory at least twice a week.

► Blood

- » Specimens 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 and blood.** Aliquots of CSF should ideally be stored at -70°C, or at -20°C if -70°C storage is not available, for referral to the national or regional reference laboratory for PCR testing.
- **Isolates of *N. meningitidis*.** Store isolates frozen at -20°C to allow for further testing in the future (serogrouping, molecular characterization and susceptibility testing). Do not thaw frozen tube. Subculture should be performed by scratching the surface of the frozen material instead of thawing.



LABORATORY TESTING

METHODS FOR IDENTIFYING CONFIRMED CASES: CULTURE OR PCR

Culture is the gold standard but has low sensitivity due to early antibiotic use or laboratory capacity (1).

- CSF and blood specimens should be cultured on blood agar plates (BAP) and supplemented chocolate agar plates (CAP) that are prepared with 5–10% sheep or horse blood (NOT human blood).
- For maximum yield of isolates from blood culture, all negative cultures from probable IMD cases should be subcultured after five days of incubation before they are discarded.

PCR is recommended on all patients with a clinical diagnosis of meningitis or septicemia, as bacterial culture might be inhibited if the case had already received antibiotics. As PCR capacities are not always available at district or hospital level, it is recommended that any remaining volume of CSF should be frozen and sent to either a national or regional reference laboratory for further testing.

Training of clinical and laboratory staff is important in assuring that CSF and blood are collected and processed in a consistent and sterile manner in clinically suspect cases.

METHODS FOR IDENTIFYING PROBABLE CASES: GRAM STAIN AND LATEX AGGLUTINATION TESTING

In some settings, rapid point-of-care tests such as latex agglutination testing (LAT) can be used since they also increase yield and provide results quickly for clinical care and outbreak identification. Rapid diagnostic tests (RDTs) identify the three primary causative pathogens of bacterial meningitis within hours: *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*. In general, RDTs only identify the species and not the serotype or serogroup. LAT should be performed according to manufacturer's instruction with quality control strains. LAT kits often have a short shelf life, and expired kits should not be used.

Gram stain may be done on CSF, blood, skin aspirate or other specimens such as synovial fluid. Bacteria may be located intracellularly or extracellularly in polymorphonuclear leukocytes, and will appear as gram-negative coffee bean-shaped diplococci.

STRAIN CHARACTERIZATION

All confirmed cases should have the serogroup designated in order to focus vaccination efforts for public

health response and understand the local epidemiology of *N. meningitidis*.

Serogrouping can be done on a bacterial isolate (if available from culture) or on PCR-positive clinical specimens.

Specimens or isolates from confirmed or probable cases should be stored for further strain characterization.

Strain characterization or whole genome sequencing (WGS) should be performed at national, regional or global reference laboratories (such as a WHO collaborating centre for meningococcal meningitis) where capacity is available for public health investigations and research purposes.

ANTIMICROBIAL RESISTANCE (AMR) TESTING

AMR testing should also be performed to monitor emerging resistance during outbreaks and for sporadic cases, as laboratory capacity allows. Determination of antimicrobials used for AMR testing should be based upon those used in the treatment and chemoprophylaxis of IMD as per national or regional guidelines.

- If WGS is performed, AMR-related genes should be characterized.
- National and regional reference laboratories and WHO collaborating centres can be utilized for these purposes when necessary.

QUALITY ASSURANCE SYSTEMS

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

LABORATORY NETWORKS

The Global Invasive Bacterial Vaccine-Preventable Diseases (IB-VPD) Laboratory Network is a global network of more than 100 laboratories that support surveillance of invasive bacterial disease, including IMD (2). 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

- » Demographics
 - Name (if confidentiality is a concern the name can be omitted so long as 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
 - Hemorrhagic rash
 - Date of symptom onset
 - Date of admission
 - Treatment
 - Patient outcome (survived without sequelae, survived with sequelae, died)
 - Date of death
- » Vaccination history
 - Source of information
 - Meningococcal vaccine. If yes,
 - Number of doses received
 - Date(s) received
 - Type and formulation of meningococcal vaccine
- » Laboratory Data
 - Type of specimen (CSF, blood, other normally sterile fluid)
 - Date of specimen collection
 - Date of reception of specimen in the laboratory
 - Laboratory methods for species and serogroup determination (culture/antigen/gram stain/PCR)

- Results
 - Culture done
 - * Culture results
 - Gram stain done
 - * Gram stain result
 - LAT done
 - * LAT result
 - PCR done
 - * PCR results
 - Meningococcal capsular group
 - * Date of confirmation of specimen in the laboratory
- » Epidemiological
 - Date of notification/reporting to the public health authorities
 - Name of reporter
 - Date of investigation
 - Epidemiological link to another case (yes/no)
 - History of travel/attendance at a mass gathering
 - Final case classification

► Additional useful data elements

- » Clinical presentation/symptoms
- » Antibiotic use prior to specimen collection
- » Risk factors such as university student, men who have sex with men (MSM), HIV+ or other immunosuppression, asplenia, complement deficiency (acquired or congenital) including treatment with eculizumab, or other complement inhibitors
- » Co-morbidities
- » Race/ethnicity

REPORTING REQUIREMENTS AND RECOMMENDATIONS

Probable and confirmed IMD cases should be notified to public health authorities within 24 hours, or per national or regional guidelines. Although cases of IMD are not required to be reported to WHO through International Health Regulations (IHR), reporting is required for IMD outbreaks deemed to be a public health event of international concern (3).

RECOMMENDED DATA ANALYSES

- Number of confirmed and probable cases by age group and area, separated by serogroup
- Incidence by age group and area, by serogroup
- Case fatality ratio
- Vaccination status of cases and proportion of cases vaccinated

USING DATA FOR DECISION-MAKING

- Determine the local disease burden (cases, deaths, disability)
- Monitor trends in disease epidemiology
- Prioritize IMD among other diseases of public health importance
- Advocate for and implement proper control strategies such as vaccination, including targeted strategies for populations determined to be at increased risk
- Evaluate the impact of vaccination services and identify areas with weak performance



SURVEILLANCE PERFORMANCE INDICATORS

LABORATORY

External Quality Assessment (EQA) and Quality Control (QC) of the laboratory should be completed annually.

There is no minimum number of cases that should test positive for meningococcus, since it varies widely among countries and depends on meningococcal conjugate vaccine use.

TABLE

1

Surveillance performance indicators for *N. Meningitidis*

SURVEILLANCE ATTRIBUTE	INDICATOR	SUGGESTED TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)
Laboratory performance indicators			
LABORATORY CONFIRMATION WITH SEROGROUP DETERMINATION	Percent of <i>N. meningitidis</i> confirmed cases with serogroup designation	> 80%	# of laboratory-confirmed cases with serogroup determined / # of laboratory-confirmed cases x 100
SPECIMEN TRANSPORT TO REFERENCE LABORATORY	Percent of specimen received at the national reference laboratory in appropriate media	≥ 80%	# of specimens received at national reference laboratory in appropriate media / # of cases with specimen collected x 100
TIME FOR SPECIMEN TRANSPORT TO FIRST LEVEL LABORATORY	Percent of cases with < 24 hours between specimen collection date and reception at first level laboratory	≥ 80%	# of specimens delivered < 24 hours / total # specimens x 100
TIME FOR SPECIMEN TRANSPORT TO NATIONAL LABORATORY	Percent of cases with < 4 days between specimen collection date and reception at the national reference laboratory	≥ 80%	# of specimens delivered < 4 days to national reference laboratory / total # specimens x 100.
TIME FOR SPECIMEN TRANSPORT AND RESULT AVAILABLE AT REFERENCE LABORATORY	Percent of cases with < 7 days between specimen collection and result given by the national reference laboratory	≥ 80%	# of specimens delivered < 7 days between collection and result from national reference laboratory / total # specimens x 100.
Data management performance indicators			
TIMELINESS OF CASE REPORTING	Percent of cases reported within < 24 hours (or per national or regional guidelines)	≥ 80%	# of cases reported within < 24 hours / # of total cases reported (or # total cases) x 100
COMPLETENESS OF OUTCOME	Percent of enrolled cases with outcome recorded	≥ 80%	# of enrolled cases with outcome recorded / # of enrolled cases x 100
COMPLETENESS OF VACCINE STATUS	Percent of cases with vaccine status reported	≥ 80%	# of enrolled cases with vaccine status reported / # of enrolled cases x 100



CLINICAL CASE MANAGEMENT

Treat all cases of IMD as quickly as possible, using appropriate antibiotics and isolation procedures according to national treatment protocols. A pharyngeal swab of each case is not recommended.

Specimens for laboratory confirmation of IMD should be obtained before antibiotic treatment, if possible. However, patients should be treated presumptively with antibiotics without waiting for laboratory results.

Some areas with higher prevalence of IMD in Africa also harbor endemic haemorrhagic viruses, which might be confused clinically with the haemorrhagic rash of IMD. Laboratory diagnosis is important in distinguishing these diseases.



CONTACT TRACING AND MANAGEMENT

Close contacts of IMD cases are at increased risk of IMD disease. Close contacts include those living in the same household or who have an equivalent level of contact, those in the same childcare or preschool settings, travel contacts (such as persons sitting next to IMD case on a long flight) and anyone directly exposed to respiratory or oral secretions of a case in the seven days before disease onset. Vaccination and chemoprophylaxis of close contacts should follow

national guidelines. If chemoprophylaxis with antibiotics is given, it should be done as soon as possible, preferably within < 24 hours after identification of the index case, as most secondary disease occurs within 72 hours of presentation of the index case. Specific antibiotics that clear pharyngeal carriage of meningococci are recommended for chemoprophylaxis (4) (5).



SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

DEFINITION OF AN OUTBREAK

Outbreak definitions are specific to each country and depend on the local IMD epidemiology. Outbreaks can be defined as follows:

- **Cluster:** The occurrence of a number of cases close in time and within a defined geographical area or population (in the community or in institutions such as university settings, schools or prisons), but not meeting the definition of an outbreak. A cluster can be two or three cases.
- **Outbreak:** The occurrence within a defined time period of a minimal number of cases (of the same serogroup/strain, if possible to identify), or of a minimal attack rate above a defined threshold, usually expressed as the number of cases per 100,000 population. These thresholds are specific to each setting.
- **Hyperendemic situation:** Persistent, high levels of disease occurrence. Typically, this happens in the African meningitis belt between epidemics.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK

Surveillance should be intensified during IMD outbreaks. To increase detection and improve case finding, a suspected case definition may be implemented according to the main symptoms encountered. Community-based surveillance and active surveillance may also be considered.

PUBLIC HEALTH RESPONSE

Each country should define specific actions that need to be undertaken during clusters or outbreaks, including further investigation, active case finding and outbreak control measures. These differ depending on

specific factors including the extent of the outbreak and serogroup type. Control measures may include the organization of case management structures, vaccination of the population at risk and antibiotic prophylaxis to contacts. To ensure a robust and efficient public health response to an outbreak, consider implementing an operational threshold strategy. In some settings, operational thresholds have been defined by modeling historical disease data to help identify populations at risk for epidemics. For example, a predictive “alert” threshold might trigger the reinforcement of surveillance, while crossing a predictive “epidemic” threshold might trigger mass control measures such as vaccination campaigns (6).



SPECIAL CONSIDERATIONS FOR MENINGOCOCCAL SURVEILLANCE

- Mass gatherings have been settings for IMD outbreaks. Report cases related to mass gatherings through IHR.
- Serosurveys should be limited to research activity and are not part of the surveillance recommendations.
- Carriage studies are not routinely used as part of IMD surveillance, but it may be beneficial to investigate circulating capsular groups or clonal complexes, especially prior to or post vaccine introduction. They may also be conducted to provide additional information on age groups to target for potential vaccination.
- In the context of serogroup B meningococcal (MenB) vaccine use, there may be cross protection of non-B serogroups.
- Investigation of vaccine failures should be considered in the context of new vaccine introduction. Investigation should confirm vaccine status and detailed laboratory confirmation including serogroup, and may also include immunologic response to vaccine.
- Evaluate the ability of the surveillance system to detect and report all IMD cases by using capture-recapture studies.



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In countries with significant meningococcal disease burden or limited ability perform laboratory-based IMD surveillance, syndromic meningitis surveillance should be implemented. Typically, this applies to the African meningitis belt countries and is part of the AFRO IDSR surveillance. Unlike IMD surveillance, meningitis surveillance is not targeted at only one pathogen, and covers the three vaccine preventable disease pathogens associated with bacterial meningitis: *N. meningitidis*, *S. pneumoniae* and *H. influenzae*. Please refer to the chapters on surveillance standards for *S. pneumoniae* and *H. influenzae* for a more complete description of this approach to surveillance.

MAIN OBJECTIVES

The objectives of meningitis surveillance are to:

- detect outbreaks in order to initiate a rapid response to meningitis epidemics
- evaluate the effectiveness and impact of specific vaccines.

CASE DEFINITIONS

Suspected meningitis case: Any person with sudden onset of fever ($> 38.5^{\circ}\text{C}$ rectal or 38.0°C axillary) and altered consciousness or neck stiffness or other meningeal signs, including bulging fontanelle in infants.

Probable meningitis case: Any suspected case with macroscopic aspect of cerebrospinal fluid (CSF) turbid, cloudy or purulent; or with a CSF leukocyte count > 10 cells/mm³; or with bacteria identified by Gram stain in CSF; or antigen detected by immunochromatographic dipstick or latex agglutination.

In infants: Any suspected case with CSF leukocyte count > 100 cells/mm³; or CSF leukocyte count 10–100 cells/mm³ and either an elevated protein (> 100 mg/dL) or decreased glucose level (< 40 mg/dL).

Confirmed meningitis case: Any suspected or probable case that is laboratory-confirmed by culturing or identification (for example, by polymerase chain reaction) of the principal bacterial pathogens (*N. meningitidis*, *S. pneumoniae*, *H. influenzae*) in the CSF or blood. Future laboratory capacity might include diagnosis of other bacterial causes of meningitis such as listeria, Group B streptococcus, *E. coli*, etc.

APPROACH TO SURVEILLANCE

Bacterial meningitis surveillance is based on the identification of patients with clinically suspected meningitis. The clinician suspecting the disease is the starting point for inclusion in surveillance, followed by laboratory confirmation, which is performed with various degrees of intensity.

To detect and respond to outbreaks, surveillance:

- Should be nationwide or in subnational areas where the risk of outbreak exists.
- Does not necessarily need individual-level data as reported cases may be aggregated by area and time units, according to the definition of outbreak (time and place) used in the country. Age is useful with aggregate meningitis data. At a minimum, use the categories < 5 years of age and ≥ 5 years of age, but preferably 0–23 months, 2–4 years, 5–14 years, 15–29 years, 30+ years).
- Should include sufficient laboratory information (serogroup) to inform choice of specific vaccine for outbreak response. Not all cases need to have a laboratory confirmation; however, the sample of suspected cases selected for specimen collection and laboratory confirmation should be representative of the outbreak situation.

To evaluate the effectiveness and impact of specific vaccines, surveillance:

- should be case-based, and the collected information should include epidemiological confirmation data, including applicable vaccine history and laboratory confirmation data for each patient
- should be population-based so that the defined catchment target population allows incidence calculations
- may be nationwide or focused on a specific subnational area according to the country capacity and estimated sample size necessary to determine significant vaccine impact
- may be sentinel or hospital-based, with sites chosen according to these criteria:
 - » highest burden of disease
 - » laboratory capacity (capacity to perform confirmatory testing by PCR/culture, timeliness of specimen shipment to the laboratory)
 - » well-defined catchment area
 - » data management allows linkage between clinical and laboratory data.
- may cover a specific target age or all age groups, as a function of the main pathogen that is targeted for surveillance.