Guide for the Investigation of *Neisseria meningitidis* Serogroup A Cases in the Meningitis Belt

MenAfriNet

Toolkit

This document provides standardized guidance for public health authorities to investigate reports of serogroup A meningococcal disease in countries that have introduced meningococcal A conjugate vaccine (MACV, MenAfriVac™)

INTRODUCTION

Since the progressive introduction of meningococcal serogroup A conjugate vaccine (MACV) in the meningitis belt of sub-Saharan Africa starting in 2010 via mass vaccination campaigns, 19 countries have completed mass preventive campaigns and 260 million persons have been vaccinated. Surveillance data and studies have documented a dramatic impact of the vaccine, reducing serogroup A *N. meningitidis* (NmA) incidence. In order to sustain the success of the mass campaigns, introduction of MACV into Expanded Programme for Immunizations (EPI) programs started in 2016.

Epidemiological surveillance has shown that, despite the success of MACV campaigns and the dramatic reduction of NmA epidemics in the belt, NmA cases have continued to occur, typically reported as isolated cases or small clusters. This finding indicates that the pathogen is still circulating, mainly in pockets where MACV coverage has been lower. Furthermore, the number of susceptible people has increased, as children born after mass campaigns and prior to the integration of MACV into EPI programs have not been vaccinated. Influx of new residents in a community may also influence the number of people at risk. It is therefore important to monitor the incidence of NmA and implement the vaccination of new cohorts of susceptible people as soon as possible.

Epidemiologic evaluation and microbiologic confirmation of every NmA case is necessary in order to:

- Confirm the isolate pathogen
- Understand the primary reason for the occurrence of a NmA case in a vaccinated area (which would include whether the person was unvaccinated or if there was a vaccine failure)
- Understand the potential risk for the population in the area

This information is needed to inform an eventual public health intervention, and is also crucial to document the duration and strength of protection of MACV.

PURPOSE OF THE DOCUMENT

This document aims to provide standardized guidance for public health authorities at all levels to plan and conduct the investigation of every NmA case. This guidance applies to all countries and areas that have introduced MACV.

This document does not intend to provide comprehensive guidance on the control measures that need to be implemented in response to the identification of an NmA case.

Objectives of the investigations of NmA cases

The systematic investigation of a case of NmA aims to:

- Confirm the diagnosis of NmA in the suspected case
- Determine the vaccination status of the suspected case and identify any potential vaccination failure
- Determine if the case is part of an unreported cluster of NmA cases
- Identify groups of people at increased risk of infection (unvaccinated/accumulation of susceptible) for whom catch-up vaccination is needed
- Inform assessment of MACV effectiveness and vaccine impact

Methods

Two categories of activities need to be undertaken to manage newly identified NmA cases:

☐ Field investigation of the case for epidemiological data collection

☐ Microbiologic confirmation and molecular characterization of the infecting strain

A laboratory determining a positive result for NmA (suspected or confirmed) should inform the regional and national public health authorities immediately (within 24 hours). The health authorities should then immediately:

- Ask the laboratory to provide details on the laboratory methods used
- Obtain the Integrated Disease Surveillance and Response (IDSR) form of the case(s)
- Inform the World Health Organization (WHO)

The field investigation of the case should be performed as quickly as possible (within one week of the report) and laboratory confirmation should be sought on any suspected meningitis case.

1. Epidemiologic field investigation of NmA cases

The following key steps should be implemented

- **Prepare for the investigation:**
  - A multidisciplinary field investigation team should be assembled with members having experience in epidemiology and laboratory diagnosis.
  - Preliminary background information (including any previous reports, case information, laboratory confirmation, etc.) should be collected and necessary materials (forms, guidelines, any materials to reinforce surveillance, if needed) assembled.
  - Gather maps and epidemiological information on meningitis incidence and serogroup distribution for areas where you have suspected cases.
- **Review the available information:** The investigation team should review carefully the standard IDSR notification form completed for the case and transmitted from the field to determine whether the demographic, clinical, and epidemiological information is complete. Review clinical information to confirm whether the suspect case meets the case definition for bacterial meningitis (see Box 1). If confirmation is not possible with the given information, verify the clinical symptoms during the patient interview.
- **Conduct the field investigation:** Essential information to be collected for a suspected or confirmed NmA case (use **NmA Case Investigation Form**, the specific form for the investigation of meningitis cases with serogroup A meningococci)

1. Patient identification and demographic information:
   - Unique patient ID number (e.g., EPID)
   - Name
   - Sex
   - Birth date/age
   - Place of residence and contact information
   - Name of proxy interviewed and relationship to the patient (if applicable)
2. Travel history of patient within 10 days of disease onset
3. Clinical information:
   - Date of consultation
   - Date of specimen collection
   - Date of onset of symptoms
   - Symptoms
   - Treatment
   - Hospital admission and discharge dates
   - Patient outcome
4. Vaccination status (MACV)
   - Ask for the vaccination card and take a picture of the card
   - Date and place of vaccination
   - Vaccine batch number
   - If card not available, attempt to complete the information by reviewing vaccination registries
   - If no written information can be found, a careful interview must be conducted including a cross-validation with another person to ensure the vaccination status
5. Other persons in the household or close community (i.e., concession) meeting the suspected bacterial meningitis case definition:
   - Name, age, and vaccination status
   - These suspected meningitis cases from the community should be cross-checked with health center patient records and then categorized (see classification).
6. Laboratory investigation
   - Date and health facility where lumbar puncture performed
   - Laboratory name and type of test performed
     - » Test results
     - » Final laboratory diagnosis (classification)
     - » Availability of laboratory material of the case Cerebrospinal fluid (CSF), aliquot isolate in culture)

In addition to the medical staff, the investigation team should locate and interview the patient.

During the interviews, all information should be collected (use **NmA Case Investigation Form**). Information should also be sought on persons who came in close contact with the patient, such as individuals living in the same household, travel contacts (such as persons sitting next to patient on a long bus ride), or others directly exposed to respiratory or oral secretions in the 7 days before the patient's disease onset.

Active case-finding: A review of health facility patient records (i.e., log book, register) should be conducted to ensure that all persons meeting the suspect case definition for meningitis have been reported and that any specimens that have been taken are tested and followed up on. The areas that should be surveyed include the village of residence of the patient as well as areas where the patient may have acquired the infection (if the patient travelled within 10 days before disease onset).

- **Reinforce surveillance:** Surveillance should be reinforced in the area where the case was reported to ensure detection, specimen collection, laboratory diagnosis, and reporting of subsequent cases.

2. Laboratory confirmation of NmA

All NmA cases require laboratory confirmation by culture and/or PCR at the National Reference Laboratory (NRL). If the specimen is still available and has not been tested at the NRL, it should be referred to the NRL for confirmatory testing within 48 hours. If culture or PCR is not available at the national level, the specimen should be sent to a WHO Collaborating Centre for testing.

The NRL should rapidly communicate the laboratory results to the national surveillance unit, which should provide feedback to the concerned district, region, and WHO immediately.

If results are inconclusive or tests are contradictory, the specimen should be sent to a WHO Collaborating Centre for confirmatory testing.

In addition, all available NmA bacterial isolate specimens should be referred to a WHO Collaborating Centre for confirmatory testing and sequence typing by whole genome sequencing of available isolates. If only a clinical specimen is available, the specimen may be referred to a WHO Collaborating Centre for metagenomic sequence typing. For large clusters (i.e., more than 100 NmA cases), a representative subset may be sampled for shipment.

Classification of the case

As soon as confirmatory laboratory results are available from the NRL and/or the WHO Collaborating Centre, these results should be integrated into the final investigation report, providing a final case classification and an understanding of the cause of the infection:

- ***NmA not confirmed***
  - Lab is not conclusive
  - Specimen is no longer available and the specimen has not been tested at the NRL or a WHO Collaborating Centre
- ***NmA confirmed*** (laboratory confirmed)
  - Patient not vaccinated (indicate whether the patient was eligible or not eligible for vaccination at the time of the campaign)
  - Vaccination failure (patient vaccinated)
  - Not conclusive (vaccination status not determined)

Box 1. Case definitions for bacterial meningitis

Suspected meningitis case:
Sudden onset of fever (>38.5°C rectal or 38.0°C axillary) AND neck stiffness or other meningeal signs, including bulging fontanelle in infants.

Probable meningitis case:
Any suspected case with macroscopic aspect of CSF turbid, cloudy or purulent; or with a CSF leukocyte count >10 cells/mm^3; or with bacteria identified by Gram stain in CSF.

In infants ≤12 months of age: CSF leucocyte count >100 cells/mm^3; or CSF leucocyte count 10–100 cells/mm^3 AND either an elevated protein (>100 mg/dl) or decreased glucose (<40 mg/dl) level.

Confirmed meningitis case:
Any suspected or probable case that is laboratory confirmed by culture or identification (e.g., by polymerase chain reaction [PCR], immunochromatographic dipstick or latex agglutination) of *Neisseria meningitidis*, *Streptococcus pneumoniae,* or *Haemophilus influenzae* in the CSF or blood.

For the purposes of this NmA investigation protocol use the following case definitions:

Suspected *N. meningitidis* serogroup A case:
Laboratory findings consistent with NmA at subnational level, including identification by latex agglutination, immune-chromatographic rapid test, PCR, or culture.

Confirmed *N. meningitidis* serogroup A case:
Laboratory findings by PCR and/or culture, consistent with NmA, at the National Reference Laboratory and/or Regional Reference Laboratory.

For cases identified in the household (epi link) of a confirmed NmA case, they should be categorized as follows:

- Case already reported in the health system and either a negative NmA laboratory result or confirmed with another pathogen: ***discarded***
- Case already reported in the health system and there is neither a lumbar puncture nor a negative NmA laboratory result: ***suspected NmA case***
- Case not reported in the health system: ***suspected NmA case***

Investigation report and dissemination

A detailed report of the case investigation findings should be composed and shared with health authorities at district, regional, and national levels, as well as with partners (e.g., WHO, CDC). This report should contain a descriptive analysis of the case(s) (person, time, and place). It is essential that information on vaccination status for all identified NmA cases be presented. For investigations that yield multiple cases of NmA, graphical/tabular descriptions of cases by date of onset, geographic location, age, and vaccination status should be developed. Any key observations and recommendations on strengthening case detection, notification, data management, laboratory confirmation, or other aspects of the surveillance process should be noted. Reports shared with public health authorities outside the national system should not contain potentially identifiable information on individual patients. It is advised that unique patient ID number such as an EPID be used with links to patient information maintained by national public health authorities. The report of the field investigation containing this information and analysis should be disseminated within 7 days of returning from investigation.

The conclusion from this final report should be discussed among national authorities and partners in order to decide whether additional evaluations/studies and any response measures should be implemented.

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NmA Case Investigation Form

Health Facility: **District:** **Region:**

Date of investigation: _____/_____/_____ *(dd/mm/yyyy)* **Name of investigator:**

Date seen at health facility: _____/_____/_____ *(dd/mm/yyyy)*

Date of MACV campaign in the District: _____/_____/_____ *(dd/mm/yyyy)* (Year : _____)

UNIQUE IDENTIFIER NUMBER (EPID): (TO BE ASSIGNED AT DISTRICT LEVEL)

COUNTRY	REGION	DISTRICT	YEAR	DISEASE	CASE NUMBER

PATIENT DETAILS

Surname: **First name:** **Sex:** ☐ Female ☐ Male

Date of birth: _____/_____/_____ *(dd/mm/yyyy)* OR **Age in years:** OR **Age in months (if <12 months):**

Residential address: **Village:** **District:**

Name of parent(s): **Telephone of patient or parent(s):**

Did the patient travel to any other location (other than their District of residence) 10 days before onset of symptoms?

☐ Yes ☐ No ☐ Don't know If yes, specify where:

Date of onset of symptoms: _____/_____/_____ *(dd/mm/yyyy)*

Hospitalization: **Was the patient admitted to hospital?** ☐ Yes ☐ No **Name of hospital:**

Date of admitted to hospital: _____/_____/_____ *(dd/mm/yyyy)* **Date of discharged from hospital:** _____/_____/_____ *(dd/mm/yyyy)*

Outcome: ☐ Recovered ☐ Died ☐ Still in hospital ☐ Don't know

Signs and symptoms:

☐ Fever (specify T°= _____) ☐ Neck stiffness ☐ Headache ☐ Bulging fontanel
☐ Seizure/Convulsion ☐ Altered consciousness ☐ Rash ☐ Photophobia
☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Other (*Specify*): _____ ☐ Unknown

Are there other cases known among the patients contacts? ☐ Yes ☐ No If yes, how many?:

(Please complete Case Search Among Contact Details *on page 2)*

VACCINATION STATUS

Vaccine		*Date of last dose*	*Lot number*	*Source of vaccination information*		
MenA conjug. (MACV)	☐ Yes	Date: _____/_____/_____ *(dd/mm/yyyy)*	Lot number:	☐ Card	☐ Verbal	☐ Unknown
MenAC (PS)	☐ Yes	Date: _____/_____/_____ *(dd/mm/yyyy)*	Lot number:	☐ Card	☐ Verbal	☐ Unknown
MenACW (PS)	☐ Yes	Date: _____/_____/_____ *(dd/mm/yyyy)*	Lot number:	☐ Card	☐ Verbal	☐ Unknown
MenACWY (PS)	☐ Yes	Date: _____/_____/_____ *(dd/mm/yyyy)*	Lot number:	☐ Card	☐ Verbal	☐ Unknown

CSF SPECIMEN

Date of lumber puncture: _____/_____/_____ *(dd/mm/yyyy)*

Name of Facility where CSF taken:

Appearance of CSF: ☐ Clear ☐ Turbid ☐ Bloody ☐ Xanthochromic ☐ Viscous ☐ Purulent ☐ Not done

Date of injection in the transport medium: _____/_____/_____ *(dd/mm/yyyy)*

Transport medium: ☐ Dry tube ☐ Trans-Isolate ☐ Cryotube ☐ Other (specify):

RESULTS OF THE FIRST LABORATORY REPORTING THE CASE OF NmA

Name of laboratory:

Latex:	☐ Not done	☐ Negative	☐ NmA	
Culture:	☐ Not done	☐ Negative	☐ NmA	
PCR:	☐ Not done	☐ Negative	☐ Contaminated	☐ NmA
Rapid test:	☐ Not done	☐ Negative	☐ Contaminated	☐ NmA

Other tests (glucose, etc):

Is the patient's specimen still available: **If yes, where?:**

NmA Case Investigation Form

UNIQUE IDENTIFIER NUMBER (EPID): (TO BE ASSIGNED AT DISTRICT LEVEL)

COUNTRY	REGION	DISTRICT	YEAR	DISEASE	CASE NUMBER

RESULT FROM REFERENCE LABORATORY

(Do not complete if it is the laboratory that reported the case)

Date specimen received: _____/_____/_____ *(dd/mm/yyyy)*

Appearance of CSF:

Gram stain: ☐ Not done ☐ Negative ☐ DGP ☐ DGN ☐ BGP ☐ BGN ☐ Other bacteria:

Latex: ☐ Not done ☐ Negative ☐ NmA ☐ NmW/Y ☐ NmX ☐ NmC ☐ NmB/*E. Coli* ☐ *S. pneumoniae* ☐ Hib

Culture: ☐ Not done ☐ Negative ☐ Contaminated ☐ NmA ☐ NmW ☐ NmX ☐ NmC ☐ NmY ☐ NmB
☐ Nm indeterminate ☐ *S. pneumoniae* ☐ Hib ☐ Hi non-b ☐ Other bacteria

PCR: ☐ Not done ☐ Negative ☐ Contaminated ☐ NmA ☐ NmW ☐ NmX ☐ NmC ☐ NmY
☐ Nm indeterminate ☐ *S. pneumoniae* ☐ Hib ☐ Other bacteria:

Other tests (glucose, etc.):

Is the patient's specimen still available: ☐ Yes ☐ No **If yes, where?:**

RESULTS FROM WHO COLLABORATING CENTRE (LABORATORY)

Date specimen received: _____/_____/_____ *(dd/mm/yyyy)*

Culture: ☐ Not done ☐ Negative ☐ Contaminated Result:

PCR: ☐ Not done ☐ Negative ☐ Contaminated Result:

Molecular typing results: ☐ Not done ☐ Negative ☐ Contaminated Result:

CASE SEARCH AMONG CONTACT DETAILS

(i.e., household or community, alive or dead)

1. Name of contact: **Age:**

Vaccinated? ☐ Yes (*specify*): ☐ Card ☐ Verbal ☐ No ☐ Don't know

If yes, vaccinated with MACV only? ☐ Yes ☐ No

Date of last vaccination: _____/_____/_____ *(dd/mm/yyyy)* Place of vaccination:

Cross-checked with health facility? ☐ Yes ☐ No

Classification: ☐ Discarded ☐ Suspected NmA ☐ Confirmed NmA

If suspected or confirmed, has a separate NmA Case Investigation Form been initiated? ☐ Yes ☐ No

2. Name of contact: **Age:**

Vaccinated? ☐ Yes (*specify*): ☐ Card ☐ Verbal ☐ No ☐ Don't know

If yes, vaccinated with MACV only? ☐ Yes ☐ No

Date of last vaccination: _____/_____/_____ *(dd/mm/yyyy)* Place of vaccination:

Cross-checked with health facility? ☐ Yes ☐ No

Classification: ☐ Discarded ☐ Suspected NmA ☐ Confirmed NmA

If suspected or confirmed, has a separate NmA Case Investigation Form been initiated? ☐ Yes ☐ No

Note: If there are more than 2 contacts, add additional contact information with identifying EPID number on separate sheet.