

Investigation of a *Neisseria meningitidis* Serogroup A Case in the Meningitis Belt

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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 vaccinated. Surveillance data and studies have documented a dramatic impact of the vaccine, reducing serogroup A *N. meningitidis* (Nm A) incidence. In order to sustain the success of the mass campaigns, the introduction of MACV into EPI programs has started in 2016.

Epidemiological surveillance has shown that despite the large success and the dramatic reduction of Nm A epidemics in the belt, Nm A cases have continued to occur, 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. Since countries implemented their mass campaigns, new born cohorts went unvaccinated and the number of susceptible individuals has increased. Influx of new population may also influence the number of people at risk. It is therefore important to monitor the incidence of Nm A and implement the vaccination of new cohorts as soon as possible.

Epidemiologic evaluation and microbiologic confirmation of every Nm A case is necessary in order to make sure that Nm A was the isolated pathogen, understand the primary reason for the occurrence of a Nm A case in a vaccinated area (basically whether the person was not vaccinated or if it was a vaccine failure) and understand the potential risk for the population in the area to inform an eventual public health intervention. It is also crucial to document the duration and strength of protection of the MACV.

Purpose of the document

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

Objectives of the investigations of Nm A cases

The systematic investigation of a case of Nm A aims:

- to confirm the diagnosis of *Neisseria meningitidis* serogroup A in the suspected case
- to determine the vaccination status of the case and to identify any potential vaccination failure
- to detect an unreported cluster of Nm A cases
- to identify high-risk areas (unvaccinated/accumulation of susceptible) to eventually recommend catch-up vaccination
- to inform MACV vaccine effectiveness and vaccine impact

Case definition for Nm A

For the purpose of the investigation,

- An Nm A case is *suspected* on the basis of laboratory findings (including identification by latex agglutination, immune-chromatographic rapid test, PCR, or culture) at subnational level
- An Nm A case is *confirmed* by PCR and/or culture by the National Reference Laboratory and/or Regional Reference Laboratory.

Methods

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

- Field investigation of the case for epidemiological data collection
- Microbiologic confirmation and molecular characterization of the strain

A laboratory getting 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:

- request the laboratory to provide details on the laboratory methods used
- get the Integrated Disease Surveillance and Response form of the case(s).
- inform WHO

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

1. Epidemiologic field investigation of Nm A cases

The following key steps should be implemented

a. **Prepare for the investigation:**

- A multidisciplinary field investigation team should be assembled with members having experience at least 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.
- Maps of the concerned area and epidemiological information on meningitis incidence and serogroup distribution in the area should be gathered.

- b. **Review the available information:** The investigation team should review carefully the standard IDSR notification form filled for the case and transmitted from the field to determine whether the demographic, clinical, and epidemiological information is complete. Assess whether the suspect case definition for bacterial meningitis was correctly used (box). If not possible with the given information, verify the clinical symptoms during the patient interview.

Standard case definitions for bacterial meningitis

Suspected meningitis case:

Any person with sudden onset of fever ($>38.5^{\circ}\text{C}$ 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; with a CSF leukocyte count >10 cells/ mm^3 ; or with bacteria identified by Gram stain in CSF; or positive antigen detection (for example latex agglutination) in CSF

In infants: CSF leukocyte count >100 cells/ mm^3 ; or CSF leukocyte 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 culturing or identifying of (i.e. by polymerase chain reaction) a bacterial pathogen (*Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* type b) in the CSF or blood.

c. Conduct the field investigation:

Essential information to be collected for a suspected or confirmed Nm A case

1. Patient identification and demographic information:
 - Patient ID number, name, sex, birth date/age
 - Place of residence and contact information
 - Name of person and relationship to the patient if a proxy is interviewed
2. Travel history of patient within 10 days of disease onset
3. Clinical information:
 - Date of consultation
 - Date of sample collection
 - Date of onset of symptoms
 - Symptoms
 - Treatment
 - Hospitalization including date of admission and duration
 - Outcome of the patient
4. Vaccination status (MACV)
 - Ask for the vaccination card and take a picture of the card
 - Date and place of vaccination
 - Batch number
 - If card not available, check out for registers.
 - 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 cases (meeting the suspected bacterial meningitis case definition) in the household or close neighbourhood: name, age, and vaccination status. These cases should be sought for cross check at the health centre and then categorized (see classification).
6. Laboratory investigation
 - Date and place of lumbar puncture
 - Place and kind of tests conducted

- Test results
- Final laboratory diagnosis (classification)
- Availability of lab material of the case (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 (form for NmA case investigation in annex). Information should also be sought on contacts (and neighbors or others surrounding) who may meet the suspect case definition for bacterial meningitis.

Active case-finding: A review of health facility registers should be conducted to ensure that all persons meeting the suspect case definition for meningitis have been reported and that any samples that may have been taken are tested and followed-up. The areas that should be surveyed should include the village of residence of the patient as well as area where the patient may have acquired the infection (in case patient travelled within 10 days of disease onset).

- d. 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 Nm A

All Nm A cases should undergo culture and/or PCR for confirmation at the national reference laboratory (NRL). If the specimen is still available and was not tested at the NRL, it should be referred to the national reference laboratory for confirmatory testing within 48 hours. If culture or PCR method is not available at the national level, the specimen should be referred to a WHO Collaborating Centre.

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

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

In addition, all or a subset (if large cluster) of NmA samples should be referred to a WHO Collaborating Centre for confirmatory testing and whole genome sequencing of available isolates. If only a clinical specimen is available, multilocus sequence typing may be attempted for determination of sequence type.

Classification of the case

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

- **Nm A not confirmed**
 - Lab is not conclusive
 - Sample is not available anymore and the sample has not been tested at the NRL or a WHO Collaborative Centre
- **Nm A confirmed** (laboratory confirmed)
 - patient not vaccinated
 - inform 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)

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

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

Investigation report and dissemination

A detailed report of the case investigation findings should be elaborated and shared with health authorities and district, regional and national levels, as well with partners. 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 Nm A cases be presented. For investigations that yield multiple cases of Nm A, graphical/tabular descriptions of cases by date of onset, geographical location, age, and vaccination statuses should be developed. Any key observations and recommendations on the case detection, notification, data management, laboratory confirmation, or other aspects of the surveillance process to be strengthened should be noted. The report of the field investigation containing this information and analysis should be disseminated within 7 days of the completion of the mission.

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

Specific form for investigation of meningitis cases with serogroup A meningococci

Health Facility : _____		LGA : _____		State: _____	
Date of MenAfriVac campaign in the LGA (Year :_____)					
EPID No. :	/	_ _ _ _	/	_ _ _ _	/
		Country		State	
		LGA		Year	
		Disease		Case No.	
PATIENT DETAILS					
Surname: _____		First name : _____		Sex : <input type="checkbox"/> Female <input type="checkbox"/> Male	
Date of birth : ____/____/____		or Age in years : ____		or Age in months (if <12 months) ____	
Residential address : _____		Village : _____		LGA: _____	
Name of Parent(s) : _____		Telephone of patient or parent(s) : _____			
Did the patient travel to another location 10 days before onset of symptoms? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know					
If yes, specify where: _____					
Date seen at health facility: ____/____/____			Date of onset of symptoms: ____/____/____		
<input type="checkbox"/> Was the patient admitted?		Outcome: <input type="checkbox"/> Recovered <input type="checkbox"/> Died <input type="checkbox"/> Still on admission <input type="checkbox"/> Don't know			
Major symptoms: <input type="checkbox"/> Neck stiffness		<input type="checkbox"/> Fever (T°= _____)		<input type="checkbox"/> Loss of consciousness	
Other symptoms: _____					
VACCINATION STATUS					
<i>Vaccine</i>	<i>Date of last dose</i>	<i>Source</i>	<i>Lot N°</i>	<i>Place of vaccination</i>	
MenA conjug. (MenAfriVac)	<input type="checkbox"/> Yes, Date: ____/____/____ <input type="checkbox"/> No	<input type="checkbox"/> card <input type="checkbox"/> verbal	_____	_____	
MenAC (PS)	<input type="checkbox"/> Yes, Date: ____/____/____ <input type="checkbox"/> No	<input type="checkbox"/> card <input type="checkbox"/> verbal	_____	_____	
MenACW (PS)	<input type="checkbox"/> Yes, Date: ____/____/____ <input type="checkbox"/> No	<input type="checkbox"/> card <input type="checkbox"/> verbal	_____	_____	
MenACWY (PS)	<input type="checkbox"/> Yes, Date: ____/____/____ <input type="checkbox"/> No	<input type="checkbox"/> card <input type="checkbox"/> verbal	_____	_____	
CASE SEARCH (alive and dead) :					
Are there other cases known to the patient? /_____ Yes 2= No If yes, How many?_____					
1. Name of case: _____ Age :_____					
Vaccinated? : <input type="checkbox"/> yes, card <input type="checkbox"/> yes, verbal <input type="checkbox"/> No <input type="checkbox"/> Don't know					
If yes (MenAfrivac only?) :					
date of last vaccination ____/____/____		Lot N°: _____		Place of vaccination_____	
2. Name of case: _____ Age :_____					
Vaccinated? : <input type="checkbox"/> yes, card <input type="checkbox"/> yes, verbal <input type="checkbox"/> No <input type="checkbox"/> Don't know					
If yes (MenAfrivac only?) :					
date of last vaccination ____/____/____		Lot N°: _____		Place of vaccination_____	

CSF SAMPLE**Date of Lumber Puncture:****Appearance of CSF:** _____

Date of injection in the transport medium: ____/____/____

Transport medium : ☐ Dry tube ☐ Trans-Isolate ☐ Cryotube ☐ Others : _____**RESULTS OF THE FIRST LABORATORY REPORTING THE CASE OF Nm A****Name of Laboratory :****Latex:** Not done ☐ Negative ☐ NmA ☐**Culture:** Not done ☐ Negative ☐ NmA ☐**PCR :** Not done ☐ Negative ☐ Contaminated ☐ NmA ☐**Rapid Test :****Other tests (glucose, etc):** _____**Is the patient's sample still available:** _____ **If yes, where?** _____**RESULT FROM REFERENCE LABORATORY (Do not complete if it is the laboratory that reported the case)****Date sample received :****Appearance of CSF:** _____**Gram :** Not done ☐ Negative ☐ DGP ☐ DGN ☐ BGP ☐ BGN ☐ Other bacteria ☐ _____**Latex:** Not done ☐ Negative ☐ NmA ☐ NmW/Y ☐ NmX ☐ NmC ☐ NmB/E. Coli ☐ S. pneumo ☐ HiB ☐**Culture:** Not done ☐ Negative ☐ Contaminated ☐ NmA ☐ NmW ☐ NmX ☐ NmC ☐ NmY ☐ NmB ☐Nm Indeterminate ☐ S. pneumo ☐ HiB ☐ H. influenzae (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 sample still available:** _____ **If yes, where?** _____**RESULTS FROM WHO COLLABORATING CENTRE (LABORATORY)****Date sample received :** ____/____/____**Culture:** Not done ☐ Negative ☐ Contaminated ☐ Result : _____**PCR :** Not done ☐ Negative ☐ Contaminated ☐ Result : _____**Molecular typing results:**

