Collecting evidence on intervention thresholds and antibiotic regimens
WHO protocol to inform the revision of meningitis outbreak response guidelines

1. Background

The meningitis belt, a region in sub-Saharan Africa which stretches from Senegal to Ethiopia, is particularly susceptible to epidemics of meningococcal meningitis. *Neisseria meningitidis* serogroup A (NmA) has been the cause of the majority of invasive meningococcal infections in the meningitis belt for over 100 years, although other strains such as serogroups C, X and W have also caused epidemics\(^1\), and other pathogens such as *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (Spn) are also responsible for meningitis cases. The most recent large-scale epidemic was in 2012 with over 22,000 cases and 1,931 deaths\(^2\).

The predominance of the Nm A pathogen has been behind policies for epidemic surveillance and response including mass vaccination with polysaccharide vaccines, and has driven the development of a new serogroup A meningococcal conjugate vaccine (MenAfriVac). Polysaccharide vaccines have reduced the number of cases during epidemics but have not reduced the number of epidemics due to the vaccine’s inability to induce long-term protection, especially in children\(^3\). MenAfriVac as a conjugate vaccine triggers an immune response against meningococcal serogroup A that is more persistent than the immune response induced by a corresponding polysaccharide vaccine\(^1\). Since introduction of MenAfriVac in 2010, over 100 million people in 10 countries in the meningitis belt have been vaccinated. This has led to changes in the epidemiology of the disease such as a decrease in the number of overall cases, epidemics and a greater proportion of non Nm A pathogens (Nm W, X, C, Hib and Spn)\(^2\).

The World Health Organization (WHO) currently recommends that countries with high or frequent epidemic rates of meningococcal disease should implement large-scale vaccination programs in order to prevent and/or control the epidemic, depending on the country’s resources\(^1\). It also recommends that countries with less frequent epidemics have immunization programs for high-risk groups such as children and youth who live in closed communities. The introduction of the MenAfriVac poses new challenges in disease surveillance and control of outbreaks caused by non-Nm A pathogens. A comprehensive
review of surveillance data from the meningitis belt data is needed to inform detection and response to meningitis epidemics, and to determine future immunization schedules. A process to revise the existing guidelines on meningitis detection and response was initiated by WHO. The development proposal, approved by the WHO Guidelines Review Committee contains four major questions, two of which are included in this protocol (referred to as PICO 1 and 3). The other two (use of rapid diagnostic tests and prophylaxis for household contacts) are described in separate protocols.

2. Objectives

2.1. Collect and analyze data to answer the following question: In outbreaks of meningococcal meningitis due to vaccine preventable serogroups, how many cases and deaths are potentially averted when mass vaccination is implemented at different thresholds? (PICO 1)

2.2. Collect and analyze data to answer the following question: Should single dose antibiotic regimens continue to be recommended for suspected cases of meningitis during a meningococcal meningitis outbreak, and, if so, in what circumstances? (PICO 3)

3. Definitions

For the purpose of this study, the terms “meningitis belt” and “sub-Saharan Africa” will be used indifferently and include the following 26 countries: Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Côte d’Ivoire / Ivory Coast, Democratic Republic of the Congo, Eritrea, Ethiopia, Ghana, Gambia, Guinea, Guinea Bissau, Kenya, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sudan, South Sudan, Tanzania, Togo and Uganda.

Standard case definitions will be used as per current WHO recommendations\(^4\) (Appendix A) but for the purpose of this study, probable cases must be recorded as suspected cases.

A meningitis epidemic is currently defined as crossing an epidemic threshold of 10 suspected cases per 100,000 inhabitants per week, in a population greater than 30,000, in a given district\(^4\). An epidemic period is the period when the incidence of meningitis suspected cases is greater than or equal to the epidemic threshold for at least a week. A
non-epidemic period is when the incidence of meningitis suspected cases has
descended below the alert threshold for at least 2 weeks.

Epidemics will be considered caused by a given pathogen when it is responsible for at
least 50% of the confirmed cases. When the proportion of confirmed cases due to a
single pathogen is lower than 50%, the epidemic is considered “mixed”.

4. Data needs

4.1. PICO 1: characterize the number of cases and deaths averted during non-Nm A
epidemics of meningococcal meningitis should new intervention criteria be used
by collecting aggregated data on:

- the weekly incidence of meningitis suspected cases and deaths at district
  and sub-district levels in order to compute the duration of non Nm A
  meningitis epidemics;

- the type and number of micro-organisms identified in meningitis
  confirmed cases through cerebrospinal fluid (CSF) in order to determine
  the pathogen responsible for the epidemic;

- the lag time to launch reactive immunization campaigns, its comparison
  with the time for the epidemic to peak, and the duration of protection
  provided in order to factor in the efficiency of containment measures.

4.2. PICO 3: characterize the number of meningitis suspected cases who would
receive inappropriate antibiotic treatment should the treatment strategy remain
unchanged by collecting age-specific data on:

- the incidence of meningitis cases and deaths in order to compute and
  compare the CFRs of meningitis cases during Nm A and non Nm A
  epidemics before and after introduction of MenAfriVac;

- the type and number of micro-organisms identified in meningitis
  confirmed cases before and after the introduction of MenAfriVac in order
  to compute and compare the age-specific pathogen distribution (Nm of all
  serogroups, Hib, Spn) of meningitis cases before and after introduction of
  MenAfriVac;
• the distribution of pathogens over time in order to assess whether it changes during the course of epidemics, and during epidemic and non-epidemic periods

• the status and coverage obtained from immunization with the Men A (mass immunization), Hib and Sp vaccines (routine) in order to factor in the impact of the protection provided on pathogens’ distribution.

5. Data search

5.1. A comprehensive search involving (i) the African Regional Office of the WHO (AFRO), Ministries of Health in countries of meningitis belt, (ii) CDC, NGOs, other partners (iii) published and unpublished literature, for meningitis surveillance data on epidemics and non-epidemic periods from all countries of the meningitis belt since 2002.

5.2. Data from AFRO and Ministries of Health in the meningitis belt (lead Clement Lingani)

5.2.1 Meningitis surveillance datasets from all countries of sub-Saharan Africa will be sought and authorization for access will be requested from each Ministry of Health using an official letter.

The search will span over 3 disease surveillance and control systems (enhanced surveillance, case-based surveillance and epidemic investigation) since 2002.

Enhanced surveillance data will include aggregated count data (number of cases and deaths per district and per week) and laboratory information when existing (number of pathogen identified at available temporal and spatial scale). Case-based surveillance data will include individual epidemiological and laboratory data with age specific information (week of disease onset, district, sub-district, facility, age, immunization status for MenAfriVac, pathogen identified, disease outcome). Epidemic investigation datasets will include individual data on all investigated cases (week of disease onset, district, sub-district, facility, age, pathogen identified, disease outcome; immunization status for MenAfriVac will be sought if the epidemic occurred in an area where MenAfriVac was introduced).
For each of these datasets, the year of implementation of enhanced and case-based surveillance will be indicated when applicable.

Information prior to January 1\textsuperscript{st} 2002 will be excluded. All datasets containing meningitis surveillance data on epidemics and non-epidemic periods from all countries of the meningitis belt since implementation of enhanced surveillance will be included.

5.2.2 Data on the introduction of MenAfriVac in all countries of the meningitis belt will be sought from AFRO.

Datasets will include data on MenAfriVac introduction status (yes/no), introduction approach (nationwide or in specific districts), list of districts where introduced unless nationwide, date of introduction in each area (mmm/yyyy), vaccine coverage through introduction in each area by age groups (%) and computation (administrative coverage or survey). Age will be categorized by group of age in years (1-4y; 5-14y; 15-29y) if not available per year after 12 months.

Information prior to January 1\textsuperscript{st} 2010 will be excluded. All information from countries of the meningitis belt since 2010 will be included.

5.2.3 Data on children routine immunization against Hib and Spn vaccine in countries of the meningitis belt will be sought from AFRO and the WHO vaccine-preventable diseases monitoring system (2013 global summary), available at: http://apps.who.int/immunization_monitoring/globalsummary.

Assuming nationwide introduction, datasets will include: Hib and Spn vaccine introduction status (yes/no), date of introduction (mmm/yyyy), vaccine coverage (%) and computation (administrative coverage or survey).

Information prior to January 1\textsuperscript{st} 2002 will be excluded. All information from countries of the meningitis belt since 2002 will be included.

5.3. **Data from partners (lead Laurence Cibrelus)**

Meningitis datasets will be requested from partner organizations such as CDC, AMP, MSF, Imperial College or John Hopkins who are known to have, or likely to have, relevant data using a standard letter.
Partners will be identified from previous collaborations with WHO and/or from participation to one of the WHO guideline groups involved in the revision of the guidelines for epidemic response. Partners will also be asked to identify other resource persons and/or relevant sources of information, who will be contacted as well.

Datasets sought will cover two main types of information since 2002: aggregated surveillance data that could not be obtained from AFRO or the Ministries of Health (particularly sub-district level information and epidemic investigations), and age-specific count and laboratory data, using the formats described in 5.2.1.

There will be no restriction on the language, type of study and details of design generating the data (eg, prospective studies or trials including testing of diagnostic tests or vaccine development, retrospective hospital inpatients studies etc.). For each of these datasets, the type of study, details of design, data collection start and end dates (dd/mmm/yyyy) will be indicated. The year of implementation of enhanced and case-based surveillance will be provided when applicable.

Information prior to January 1st 2002 will be excluded. All information from countries of the meningitis belt since 2002 will be included.

5.4. Literature search (lead Guen Gwanyalla)

5.4.1. Search strategy

The following electronic literature databases will be searched for publications since 2002 without language restriction:

- PubMed (Medline)
- EMBASE -OVID
- African Index Medicus
- Global Index Medicus
- CAB/Global Health
- WHO Regional databases
- Grey literature (using Google with country filters eg meningitis site:gov.ng)

5.4.2. Search terms

A. General search for meningitis in Africa

AND


B. Sub-search within (A)


5.4.3. Criteria for selection

Whatever the date of publication, we will exclude surveillance data before 1st January 2002.

All papers containing meningitis surveillance data on epidemics and non-epidemic periods from all countries of the meningitis belt since 2002 will be included.

A database of references will be created from the main search. The sub-search will then be conducted. Abstracts will be screened independently by the principal researcher (GG) and a second researcher (LC). Discrepancies will be discussed by the 2 researchers. If there is no agreement, the senior reviewer will make the final decision. Discrepancies and outcome of discussions will be documented. The full text of all
relevant articles will be obtained, with assistance from Columbia University library where necessary.

5.5. **Time for vaccine response (lead Katya Fernandez)**

Data from 2006 to 2013 of ICG requests approved for vaccine supply for outbreak response will be used to analyze time from reaching the epidemic threshold to vaccination.

Data set compiled from ICG requests will include time of vaccination campaign implementation (start and end dates/epidemiological week) per district, type of vaccine used and administrative vaccine coverage (%) per district. Data on date/epidemiological week of epidemic threshold crossing and on peak of epidemic will be extracted from the meningitis surveillance data sets from countries (described in 5.2.1). Ready availability of vaccine will be noted (Yes/No). Missing data on vaccination campaign implementation and coverage will be sought from countries.

Information prior to January 1st 2006 will be excluded. All information from countries of the meningitis belt since 2006 will be included.

6. **Data Extraction**

6.1. After piloting data extraction forms in ExCel for ease of use and data capture capability, they will be used to extract (i) aggregated surveillance data (number of cases per district and per week) (ii) individual case-based surveillance (with age specific information) (iii) laboratory-aggregated data (iv) laboratory data with age-specific information and (iv) data related to reactive immunization.

6.2. Databases will be constructed by country of (i) surveillance data including information on suspected cases, CSF, laboratory test results, pathogen, date, age distribution, epidemics and non-epidemic periods, (ii) data sources and contacts, and (iii) contextual material such as date of implementation of immunization programs with MenAfriVac, Hib, pneumococcal conjugate vaccines. Age will be categorized by month up to one year then by group of age in years (1-4y; 5-14y; 15-29y;≥30y) if not available per year after 12 months.

6.3. For *data extracted from the literature search*, a second reviewer (LC) will check data for accuracy and completeness. If there are discrepancies, discussion with GG will be held to resolve. If there is no agreement, the second reviewer will
make the final decision. Disagreements and agreements on all data outcome will be documented. For each study, duplication with data obtained from other sources (countries, partners) will be checked (LC). If not duplicated and if the authors have not already been requested for the same data, an author will be contacted to gain permission to access the original data and request additional data on similar studies.

6.4. Data quality. Data will be cleaned before analysis. No restriction will be placed on completeness of data. Absent or low percentage of reporting, e.g. on age, pathogen will be taken into account through sensitivity analysis.

7. Data Analysis

7.1. PICO 1. (Lead LC/CT) Descriptive analysis of non-Nm A surveillance data will include weekly meningitis incidence by district (and sub-district where available) by country by predominant pathogen, CFR, duration of epidemics. Using the available weekly case counts on the course of epidemics, we will investigate the potential number of cases and deaths averted by using a range of lower alert and epidemic thresholds compared to the current standard, taking into account the effect of any mass vaccination in that population. This will take into account the time estimated to deliver a vaccination campaign and for the vaccine to take effect. Sensitivity analysis will include the % of suspected cases not laboratory confirmed.

7.2. PICO 3. (Lead GG/LC). We will examine age-specific incidence by Nm, Spn and Hib, and case fatality, during Nm A and Non-Nm A epidemics, before and after the introduction of MenAfriVac. Data on fluctuation of pathogen distribution during the outbreak will be included where available. Use of Hib and pneumococcal vaccines in national immunisation programmes and coverage obtained with MenAfriVAc will be taken into account. Sensitivity analyses will include examining the effect of removing or including datasets where a low proportion of cases are not laboratory confirmed.

8. Evidence profiles for outbreak response guidelines (3.1, 3.2).

Evidence will be assessed based on GRADE methodology, categorizing quality of evidence and strength of recommendation, and supported by the WHO handbook on guideline development. Evidence will be classified as high, moderate, low or
very low depending on the type, quality and results of retrieved studies and an assessment as to whether further research is likely to change confidence in the estimate of effect. As the evidence is provided by analysis of datasets not a systematic review, a modified approach will be adopted.

9. **Timelines**

<table>
<thead>
<tr>
<th>Task</th>
<th>Date</th>
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<tbody>
<tr>
<td>Data collection completed:</td>
<td>2 December 2013</td>
</tr>
<tr>
<td>Multi source dataset completed:</td>
<td>16 December 2013</td>
</tr>
<tr>
<td>Draft reports and evidence profiles:</td>
<td>20 January 2014</td>
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Appendix A: Meningitis case definitions


Suspected meningitis case:
• Any person with sudden onset of fever (>38.5 C rectal or 38.0 C axillary) and one of the following signs: neck stiffness, altered consciousness, other meningeal signs or purpura fulminans.
• Any child under 2 with sudden onset of fever (>38.5 C rectal or 38.0 C axillary) and one of the following signs: neck stiffness, or flaccid neck, bulging fontanel, convulsion, other meningeal signs or purpura fulminans.

Probable meningitis case: for the purpose of this work, probable cases should be reported as suspected cases

Any suspected case with macroscopic aspect of its cerebrospinal fluid (CSF) turbid, lousy or purulent; or with microscopic test showing Gram negative diplococci, or Gram positive diplococci, or Gram positive bacilli; or with leukocytes count greater than 10 cells/mm3.

Confirmed meningitis case:
Isolation or identification of causal pathogen (Neisseria meningitidis (Nm), Streptococcus pneumoniae (Sp), Haemophilus influenzae b (Hib)) from the CSF of a suspected/probable case by culture, PCR or rapid diagnostic test (latex agglutination, dipstick).
1 WHO. WHO position paper on meningococcal vaccines. 2011;47(86):521-540