The use of polysaccharide trivalent ACW vaccine for the control of epidemic meningococcal disease outbreaks in countries of the African meningitis belt

Recommendations from an international informal consultation
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Acknowledgements

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I. Background

Epidemic meningococcal disease (EMD) outbreaks are usually due to *Neisseria meningitidis* (*Nm*) serogroups A or C. However *Nm* serogroup W135 has recently emerged as a cause of epidemic disease. In 2002, the first major W135 meningococcal disease outbreak occurred in Burkina Faso, with 13,125 suspected meningitis cases and 1,510 deaths. The response to the 2002 epidemic in Burkina Faso was hindered by the lack of a serogroup W135-containing meningococcal vaccine due to both limited worldwide production and high cost.

In response to the unexpected W135 outbreak in 2002, the World Health Organization (WHO) sounded the alarm to the pharmaceutical industry, asking their assistance to make a W135-containing polysaccharide (PS) vaccine available at an affordable price for African countries. GlaxoSmithKline (GSK) responded favourably and developed 3 million doses of a new ACW meningococcal PS vaccine for evaluation and limited use in Africa in 2003. This vaccine was licensed by the Belgian National Regulatory Authority by the end of January 2003 and can be exported to countries that authorize its use.

During the 2002-2003 season, Burkina Faso was affected by a mixed *Nm* A-W135 epidemic (7,900 cases). In response to the outbreak, two million people were vaccinated with the new trivalent vaccine. At the same time, an increased proportion of *Nm* W135 isolates was reported by several African meningitis belt countries, suggesting that W135 could be the cause of further outbreaks in the region (alone or together with serogroup A).

WHO recently reached an agreement with GSK for the production of 6 million doses of PS trivalent ACW vaccine at 1 Euro per dose. However to ensure production, WHO would have to raise the required funds before the beginning of the epidemic season. The funds obtained will be used for establishing a revolving emergency stock. No additional supply of this vaccine is expected to be available for the 2003–2004 epidemic season.

The recommended strategy for EMD outbreak control in the African meningitis belt is based on reactive mass vaccination with the meningococcal PS vaccine and effective case management. While the case management strategy does not differ according to the strain, the vaccination strategy to be adopted is less clear. Indeed, in the current context of a limited supply of PS trivalent ACW vaccine, the use of the vaccine must be carefully evaluated.

In making informed and optimal decisions regarding outbreak response, two issues must therefore be urgently addressed: (i) determining the most appropriate meningococcal PS vaccine to be used in the affected areas; and (ii) developing an optimal vaccination strategy for the use of the PS trivalent ACW vaccine in the field.

The recommendations presented in this document are the result of an informal consultation organized by WHO in March 2003 to obtain technical advice from various experts on the two issues mentioned above.
II. Current Strategy for Outbreak Response

The current WHO recommendations for EMD outbreak control are based on reactive mass vaccination with the meningococcal PS vaccine and effective case management. Prompt implementation of control measures in EMD depends on early detection of outbreaks through the effective application of alert and epidemic thresholds as recommended by WHO\(^1\).

The *alert threshold* is used to:

1. sound an early warning and launch a laboratory investigation at the start of an epidemic;
2. check epidemic preparedness;
3. start a vaccination campaign if there is an epidemic in a neighbouring area; and
4. prioritize areas for vaccination campaigns in the course of an epidemic.

The *epidemic threshold* is used to confirm the emergence of an epidemic so as to step up control measures, i.e. mass vaccination and appropriate case management.

In light of the recent emergence of W135 as an epidemic strain, African meningitis belt countries may be faced with three likely outbreak scenarios:

(a) an epidemic caused by *Nm A* exclusively,
(b) an epidemic caused by *Nm W135* exclusively or
(c) a mixed epidemic caused by both *Nm A/C* and *Nm W135*.

In order to design effective interventions for the above outbreak scenarios, public health authorities must determine as early as possible the type and distribution of disease-causing meningococcal serogroups. Consequently, there is an urgent need for improved surveillance and laboratory confirmation of the causal pathogen in affected populations.

In response to this need, standard operating procedures (SOPs) for enhancing epidemic meningitis disease surveillance were developed by WHO in collaboration with partners and were implemented during the 2002-2003 season by 8 countries of the region. Based on lessons learned, the SOPs will now be reviewed and adapted to fit field conditions and allow a faster identification of circulating serogroups.

Under the context of limited PS trivalent ACW vaccine, decision-makers at country level will need to make use of the best epidemiological and laboratory evidence available for choosing the most appropriate vaccine for outbreak containment, i.e. bivalent AC vaccine versus trivalent ACW vaccine.

The recommendations presented next are intended to facilitate decision-making at national and international level, by providing simple criteria and highlighting key elements that should be considered in the decision process.

III. Decisional Tree for the Use of ACW Trivalent Polysaccharide (PS) Vaccine in the African Meningitis Belt Countries

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**2 Epidemic threshold**

- Population greater than 30,000: an incidence of 15 cases per 100,000 inhabitants per week, in 1 week. However, when the epidemic risk is high (no epidemic for 3 years or alert threshold crossed early in the dry season), the recommended epidemic threshold is 10 cases per 100,000 inhabitants per week, in 1 week (see reference article for more details).
- Population less than 30,000: 5 cases in 1 week or doubling of the number of cases over a 3-week period (other situations must be evaluated in a case by case basis according to the epidemic risk).
- For operational purposes, when an epidemic is confirmed in a neighbouring area, the alert threshold also serves as the epidemic threshold.


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3 Ideally the samples should be obtained within two weeks of when the epidemic threshold was crossed.
IV. Recommendations Associated to the Use of the Decisional Tree

1. Application of the Epidemic Threshold

- Weekly meningitis incidence should ideally be calculated for areas with population ranging between 30 000 to 100 000. Incidences calculated for areas with a larger population may delay or impede the detection of localized outbreaks.

- Therefore for surveillance and response purposes areas with more than 100 000 inhabitants should be divided in smaller sub-zones (sub-district or neighbourhood within urban areas) of approximately 30 000 to 100 000 people each.

- For populations of less than 30 000, an absolute number of cases is used to define the alert and epidemic thresholds so as to avoid major incidence fluctuations due to the small population size4.

- The effectiveness of this approach depends on the quality of epidemiological surveillance, and especially on the completeness and timeliness of case reporting. Underreporting and delays in data transmission can significantly delay the detection of an epidemic.

2. Collection of Cerebrospinal Fluid Specimens

- Timely identification of the pathogen(s) circulating during a meningitis epidemic is crucial for the choice of the PS vaccine to be used for outbreak control. Therefore laboratory investigation of suspected meningitis cases should be a standard practice during the meningitis epidemic season.

- Basic material for collection, transport and testing of cerebrospinal fluid specimens (CSF) such as lumbar puncture kits, transport media vials (TIs), Gram stain and latex kits, should be made available at health facilities at the regional level (province) before the beginning of the epidemic season. In countries without intermediary level, the material should be kept at central level.

- During the pre-epidemic period collection of CSF samples at the periphery level should be stepped up, particularly in those areas that have crossed the alert threshold. Collected samples should be immediately transported to the national laboratory of reference for serogroup identification using TIs.

- Active field investigation should be conducted in areas crossing the epidemic threshold as well as in those that remain in alert for more than three weeks. Field investigation teams (epidemiologist and lab technicians) should be sent to the epidemic areas in order to assist data collection and analysis, as well as CSF specimens collection and laboratory confirmation (Gram stain, latex tests).

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Local health staff and field investigation teams should systematically collect and test CSF specimens within two weeks after the epidemic threshold was crossed. We estimate that 20 to 30 CSFs suffice to support the choice of the adequate PS vaccine and limit the number of invasive medical practices. The quicker these samples are obtained the better.

Once the epidemic has been confirmed, regular collection of CSF specimens should be maintained in selected districts\(^5\) throughout the epidemic season, in order to monitor circulating \(Nm\) serogroups. Systematic collection of samples from all suspected cases is not recommended. The number of CSF specimens to be collected weekly may vary according to local circumstances and human resources available.

### 3. Laboratory Confirmation of CSF Samples

- The identification of \(Nm\) as the main causative pathogen is essential to confirm a meningococcal meningitis epidemic. All CSF specimens collected should undergo a Gram stain at the nearest laboratory for germ determination.

- The identification of the \(Nm\) serogroup is crucial for deciding on the most appropriate PS vaccine to be used for outbreak control. \(Nm\) should therefore be confirmed from CSF specimens by either:
  - rapid latex tests that can be used at the peripheral laboratories and allow the identification of most common pathogens/serogroups; or
  - culture and serogrouping at national or regional laboratories of reference.

- The use of a latex test that allow the identification of \(Nm\ W135\) (Pastorex®) is highly recommended as they can be used at field level and substantially reduce the delay for bacteriological confirmation and decision making. Nevertheless, the field performance of this test has not been properly evaluated and its use should be limited to laboratories fulfilling the following criteria:
  - trained staff;
  - availability of an appropriate infrastructure (cold chain, centrifuge)


The following criteria could be used to select epidemic districts for CSF regular specimen collection:

#### Epidemiological criteria:
- epidemic threshold has been crossed;
- not contiguous to another epidemic district selected for sampling;
- population size approximately 100 000;

#### Operational criteria:
- distance permitting adequate shipping of specimens to the national reference laboratory with 48 hours;
- health infrastructure (operational cold chain, etc);
- motivated and well-trained personnel.

A limited number of epidemic districts per country should be selected for CSF specimen sampling (3-5). In the event that two contiguous districts are in epidemic phase, specimen collection should be carried out only in the first one that has crossed the epidemic threshold.
- TIs are necessary to transport CSF specimens to laboratories that have the capacity to perform culture and serogroup determination. SOPs procedures for the appropriate use of the TIs should be made available to the countries before the beginning of the epidemic season.

- If TIs are not available for the transport of CSF specimens to laboratories, CSF specimens should be stored in sterile tubes preferably in a freezer (-20°C) or in the refrigerator (+4°C for few weeks), and shipped in a cool box for PCR assays in national or regional reference laboratories for the determination of serogroup and genotype.

- Given the need to monitor epidemiological trends of serogroups and genotypes and better understand the spreading patterns of *Nm* epidemic complexes in the region, it is recommended to split a proportion of samples being processed at national level and to ship aliquots to WHO collaborating centres\(^6\) for genotype characterization.

**4. Laboratory Criteria for PS Vaccine Choice**

- The decision on the type of PS vaccine to be used should ideally be based on the results from at least 10 *Nm* positive specimens. In order to obtain that number of *Nm* positive specimens, we estimate that 20 to 30 CSF specimens should be collected from the affected area.

- Efforts should be made to collect and test CSF specimens in the field as early as possible in the epidemic so as to support the appropriate choice of the PS vaccine.

- The proportion of *Nm* W135 required to warrant the use of ACW trivalent PS vaccine could be defined according to the number of *Nm* positive samples available from a given affected area. The following could be suggested:

  \[
  \begin{align*}
  \text{\textgreater} & 30\% \text{ of W135 out of 10-19 Nm positive samples} \\
  \text{OR} \\
  \text{\textgreater} & 20\% \text{ of W135 out of 20 or more Nm positive samples}.
  \end{align*}
  \]

- In the total absence of laboratory evidence of *Nm* W135 the use of PS trivalent ACW vaccine should be strongly discouraged.

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- In the above mentioned situation, vaccination with the PS bivalent AC vaccine should be recommended (provided that some laboratory evidence of \( N_m A \) is available).

- In situations where a full blown epidemic is reported and where the minimum percentage of \( N_m W135 \) was not reached, the identification of one or more \( N_m W135 \) in the concerned area(s) and concurrent W135 epidemic in contiguous area(s) will justify the use of the trivalent vaccine.

- In any other situation, decisions on which PS vaccine should be used, should be evaluated in a case-by-case basis and should take into account all epidemiological and lab information available.

V. Release Mechanisms for the PS Trivalent ACW Vaccine

The trivalent vaccine is being distributed through the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG). The ICG, formed in January 1997, brings together agencies of the United Nations, non-governmental organizations, and other technical and financial institutions. The daily operational activities of the Group are delegated to an Executive Sub-Group of the ICG, comprising the International Federation of Red Cross and Red Crescent Societies, Médecins Sans Frontières, UNICEF and WHO.

The primary objective of the Group is to ensure immediate availability of vaccine stocks to reduce the delay of response. Countries wishing to obtain the trivalent vaccine must submit a formal request to the ICG. The requests are then reviewed and vaccine distributed only to those countries which meet key epidemiological and operational criteria established by the ICG.

Submission of requests to the ICG
Countries facing epidemics of meningococcal meningitis should send their request for vaccine and materials through the WHO country representatives or through the offices of the other partners involved, to WHO Headquarters. A consensus decision will be taken by the ICG Executive Sub-Group within 48 hours, based upon agreed criteria.

In order to consider a country request, countries should submit the following information:

- **epidemiological data**: weekly number of cases and deaths, attack rates and case-fatality ratio by district, age distribution of cases;
- **laboratory data**: number of CSF samples and distribution of causative pathogens;
- **microplanning**: detailed information by district on target population, vaccine and injection material required for implementation of vaccination campaigns;
- **storage conditions**: assurance of availability of proper storage conditions for the vaccine and indication of the exact amount of vaccine already available in stock.
In addition to the epidemiological and laboratory criteria mentioned above, the ICG decision for the release of vaccine and other materials will take into consideration the following criteria:

- the timeliness of the immunization intervention;
- the epidemiological context in the region
- the stocks of vaccine currently available; and
- the country capacity to ensure the conditions for proper administration of the vaccine.

V. Conclusions

With the emergence of epidemic *Nm* W135 disease and the recent establishment of an emergency stock of trivalent *Nm* ACW PS vaccine, criteria are needed to guide the proper use of this stock and highlight the fact that trivalent vaccine is not meant to replace the bivalent *Nm* AC PS vaccine as the vaccine of choice in responding to epidemic meningococcal disease.

The purpose of the informal consultation was to determine the minimum information that can support the choice of the most appropriate PS vaccine for EMD outbreak control.

The recommendations presented in this document are aimed to facilitate decision-making at national and international level, by providing simple criteria and highlighting key elements that should be considered in the decision process.

The criteria detailed in this document only apply to the current context characterized by limited worldwide availability and the high cost of the PS trivalent ACW vaccine in order to make the best use of the available vaccine reserve.