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Standardized treatment of bacterial meningitis in Africa in epidemic and non epidemic situations

EPIDEMIC AND PANDEMIC
ALERT AND RESPONSE

World Health Organization

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Contents

Abbreviations

CFR	Case-fatality rate
CSF	Cerebrospinal fluid
EMGM	European Monitoring Group of Meningitis
IMCI	Integrated management of childhood illness
MDSC	Multi-Disease Surveillance Centre [Ouagadougou, Burkina Faso]
MIC	Minimum inhibitory concentration
NPHL	National public health laboratory
OC	Oily chloramphenicol
SOP	Standard operating procedure
TI	Trans-isolate
WHO	World Health Organization

Aim of this document

The current strategy for managing an outbreak of meningitis caused by *Neisseria meningitidis* (the meningococcus) in the African meningitis belt is based on early case detection and confirmation, reactive mass vaccination, and effective case management. Case management is based on the pre-positioning of a free, standardized, presumptive treatment.

Since 1996, the World Health Organization (WHO) has recommended the use in peripheral health centres of oily chloramphenicol (OC) for the presumptive treatment of meningococcal epidemics. Subsequently, studies have demonstrated that a single dose of ceftriaxone (100 mg/kg) cures meningitis due to *N. meningitidis*. Ceftriaxone is now more readily available for the treatment of bacterial meningitis and has proved its efficacy as a single dose in presumptive treatment of meningococcal meningitis in epidemic situations in the African meningitis belt.

Thus the aim of this document is:

- to update recommendations for the presumptive treatment of bacterial meningitis in epidemic and non-epidemic situations in the African meningitis belt;
- to outline the operational issues before, during, and after a meningitis epidemic;
- to make recommendations to prevent the emergence of antimicrobial resistance;
- to make recommendations concerning laboratory isolation of meningitis pathogens and surveillance of antimicrobial resistance.

The preparation of this document was assisted by an informal consultation of experts convened by WHO in July 2006 (see Annex 1).

Expected readership

The document is intended for ministries of health in countries of the African meningitis belt and other health professionals involved in the treatment of meningitis in the African meningitis belt.

Background

Epidemic meningococcal disease remains a major public health challenge in the African meningitis belt, an area that extends from Senegal to Ethiopia with an estimated total population of 400 million. These epidemics classically occur in the dry season, between October and April. The estimated number of cases of meningitis in the last 10 years is approximately 700 000 of whom about 10% succumbed to the disease. In addition, in countries like Burkina Faso, the frequency of epidemic years has markedly increased since 1996. This change has challenged the country's resources significantly and complicated preparedness and response efforts.

In epidemic periods

N. meningitidis is the main cause of meningitis epidemics in the African meningitis belt and accounts for as many as 80–95% of cases of bacterial meningitis admitted to health centres (Nathan et al., 2005; WHO, 2005). Most of remaining cases are caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

In non-epidemic situations

Up to 50% of cases of bacterial meningitis are due to *N. meningitidis* overall in the population (Leimkugel et al., 2005, Parent Du Chatelet et al., 2005), and this percentage is lower in neonates and young children where *S. pneumoniae*, *H. influenzae* and neonate-associated organisms (*Streptococcus agalactiae*, *Streptococcus pyogenes*, Enterobacteria) are the most common (Molyneux et al., 1998; Tunkel et al., 2004).

Age also plays a role

Surveillance studies conducted in Ghana and Niger showed that the incidence of meningococcal meningitis was similar in all age groups under 20 years of age (average annual incidence 30–40 cases per 100 000). The highest attack rates of pneumococcal meningitis occurred among children under the age of 1 year (43–150 cases per 100 000). The peak incidence of *H.influenzae* meningitis occurred among children aged 5–6 months and was negligible in persons > 5 years old.

Case-fatality rates (CFRs)

Between 2003 and 2005, annual overall CFRs of suspected meningitis cases in the African meningitis belt were 4–26 % according to the country (WHO Weekly Epidemiological Record 2005). They also varied in relation to the causative agent of the meningitis. In Niamey, Niger, the CFR associated with *N. meningitidis* was 11.7% in the period 1989–1996, and 8.8% in 2003–2006. In Ghana and Burkina Faso, the CFRs associated with *S. pneumoniae* and *H. influenzae* infections varied from 30–50% and were 5–8 times higher than those attributed to *N. meningitidis* (7–12%) (Hodgson et al., 2001; Yaro et al., 2006).

Bacterial meningitis also carries a significant rate of sequelae although data on these in the African meningitis belt are few.

Additional data on incidence and case-fatality rates can be found in Annex 2.

Presumptive treatment of bacterial meningitis at the peripheral level in the African meningitis belt

In epidemic situations

During a meningitis epidemic, rapid identification of the pathogen(s) circulating is crucial for an effective response. The prognosis of bacterial meningitis varies according to the causative agent, the age of the patient, and case management. Therefore laboratory investigation of suspected meningitis cases should be standard practice at the beginning of the meningitis epidemic season. After identification of *N. meningitidis* as the causative agent of an outbreak, 95% of cases of bacterial meningitis seen in health centres will be meningococcal. Therefore systematic laboratory confirmation is no longer necessary, and treatment should be adapted to the most probable causative pathogen, i.e. *N. meningitidis*. This is the principle of presumptive treatment.

In non-epidemic situations

Ideally, in a non-epidemic situation, lumbar puncture and laboratory identification of the bacteria in cerebrospinal fluid (CSF) should be done systematically to guide antibiotic treatment. However, in some countries within the African meningitis belt, laboratory investigation of suspected meningitis cases is often unavailable. Thus, in non-epidemic situations, in the absence of laboratory support, treatment should be adapted to the most probable causative pathogen according to age of the patient (see Table 1).

Oily chloramphenicol as presumptive treatment

Since 1996, WHO has recommended the use of oily chloramphenicol (OC) for the presumptive treatment of meningococcal epidemics in peripheral health centres. OC is:

- effective as a single dose (100 mg/kg)
- easy to use at district level (one intramuscular injection)
- has a low risk of misuse due to its limited indication.

However, it also has some drawbacks:

- it cannot be used in pregnant or lactating women
- it cannot be used in children less than two months of age
- side effects, although rare, can be serious
- there is only one manufacturer, thus there is a risk of production disruption.

Ceftriaxone as an alternative to OC as presumptive treatment

Ceftriaxone, a third-generation cephalosporin, is the recommended treatment for bacterial meningitis in many developed countries because it has a wide spectrum of action and a long half-life (8 hours in blood, 14 hours in CSF). It has been recommended by WHO as treatment for meningitis since 1997. However, until recently, ceftriaxone was considered in developing countries as second-line treatment for bacterial meningitis in all age groups due to the high cost of the patented drug. The patent has now expired and generic versions of good quality are available.

During meningococcal meningitis outbreaks

N. meningitidis is responsible for most of the bacterial meningitis and so the risk of treatment failure with ceftriaxone (due to infections caused by other bacteria) is low. Ceftriaxone can be used at district level (one intramuscular injection), there is no restriction on its use in children or in pregnant or lactating women and thus it is a good alternative to OC for presumptive treatment.

In non-epidemic situations

Presumptive treatment with a single dose of ceftriaxone is not appropriate. Studies have shown (Pecoul et al., 1991; Tunkel et al., 2004; Nathan et al., 2005) that *S. pneumoniae* and *H. influenzae* meningitis cannot be treated with a single dose of ceftriaxone but need several days of treatment in order to generate a stable concentration sufficient to sterilize the CSF.

Concerns about increasing the use of ceftriaxone

While making the above recommendations for the use of ceftriaxone as presumptive treatment for meningococcal meningitis, there are several concerns, namely:

- The use of a single dose of ceftriaxone for the treatment of bacterial meningitis may become generalized regardless of the suspected pathogen, the age of the patient, or the epidemic/non-epidemic situation.
- The massive use of a single-dose treatment with ceftriaxone in epidemic situations may have an impact on the antibiotic susceptibility of *N. meningitidis*.
- Since ceftriaxone is used for several other indications, notably for sexually-transmitted diseases, its widespread availability and use in developing countries may lead to rapid emergence of resistance in other pathogens.

To address these concerns, recommendations are made for the prevention of emergence of resistance (see page 15) and the laboratory surveillance of antimicrobial susceptibility (see page 17).

Choosing the appropriate treatment

A decision tree has been drawn up to guide the choice of treatment (see Figure 1), this is then set out in detail in Tables 1–4.

Figure 1: How to choose a treatment – a decision tree according to the situation and the age of the patient

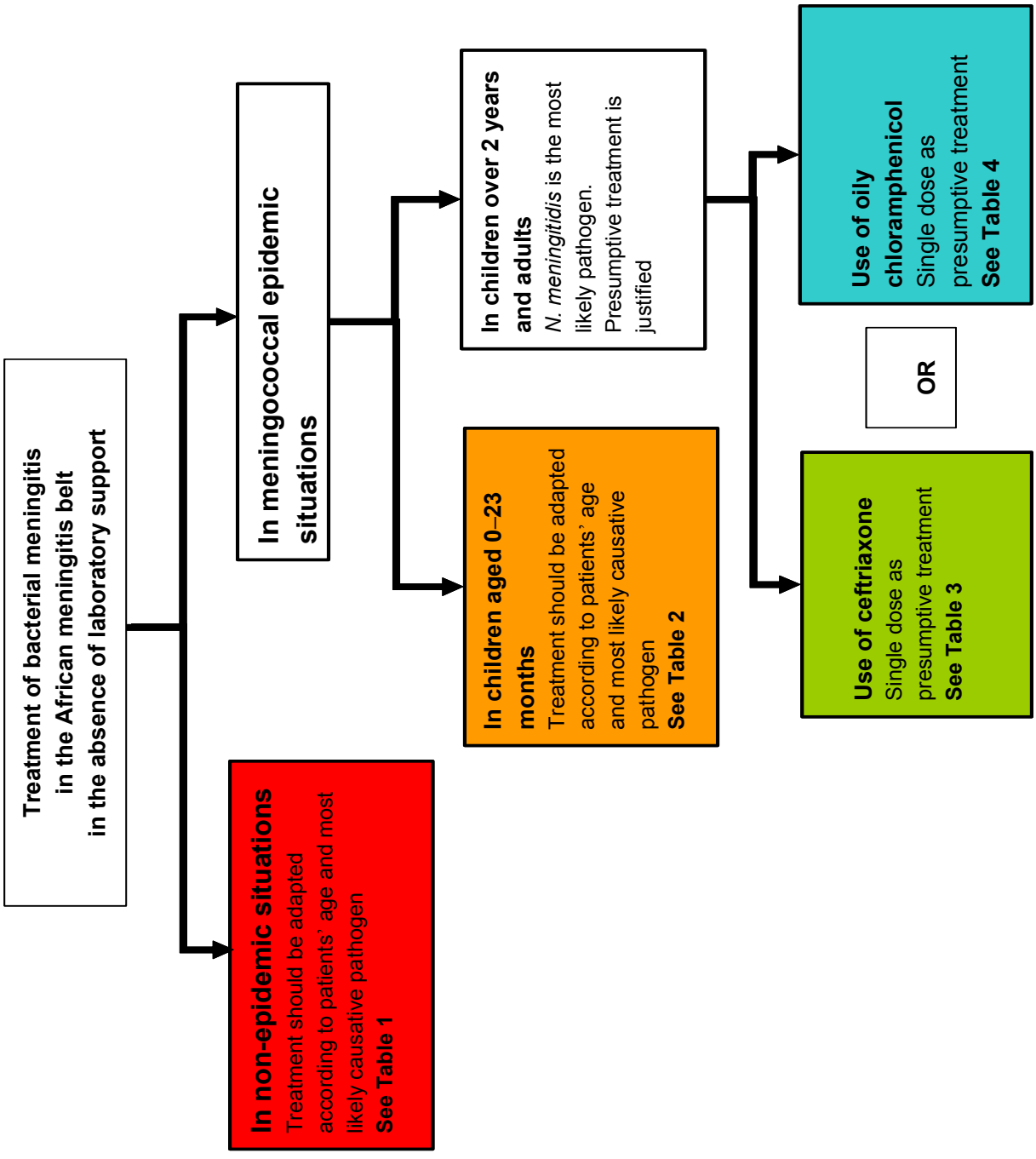

Table 1
Non-epidemic situations: presumptive treatment of bacterial meningitis in the absence of laboratory support

Age group	Principal causes	Treatment	Monitoring
< 2 months	*S. agalactiae* *S. pyogenes* Enterobacteria	Ceftriaxone 100 mg/kg /day once daily for 7 days IV/IM possible[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h
2–23 months	*S. pneumoniae* *H. influenzae* *N. meningitidis* Enterobacteria	Ceftriaxone 100 mg/kg/day once daily for 5 days IM or IV[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h
2–5 years	*S. pneumoniae* *H. influenzae* *N. meningitidis*	Ceftriaxone 100 mg/kg/day once daily for 5 days IM or IV[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h
> 5–14 years	*S. pneumoniae* *N. meningitidis*	Ceftriaxone 100 mg/kg/day (max. 2 g) once daily for 5 days IM or IV[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h[4]
> 14 years	*S. pneumoniae* *N. meningitidis*	Ceftriaxone 2 g/day once daily for 5 days IM or IV[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h[4]

[1] At peripheral level, only intravenous (IV) ceftriaxone with aqueous solvent should be supplied to be used in IV or intramuscular (IM) injection;
[2] Give first dose of antibiotic before referral;
[3] Criteria used by the Integrated Management of Childhood Illnesses (IMCI);
[4] i.e. repeated convulsions, fever > 38.5 ^{0}C after 48 h, appearance or aggravation of a reduced level of consciousness since admission, appearance or aggravation of neurological signs since admission.

Table 2
Meningococcal epidemic situations: presumptive treatment of bacterial meningitis in neonates and young children in the absence of laboratory support

Age group	Principal causes	Treatment	Monitoring
< 2 months	*S. agalactiae* *S. pyogenes* Enterobacteria	Ceftriaxone 100 mg/kg /day once daily for 7 days IV/IM possible[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h
2–23 months	*S. pneumoniae* *H. influenzae* *N. meningitidis* Enterobacteria	Ceftriaxone 100 mg/kg/day once daily for 5 days IM or IV[1]	Clinical reassessment at 24, 36 and 48 h Refer patient[2] 1) if coma or repeated convulsions[3] 2) if no improvement after 48 h[4]

[1] At peripheral level, only intravenous (IV) ceftriaxone with aqueous solvent should be supplied to be used in IV or intramuscular (IM) injection;
[2] Give first dose of antibiotic before referral;
[3] Criteria used by the Integrated Management of Childhood Illnesses (IMCI);
[4] i.e. repeated convulsions, fever > 38.5 ^{0}C after 48 h, appearance or aggravation of a reduced level of consciousness since admission, appearance or aggravation of neurological signs since admission.

Table 3
Meningococcal epidemic situations: presumptive treatment of bacterial meningitis with ceftriaxone in children over 2 years of age and in adults, in the absence of laboratory support

Age group	Principal causes	Treatment	Monitoring
2–5 years	*S. pneumoniae* *H. influenzae* *N. meningitidis*	Ceftriaxone 100 mg/kg single dose IM[1]	Clinical monitoring at 24 and 48 h If no improvement:[2] - after 24 h, give second dose of ceftriaxone 100 mg/kg - after 48 h, treat for total of 5 days with ceftriaxone, or refer
> 5–14 years	*N. meningitidis* *(S. pneumoniae)*	Ceftriaxone 100 mg/kg single dose IM[1]	Clinical monitoring at 24 and 48 h If no improvement:[2] - after 24 h, give second dose of ceftriaxone 100 mg/kg - after 48 h, treat for total of 5 days with ceftriaxone, or refer
> 14 years	*N. meningitidis* *(S. pneumoniae)*	Ceftriaxone 100 mg/kg (max. 4 g) single dose IM[1]	Clinical monitoring at 24 and 48 h If no improvement:[2] - after 24 h, give second dose of ceftriaxone 100 mg/kg or 2 g for an adult - after 48 h, treat for total of 5 days with ceftriaxone, or refer

[1] At peripheral level, only intravenous (IV) ceftriaxone with aqueous solvent should be supplied to be used in IV or intramuscular (IM) injection;
[2] i.e. repeated convulsions, fever > 38.5 ^{0}C after 48 h, appearance or aggravation of a reduced level of consciousness since admission, appearance or aggravation of neurological signs since admission.

Table 4
Meningococcal epidemic situations: presumptive treatment of bacterial meningitis with oily chloramphenicol (OC) in children over 2 years of age and in adults, in the absence of laboratory support

Age group	Principal causes	Treatment	Monitoring
2–5 years	*S. pneumoniae* *H. influenzae* *N. meningitidis*	OC 100 mg/kg single dose IM	Clinical monitoring at 24 and 48 h If no improvement after 24 h:[1] - give second dose of OC 100 mg/kg, or refer
> 5–14 years	*N. meningitidis* *(S. pneumoniae)*	OC 100 mg/kg single dose IM	Clinical monitoring at 24 and 48 h If no improvement after 24 h:[1] - give second dose of OC 100 mg/kg, or refer
> 14 years	*N. meningitidis* *(S. pneumoniae)*	OC 100 mg/kg (max. 3 g) single dose IM	Clinical monitoring at 24 and 48 h If no improvement after 24 h:[1] - give second dose of OC 100 mg/kg (max. 3 g), or refer

OC, oily chloramphenicol; IM, intramuscular
[1] i.e. repeated convulsions, fever > 38.5 ^{0}C after 24 h, appearance or aggravation of a reduced level of consciousness since admission, appearance or aggravation of neurological signs since admission.

Recommendations for management of drug availability

In non-epidemic situations

In non-epidemic situations, the recommended treatment for bacterial meningitis at district level is ceftriaxone once a day for 5–7 days, the patient assumes the cost of this treatment, and the availability of ceftriaxone in health structures is under the responsibility of the national authorities.

In epidemic situations

During an epidemic, early treatment is essential to reduce mortality and sequelae. The principle is a free, simple presumptive treatment, available at peripheral level. Countries may continue to use OC when available and as recommended by national protocol or choose ceftriaxone.

Countries should add ceftriaxone to their national list of essential drugs for epidemic meningitis for peripheral health centres, define a national strategy for the introduction and monitoring of ceftriaxone, and obtain from WHO a list of certified ceftriaxone manufacturers.

To be available in time and in sufficient quantities at peripheral level, presumptive treatment must be pre-positioned before the epidemic season and a strategy of distribution, stock management, and evaluation must be defined. After the epidemic, remaining treatments must be centralized.

Operational issues before the epidemic season

Monitoring tools must be prepared: i.e. national tables with province and district names; population and number of doses of antibiotics to be released; date of shipment to the province and to the districts.

Pre-positioning

Before the epidemic season, treatments must be pre-positioned in sufficient quantity to permit complete treatment coverage of the affected districts. Pre-position sites and times of delivery must be defined.

Pre-positioning of presumptive treatment (OC or ceftriaxone) in the provinces must be done according to the distribution plan. To avoid the misuse of the stock of meningitis outbreak treatment, it must be kept in a location other than the health facilities, where doctors or nurses could use it for other treatment purposes. At regional level, the presumptive treatment stock must be kept at the regional health dispensary outside of the hospital. At district level, the stock should be with the district management team outside of the hospital. At the beginning of the epidemic season, treatments for five bacterial meningitis cases should be distributed to each health facility.

Apart from treatment of meningitis, OC indications are limited. Consequently the only problem created by the pre-positioning of OC stocks in health facilities is the possible misuse of single dose treatment in non-epidemic periods. With ceftriaxone, the problem is more acute because third-generation cephalosporins have many indications and could be used for infections other than meningitis. To avoid disruption of pre-positioned stocks for meningitis

outbreaks, the availability of ceftriaxone should be guaranteed between the time of pre-positioning and use when the epidemic occurs.

Treatment kits

Pre-positioning is recommended at peripheral level of a treatment kit composed of OC or ceftriaxone, its solvent (e.g. ceftriaxone + aqueous solvent), injection materials (syringe, needle, safety box) and an antipyretic (paracetamol). For the hospital level, complementary kits with drugs and materials recommended in national protocols (e.g. supplementary ceftriaxone, antimalarials, diazepam) should be pre-positioned.

Estimation of adequate quantity of antibiotics to order

To avoid shortage of antibiotics, the needs have to be estimated according to the number of expected cases.

Estimation must be made according to the cumulative annual incidence levels which may vary according to the region or district or between districts. The best way to estimate the needs is to consider the average incidence of the five previous years. Where this information is not available, an incidence of 150–300 cases per 100 000 inhabitants can be used, which is a reasonable average for a district in the African meningitis belt. Other factors to consider are the level of immunization of the population and the delay in shipment to the health facilities. A security stock must be anticipated to respond to a high attack rate or an increase in the exposed population (migration, refugees).

Table 5 shows an example of an estimation of needs. For a population of 500 000 inhabitants with an average attack rate of 300 per 100 000 inhabitants, 1500 cases are expected. If 100 cases have been recorded, 1400 treatments at least are necessary. To anticipate a possible underestimation of the incidence, the breakage of some vials and the possible delay in shipment, a security margin of 25% should be adopted to avoid shortage of treatment during the outbreak. In the example in Table 5 this represents a supplement of 350 treatments.

Table 5
Example of the estimation of needs according to the number of expected cases

	Estimation
a. Population at risk	500 000
b. Attack rate (per 100 000 population)	300/100 000
c. Estimated cases (a x b)	1500 cases
c. Cases already declared at the period	100 cases
d. Number cases considered (b - c)	1400 cases
e. Security stock (25% of d)	350
f. Number cases to estimate needs (d + e)	1750 cases
g. Quantity: no. of vials needed (1 treatment = 4* vials)	7000

*1vial = 1 g

Operational issues during the epidemic season: distribution of the treatment

At district level, a focal person must be identified who will centralize the distribution in the district. The focal person will be responsible for distribution of kits of 5–10 treatments (i.e. 20–40 vials) to hospitals and health facilities that first declare cases, then kits of 5 treatments (i.e. 20 vials) to health facilities with 0 cases declared (in epidemic districts or in neighbouring areas). After the beginning of an epidemic, the quantities to be distributed should be based on:

- the number of cases reported weekly and the CFR
- the epidemic curve and the population figures
- frequency of provision, accessibility of health facilities and existing stocks.

Monitoring and distribution should be done based on these data, ideally on a weekly basis, or as frequently as required, the objective being to guarantee a continuous supply based on the epidemiological situation.

The focal person should update the available stock weekly, by using stock management forms to record the entries (origin, quantity, batch number and date of entry) and the outgoings (destination, quantity, batch number and date of delivery). The focal person should also define the minimum level of stock that should trigger a new order (e.g. 50 % of stocks).

Operational issues after the epidemic season

After the epidemic season, all remaining treatments should be sent to the regional level to avoid misuse of OC and to avoid use of ceftriaxone for other bacterial diseases.

An evaluation of the plan of action should be undertaken. Some indicators of the management of the distribution system (indicators of efficiency) and the impact of the strategy (indicators of effectiveness) are proposed below.

Indicators of efficiency

- number of days/weeks of shortage of drugs during the course of the epidemic season
- proportion of health facilities supplied during the epidemic season
- proportion of health facilities with treatment protocol available
- proportion of health facilities complying with the national protocol
- ratio of number of vials used to number of patients treated
- delay between the crossing of the alert threshold and the first availability of treatment in hospital or peripheral health centres.

Indicators of effectiveness

- impact of treatment, e.g. CFR by age group, sex, pathogen
- proportion of patients receiving a second dose of ceftriaxone
- proportion of patients who failed treatment
- proportion of patients referred to a higher level.

Recommendations for preventing the emergence of resistance to antibiotics

Train health professionals

Reducing the misuse of antibiotics is the main concern in order to decrease the probability of drug resistance emerging. In health facilities personnel must be trained in the use of antibiotics. Emphasis must be put on the management of common infectious diseases and their etiologies according to age in order to reduce the inappropriate use of antibiotics.

Decrease the use of antibiotics by immunization against the main causative pathogens of bacterial meningitis

S. pneumoniae and *H. influenzae* have already shown a decrease in their susceptibility to OC and ceftriaxone. Apart from *S. pneumoniae* meningitis outbreaks which can affect all age groups, *S. pneumoniae* and *H. influenzae* are more frequent in children and systematic immunization of children against these pathogens decreases the incidence of these infections in this age group and therefore decreases the use of antibiotics.

Educate the population

Clear educational messages should be given to the population on the appropriate use of antibiotics to decrease self-medication which is often inappropriate and ineffective. Generally, dose and treatment duration are incorrect and this is a factor in the emergence of drug resistance. The situation is aggravated by the use of medicaments bought in the street where they are often of questionable quality.

Implement bacteriological diagnosis

With a single dose treatment (OC or ceftriaxone), the risk of emergence of drug resistance is more likely in *S. pneumoniae* and *H. influenzae* than in *N. meningitidis*. Since *S. pneumoniae* and *H. influenzae* cause only about 5% of bacterial meningitis during epidemic periods in epidemic districts, the risk therefore is small. However, in non-epidemic situations, where *S. pneumoniae* and *H. influenzae* could be responsible for most of the cases, the single dose treatment must not be used because it will increase the exposure of these pathogens to inappropriate doses of antibiotics and thus increase the selection of resistant strains.

Performing lumbar punctures and examining CSF allows the bacteriological identification of the causative pathogen. Treatment can then be adapted appropriately, thus avoiding the selection of resistant strains. Unfortunately, there is a lack of systematic use of the laboratory for confirmation of cases of meningitis in the countries of the African meningitis belt. Particular emphasis should be put on strengthening laboratory capacity for the confirmation of causative pathogens (and serogroups of *N. meningitidis*) as well as for monitoring antibiotic resistance. There is a need to conduct rapid laboratory tests to adapt the treatment (antibiotic, dose, duration of treatment) appropriately.

The following laboratory tests should be conducted, depending on the organizational level of the health facility (national, regional, district) and the technical capacity of the laboratory at that level:

- Gram stain and cell counts of CSF at district laboratory, or at the health facility with appropriate equipment;
- rapid latex tests at district laboratory level where a cold chain is available.

The laboratory technicians should be trained to perform and interpret Gram stains and latex agglutination tests correctly, and good quality reagents must be available. The added value of latex tests is that they can be used at field level and substantially reduce the delay for bacteriological confirmation and therefore aid treatment decision-making.

Recommendations for monitoring antibiotic susceptibility of causative pathogens of bacterial meningitis

Enhanced epidemic meningitis surveillance focuses on systematic weekly collection, compilation and analysis of epidemiological data, as well as the adequate collection, transportation and analysis of laboratory specimens. Reliable laboratory data are essential for the choice of appropriate vaccine and drugs.

Currently, the main concern of decreased susceptibility associated with introduction of single dose ceftriaxone as presumptive treatment is the impact on *S. pneumoniae*. However, with the continuing OC misuse, and the increased use of third-generation cephalosporins in Africa (within and outside health structures), there are some concerns about the evolution of susceptibility of *N. meningitidis* in the future. To respond to these concerns there should be a monitoring process in place with the aim to detect the emergence of drug resistance.

Functional laboratory networks must be built in each country to increase the capacity for diagnosis of meningitis in national laboratories. The objective is to obtain data, strains or CSF samples throughout the year from most of the districts, in order to monitor the geographical spread of pathogens (*S. pneumoniae*, *H. influenzae* and *N. meningitidis*) and their drug resistance.

Currently, there is a lack of data about antibiotic susceptibility at country level due to difficulties in the isolation of pathogens. **At district level**, the practice of lumbar puncture and the use of trans-isolate (TI) bottles must be promoted and systems for transport of specimens need to be implemented. For each suspected case of bacterial meningitis, a TI bottle containing the CSF specimen and 2 ml of CSF collected in cryotubes must be sent to the national reference laboratory. Delays in transporting CSF specimens from some districts to the national laboratories are sometimes too long and subsequent cultures are often negative.

The technical capacities of the laboratories have to be strengthened at all levels in the country: Laboratories need to receive the support necessary in terms of:

- reagents
- training of personnel
- quality control.

Standard operating procedures (SOPs), developed by the Multi-Disease Surveillance Centre (MDSC) are available for use at national level and put particular emphasis on strengthening laboratory capacity for the confirmation of causative pathogens and their serogroups, as well as for monitoring antibiotic resistance. Further information about the organization of the monitoring scheme developed by MDSC can be found in Annex 3.

Molecular tools have been implemented in some countries to detect pathogens in cases where there is no growth from the specimens submitted. These tools have permitted more data on the etiology of bacterial meningitis to be obtained. Laboratories should establish links with WHO Collaborating Centres and other recognized meningococcal laboratories or networks, such as the European Monitoring Group of Meningitis (EMGM) (see Useful Addresses, page 20).

To analyse the data on drug susceptibility, clinical data must be collected simultaneously. Close collaboration between the laboratory and epidemiological surveillance is necessary to associate clinical data and bacterial strains.

The protocol for surveillance of antibiotic susceptibility of *N. meningitidis*, *H. influenzae* and *S. pneumoniae* needs to be strengthened **at regional level**:

- Laboratory techniques must be standardized to permit longitudinal surveillance.
- All existing laboratory networks need to collaborate and exchange data on the situation of antibiotic susceptibility. MDSC could play a role in the facilitation and the coordination of the network.
- A quality assurance scheme must be organized at regional level: 10–20 % of isolates obtained at national level should be sent regularly to one of the national reference laboratories. In the same way, regional laboratories should be quality controlled by the WHO Collaborating Centres (see Useful Addresses, page 20).

Conclusions

- During epidemics of meningococcal meningitis, presumptive treatment with a single dose of either ceftriaxone or OC is appropriate. Countries can decide to use one or the other as presumptive treatment during epidemics in their national plan of response.

- In non-epidemic situations *S. pneumoniae* and *H. influenzae* may be more prevalent than *N. meningitidis* and therefore presumptive treatment with a single dose of ceftriaxone is not appropriate. In non-epidemic situations treatment should be given for at least 5 days and the choice of antibiotic made on the basis of the age of the patient and the most likely causal pathogen.

- During epidemic seasons, early treatment is essential to reduce mortality and sequelae; a plan of distribution and tools for follow-up must be designed to allow the timely delivery of antibiotic treatment.

- Longitudinal laboratory-based surveillance of *N. meningitidis*, *S. pneumoniae* and *H. influenzae* must be implemented at national and regional level in the African meningitis belt to monitor drug resistance.

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Annex 1

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Annex 2

Additional information on the etiology of meningitis in the African meningitis belt and antimicrobial resistance

Etiological agents

Neisseria meningitidis is not the only etiological agent of bacterial meningitis and many other bacterial species can be involved, e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, Enterobacteria (e.g. *Salmonella* spp., *Escherichia coli*), and others found more specifically in neonates (*Streptococcus agalactiae*, *Streptococcus pyogenes*). The incidence and etiologies of bacterial meningitis vary through the year according to the prevailing conditions (epidemic or non-epidemic) and the age groups affected.

During non-epidemic situations in the African meningitis belt, numerous studies conducted in Burkina Faso, Ghana, Niger or Mali have shown the percentages of cases caused by the most common etiological agents, as follows:

Etiological agent	% of meningitis cases
N. meningitides	37–52
S. pneumoniae	27–43
H. influenzae	5–31

In the same way, the percentage of cases of bacterial meningitis caused by the different etiological agents differs between epidemic and non-epidemic areas during the epidemic season. In Niger, during the 2006 epidemic season, *N. meningitidis* caused 95% of cases in epidemic or in alert districts compared with 59% in non-epidemic districts. In non-epidemic districts, a third of the cases of bacterial meningitis were due to *S. pneumoniae* or *H. influenzae*.

Although recent studies from Niger and Ghana have shown that incidence rates of *S. pneumoniae* have a seasonal pattern similar to that observed for meningococcal meningitis, the relative proportion of cases due to *S. pneumoniae* remains the same in meningococcal epidemic situations.

Causes of bacterial meningitis according to age

In Niger, children less than 1 year of age accounted for 43.9% of all pneumococcal meningitis cases, with 25.6% of cases being ≤ 6 months of age and 12.5% of cases occurring during the first 3 months of life. Nearly all (96.8%) of the cases of *H. influenzae* meningitis occurred among children under the age of 5 years, 92.9% among the under 2-year-olds, and 84% during the first year of life.

In a survey conducted in Niamey, Niger, between 1981 and 1996, among 101 cases of bacterial meningitis in neonates (< 1 month of age) showed the following distribution of causes:

Etiological agent	% of cases in neonates (< 1 month of age)
S. pneumoniae	33.7
enterobacteria including *Salmonella* spp	15
H. influenzae	10
N.meningitidis	11
Streptococci other then *S. pneumoniae*	3

The observed relationship between etiological agents of bacterial meningitis and age groups can also be found in other African countries (within and outside the meningitis belt).

Case-fatality rates of bacterial meningitis in the meningitis belt

Some of the data available are summarized in the table below.

Etiological agent	Time period of study	Study population	CFR %
H. influenzae	Niger, 1989–1996		43.3
	Niger, 2003–2006		33.3
S. pneumoniae	literature review (Perrocheau et al., 2004)		8–25
S. pneumoniae	Niger, 1981–1996		52.7
	Niger, 2003–2006		53.4
All causes	Niger, 1981–1996	neonates	58

Comprehensive information is unfortunately unavailable mainly due to the absence of case-based data linking laboratory results and patient outcome. District-level epidemiological and laboratory data can however be used as a proxy for pathogen-specific CFRs. In Burkina Faso for example, among the 12 districts that crossed the epidemic threshold in 2003, the highest CFRs (14–26%) were reported in districts where the proportions of *S. pneumoniae* were highest, as compared to the districts with low CFR (< 10%).

Long-term sequelae due to *S. pneumoniae* meningitis have been poorly studied in Africa and as a result are frequently underestimated. A recent study in England showed that sequelae can be present in as many as 25% of confirmed cases of *S. pneumoniae* meningitis.

Antimicrobial resistance

Information about antibiotic susceptibility is crucial for early and effective treatment.

Chloramphenicol resistance

In Africa, the rate of decreased susceptibility to chloramphenicol among *S. pneumoniae* ranges from 0–13%. *H. influenzae* has been shown to develop resistance; in Kenya susceptibility decreased from 100% in 1994 to 28% in 2002. In Malawi and Niger in the 1990s, 25% of *H. influenzae* strains were resistant to chloramphenicol. For *N. meningitidis*, chloramphenicol resistance has been described only in serogroup B meningococci which are uncommon in the meningitis belt.

The indiscriminate use of oily chloramphenicol (OC) in non-epidemic situations, regardless of the etiology, is certainly responsible in part for the high CFR associated with *S. pneumoniae* and *H. influenzae* infections.

Resistance to third-generation cephalosporins including ceftriaxone

A review of the literature shows that reduced susceptibility to 3 g doses of cephalosporin definitely occurs among clinical isolates of *S. pneumoniae* but has never been recorded for *N. meningitidis* and *H. influenzae* in Africa. According to different studies in Africa, the rate of decreased susceptibility of pneumococci to third-generation cephalosporins ranges from 0–6.3%. Even in the worst affected areas, reduced susceptibility to third-generation cephalosporins has not gone much beyond 5–6%. *S. pneumoniae* serotype 1 mainly encountered in African countries and responsible for the increased incidence of bacterial meningitis in Ghana, is not frequently encountered in the carriage state and consequently is less exposed to antibiotic pressure and less likely to develop resistance. Nevertheless, the choice of ceftriaxone as a first-line treatment for meningitis during epidemics should follow the establishment of a monitoring process capable of detecting a significant increase of resistance.

The risk of antibiotic resistance expansion in Africa with the extensive use of ceftriaxone is currently mainly limited to *S.pneumoniae*. This risk is higher with single dose treatment. When *S. pneumoniae* has been identified or is suspected clinically, a 5-day course of ceftriaxone is needed to decrease the risk of selection of a resistant strain. However, in epidemic periods, when the most frequent agent of bacterial meningitis is *N. meningitidis*, presumptive treatment with a single dose of ceftriaxone is appropriate.

In a recent study on generic formulations of ceftriaxone, Schito and Keenan (2005) have shown that several products appeared to be inferior to the original Roche formulation (Rocephin) in achieving required pharmacokinetic/pharmacodynamic parameters for successful treatment of *S. pneumoniae* infections. As a consequence, some generic formulations of ceftriaxone may increase the risk of clinical failure and/or emergence of resistant isolates. Particular emphasis must be put on ensuring the provision of generic formulations of good quality.

Annex 3

Organization of the monitoring system developed by the MDSC

The WHO Multi-Disease Surveillance Centre (MDSC) in Ouagadougou, Burkina Faso, supervises the implementation of standard operating procedures (SOPs) at country level and coordinates all meningitis surveillance activities. These include standardization of data collection, analysis of the data at regional level, prepositioning of laboratory supplies in countries, training of health personnel at various levels, as well as assessing country preparedness.

The results of the compiled epidemiological and laboratory data are synthesized in a weekly feedback bulletin and disseminated to countries and partners. In addition, the circulation of meningitis strains is monitored year-round with the technical support of the WHO Collaborating Centres for meningococci and through collaborations that have been developed directly with national laboratories or research institutes.

Objectives of the MDSC are to:

- monitor antimicrobial susceptibility of bacteria that cause meningitis;
- develop a network of national public health laboratories (NPHLs) in selected countries;
- offer facilities for quality assurance and diagnostic services to selected laboratories.

MDSC has developed strategies to:

- harmonize diagnosis and detection techniques for antimicrobial resistance of meningitis bacteria: technical guides have been disseminated; in-country training organized; quality assurance programmes are currently being implemented with special emphasis on external quality assurance by reference laboratories;
- provide essential reagents for outbreak investigation in countries;
- sensitize NPHLs to collect bacteriological data/samples and send isolated pathogens to MDSC for analysis;
- work with WHO Collaborating Centres for pathogen identification and susceptibility, and for quality assurance;
- ensure feedback to all participants and collaborators.

Roles of national laboratories, MDSC laboratory and WHO Collaborating Centres:

National reference laboratories should collect the strains isolated from bacterial meningitis, to make a preliminary identification (including serological type) and apply standard techniques for antimicrobial testing. They should send to the MDSC a representative sample of these strains. To this end, national reference laboratories need to receive the necessary support in terms of reagents, training of personnel, and quality control by the MDSC.

The MDSC laboratory collects the samples from countries for analysis, confirmation of the identification of strains and feedback.

WHO Collaborating Centres confirm strains sent by MDSC or countries, characterize the strains and determine antibiotic resistance factors.

Perspectives:

Currently four countries are involved in the monitoring systems develop by the MDSC: Benin, Burkina Faso, Mali and Niger. The Central African Republic and Ghana are soon to join the network and in 2007, they will be followed by Chad, Ethiopia and Nigeria.