

## MEMORANDUM

**From:** Coordinator, ERI      **To:** Dr S. Hill, PAR      **Date:** 22 June 2007  
**Our ref:** ERI/EPR/WP/cg      **Attention:**  
**Your ref:**      **Through:**  
**Originator:**      **Subject:** REVIEW OF CHLORAMPHENICOL  
INJECTION - EXPERT CONSULTATION ON  
ESSENTIAL MEDICINES FOR CHILDREN -  
GENEVA, 9 - 13 JULY 2007

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On the basis of a report on the comparative effectiveness and safety of chloramphenicol injection, it is proposed that this drug no longer be listed as a first line treatment for "bacterial meningitis or for meningococcal meningitis epidemics". This recommendation is mainly based on the fact that there would be a dramatic rise in bacterial resistance to chloramphenicol in the countries still using this drug. At the same time, it has been proven that ceftriaxone was a valuable therapeutic alternative and that the price of this drug was no longer an issue in developing countries.

### Review of the technical report

The review reveals several confusions and approximations, mostly:

- The different bacteria responsible for meningitis are numerous and their distribution depends on the age of the patient and the situation (epidemic/ non-epidemic). The document reports only two aetiologies of bacterial meningitis: *Haemophilus influenzae* (Hib) and *Neisseria meningitidis* (Nm). Throughout the document, it is assumed that "Bacterial meningitis" is equivalent to "Hib meningitis". The role of Nm is evoked only in the paragraph dedicated to the use of oily chloramphenicol (OC) during meningitis epidemics.
- Most of the presented data on a high level of resistance to OC, refer to Hib. It is also reported that there has been increasing resistance of Nm to OC for 20 years but with reference to only one article published in 1998 and concerning 11 strains of Nm serogroup B collected in France and Vietnam. This serogroup has never been found in Sub-Saharan Africa.
- The author makes the difference between sporadic "bacterial meningitis", where OC alone was shown as not being efficient enough and the Nm outbreak situation, where a treatment by single injection of OC remains appropriate (even if single-dose ceftriaxone can be an alternative treatment). However the conclusion of the report does not reflect this distinction and proposes to withdraw OC from the Model List for both indications.

cc: Director, EPR  
Director, PSM

### The current WHO strategy

Since 1996, the World Health Organization has recommended the use of oily chloramphenicol in peripheral health centres for the presumptive treatment of meningitis during epidemics in Africa. Indeed, 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.

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.

Considering that there was a risk of OC production disruption (there is only one manufacturer) and that the place of ceftriaxone in the therapeutic means should be clarified, the Epidemic and Pandemic Preparedness and Response department (EPR), CDS/WHO, decided to review the recommendations related to the presumptive treatment of bacterial meningitis in Africa, in epidemic and non epidemic situations<sup>1</sup>. In July 2006, a consultation of experts was convened. The main conclusions of this consultation are the following:

1. In non-epidemic situations (sporadic bacterial meningitis), the main responsible agents are *S. pyogenes*, *S. pneumoniae*, Hib, Nm and enterobacteria. In the absence of bacterial identification, Ceftriaxone was recommended as first line presumptive treatment for at least 5 days.
2. In epidemic situations, Nm is the main responsible agent. A presumptive treatment with a single dose of either ceftriaxone or OC was considered appropriate. **Indeed the surveillance of the Nm strains circulating in Africa has not showed any resistance to chloramphenicol.** Resistance to this antibiotic has been only reported among serogroup B which is absent in Sub-Saharan Africa.

**Despite the fact that ceftriaxone has been proven to be as efficient as OC as first line treatment during epidemics and is now cheaper than OC, the experts considered there was still a need for maintaining OC as an option in epidemic situation** for the following reasons:

- there is a risk of increasing bacterial resistance to ceftriaxone in Africa. Since this drug 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. Moreover, it could have an impact on the antibiotic susceptibility of Nm in the future.
- as early treatment is essential to reduce mortality, WHO recommends to pre-position first line treatments at district level before the epidemic season. In pre-positioning a broad-spectrum antibiotic like ceftriaxone, there is a risk of misuse and consecutive shortage when the epidemic will occur.

<sup>1</sup> "Standardized treatment of bacterial meningitis in Africa in epidemic and non epidemic situations" ERP/CDC/WHO. 2007. Available on [www.who.int/csr/resources/publications/](http://www.who.int/csr/resources/publications/)

Moreover, previous tensions on OC availability demonstrated how it was tricky to depend on one single drug for meningitis epidemic containment. Removing OC from the Model List will likely cause the last manufacturer to stop the production, leaving *de facto* only one drug (ceftriaxone) for the first line treatment during epidemic.

Conclusion and recommendations

The Epidemic and Pandemic Preparedness and Response Department, CDS considers that:

- using oily chloramphenicol as first line treatment during epidemic meningitis is still justified by the nature of the main causal pathogen in this situation as well as its sensitivity to this antibiotic.
- even if ceftriaxone has been proven to be as efficient as OC in this indication and is now cheaper, both options should be kept in order to not depend on a single drug

**Consequently, EPR strongly recommends to maintain Oily Chloramphenicol in the Model List of Essential Medicines for Children with the single following indication: first line presumptive treatment during a meningitis epidemic.**



Dr William Perea