Introduction

The WHO Guidelines for the Treatment of Malaria (MTGs), the current edition of which is available in English, French and Spanish, provides comprehensible, global and evidence-based guidelines for the formulation of policies and protocols for the treatment of malaria. It was first published in 2006 and a revised edition (2nd edition) was published in 2010. The guidelines are available both in hard and electronic (web-based) versions. The MTGs have been produced under the guidance of the Technical Expert Group (TEG) on Malaria Chemotherapy, convened by the WHO Global Malaria Programme. Following the creation of the Malaria Policy Advisory Committee (MPAC) in early 2012, the TEG on Malaria Chemotherapy now reports to and makes recommendations to the MPAC.

Major comprehensive review for an updated edition of the Guidelines is undertaken after at least 3 years following the most recent publication. In between this review period, specific section updates can be undertaken at any time on an ad-hoc basis when sufficient evidence supports such, and it is of major public health significance. These ad-hoc reviews are incorporated into the web-based version until the next major review. The most recent ad-hoc review for the MTGs was with regard to the recommendation for the use of parenteral artemesunate in preference to IV quinine.

The purpose of this pre-read is to inform the MPAC about the upcoming review process, and offer MPAC members an opportunity to discuss and make recommendations on the structure or content to the TEG on Malaria Chemotherapy and WHO-GMP.

The purpose and objectives of the current edition of the MTGs

- provide analysis of the current evidence regarding malaria diagnosis and treatment to inform and guide decisions
- provide a framework for development of specific malaria diagnosis and treatment protocols in countries
  - Taking into account national and local malaria drug resistance pattern and health services capacity
It should be noted that the MTGs are not meant to be used as a clinical manual for the treatment of malaria, but rather clinical manuals are derived from the MTGs.

**The current content and scope of the MTGs**

- Malaria diagnosis and treatment – policies and strategies from a clinical and a public health perspective
- What to use – in diagnosis, curative treatment (uncomplicated and severe malaria, including in special risk groups)
- How and where to use
  - Indications, contraindications and precautions
  - Best practices in clinical management, including special patient groups
  - Strategies for the use of medicines at population level

**Target audience**

- primarily policy-makers in ministries of health, who formulate national treatment guidelines.
- in addition, the following groups should also find them useful:
  - public health and policy specialists working in hospitals and primary health-care services, research institutions, medical schools, nongovernmental organizations and agencies working on malaria diagnosis and treatment, the pharmaceutical industry and health professionals, clinicians and managers of health services in endemic countries.

**Evidence for recommendation**

In 2008 WHO adopted the GRADE methodology for evaluating evidence for policy and guideline recommendations. So for the 2010 update (*second edition*) of these guidelines, all new recommendations have been subjected to the GRADE process.

- The GRADE (Grading of Recommendations Assessment, Development and Evaluation system), is a uniform approach that is being widely adopted for evaluating the strength of a recommendation based on the robustness of the evidence relating to a specific clinical question.
  - The GRADE methodology involves a four-step process:
    - identification of the clinical questions, and the critical and important outcomes to answer these questions;
• systematic reviews of the evidence (using Cochrane methodology) focusing on these outcomes;
• construction of GRADE tables to summarize the data and to assess the quality (or robustness) of the evidence;
• interpretation of the GRADE tables and the formulation of recommendations.

**Formulation of recommendations**

In the formulation of recommendations, all available evidence irrespective of the level (even where it was not suitable to apply the GRADE methodology) is included in the discussions for formulating recommendations. The key policy considerations are:

• evidence on safety, efficacy and overall benefits
  – from a clinical and public health perspective
• Considering, in the case of a medicine, procedure or a strategy, the benefits against the risks,
  – the implications for the health system,
  – the feasibility of implementation

**Scope of review (3rd edition)**

The review for the production of a 3rd edition, will include a comprehensive of existing recommendations in the light of any new evidence which might affect the recommendation in its totality, or with regard to the strength of the recommendation. In addition, specific areas have been identified for in-depth review, these are listed below:

• Review of existing treatment options for safety, efficacy and context of use, e.g.
  – Cardiotoxicity of quinolone antimalarials (following the assessment of prolongation of QTc of Eurartesim by EMA)
• New antimalarial molecules or combination options, e.g.
  – Arterolane-piperaquine
  – Artesunate + pyronaridine
• Preventive use of antimalarials
  – chemoprophylaxis for travellers
  – chemoprevention in special risk groups (IPTp, IPTi and SMC)
• Updates based on the recent review of the ERG,
  – Use of primaquine as gametocytocidal agent for *P. falciparum*,
• Safety of mefloquine in pregnancy, based on the USFDA evaluation of this medicine and possibly the access to the pregnancy registry of Hoffmann-La Roche.
• Systematic testing for malaria of children presenting with anaemia in areas of high transmission
  – Criteria for determination of malaria risk in the context of IMCI and iCCM
  – Interaction between iron and malaria, and its implications in the management of malaria in the context of IMCI
• Review of the potential role of multiple first line therapies within and across countries as a resistance management tool (together with the TEG on Drug Resistance and Containment)
• Highlight areas of gaps where there is urgent need for
  – new molecules to address the burden of disease,
  – more robust data / evidence to strengthen the certainty of recommendations.

**Review process and timelines**

• The review process is based on the WHO Guidelines for Guidelines development which is overseen by a WHO Guideline Review Committee (GRC). The guideline development or review process takes between 18-24 months, depending on the scope and the prior availability of the evidence in a systematic review format to which the GRADE methodology can easily be applied. Below is a summary of the process:
  – Establishment of a Guideline Steering Group. This is a WHO in-house committee comprised of members from relevant WHO departments involved in development of guidelines related to case management of malaria, to oversee the general process of the guidelines development to ensure that the WHO processes is being adhered to. For the previous editions, members of this group have included representatives from the department of Maternal Newborn Child and Adolescent Health, and TDR.
  – Agreement on the review topic / questions, and subsequent commissioning of evidence review and development of GRADE tables
    • TEG (malaria Chemotherapy) – 1st quarter 2013.
    • Systematic review and construction of GRADE Tables - Cochrane review group (six months)
  – Review and formulation of draft recommendations
    • TEG (last quarter of 2013)
  – Review by External experts and potential end/users of the guidelines (last quarter of 2013)
  – Finalization of the guidelines and submission to MPAC (first quarter 2014)
  – Approval from MPAC (March 2014)

* the timeframe included above is the anticipated minimal projections based on the previous experience of the Guidelines development process. The GRC advises that at least a minimum of 24 months is required to produce or update a standard comprehensive Guideline.
– Final clearance through the WHO GRC and other WHO in-house processes second quarter 2014
– Publication, translations and dissemination (June 2014)

It is projected that the 3rd edition of the MTGs will be ready for printing by June 2014

A simplified illustration of the process is presented below.