

Updating the WHO Guidelines for the Treatment of Malaria (MTGs)*

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1. INTRODUCTION

The WHO Guidelines for the Treatment of Malaria (MTGs), provides comprehensible, global and evidence-based guidelines for the formulation of policies and national guidelines for the treatment of malaria. It was first published in 2006 and the 2nd edition was published in 2010. The MTGs have been produced under the guidance of the Technical Expert Group (TEG) on Malaria Chemotherapy.

A draft plan for revision and update of the 2nd edition was presented and endorsed at the meeting of the Malaria Policy Advisory Committee (MPAC) in September 2012, and updates of the review process presented to the MPAC at the March 2013 and March 2014 meetings.

The recommendations in the third edition of these guidelines as in previous editions, aim to provide recommendations on malaria treatment, including a new section on intermittent preventive treatment based on the latest scientific evidence of in vitro antimalarial susceptibility, safety, and the pharmacokinetic and pharmacodynamic properties of the different antimalarial medicines. It takes into account areas where levels of drug resistance and background immunity vary as well as operational and feasibility aspects even in severely resource-constrained settings.

An online survey was carried out to obtain feedback from end-users of the current edition (2nd edition) of the Guidelines for the treatment of malaria with the main objective to assess satisfaction of the end-users with the document's scope, content and suitability for their needs, and sought input and specific suggestions regarding the format, presentation, content, accessibility, and overall user-friendliness of the MTGs. The main target audience for the survey included policy makers in ministries of health, public health and policy specialists, and health professionals, clinicians and managers of health services in endemic countries, who have consulted and used the WHO MTGs.

Overall, respondents expressed satisfaction with the current scope, content and format of the MTGs. All sections of the guidelines were considered very important, and it was considered equally important to retain evidence for existing recommendations in future editions of the guidelines. GRADE tables and key references were regarded the most useful format for presenting evidence. The respondents however suggested expansion on certain topics (such as antimalarial resistance and chemoprophylaxis) and the inclusion of more visual aids, graphs and images and a different colour scheme. Based on these results of the survey, the overall format of presentation of the MTG has been retained as in the past editions.

The recommendations of the updated MTGs (3rd edition) have been finalised at the last malaria chemotherapy TEG held in June 2014 and are presented to MPAC for ratification.

2. CONSOLIDATED KEY RECOMMENDATIONS

The following set of core principles, held by the guideline panel, form the foundation for the recommendations.

* This document was prepared as a pre-read for the September 2014 meeting of the Malaria Policy Advisory Committee (MPAC) and is not an official document of the World Health Organization.

A. Prompt diagnosis and effective treatment

Universal access to parasitological diagnosis of malaria beyond the reach of quality controlled microscopy, is possible with deployment of quality assured rapid diagnostic tests (RDTs), appropriate for use in primary healthcare and community settings.

Uncomplicated malaria can progress rapidly to severe forms of the disease if left untreated, especially in people with no or low immunity. Severe malaria is almost always fatal without treatment and patients may die within hours. Therefore, programs should ensure access to prompt diagnosis and effective treatments within 24–48 hours of the onset of malaria symptoms.

B. Combination therapy

Preventing or delaying resistance is essential to the success of both national and global malaria control strategies. To help protect the current and future antimalarial medicines, all episodes of malaria should be treated with at least two antimalarials with different mechanisms of action (combination therapy). To improve adherence to treatment fixed-dose combinations are highly preferable to co-blistered or co-dispensed combinations.

C. Rational use of antimalarials

To reduce the spread of drug resistance, limit wastage of precious artemisinin-based combination therapies and better identify other febrile illnesses in the context of changing malaria epidemiology, there is a strong need to dispense antimalarials only to those who truly have malaria and promote adherence to full treatment course.

2.1 Summary of key recommendations

Diagnosing malaria
All people with suspected malaria should have a parasitological test to confirm the diagnosis.
Treating uncomplicated <i>P. falciparum</i> malaria
Treat adults and children (including infants, pregnant women in their second and third trimesters, and breastfeeding women) with uncomplicated <i>P. falciparum</i> malaria with an ACT. The current recommended first or second-line ACT treatment options are: <ul style="list-style-type: none">Artemether plus lumefantrine; Artesunate plus amodiaquine; Artesunate plus mefloquine; Dihydroartemisinin plus piperazine; Artesunate plus sulfadoxine-pyrimethamine. <p style="text-align: right;"><i>Strong recommendation, High quality evidence</i></p> All ACTs should contain at least three days treatment with an artemisinin-derivative. <p style="text-align: right;"><i>Strong recommendation, High quality evidence</i></p> In low transmission areas, also provide a single dose of 0.25mg/kg primaquine to reduce onward transmission of <i>P. falciparum</i> , without the need for G6PD testing (excluding pregnant and breastfeeding women and infants aged < 1 year). <p style="text-align: right;"><i>Strong recommendation, Low quality evidence</i></p>

Treating uncomplicated *P. falciparum* malaria in special risk groups

- Treat pregnant women with uncomplicated *P. falciparum* or chloroquine resistant *P. vivax* malaria in the first trimester with seven days of quinine plus clindamycin (if unavailable use an ACT).
- Treat infants weighing less than 5 kg with uncomplicated *P. falciparum* malaria with an ACT dosed at the same mg/kg target as for children weighing 5 kg.
- In HIV positive people with uncomplicated *P. falciparum* malaria avoid AS+SP if on treatment with co-trimoxazole, and avoid AS+AQ if on treatment with efavirenz.
- Treat travellers returning to non-endemic settings with uncomplicated *P. falciparum* malaria with an ACT.
- People with *P. falciparum* hyperparasitemia are at increased risk of death and require close monitoring in addition to an ACT.

Conditional recommendation, Low quality evidence

Treating uncomplicated non-falciparum malaria

In areas with chloroquine susceptible *P. vivax*, treat adults and children with uncomplicated non-falciparum malaria using either chloroquine or an ACT.

Strong recommendation, High quality evidence

In areas with chloroquine resistant *P. vivax*, treat adults and children with uncomplicated *P. vivax* malaria with an ACT (including infants, lactating women, and pregnant women in their second and third trimesters).

Strong recommendation, High quality evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria

To prevent future relapse, treat people (excluding pregnant or breastfeeding women, and people with G6PD deficiency) with *P. vivax* or *P. ovale* malaria with a 14-day course of primaquine.

Strong recommendation, Moderate quality evidence

In people with mild to moderate G6PD deficiency, consider relapse prevention with primaquine 0.75 mg base/kg once a week for 8 weeks.

Conditional recommendation, Very low quality evidence

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding is complete, then treat with 14 days of primaquine to prevent future relapse.

Conditional recommendation, Moderate quality evidence

Treatment of suspected severe malaria pending transfer to higher level facilities (Pre-referral treatment)

In settings where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single dose of intramuscular artesunate and refer to an appropriate facility for further care. Use artemether or quinine if artesunate is not available

Strong recommendation, Moderate quality evidence

In settings where intramuscular injections are unavailable, treat children below the age of six years with a single dose of rectal artesunate and refer immediately to an appropriate facility for further care.

Strong recommendation, Moderate quality evidence

Treating severe malaria

Treat adults and children with severe malaria with intravenous or intramuscular artesunate for at least 24 hours (including infants, pregnant women in all trimesters, and lactating women).

Strong recommendation, High quality evidence

Children weighing less than 20 kg should receive a higher dose of artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose) to ensure an equivalent drug exposure.

Strong recommendation based on pharmacokinetic evaluation

Once the patient has received at least 24 hours of parenteral therapy, AND is able to tolerate oral therapy, complete treatment with three-days of an ACT

Strong recommendation, High quality evidence

Chemoprevention for special risk groups

In areas with highly seasonal malaria transmission, provide seasonal malaria chemoprevention with monthly AQ+SP for all children below the age of six years during each transmission season.

Strong recommendation, High quality evidence

In areas of moderate to high malaria transmission where SP is still effective, provide intermittent preventive treatment of infants with SP (SP-IPTi) alongside DTP2, DTP3, and measles vaccinations.

Evidence not graded

In malaria endemic areas, give Intermittent Preventive Treatment with SP to all pregnant women in their first or second pregnancies at every scheduled antenatal visit commencing at the start of the second trimester. Each SP dose should be given at least one month apart.

Strong recommendation, High quality evidence

3. ADDITIONAL RECOMMENDATION / CHANGES IN THE REVISED EDITION

3.1 Dosage Recommendations

Identification of the dose regimens of each antimalarial that provide the best balance between tolerability, safety and efficacy (therapeutic ratio) is a main objective of the development of this guidelines. Under-dosing is dangerous both for the patient and the community; it increases the individual risk of treatment failure and it accelerates the spread of resistance. The randomised controlled trials which are the basis for efficacy and safety evaluation and drug registration typically provide clinical data for a single dose regimen, and often do not provide enough information on important sub-groups such as young children and pregnant women. The application of target dose and

therapeutic ranges derived from these studies, in some cases has resulted in dose recommendations which were too low for specific groups at risk.

The therapeutic objective of treatment is to ensure adequate and optimal antimalarial drug exposures across all patient groups. Based on pharmacokinetic studies and modelling, if a sub-group of patients is found to have consistently lower drug blood levels than in main sub-groups in whom the dose has been established, then provided there is no safety concern, these guidelines have recommended dose adjustment to achieve comparable antimalarial drug exposure.

Principles underlying the recommendations on dosing of antimalarial medicines

- In all patients, malaria parasites need to be exposed to therapeutic antimalarial drug blood levels.
- ACT regimens should be deployed using optimal dosing strategies that prolong the useful therapeutic life, i.e. maximize the likelihood of rapid clinical and parasitological cure and retard drug resistance, including transmission of resistant strains.
- While age-based dosing may be more practical, it carries the risk of potentially under-dosing or over-dosing unless region-specific weight-for-age databases are available to guide dosing in specific regions.

The dosage recommendations in the MTGs are derived from the dose response and the drug exposure profiles (pharmacokinetic and pharmacodynamics data) of recommended drugs – in all target populations, and awareness of dose related toxicity. Based on the review of this data for all main antimalarials, the new guidelines propose a change in the dosing schedule recommended target doses of two specific antimalarials for small children to ensure the recommended target doses and thus adequate drug blood levels is achieved. This change was necessary and made for:

- Dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria,
 - Though the overall cure rates achieved with the manufacturers' dosing recommendations are generally high (> 95%), a sub-analysis shows that these doses are sub-optimal in children aged 1 to 4 years who are at a three-fold increased risk of treatment failure. This is attributed to many young children currently being dosed below the minimum recommended targeted piperaquine dose of 16 mg/kg per day. Also pharmacokinetic differences resulting in this age group having significantly lower drug concentrations than older children and adults given the same mg/kg dose. This means that these young children require a higher mg/kg dose of at least 54–59 mg/kg (i.e. 18-20 mg/kg per day) to achieve the recommended target dose.
- Artesunate injection for the treatment of severe malaria.
 - Pharmacokinetic studies in children with severe malaria receiving intramuscular artesunate suggest that there is underexposure relative to older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin (DHA) in young children. Body weight has also been identified as a significant covariate in studies of oral and rectal artesunate pharmacokinetics. As absorption of intramuscular artesunate is rapid and reliable this suggests that young children have a larger apparent volume of distribution for both compounds, and therefore need a slightly higher dose of parenteral artesunate to achieve comparable exposures to older children and adults. The recommendation was thus modified as
 - In children ≤ 20 Kg give 3mg/kg/dose of injectable at 0,12 and 24 hours and continue once daily until oral administration is feasible

- In children with weight >20Kg and adults give 2.4mg/kg/dose injectable artesunate at 0,12 and 24 hours and continue once daily until oral administration is feasible

3.2 New Sections included in the 3rd Edition of the Malaria Treatment Guidelines

- Intermittent Preventive Treatment in pregnancy
- Intermittent preventive Treatment in infants
- Seasonal Malaria Chemoprevention

Review process and timelines

September 2014	Approval from MPAC.
Q4 2014	Final clearance through the WHO GRC and other WHO in-house processes.
Q1 2015	Release and Launching, Web Publication, translations and dissemination.