

Position of WHO's Roll Back Malaria Department on malaria treatment policy

Background

Global malaria control is being threatened on an unprecedented scale by rapidly growing resistance of *Plasmodium falciparum* to conventional monotherapies such as chloroquine, sulfadoxine-pyrimethamine (SP) and amodiaquine. Multi-drug resistant falciparum malaria is widely prevalent in South-East Asia and South America. Now Africa, the continent with highest burden of malaria is also being seriously affected by drug resistance.

WHO recommendations

As a response to the antimalarial drug resistance situation, WHO recommends that treatment policies for falciparum malaria in all countries experiencing resistance to monotherapies should be combination therapies, preferably those containing an artemisinin derivative (ACT - artemisinin-based combination therapy).

Following are the therapeutic options currently recommended by WHO:

1. artemether/lumefantrine
2. artesunate plus amodiaquine
3. artesunate plus sulfadoxine/pyrimethamine (in areas where SP efficacy remains high)
4. amodiaquine plus sulfadoxine/pyrimethamine, in areas where efficacy of both amodiaquine and sulfadoxine/pyrimethamine remains high (mainly limited to West Africa).
5. artesunate plus mefloquine, an additional recommended combination treatment which is reserved for areas of low transmission.

The current WHO policy on antimalarial treatment is based on the recommendations and conclusions of two consultations of international experts on malaria chemotherapy, held in November 2000 and April 2001 (see ANNEX I).

WHO strategic position on expanding access to ACT

Over the last three years around 20 countries (7 in Africa) have updated their treatment policies to include ACTs as 1st-line or 2nd-line treatment of malaria. This was based on WHO advice, and was made possible with the participation of RBM partners and increased mobilization of international funding.

In 2002 the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) was established, and it has become one of the main international funding mechanism to support the implementation of highly effective interventions for the control of these three diseases in endemic developing countries. The GFATM has become the largest financial supporter of ACTs in countries. A total of US\$30 million has been committed over the full 5-year life of GFATM Board-approved proposals from African

countries for the purchase of ACTs in three proposal rounds. Moreover, as a result of flexibility in the use of funds committed to these programmes, even more funds may be allocated to purchase ACTs as countries continuously evaluate their drug policies and how to best utilize grants from the GFATM. Indeed a number of recipient countries in Africa, which originally requested funding for chloroquine, are already in the process of re-evaluating their drug policies towards the use of ACTs, examples being Senegal, Ghana, Benin, Mali, Chad, and The Gambia. In addition to the GFATM, national Governments and RBM partners, such as UN Organizations, Bilateral Agencies and NGOs (MSF in particular) have contributed to the sourcing and financing of ACTs.

The single non artemisinin-based combination therapy (amodiaquine plus SP), listed among WHO recommended options is reserved for countries which, for whatever reason, are unable to move into ACTs. However, the following limitations of this option should be noted:

1. The number of countries where efficacy is high of both amodiaquine and SP is limited and mainly restricted to West Africa.
2. As both amodiaquine and SP are currently in wide usage as monotherapies it is unlikely that the adoption of this combination therapy will significantly delay the spread of resistance to either drug. Therefore, the adoption of CT with amodiaquine plus SP is likely to be a short-term solution.
3. Even in areas where the efficacy of both amodiaquine and SP remain high, their combined use will compromise the useful therapeutic life of both, and thus endanger their potential use as partner drugs for artesunate in ACTs.
4. There is currently no replacement for SP as a drug for Intermittent Preventive Treatment (IPT) in pregnancy. Rather than compromise its therapeutic life by using it as a component of a CT, SP should be reserved for IPT.
5. As the process of drug policy change and implementation is resource- and time-intensive (experience shows it to take from one to three years), all efforts for improving access to treatment should be directed towards implementing the most effective and durable treatment policy.

One of the principal reasons for countries wishing to adopt non artemisinin based combinations (CTs) is their lower price. However, multiple financial mechanisms are now available in countries, and international support is being mobilised to help countries adopt ACTs, and an increasing number of countries are now replacing ineffective monotherapies with ACTs.

To facilitate access to ACTs, WHO has, in collaboration with UNICEF, established a system for pre-qualification of manufacturers of artemisinin derivatives, negotiated price agreements with manufacturers, engaged in international procurement, and set up systems of pharmacovigilance. A service for malaria medicines and supplies is now being established by WHO and RBM partners to facilitate access to ACTs. This will be a component of a larger facility for improving access to medicines and supplies for HIV-AIDS, TB and Malaria.

Conclusions

Consistent with WHO recommendations, malaria endemic countries which are experiencing resistance to currently used antimalarial drug monotherapies

(chloroquine, sulphadoxine/pyrimethamine or amodiaquine) should change treatment policies to the highly effective artemisinin-based combination treatments (ACTs).

We call on all RBM partners to unite in a global coalition to mobilise expertise and resources to support countries to access ACTs and to make these drugs affordable to the people in need.

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ANNEX I

WHO Informal Consultation on the Use of Antimalarial Drugs (13-17 November 2000)¹

The meeting reviewed and updated recommendations on the use of antimalarial drugs for malaria prevention and treatment of uncomplicated malaria, and to assess the implications of latest drug developments for national treatment policies. The experts elaborated a specific definition of antimalarial combination therapy, and highlighted the strategic value of drug combinations for national malaria control programmes and those involved in implementing antimalarial treatment policies.

In particular, the experts recognized and widely accepted:

"the potential value of drug combinations, notably those containing an artemisinin derivative, to improve efficacy, delay development and selection of drug-resistant parasites and thus prolong the therapeutic life of existing antimalarial drugs. Combinations that do not contain an artemisinin derivative could be a preferred option for reasons of cost and accessibility in some countries."

WHO Technical Consultation on Antimalarial Combination Therapy (4-5 April 2001)²

In view of the recognition of the role of combination therapy, WHO convened a technical consultation to review existing evidence on combination therapy for malaria and to make specific choices on appropriate combinations for use.

The Technical Consultation strongly endorsed the potential of combination therapy for use in Africa. It recommended the following four combination therapies with potential for deployment, on the basis of the available safety and efficacy data, which are listed below in prioritized order, if costs were not an issue:

1. artemether/lumefantrine;
2. artesunate (3 days) plus amodiaquine;
3. artesunate (3 days) plus sulfadoxine/pyrimethamine (SP), in areas where SP efficacy is high;
4. amodiaquine plus SP, in areas where efficacy of both drugs remains high - mainly limited to countries in West Africa.

The consultation recognized that increased funding would be required to facilitate the appropriate exploration of use and purchase of optimal antimalarial drugs. Failure to assure funding for antimalarial drugs will provide a major obstacle for many countries in Africa in moving to combination therapy.

Options that were not recommended for policy included:

- a. chloroquine-based combinations (CQ + SP and CQ + artesunate)
- b. one-day treatment of artesunate + SP
- c. mefloquine-based combinations (e.g. mefloquine plus artesunate) in areas of high malaria transmission
- d. one-day treatment of artesunate plus mefloquine in the acute phase of a complex emergency or malaria epidemics

The committee also recommended the accelerated development of other artemisinin-based combination therapies which are in the pipeline, in particular of:

- i. piperazine/dihydroartemisinin,
- ii. chlorproguanil/dapsone/artesunate and
- iii. pyronaridine/artesunate.

¹ WHO (2000) *The Use of Antimalarial Drugs*. Report of a WHO Informal Consultation. WHO unpublished report. WHO/CDS/RBM/2001.33.

² WHO (2001). *Antimalarial Drug Combination Therapy*, Report of a WHO Technical Consultation. WHO unpublished report. WHO/CDS/RBM/2001.35.