



FACTs on ACTs (Artemisinin-based Combination Therapies) An update on recent progress in policy and access

Malaria burden, drug resistance, and patterns of drug use

Recent estimates of the global malaria burden have shown increasing levels of malaria morbidity and mortality, reflecting the deterioration of the malaria situation in Africa during the 1990s. About 90% of all malaria deaths occur in Africa south of the Sahara, and the great majority of them in children under five (1).

Key among the factors contributing to the increasing malaria mortality and morbidity is the widespread resistance of *Plasmodium falciparum* to conventional antimalarial drugs, such as chloroquine, sulfadoxine-pyrimethamine (SP) and amodiaquine. Multidrug-resistant *P. falciparum* malaria is widely prevalent in south-east Asia and South America. Now Africa, the continent with highest burden of malaria, is also being affected. Resistance to inexpensive monotherapies such as chloroquine and SP has developed or is developing rapidly, with increased mortality as a result.

The inappropriate use of antimalarial drugs during the past century has contributed to the current situation: antimalarial drugs were deployed on a large scale, always as monotherapies, introduced in sequence, and were generally poorly managed in that their use was continued despite unacceptably high levels of resistance. In addition, there has been over-reliance on both quinoline compounds (i.e. quinine, chloroquine, amodiaquine, mefloquine and primaquine) and antifolate drugs (i.e. sulfonamides, pyrimethamine, proguanil and chlorproguanil), with consequent encouragement of cross-resistance among these compounds.

Over the past decade, a new group of antimalarials – the artemisinin compounds, especially artesunate, artemether and dihydroartemisinin – have been deployed on an increasingly large scale. These compounds produce a very rapid therapeutic response (reduction of the parasite biomass and resolution of symptoms), are active against multidrug-resistant *P. falciparum* malaria, are well tolerated by the patients and reduce gametocyte carriage (and thus have the potential to reduce transmission of malaria). To date, no parasite resistance to these compounds has been detected. If used alone, the artemisinins will cure *falciparum* malaria in 7 days, but studies in south-east Asia have shown that combinations of artemisinin compounds with certain synthetic drugs produce high cure rates on just 3 days of treatment. Furthermore, there is some evidence that use of such combinations can greatly retard development of resistance to the partner drug.

WHO recommendations on malaria treatment

As a response to increasing levels of antimalarial resistance, WHO recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine-pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies) for *falciparum* malaria (2, 3).

As yet another step towards combating drug resistance in Africa, WHO has lowered the resistance-threshold for treatment policy change from 25% to 15% as assessed by standard WHO protocols, in children under 5 years of age (4), meaning that a more effective treatment should be adopted before 15% resistance to the old treatment is reached.

WHO currently recommends the following therapeutic options:

- artemether-lumefantrine,
- artesunate plus amodiaquine,
- artesunate plus sulfadoxine-pyrimethamine (in areas where SP efficacy remains high),
- artesunate plus mefloquine (in areas with low to moderate transmission), and
- amodiaquine plus sulfadoxine-pyrimethamine, in areas where efficacy of both amodiaquine and SP remains high (mainly the countries of west Africa). This non-artemisinin-based combination therapy is reserved as an interim option for countries that, for whatever reason, are unable immediately to move to ACT (5)

Malaria endemic countries adopt combination therapies

Since 2001, 34 countries have adopted one of the above five combination therapies, several as first-line treatment and a few as second-line. Many others are in the process of policy change (see table below). WHO has provided continuous technical cooperation to ministries of health on all aspects of national treatment policy change – monitoring the therapeutic efficacy of medicines, and updating and implementing ACT-based treatment policies.

	Number of countries in	
	Africa	rest of the world
Changed treatment policy to ACT ^a	15 ^b	14 ^c
Changed treatment policy to CT	3	1
In process of treatment policy review	9	7
Studying efficacy of ACT options	4	1

^a Adoption does not immediately translate into implementation: In Africa only 6 out of the 15, and outside Africa 10 out of 14 countries which have adopted ACTs are deploying these drugs in the public sector.

^b Benin, Burundi, Cameroon, Comoros, Côte d'Ivoire, Equatorial Guinea, Gabon, Ghana, Kenya, Mozambique, Sao Tome and Principe, Senegal, South Africa, Republic of Tanzania, Zambia: all but four changed to artesunate plus amodiaquine

^c Bhutan, Bolivia, Cambodia, Ecuador, Guyana, Indonesia, Lao People's Democratic Republic, Myanmar, Papua New Guinea, Peru, Philippines, Suriname, Thailand, Viet Nam: all but five changed to artesunate plus mefloquine

Supply and demand for ACTs

The exponential increase in the number of countries adopting ACTs is leading to a rapid increase in demand for artemisinin and its derivatives.

Artemisinin compounds are derived from a raw substance extracted from the plant *Artemisia annua*. Cultivation of the plant requires a minimum of 6 months, and extraction, processing and manufacturing of the final products require at least 2 to 5 months depending on the product formulation. Agricultural production is not a limiting factor. However, if the very rapid increase in demand for the pharmaceutical products is not predicted in time to allow for agricultural production, there could be temporary shortages in supply. Reliable forecasting of global ACT requirements is thus essential.

WHO forecasts that at least 30 000 000 adult ACT courses will be required globally in 2004 and 132 000 000 courses by the end of 2005 (see Fig. 2). UNICEF and WHO will convene a meeting with manufacturers in April 2004 to discuss the need to increase production in 2005 by at least 100 000 000 treatments.

Fig. 1 Countries moving to ACTs in Africa ^a

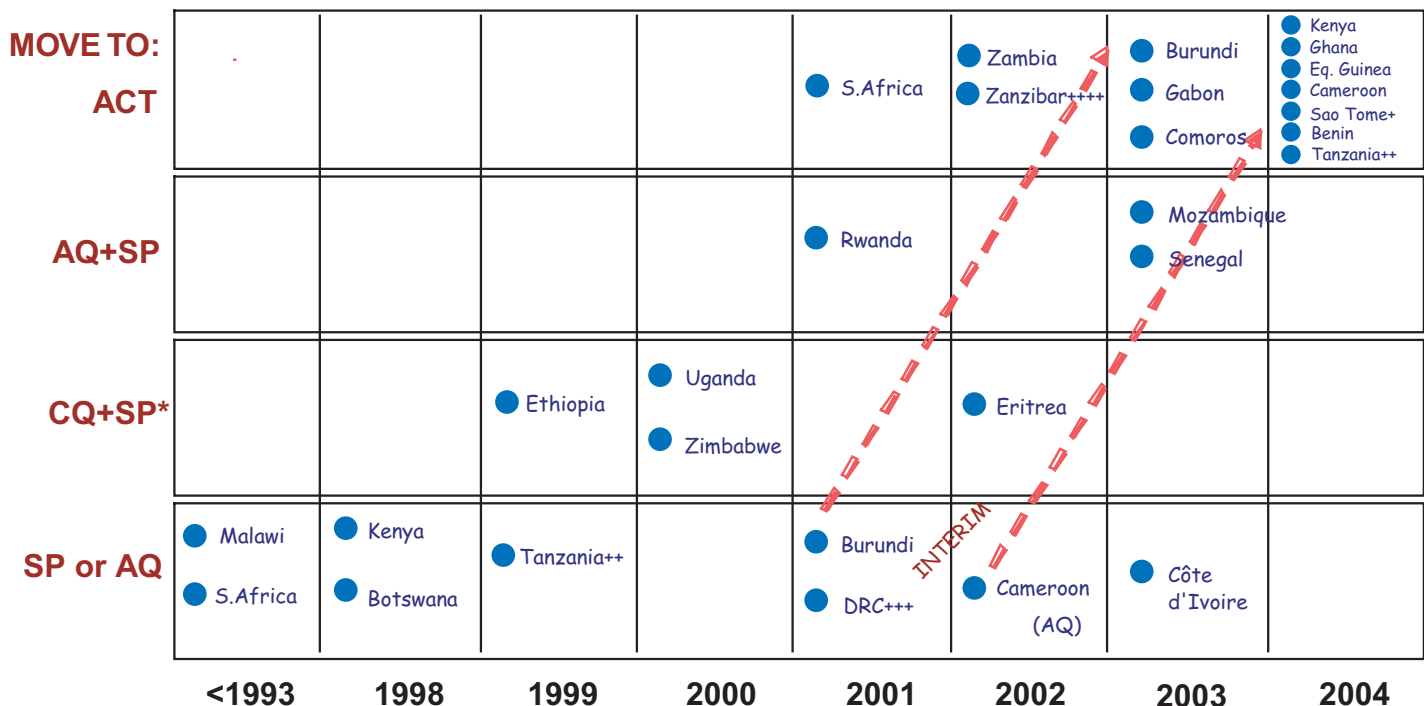


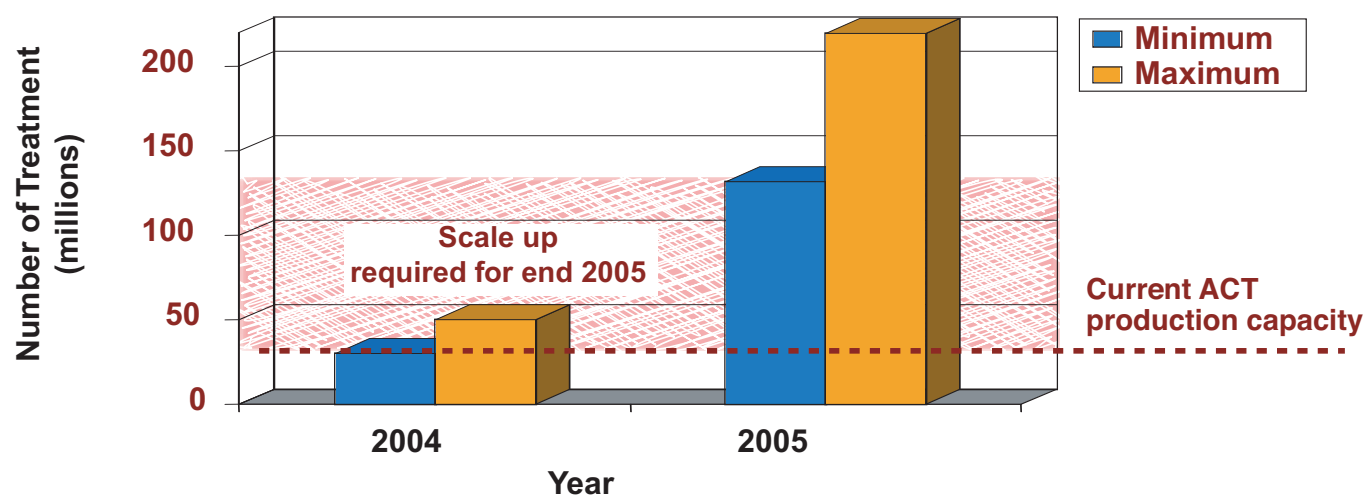
Figure 1 shows how and when African countries moved away from monotherapies to ACTs as first-line treatment.

^a Based on information available to WHO up to March 2004. Chloroquine (CQ); sulfadoxine-pyrimethamine (SP); amodiaquine (AQ); red arrows show the transition from an interim policy with SP to an ACT.

* Not recommended by WHO since 2001.

+ Sao Tome and Principe ++ Republic of Tanzania (mainland) +++ Democratic Republic of Congo ++++ Zanzibar, Republic of Tanzania

Fig. 2 Global forecasts of ACT requirements^a



^a WHO forecast of ACT requirements has been based on: (1) timing of adoption of ACT and of expected change in countries that are in process of changing treatment policy to ACTs; (2) estimated malaria incidence per country (WHO/RBM estimates); (3) delivery through only public services or public-private sectors (minimum and maximum estimates, respectively). Assumptions made were: (1) financial resources available; (2) nationwide implementation 9 months after adoption of the new policy.

How access to ACTs is being ensured

<p>Quality assurance</p> <p><i>Pre-qualification and Sourcing Project</i></p>	<p>In May 2002, in collaboration with other United Nations agencies, WHO established an international mechanism to pre-qualify manufacturers of artemisinin compounds and ACTs on the basis of compliance with internationally recommended standards of manufacturing and quality (8). Products and manufacturers that meet these standards are included in a list considered acceptable for procurement by United Nations agencies. The list is published as a guide to governments, NGOs and other partners, e.g. the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), procuring ACTs. To date, one ACT – artemether–lumefantrine (Coartem[®]) – has been pre-qualified.</p>
<p>WHO and UNICEF call for tenders of ACTs</p>	<p>WHO and UNICEF have called for tenders of co-blistered products of the following combinations for which there are as yet no pre-qualified manufacturers:</p> <ul style="list-style-type: none"> – artesunate plus amodiaquine – artesunate plus sulfadoxine–pyrimethamine – artesunate plus mefloquine – amodiaquine plus sulfadoxine–pyrimethamine.
<p>Negotiated prices and centralized procurement</p> <p><i>artemether–lumefantrine (Coartem[®])</i></p>	<p>WHO and Novartis, the manufacturer of artemether–lumefantrine (Coartem[®]), have entered into a special pricing agreement: Novartis provides the drug at cost price (US\$ 0.9 and 2.4 per child and adult treatment course respectively) for use in the public sector in malaria-endemic countries (9). WHO, through a panel of experts, reviews requests for supplies of Coartem[®], and procures the drug for governments of malaria-endemic countries, United Nation agencies, bilateral agencies, and NGOs.</p>
<p>Financing of ACTs (10)</p> <p><i>Global Fund expenditure on ACTs</i></p>	<p>GFATM, established in 2002, is now the largest funder of ACTs in countries. In first three rounds of funding, a total of US\$ 30 million has been committed over the full 5-year life of GFATM Board-approved proposals for the purchase of ACTs in African countries. In the fourth round of GFATM funding:</p> <ul style="list-style-type: none"> – Countries have been requested to apply for the most effective treatments to roll back malaria. – Provision is made for recipients of approved grants of funding for chloroquine or SP to convert to the use of ACTs in case of documented resistance to these medicines. <p>Other sources of funds for ACT purchases available to countries include development banks, multilateral and bilateral agencies and NGOs.</p>

The cost of the estimated global ACT requirements far exceeds the current level of ACT financing by the GFATM. An enhancement of the financial resources for purchasing ACTs is thus urgently required to both encourage endemic countries to adopt these effective treatment policies and to stimulate the market.

Malaria is a highly treatable disease, and very effective treatment is available in the form of ACTs. WHO calls on all RBM partners to unite in a global coalition to enable countries to accelerate access to ACTs and make these life-saving medicines affordable to the people in need.

References

1. *The Africa malaria report 2003*. Geneva, World Health Organization, 2003 (WHO/CDS/MAL/2003.1093).
2. WHO (2001). *The use of antimalarial drugs: report of a WHO informal consultation, 13–17 November 2000*. Geneva, World Health Organization, 2001 (WHO/CDS/RBM/2001.33).
3. *Antimalarial drug combination therapy: Report of a WHO technical consultation, 4–5 April 2001*. Geneva, World Health Organization (WHO/CDS/RBM/2001.35).
4. *Meeting on goal of malaria treatment policy in the Africa Region, 14–15 August 2003, Harare, Zimbabwe*. Harare, World Health Organization, (in preparation).
5. *Position of WHO's Roll Back Malaria Department on malaria treatment policy*. Geneva, World Health Organization http://mosquito.who.int/cmc_upload/0/000/017/113/who_recommended.htm
6. *Framework for developing, implementing and updating antimalarial treatment policy in Africa: a guide for country malaria control programmes*. Harare, World Health Organization (in press).
7. *Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria*. Geneva, World Health Organization, 2003 (WHO/HTM/RBM/2003.50).
8. *Procurement, quality and sourcing project: access to artemisinin-based combination antimalarial drugs of acceptable quality*. Geneva, World Health Organization (<http://mednet3.who.int/prequal/mal/maldefault.shtml>).
9. *Procurement of artemether/lumefantrine (Coartem®) through WHO*. Geneva, World Health Organization (http://rbm.who.int/cmc_upload/0/000/015/789/Coa_website5.pdf).
10. *Report of the Expert Consultation on the Procurement and Financing of Antimalarial Drugs, 15–16 September 2003*. Washington, DC, World Bank.



WHO

This factsheet has been prepared by the Roll Back Malaria Department of the World Health Organization.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.



Roll Back Malaria is a global partnership initiated by WHO, UNDP, UNICEF and the World Bank in 1998. It seeks to work with governments, other development agencies, NGOs, and private sector companies to reduce the human and socioeconomic costs of malaria.

Roll Back Malaria Partnership, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland
Tel: +41 22 791 2891 E-mail: rbm@who.int

www.rbm.who.int