



FACTS ON ACTS (ARTEMISININ-BASED COMBINATION THERAPIES)

JANUARY 2006 UPDATE

I. 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 80% 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 *falciparum* malaria is widely prevalent in south-east Asia and South America. Now Africa, the continent with highest burden of malaria, is also 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.

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*, are well tolerated by the patients and reduce gametocyte carriage (and thus have the potential to reduce transmission of malaria). To date, no resistance to artemisinin or artemisinin derivatives has been reported, although some decrease in sensitivity *in vitro*

has been detected in China and Viet Nam (2). If used alone, the artemisinins will cure *falciparum* malaria in 7 days, but studies have shown that in combination with certain synthetic drugs they produce high cure rates in 3 days with higher adherence to treatment. Furthermore, there is some evidence that use of such combinations in areas with low to moderate transmission can retard the development of resistance to the partner drug.

II. WHO RECOMMENDATIONS ON MALARIA TREATMENT

As a response to increasing levels of resistance to antimalarial medicines, 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 (3, 4).

As yet another step towards combating drug resistance in Africa, WHO has lowered the resistance–threshold recommended for treatment policy change from 25% to 10% as assessed by standard WHO protocols in children under 5 years of age (5), meaning that a more effective treatment should be adopted when the proportion of treatment failures to the old treatment reaches 10% .

WHO currently recommends the following combination therapies (in alphabetical order):

1. artemether/lumefantrine,
2. artesunate plus amodiaquine¹
3. artesunate plus mefloquine²
4. artesunate plus sulfadoxine/pyrimethamine³.

Note: Amodiaquine plus sulfadoxine–pyrimethamine may be considered as an interim option where ACTs cannot be made available, provided that efficacy of both is high.

¹ In areas where the cure rate of amodiaquine monotherapy is greater than 80%

² Insufficient safety data to recommend its use in Africa

³ In areas where the cure rate of sulfadoxine/pyrimethamine is greater than 80%

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III. MALARIA ENDEMIC COUNTRIES ADOPT COMBINATION THERAPIES

WHO provides technical cooperation to ministries of health on all aspects of national treatment policy change – monitoring the therapeutic efficacy of medicines, updating, implementing and monitoring ACT-based treatment policies. Adoption is not immediately followed by implementation: in Africa a total of 10 out of the 34 (29%), and outside Africa 13 out of the 20 countries (65%) which have adopted ACTs are deploying these medicines in the public sector.

The countries which are currently deploying ACT in the general health services to some extent

are the following:

- In Africa: Burundi, Comoros, Ethiopia, Liberia, Mozambique, Sao Tome and Principe, Sierra Leone, South Africa, Sudan, Zambia, Zanzibar;
- Outside Africa: Bangladesh, Bolivia, Cambodia, Ecuador, Guyana, Indonesia, Lao PDR, Myanmar, Papua New Guinea, Peru, Philippines, Surinam, Thailand, Viet Nam.

Since 2001, a total of 56 countries have adopted one of the WHO recommended artemisinin-based combination therapies, several as first-line treatment and a few as second-line (see table below, last updated on 1st November 2005).

Continent	Countries	Options	Line
AFRICA	Burundi, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Ghana, Guinea, Liberia, Madagascar, Senegal, Sao Tome and Principe, Sierra Leone, Sudan (S), Zanzibar	AS + AQ	1st
	Angola, Benin, Burkina Faso, Comoros, Ethiopia, Gambia, Guinea Bissau, Kenya, Mali, Namibia, Niger, Nigeria, Rwanda, Uganda, South Africa (Kwa Zulu Natal), Tanzania, Togo, Zambia	AL	1st
	Côte d'Ivoire, Gabon, Mozambique, Sudan (N), Sao Tome and Principe, Zanzibar	AL	2nd
	Mozambique, Sudan (N), South Africa (Mpumalanga)	AS + SP	1st
ASIA	Cambodia, Thailand	AS + MQ	1st
	Bangladesh, Bhutan, Laos, Myanmar	AL	1st
	Indonesia	AS + AQ	1st
	Afghanistan, India (5 Provinces), Iran, Tajikistan, Yemen	AS + SP	1st
	Viet Nam	DP	1st
	Papua New Guinea	AS + SP	2nd
	Philippines, Iran	AL	2nd
SOUTH AMERICA	Ecuador, Peru	AS + SP	1st
	Bolivia, Peru, Venezuela	AS + MQ	1st
	Brazil, Guyana, Suriname	AL	1s

AS+AQ = artesunate+amodiaquine; AS+SP = artesunate+sulfadoxine/pyrimethamine;
AS+MQ = artesunate+mefloquine; AL = artemether/lumefantrine; DP = dihydroartemisinin/piperazine

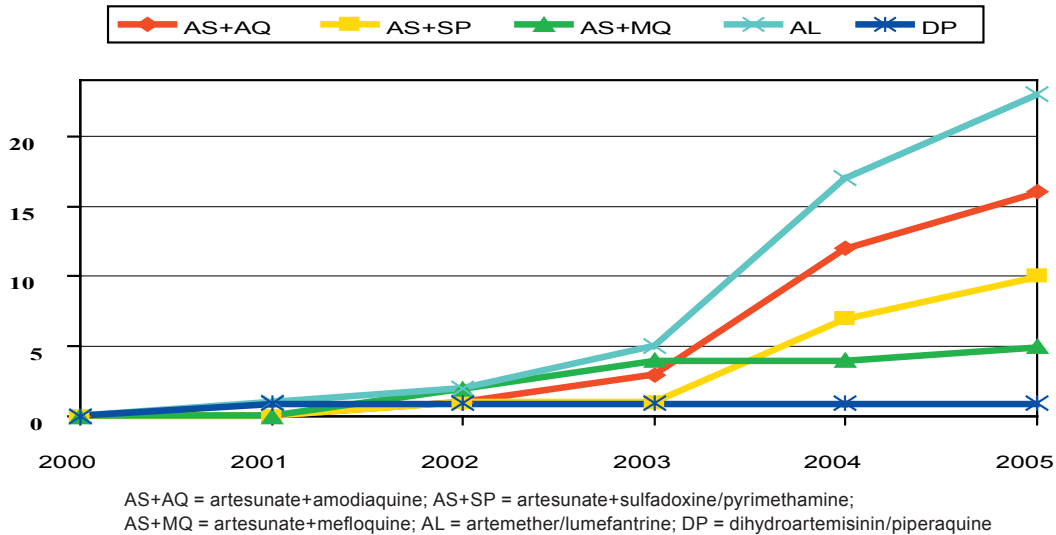


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The Figure 1 shows the trend of adoption of ACTs as first-line treatment (the line represents the cumulative number of countries).

Figure 1



IV. SUPPLY AND DEMAND FOR ACT

The exponential increase in the number of countries adopting ACTs has led to a rapid increase in demand for artemisinin and its derivatives. The global consumption of ACTs has increased from a few hundred thousands in 2001 and 2002 to tens of millions in 2005. The rapid increase in demand produced a global supply shortage of artemether/lumefantrine⁴, the product which was in greatest demand. This shortage which lasted for a period of about 12 months has been overcome by its manufacturing company by introducing major changes in the critical steps of manufacturing, from sourcing to supply chain management. No supply shortages are foreseen for any of the ACTs in the near future.

Artemisinin compounds are derived from a raw substance extracted from the plant *Artemisia annua*. Cultivation of the plant requires a minimum of 6-8 months from planting to harvesting, and extraction, processing and manufacturing of the final products require at least 2 to 5 months depending on the product formulation. In 2005, there has been a major expansion of the agricultural production and extraction facilities from the existing sites and sources in China and Viet Nam to several in Africa and other parts of the world.

WHO forecasts that for 2006 at least 120 million ACT treatment courses will be required globally. The Roll Back Malaria Medicines and Supply Services (<http://www.rollbackmalaria.org/mmss>) is consolidating all ACT country forecasts, including anticipated demands from international funding institutions and procurement agencies and plans to make this information publicly available in early 2006. The sources of information and estimations for these forecasts will be provided to help both manufacturers and health development partners.

- The cost of the estimated global ACT requirements far exceeds the current level of ACT financing by the GFATM and the new funding initiatives are a very important step towards increasing access to ACTs. However, mechanisms for increased and sustained financing are urgently required to both encourage endemic countries to scale-up implementation of effective treatment policies and to guarantee production of these medicines.
- Agricultural production, extraction of artemisinin raw material, the processing of the semi-synthetic derivatives and manufacturing of finished products, all need to be informed by reliable forecasting of global ACT requirement and stable sources of financing.
- Malaria is a highly treatable disease, and now, 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.

⁴ Coartem® is the only ACT prequalified by WHO to date.

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V. HOW ACCESS TO ACT IS ENSURED

<p>QUALITY ASSURANCE Prequalification and Sourcing Project</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 (6). 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-UNICEF CALL FOR TENDERS OF ACT</p>	<p>WHO and UNICEF place regular calls for tenders of co-blistered combinations of the following products for which there are not yet pre-qualified manufacturers: i) artesunate plus amodiaquine; ii) artesunate plus sulfadoxine/pyrimethamine; iii) artesunate plus mefloquine; and iv) amodiaquine plus sulfadoxine/pyrimethamine. Several manufacturers have been inspected by WHO, and GMP-certified products for all of the above ACT are being procured by both WHO and UNICEF, including for GFATM supported programmes.</p>
<p>NEGOTIATED PRICES AND CENTRALIZED PROCUREMENT artemether/lumefantrine (Coartem®)</p>	<p>WHO and Novartis, the manufacturer of artemether/lumefantrine (Coartem®), have a special pricing agreement since 2001: 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 (7). WHO, through a panel of experts, reviews requests for supplies of Coartem®. Through the special price agreement WHO and UNICEF procure the drug for governments of malaria-endemic countries, United Nation agencies, bilateral agencies, and NGOs.</p>
<p>FINANCING OF ACT Global Fund expenditure on ACT</p>	<p>GFATM, established in 2002, is up to now the largest funder of ACTs for public health. In first four rounds of funding, a total of US\$ 230 million has been approved over the first 2 years of GFATM Board-approved proposals for the purchase of ACTs, mostly for African countries.</p> <p>Since January 2004, the GFATM has promoted:</p> <ul style="list-style-type: none"> • The deployment of the most effective treatments to roll back malaria. • The reprogramming of approved grants to procure ACTs instead of chloroquine or SP where there is documented resistance to these medicines. <p>Other sources of funds for ACT purchases available to endemic countries include development banks, multilateral and bilateral agencies and NGOs. Recent new and expected sources of funding for malaria control include the World Bank's Booster Programme for Malaria Control, which amounts to between US\$500 million and US\$1 billion over the next five years, and USA's President's Malaria Initiative (PMI) for US\$1.2 billion over five years for 15 countries. It is expected that some of these funds will be available for the purchase of ACTs.</p>

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