ACT NOW

To get malaria treatment that works to Africa

Access to Essential Medicines Campaign

Released by Médecins Sans Frontières in avril 2003

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Campaign for Access to Essential Medicines

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Printing: Editions Européennes, Brussels, Belgium

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Published by Médecins Sans Frontières Access to Essential Medicines Campaign April 2003

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ACT Now. This is an urgent call to international donors to join African countries in implementing World Health Organization (WHO) treatment guidelines for malaria. On the advice of international experts, WHO recommends African countries facing resistance to classical antimalarials to introduce drug combinations containing artemisinin derivatives – artemisinin-based combination therapy, or ACT for short.

Artemisinin derivatives have attributes that make them especially effective: they are highly potent, fast-acting (parasite clearance is fast and people recover quickly), very well tolerated and complementary to other classes of treatment.

Implementation of new malaria recommendations is a matter of life and death in Africa, where malaria kills between 1 and 2 million people each year. Sickness and death from malaria account for 30-50% of hospital admissions and a yearly loss of US$12 billion on the African continent.

The WHO-led global malaria eradication programme launched in the 1950s sought to eliminate the disease via vector control and effective treatment. The eradication programme was successful in some parts of Asia, North America and Europe, but bypassed sub-Saharan Africa. In 1969, the focus switched to the less ambitious goal of control through treatment. At the time, the treatment of choice was chloroquine, dispensed in a three-day course. This effective treatment campaign led to falling death rates through to the early 1980s.

However, since the early eighties, the situation has stopped improving, and has in fact been getting dramatically worse. Average annual cases were four times higher between 1982 and 1997 compared to the period 1962-1981. Death rates have also jumped: hospital studies in various African countries have documented a two- to three-fold increase in malaria deaths. The continuing use of ineffective drugs despite spectacular levels of resistance is leading to increased treatment failure.

While African countries are heeding the advice of world experts to switch from old failing single-drug treatments to combination treatments, they are being forced to switch to stop-gap, less expensive combinations because of a lack of resources.

Summary «««

Why is MSF so focused on treatment?

Effective malaria control requires strong political will from endemic country governments that translates into implementation of comprehensive prevention and treatment programmes. But while the international community has been willing to do everything possible to augment prevention, there has so far been no concerted drive to support improved treatment.

In its projects MSF supports prevention as an integral part of effective malaria control. There is no controversy there. The debate that we think needs to be stimulated is on treatment.

After extensively documenting resistance to current treatments in MSF projects and carefully considering data gathered by ministries of health in endemic countries that MSF decided to switch to ACT in all its programmes. The decision was articulated in an October 2002 internal MSF malaria policy paper:

To ensure good patient care now and in the future, and to prevent the further spread of the disease in intensity and into new populations, MSF believes it is essential to use artemisinin-based combination therapy (ACT) in all our programmes where there are patients with falciparum malaria, and to explore all avenues open to MSF to assist governments to do the same in affected countries.

Since October 2002, implementation of this policy has focused simultaneously on switching to ACT in all MSF projects, and on advocating for and giving technical support towards increasing the availability of quality ACT drugs.

Médecins Sans Frontières (MSF) is seeking to change the current dynamic in which some international donor countries, such as the US and UK, are supporting a "leave it alone" approach while other countries have no publicly articulated policy. This report debunks detractors' arguments by demonstrating that ACT is safe and effective.

The lack of political and financial support on the part of donors means that endemic countries are often encouraged to "leave alone" failing malaria treatment and are not given financial and technical help to implement more effective strategies.

Without successful implementation of ACT therapies in the next decade, significant progress in controlling malaria will be impossible. This is because there are no miracle non-ACT combinations waiting in the wings, and because malaria control using prevention without effective treatment is doomed to failure.

How can we "leave alone" malaria treatment when one African child dies of malaria every thirty seconds?

This report defines **The Malaria Problem**, looks at **What Works** in malaria treatment and outlines what needs to be done to **Make ACT a Reality**.

Our recommendations convey what MSF thinks needs to be done to stem the tide of unnecessary malaria deaths in Africa.

The idea is a simple one. **Restock Africa with a malaria medicine that works.**

- The World Health Organization must push for implementation of its own recommendation to switch to ACT
- Donors must stop wasting their money funding drugs that don't work and help fund efforts of endemic countries to make the switch to ACT
- Endemic countries need to back up their will to improve malaria control with increased budget allocations
- ACT must be provided to individuals free of charge, or at an affordable price
- International agencies and donors must provide technical support to facilitate both treatment implementation and upgrading international and domestic drug suppliers

"Malaria is like the common cold, except that it's a killer"

MSF doctor, Kajo Keji, southern Sudan

- UNICEF, WHO procurement and the Global Fund for AIDS, Tuberculosis and Malaria must pool needs and make large orders to prime the drug production pump and bring down prices
- International and/or regional pre-qualification needs to be augmented to assist countries in identifying quality drug sources
- Concerned parties must undertake operational research to improve use of current tools
- Research & development for new drugs, new formulations and improved diagnostic tools must be placed high on the agenda and implemented through government supported research and non-profit initiatives such as the Medicines for Malaria Venture.

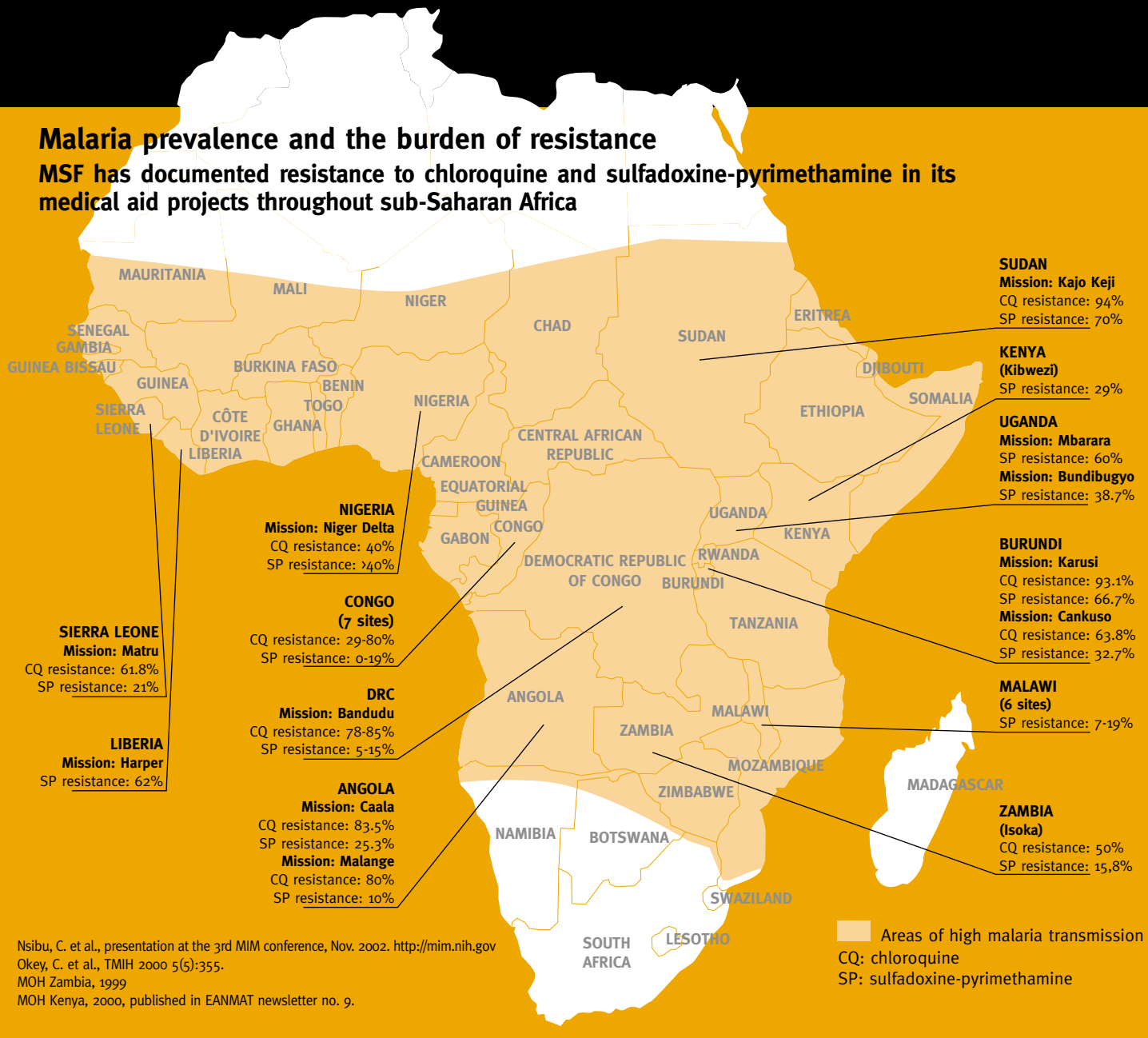
We need to implement ACT today.
We need to ACT now.

the malaria problem

Why Africa can't wait any longer for treatment that works

Malaria prevalence and the burden of resistance

MSF has documented resistance to chloroquine and sulfadoxine-pyrimethamine in its medical aid projects throughout sub-Saharan Africa



SUDAN
Mission: Kajo Keji
CQ resistance: 94%
SP resistance: 70%

KENYA
(Kibwezi)
SP resistance: 29%

UGANDA
Mission: Mbarara
SP resistance: 60%
Mission: Bundibugyo
SP resistance: 38.7%

BURUNDI
Mission: Karusi
CQ resistance: 93.1%
SP resistance: 66.7%
Mission: Cankuso
CQ resistance: 63.8%
SP resistance: 32.7%

MALAWI
(6 sites)
SP resistance: 7-19%

ZAMBIA
(Isoka)
CQ resistance: 50%
SP resistance: 15,8%

NIGERIA
Mission: Niger Delta
CQ resistance: 40%
SP resistance: >40%

CONGO
(7 sites)
CQ resistance: 29-80%
SP resistance: 0-19%

DRC
Mission: Bandudu
CQ resistance: 78-85%
SP resistance: 5-15%

ANGOLA
Mission: Caala
CQ resistance: 83.5%
SP resistance: 25.3%
Mission: Malange
CQ resistance: 80%
SP resistance: 10%

SIERRA LEONE
Mission: Matru
CQ resistance: 61.8%
SP resistance: 21%

LIBERIA
Mission: Harper
SP resistance: 62%

Areas of high malaria transmission
CQ: chloroquine
SP: sulfadoxine-pyrimethamine

Nsibu, C. et al., presentation at the 3rd MIM conference, Nov. 2002. http://mim.nih.gov
Okey, C. et al., TMIH 2000 5(5):355.
MOH Zambia, 1999
MOH Kenya, 2000, published in EANMAT newsletter no. 9.

MSF studies using 14- or 28-day follow-up; list of studies here is not exhaustive

Malaria is the "hidden" global scourge. And Africa is at its epicentre.

Where malaria thrives, people suffer and economies are drained. Malaria, a parasitic disease (see box page 8), thwarts children's cognitive development and education, and adults' ability to make a living and care for their families.[1] At a country level, it impacts on trade, tourism and foreign direct investment. There is a remarkable correlation between malaria and poverty: average GDP in malarious countries is five times lower than in non-malarious countries.[2] Malaria keeps poor people poor.

Malaria statistics read like a road map to a place where no one wants to go: 300-500 million cases a year, 90% of them in sub-Saharan Africa; 1-2 million deaths a year, mostly in Africa; US$12 billion lost every year in Africa[3]; 30-50% of all African hospital admissions[4]; and the litany goes on. Malaria is the leading killer of Africa's children.

Malaria is not an incurable disease, and treatment does not last a lifetime. It is curable in no more than three days. Treatment that works does exist. Why, then, are so many people in Africa dying of malaria? Because Africans with malaria are not benefiting from proven prevention strategies and treatment that works. Affordable, efficacious drugs are not available to them, so people continue to use older medicines that health experts know are no longer working.

In the 1950s, malaria eradication in Africa was considered impractical

Today, in many African countries chloroquine and SP are virtually useless

No secret

There is no secret about the best treatment for malaria today. Combination therapy using artemisinin derivatives is so effective that it is bringing about a revolution in the treatment of the disease, particularly in Asia, where its use is widespread. It is time to bring artemisinin-containing combination therapy, or ACT, to Africa. The World Health Organization (WHO), international donors and African governments cannot afford to let this treatment bypass the continent where malaria is taking its greatest toll.

Already bypassed once

Malaria eradication was identified as a priority in the mid-twentieth century, with the discovery in 1942 of the insecticidal properties of DDT and the establishment of the World Health Organization in 1948. The WHO-led Global Eradication of Malaria programme, launched in the 1950s, sought to eliminate the disease via vector control with DDT and through treatment with chloroquine.

Yet the campaign bypassed sub-Saharan Africa, where eradication was considered impractical because of the high level of transmission and the lack of infrastructure.[5] Malaria was, however, effectively eradicated in zones where infection was lower (areas of southern Europe, North America, Mauritius and Singapore, Hong Kong, parts of Malaysia, and elsewhere). Eventually the malaria parasite developed resistance to DDT; at the same time, concerns about the pesticide's safety emerged, and the eradication strategy was dropped. By 1969, WHO accepted the necessity of control programmes in areas where the disease was not eradicated; the focus turned to control through chloroquine treatment. For a time, this seemed to keep the disease in check, and certainly malaria mortality in Africa due to malaria declined through the early 1980s (see figure 1), due in large part to the availability of cheap and effective drugs.[6]

Malaria is roaring back

Now, however, malaria has roared back in Africa, spreading throughout almost all of sub-Saharan Africa. The average annual number of reported malaria cases in the period 1982-1997 is four times that reported in the period 1962-1981.[7] Deaths have also increased. After a steady decline from the early 1900s to the early 1980s, the annual malaria mortality rate in Africa has jumped dramatically over the last two decades, even as that of the rest of the world has declined.[8] And, since 1990, even as all-cause mortality for children has dropped in Africa, malaria-specific mortality has been on the rise.[9]

There has also been a recent, striking increase in the number of severe malaria epidemics on the continent, with epidemics in 35 areas between 1997-2002.[10] To give just one example: between October 2000 and March 2001, a severe malaria epidemic in Burundi caused around 3 million cases among a population of 6.5 million people.[11] The epidemic caused 13,000 deaths in only three provinces.

Human migration, often as a result of war or conflict, has played a role in this resurgence. People who haven't developed natural resistance to malaria increasingly migrate to regions where the disease is rife. At the same time, poverty, war and political instability have weakened

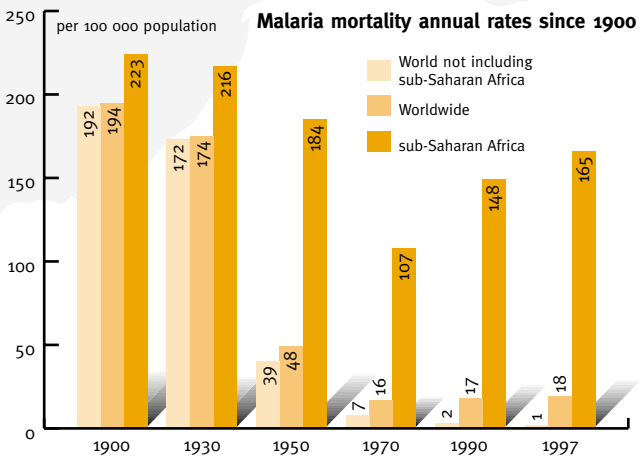


Figure 1
Source: World Health Organization, World Health Report 1999

What is malaria?

Malaria is a parasitic disease caused by four species of Plasmodium protozoa (single-cell parasites): **Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale** *and* **Plasmodium malariae**. *Of the four species,* **Plasmodium falciparum** *is responsible for the most deaths. The parasite transmission by Anopheles mosquitoes, the vector, is affected by climate and geography, and is often highest during the rainy season.*

When a malaria-infected Anopheles mosquito bites a human, the parasite passes into the person's bloodstream, where it multiplies and can cause illness or even death. When this person is bitten by another mosquito, the parasite travels from human back to insect and the cycle continues.

Symptoms of malaria include fever, shivering, pain in the joints, headaches, repeated vomiting, convulsions and coma. If left untreated, the disease – particularly that caused by P. falciparum – may progress to severe malaria and sometimes death.

In areas where the disease is endemic, repeated bouts with the disease are common. African children can get malaria many times each year. Such repeated exposure can have grave health consequences: chronic anaemia, malnutrition, retarded physical and cognitive development, and potential increases in vulnerability to other diseases.

Malaria is curable, but so ma
because they are not get

public health systems in many developing countries. Changing demographics and land use have also played a part. And most experts agree that the resurgence of the disease is due in large part to that fact that malaria parasites and its vector are increasingly developing resistance to the drugs and insecticides used to control them.

The drugs are failing

In the 1950s, the drug chloroquine was first introduced to treat malaria. Fast, effective and cheap, it seemed a miracle drug, and a potent ally in the fight to eradicate the disease. But uncontrolled and widespread use contributed to the rapid emergence and spread of resistance (see box page 9) beginning in the mid-1960s, radiating out from Southeast Asia, and hitting Africa by the late 1970s.

In response, another drug, sulphadoxine-pyrimethamine (SP, also known as Fansidar®) was widely introduced, in the 1970s in Southeast Asia (starting in 1973 in Thailand) and in Africa in the early 1990s (starting in 1993 in Malawi). Initially, it was extremely useful: it is taken as a single dose, and side-effects are very uncommon. But optimism was short-lived: within five years, resistance to this drug had already developed in much of Southeast Asia, and is now spreading rapidly through Africa.

Today, in many African countries, resistance to chloroquine and SP is so high that both drugs are virtually useless. To give only a few examples: 1999 figures show 28-97% resistance to chloroquine in Tanzania, 66-87% resistance in Kenya, and 10-80% resistance in Uganda.[12] According to EANMAT (East African Network for Monitoring Antimalarial Treatment), SP resistance reached 27% in Bondo and 42% in Kisumu in Kenya in 2000 and 17% in Kyela and 34% in Mkuzi in Tanzania in 1999.[13] It is important to note that these data represent treatment failure detected on day seven after start of treatment. Such a short follow-up underestimates resistance compared to a longer follow-up (eg, 14 or 28 days).[14] Using 14 or 28-day follow-up, MSF has documented resistance to chloroquine and SP in its medical aid projects throughout sub-Saharan Africa (see map page 6), a growing drug resistance also recognised by the World Health Organization.[15]

Treatment failure = more deaths

Ineffective drugs continue to be used despite the spectacular levels of resistance, leading to increased treatment failure. Treatment failure leads to rising rates of mortality, particularly among children: hospital studies in various African countries have documented a two- to three-fold increase in malaria deaths and hospital admissions for severe malaria, corresponding to the rise in chloroquine

resistance.[16] In Senegal, the emergence of chloroquine resistance has been directly linked to a dramatic increase in malaria mortality between 1984 and 1995 in Sahel, savannah and forest areas. This suggests that the spread of chloroquine resistance has had "a dramatic impact on the level of malaria mortality in most epidemiological contexts in tropical Africa."[17]

International guidelines to instruct countries in choosing appropriate malaria treatment were established in April 2001. The World Health Organization recommends that treatment failure rates should be less than 5%. Failure rates between 5 and 15% represent a warning period. Once treatment failure rises to between 16 and 24%, activities to initiate change of treatment protocol should start. And when treatment failure exceeds 25%, change is required.[18]

Chloroquine-resistant parasites had already been identified in all countries of tropical Africa by 1988.[19] A majority of affected African countries have now reached the 25% failure rate for chloroquine and, in many places, the SP failure rate is also worsening.

International and African leaders acknowledge the crisis

This is not all happening in a vacuum, completely unnoticed. In the late 1990s, there was recognition that something had to be done to address malaria's expanding threat. Roll Back Malaria, a global partnership, was founded in 1998 by the United Nations. Roll Back Malaria in turn convened the first-ever summit on malaria in Abuja, Nigeria, in April 2000. Senior officials from 44 affected African countries, including 19 heads of state, expressed their resolve to meet three main targets by 2005: ensure that 60% of those suffering from malaria have prompt access to correct, affordable and appropriate treatment; ensure that at least 60% of those affected by malaria benefit from suitable protective measures, such as insecticide-treated nets; and ensure that at least 60% of all pregnant women at risk for malaria receive chemoprophylaxis or presumptive intermittent treatment.[20] They reiterated their commitment to the Roll Back Malaria goal of cutting African malaria deaths in half by 2010, a commitment that was echoed by the world leaders at the 2000 G8 summit in Okinawa.

In recent years, as a result of these laudable initiatives, there has been much fanfare over attempts to implement preventive measures such as provision of insecticide treated bednets or insecticide spraying. Malaria has also been headlined for funding from the Global Fund for AIDS, Tuberculosis and Malaria. Yet so far, much of the rhetoric has not been followed up with concrete action. And, according to an external evaluation of the Roll Back Malaria partnership, in the last several years not only has there been no reduction in malaria — there may even have been an increase.[21]

Prevention efforts must be strengthened and commitments reinforced. Halving malaria mortality by 2010 will require that millions of people who do contract the disease each year receive treatment that works.

ny people in Africa are dying ting treatment that works

How does a parasite develop resistance to drugs?

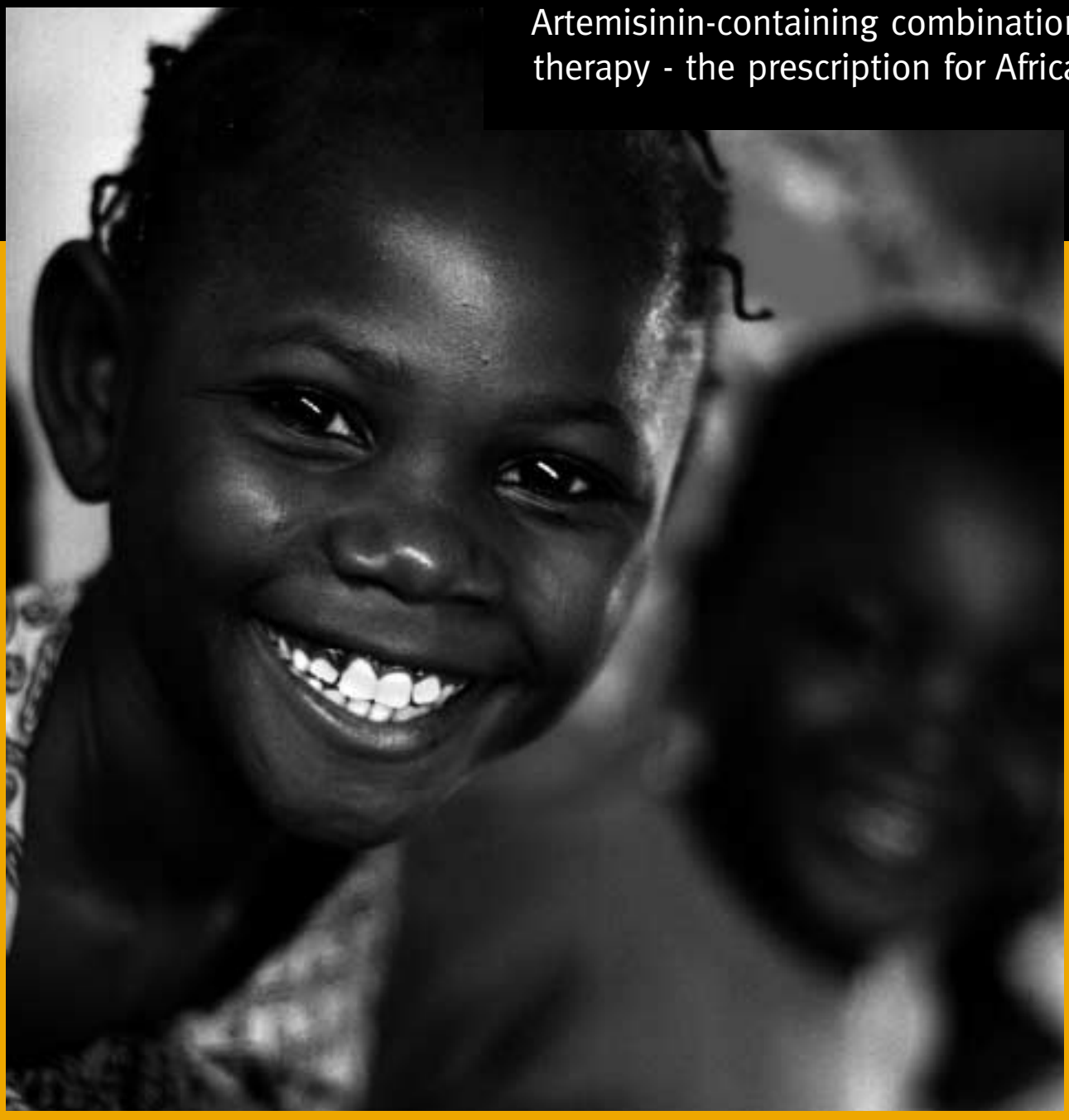
Drug resistance occurs through spontaneous genetic mutations in the parasite. When a patient is treated with a drug (eg, chloroquine), the parasites that are still sensitive to this drug are killed – but other parasites have "mutated" genes which means that they survive. The mutated parasites survive to reproduce and infect other mosquitoes and, in turn, another person. The parasites with the resistant mutation are thus favoured to survive and reproduce. Several mutations occurring in the same parasite are required to make a parasite resistant to chloroquine, while a relatively small number of mutations are required to make the parasite resistant to sulphadoxine-pyrimethamine (SP, also known as Fansidar®), which is why resistance to SP seems to develop much more quickly than resistance to chloroquine.

Among the factors that increase the likelihood of the survival and transmission of the resistant mutant are failure to complete a course of treatment, poor quality drugs that do not have adequate active ingredient, and clinical diagnosis. The typical malarial symptoms, such as fever, headache and chills, are non-specific to malaria. Basing diagnosis on clinical symptoms without using laboratory tests to confirm the presence of malaria parasites therefore means that many people who do not actually have malaria may end up being treated with antimalarial drugs.

The use of two drugs together, with different mechanisms of action, significantly decreases the likelihood of any one parasite having the mutations required to resist both drugs.

»» what works

Artemisinin-containing combination therapy - the prescription for Africa



© Remco Bohle

Despite spreading resistance and rising mortality rates (see Part 1), the malaria treatment scenario is not without hope. Effective treatments do exist. Experts agree that the best current treatment is a combination of drugs that includes artemisinin derivatives, extracts of a Chinese plant (see box page 12).[1] In widespread use to treat malaria for much of the past decade, artemisinin derivatives relieve clinical symptoms and decrease parasite load faster than any other antimalarial. A meta-analysis was undertaken by the World Health Organization's/Special Program for Research and Training in Tropical Diseases (TDR) of artemisin-based combinations vs. standard drugs in monotherapy, covering trials in Kenya, Malawi, Uganda, Senegal, The Gambia, Gabon, Sao Tomé, and Côte d'Ivoire plus several non-African countries.[2] It shouwed a clear benefit in terms of reduction of risk of treatment failure, superior pharmacodynamic action (parasite clearance and fever clearance), and reduction in gametocyte carriage. This has also been shown in studies in China, Vietnam and Thailand,[3] and in an evaluation including clinical data from province-wide use in KwaZulu Natal in South Africa[4].

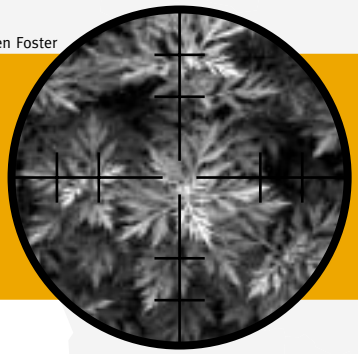
Artemisinin has several characteristics that make it an excellent malaria medicine:

1. It brings down the parasitaemia (the number of parasites in the blood) faster than any other antimalarial drug – ten times faster than the previous best, quinine.
2. It has few side-effects.
3. Two million cases of malaria are estimated to have been treated with artemisinin-based drugs with no reports of severe toxicity, suggesting that immediate and severe complications associated with this group of drugs are rare.[5]
4. Artemisinin is well absorbed by mouth and is not unpleasant to take.
5. It can also be given by intravenous or intramuscular injection, in a once-daily administration.
6. Its use is shown to markedly reduce the carriage of gametocytes, the infective form of the parasite in human blood.
7. No resistance to artemisinins has been reported, despite centuries of use in China.

Artemisinin-based combination therapy — ACT

Artemisinin derivatives should never be used alone, but always with a companion drug. There is now substantial evidence that using a combination of drugs with independent modes of action and different biochemical targets is not only more effective, but also successful in preventing or slowing the development of resistance, because the probability of parasites being simultaneously resistant to two drugs is greatly reduced. This thinking has been applied for some time to the treatment of tuberculosis and leprosy and, more recently, to HIV/AIDS.[6] In malaria treatment, using the combination drug approach with artemisinins means using artemisinin-based combination therapy, or ACT.

Photo ©2003 Steven Foster



The best current treatment is a combination of drugs that includes artemisinin derivatives, extracts of a Chinese plant

"WHO, on the advice of international experts, recommends the introduction of combinations of drugs to replace single drugs (monotherapy) in the treatment of malaria.... WHO recommends in particular, the use of drug combinations containing artemisinin compounds — artemisinin-based combination therapy — ACT for short.

"World health Organization, Statement, February 2002"

Artemisinin-based combinations have several distinct advantages in that they produce rapid clinical and parasitological cure, there is as yet no documented parasite resistance, they reduce gametocyte carriage rate, and are generally well tolerated.

Based on available safety and efficacy data, the following therapeutic options are now available:

1. *artemether-lumefantrine (Coartem™)*
2. *artesunate plus amodiaquine*
3. *artesunate plus SP in areas where SP efficacy remains high"*
4. *SP plus amodiaquine in areas where efficacy of both amodiaquine and SP remains high*

"Antimalarial drug combination therapy: Report of a WHO Technical Consultation," 4-5 April 2001, Geneva

Rediscovered cure

Although artemisinin is being acclaimed as the most important new malaria drug by top international health authorities, artemisinin and its derivatives have been around for quite a long time.

Artemisinin and artemisinin derivatives are extracts from a plant, Artemisia annua. The Artemisia plant is usually more known by its common names of sweet wormwood or Chinese wormwood. The medical benefits of an infusion of qinghaosu (the traditional name for artemisinin) were first discovered at least 2000 years ago by the Chinese, who used it to reduce fevers and other symptoms associated with malaria. However, the Chinese treatments using sweet wormwood were lost over time, and artemisinin was only recently scientifically identified as the active ingredient.

During the Cultural Revolution in China in the late 1960s, Chairman Mao Tse Tung charged Chinese scientists to investigate ancient Chinese herbal remedies. Ho Chi Minh also asked Mao to help provide new medicines to combat malaria, responsible for many deaths among Vietnamese soldiers during the Vietnam War. In the 1970s, an archaeological dig unearthed recipes for ancient medical remedies, including ones using artemisinin.

A crucial element of effective treatment of
There is an urgent need for better rapid diagno
toward treating confirmed cases only, thus sa

The Chinese studied many types of traditional malaria cures before hitting on a recipe for tea made from the Artemisia plant. Distilling the tea and adding chemicals to try to isolate the active compound in the plant, they developed the medical remedy. The Chinese manufactured artemisinin in drug form and performed tests on malaria patients. It was discovered that artemisinin cleared malaria parasites from the host bodies faster than any other antimalarial.

Artemisinin derivatives have attributes that make them especially effective: they are highly potent, fast-acting (fever clearance is fast and people recover quickly), very well tolerated and complementary to other classes of treatment. Given that a minimum of eighteen months is needed to grow the Artemisia plant from which artemisinin derivatives are extracted, harvesting large quantities of the plant is critical for worldwide drug usage. Currently, most of the cultivation, extraction and synthesis for the production of the drugs takes place in China and Vietnam, where the Artemisia plant is grown. Artemisinin production is also beginning in Tanzania and India but full-scale production will take time.

Drawn from "Health: Can a Chinese herb win the malaria war?" BBC Online Network, Thursday, October 15, 1998. http://news.bbc.co.uk/1/hi/health/194160.stm and information on www.artesunate.com.

Artemisinins act rapidly on parasites and do not remain in the bloodstream for long. Most parasites are therefore destroyed before drug concentrations drop to sub-therapeutic levels, reducing the chancesthat parasites will be exposed to low levels of the drug. In this way resistance to the drug is limited.[7] When artemisinins are combined with an additional effective antimalarial, the remaining parasites are then killed by therapeutic concentrations of this companion drug. Studies conducted in Africa have shown that, when artesunate was added to SP or amodiaquine treatment, parasite loads and gametocyte rates declined significantly faster.[8]

Combining artemisinins with a companion drug also shortens the treatment course. Given alone, a full course of treatment with artemisinins takes seven days. Because patients generally feel much better after just one or two days of treatment, it is hard for them to comply to this length of treatment. Given in combination with another effective antimalarial, the treatment is reduced to three days.

Choice of companion drug

Today, artemisinins can be used in combination with SP, amodiaquine and mefloquine. A fixed dose combination of artemether and lumefantrine also exists: Coartem™ or Riamet™. In many parts of Africa, amodiaquine would be a suitable companion drug. Where resistance to amodiaquine and SP is already high, Coartem™ may be a viable solution (see WHO recommendation box page 12).

Malaria epidemiology – including patterns of transmission, drug resistance and mosquito behavior – varies widely from country to country. Choice of treatment must be adapted to the specific setting and will depend on local drug resistance patterns, availability and price.

In several West African countries, resistance to SP has not yet reached high levels: it may still be possible to delay resistance and extend the usefulness of SP by combining it with artemisinin derivatives. In Southeast Asia, pre-existing resistance to mefloquine was stabilized and eventually reversed when it started to be used in combination with artesunate.[9]

Artemisinins reduce transmission of malaria

Not only do artemisinins help people feel better faster, they may also help reduce transmission of the disease. Artemisinin derivatives significantly reduce the load of gametocytes, the infective form of the parasite carried in the blood. By doing so, they also reduce the likelihood of transmission of the parasite. Studies in Southeast Asia suggest that the use of an artesunate-mefloquine combination reduced the incidence of *P. falciparum* malaria in the region.[10]

In 2001, when ACT Coartem™, (artemether plus lumefantrine) was implemented province-wide in KwaZulu Natal, South Africa, a study of gametocyte carriage was undertaken. In a sample of 100 patients, the gametocyte carriage rate was 2%. Two years prior, treatment of 129 patients with SP monotherapy left a 74% gametocyte carriage rate (See box page 15 for more on the KwaZulu Natal program).[11] It is not known whether results would be as dramatic in African regions of high endemicity.

Accurate diagnosis is critical

A crucial element of effective treatment of malaria is proper diagnosis of the disease. In most of Africa, diagnosing malaria based on symptoms alone is normal practice. This clinical diagnosis was actively promoted when malaria treatments were cheap, safe and easy to use and biological diagnosis was considered too complex and expensive. However this method of diagnosis is very inaccurate, as symptoms of malaria are non-specific and may indicate the presence of other febrile infectious diseases.[12] It is generally estimated that 50% of Africans who present with fever and are treated for malaria may in fact not be infected with the malaria parasite. Clinical diagnosis may therefore needlessly increase treatment costs. It may also play a role in the development of resistance.

malaria is proper diagnosis of the disease. stic tests. Rapid diagnosis will facilitate the move ving resources and helping prevent resistance

Accurate diagnosis of malaria using biological tests should be encouraged and supported as part of ACT implementation. Biological diagnosis can be done through microscopic examination or rapid tests. Mircroscopy is time-intensive, particularly when the number of parasites in the blood is low: the laboratory technician needs to examine 100 fields in the microscope to be sure a slide is negative.

Although currently expensive, rapid diagnostic tests using a simple “dipstick” can greatly facilitate diagnosis of malaria. They can be read in just minutes, are simple to interpret, and are easy to use in areas where medical and laboratory facilities are minimal or non-existent. They have some limitations in terms of accuracy, but can give an adequate sensitivity and specificity when combined with clinical diagnosis.

There is an urgent need for rapid diagnostic tests with improved performance. Rapid diagnosis will facilitate the move toward treating confirmed cases only, thus saving resources and helping prevent resistance. Prices of these diagnostics could be reduced by bulk purchasing.

Médecins Sans Frontières experience in using ACT

For good patient care now and in the future, and to prevent the further spread of the disease in intensity and into new populations, MSF has decided to implement artemisinin-based combination therapy for first-line treatment of all its malaria patients by the end of 2003.

African countries that have changed protocols in response to increasing drug resistance

MSF believes that countries who want and need to change should be offered support to move directly to ACT rather than to other sub-optimal interim protocols. These countries will incur the extra costs of changing to ACT (which are substantially more expensive that non-ACT treatment), as well as the costs involved in changing protocol. But countries choosing a non-ACT alternative are also incurring the substantial costs involved in changing protocol, yet they are still not providing individuals with the best possible treatment.

MSF has decided to implement artemisinin-based combination therapy for first-line treatment of all its malaria patients by the end of 2003

This change in policy was based on evidence of growing drug resistance in Africa and on previous experience with ACT in Asian countries including Afghanistan, Cambodia, Myanmar, Pakistan and Thailand.

In Africa, MSF is already using ACT in its projects in hospitals and therapeutic feeding centres in Angola, Sierra Leone and the Democratic Republic of Congo; in refugee camps and a focused outreach project in Zambia; in open-access clinics in Liberia, Kenya and Ivory Coast; in a sleeping sickness programme in Congo-Brazzaville; and in MSF-supported clinics in southern Sudan. Coartem™ was used very successfully in the recent malaria epidemic in Burundi.

In areas where it has been possible for MSF to start, careful monitoring is in progress to ascertain not only the efficacy of the drugs themselves, which is known to be very good, but also the effectiveness of different ways of managing drug administration and use. Compliance studies will be used to determine the best methods of managing treatment in primary care, and follow-up microscopy will show how long people remain free of parasites in endemic settings. The efficacy of treatment of patients with HIV will also be studied.

Not "if" but "how"

The right question is not "if" ACT can be effectively implemented in Africa, but "how" it can best be implemented. To refine implementation strategies, MSF is conducting operational research and urges Ministries of Health in affected countries as well as NGOs to do the same. It is only by rigorously comparing programme designs that we will be able to improve results for individual patients and communities.

Making the switch to ACT

Several African governments have decided to change protocols (see map above); KwaZulu Natal province in South Africa has successfully managed to change while Burundi, Zambia, and Zanzibar in Tanzania are preparing for implementation. Other countries, recognising the parasite resistance to their first-line protocol, have opted to change to another monotherapy or to non-ACT combinations, primarily because of a lack of funds.

MSF believes that countries who want and need to change should be offered support to move directly to ACT rather than to other, sub-optimal interim protocols; aside from the costs of the drugs themselves (see Part 3), which are substantially more expensive than non-ACT treatments, there are other significant costs involved in changing protocol which are the same regardless of the protocol chosen. Countries choosing a non-ACT alternative are incurring substantial costs while still not providing individuals with the best possible treatment.

To avoid this and others pitfalls, endemic countries will need the support of the World Health Organization and the international donor community.

KwaZulu Natal — province-wide implementation of ACT [1]

The introduction of artemisinin-based combination therapy (ACT) in South Africa's KwaZulu Natal province has already had a dramatic affect on public health in the region. The implementation of artemether–lumefantrine (Coartem™) in February 2001, together with improved vector control measures, resulted in a dramatic reduction in malaria in the province: the number of malaria cases dropped from 41,786 in 2000 to 9,443 in 2001 (78% reduction). Between 2000 and 2001, admissions to Manguzi hospital in KwaZulu Natal for malaria were cut by 82% and the number of reported malaria deaths decreased by 87%.

These remarkable improvements in malaria control and public health reflect the combined effect of residual household spraying with an effective insecticide in both KwaZulu Natal and southern Mozambique, and the replacement of sulphadoxine-pyrimethamine (SP), a drug that had become ineffective because of parasite resistance with an effective ACT as the first-line treatment of uncomplicated malaria.

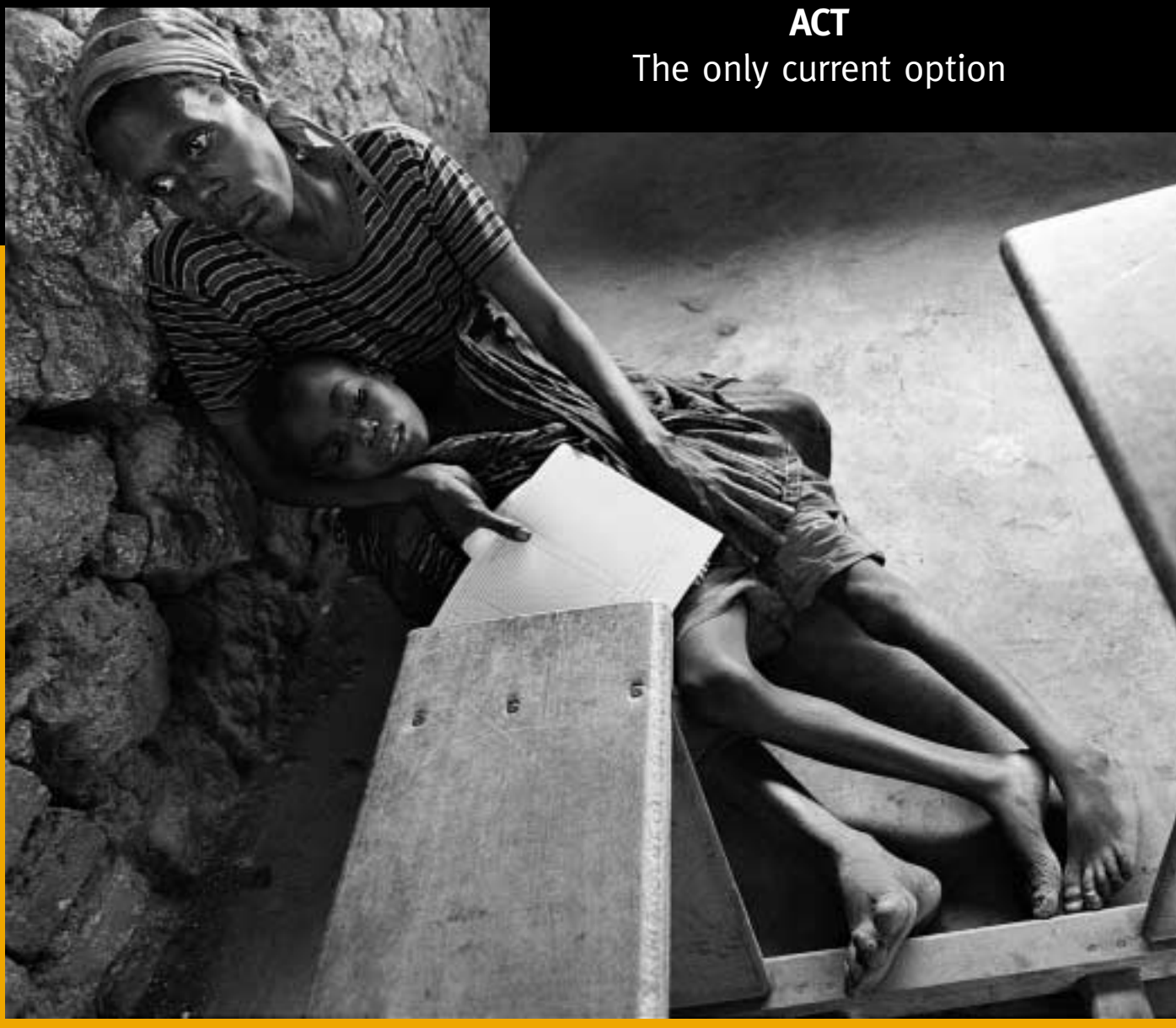
These early results from KwaZulu Natal are very encouraging. The same malaria control approach will soon be implemented in Namaacha district of southern Mozambique which will enable the gathering of data in a higher intensity transmission area.

The right question is not "if" ACT can be effectively implemented in Africa, but "how" it can *best* be implemented

The South East African Combination Antimalarial Therapy (SEACAT) evaluation is working with national malaria control programs to assess where and how best to implements ACT as first-line treatment.
They are working in South Africa, Mozambique, and potentially Swaziland.
The evaluation involves monitoring therapeutic efficacy, resistance, gametocyte carriage, drug safety, treatment seeking, drug use (especially drug availability and patient adherence), distribution and intensity of malaria transmission, and the costs and cost-effectiveness of implementing ACT.

making it a reality

ACT
The only current option



© Roger Job

"African mothers don't realise that their children are dying needlessly, that donors could choose to fund effective treatment that would save their lives."

Nick White
Chairman, Wellcome Trust Southeast Asian Tropical Medicine Research Units and
Professor of Tropical Medicine, Mahidol and Oxford Universities

Without successful implementation of ACT now, significant progress in controlling malaria will be impossible. This is because there is no miracle non-ACT combination waiting in the wings and because malaria control that consists of prevention without effective treatment is doomed to failure. Despite this reality – and despite the rising mortality rates, despite the desire of many African governments to use drug combinations that work,[1] despite endorsement by the World Health Organization,[2] ACT is still not available to the vast majority of Africans who need it. We know which treatment works – so why do so few people have access to it?

ACT treatment is currently much more expensive than other standard treatments; in addition, supplies of the drug are still limited. Yet both of these obstacles can be overcome. In fact, funding ACT treatment for all of Africa is economically feasible and scaling up production is technically possible. What is missing is political will.

Unless this changes, people will continue to die needlessly from taking drugs that no longer work.

The money problem

The cost of ACT is currently much higher than the previous "gold standard" treatments (eg, chloroquine monotherapy). The cost of treating an adult with chloroquine or SP monotherapy is around US$0.10.[3] The lowest quotes to humanitarian and government organizations for combination therapy artesunate-amodiaquine have been about $1.50.[4] Yet, based on current price trends and historical experience, MSF estimates that the price of the artesunate-amodiaquine combination should be $0.50-$0.80 by 2004-2005.[5] As orders for the drug increase, the price of ACT will go down over time, becoming more and more affordable.

The poor people who represent most of the continent's malaria disease burden cannot afford to pay much more than what they currently pay for the old treatments, so costs must be subsidized by national governments with the help of international donors.

MSF estimates that provision of ACT for all African countries that need it today would cost about $US 100-200 million a year at current drug prices.[6]

International donors must step in and assist governments in meeting these funding gaps. MSF estimates that for five countries – Kenya, Rwanda, Burundi, Uganda and Tanzania – only $19 million in total would be needed to switch to ACT instead of a sub-optimal interim protocol.[7] Nineteen million dollars may be a lot for the five countries, but with US and UK aid budgets of US $8.5 billion[8] and $5.25 billion,[9] respectively, these key international donors should easily be able to foot this bill. The US Agency for International Development spends $586 million on operating expenses alone.[10]

The Global Fund for AIDS, Tuberculosis and Malaria, established in 2001, has awarded money to Zambia, Tanzania (Zanzibar) and Burundi for projects involving ACT treatment during the first and second rounds of grants; while a promising initiative, the several millions of dollars that have so far been made available are a fraction of what is needed for effective implementation of ACT in all the African regions that need it today. The solution could come from an increase in bilateral and Global Fund money. The US$100-200 million necessary to provide ACT represents only 1-2% of the US$10 billion the Global Fund hopes to disburse yearly. To date, the Global Fund has received US$ 3.3 billion in pledges, far short of this target.

Yet, despite direct pleas from African governments, major international donors have so far been reticent to help pay for ACT implementation.[11] Are international donors denying Africa's children the malaria treatment they would give to their own sons and daughters?

Availability – Current challenges and future possibilities

Initial efforts to supply the first countries that have switched to ACT have been thwarted by a lack of supplies of needed drugs. However, scaling up has begun and is feasible. The technology needed for extracting the raw material and processing and formulating it not that sophisticated. Even putting the combination drugs into blister packs or into a single pill does not present a serious challenge to drug developers and producers. Once markets are established by pooling orders and securing financing, producers will respond to the challenge.

Funding ACT for all of Africa is economically feasible for donors

The WHO recommendation to use ACT in April 2001 was not followed up by securing the funds necessary to entice European, Indian, African, Vietnamese and Chinese producers to scale up production. The World Health Organization, donors and involved governments must work together to encourage ACT production and to work with new producers to assist them in meeting WHO quality standards. In Vietnam, where much of the Artemisia plants are grown and raw material extracted, farmers are willing to plant additional acreage of this cash crop if they can be assured of demand.[12] (See box page 20 for more on challenges for ACT producers.)

The WHO pre-qualification process, which certifies qualified producers, has made a call for "expression of interest" to producers of ACT and is currently undergoing examinations of products and facilities, but the future of the pre-qualification process is being put at risk by a lack of long-term funding.

It will take political will and expressed commitment to generate a demand-driven cycle for quality ACT raw material and finished products.

(continued page 21)

››› Unconvincing

The cost of ACT as well as the limits of existing supplies are key areas where donors, agencies and governments could potentially make a real difference. Unfortunately, until now, in terms of articulated policy the donors have fallen into two camps. The "leave it alone" countries are the United States and the United Kingdom, which have spent considerable energy chronicling the barriers to ACT introduction;[1] and the rest of the donor community, which has "no opinion." In other words, most countries have not actively supported the World Health Organization's recommendations to implement ACT now.
They have been conspicuously silent on the issue.

The "leave it alone" camp has argued:

›› We must not rush because ACT has not been proven safe and effective at the village or national level in Africa ‹‹

In fact, artemisinins have been studied more extensively than many other antimalarials,[1] and it is estimated that about 2 million people have so far been treated with ACT, with little report of gross toxicity. Not only have these drugs been used for more than ten years in Asia but there is also extensive safety as well as efficacy data from studies conducted both in Asia and Africa.[2] In a recently completed meta-analysis of artesunate-based combinations versus the standard antimalarial drug alone, which included around 5,194 patients and took place in sites in eight African countries, the combination showed a clear benefit in terms of reduction of risk of treatment failure, superior pharmacodynamic action (parasite clearance and fever clearance), and reduction in gametocyte carriage. The total number of serious adverse events was small [n=65] and was similar in both groups. Implementation of Coartem™ along with enhanced prevention measures in KwaZulu Natal have resulted in remarkable improvements in malaria control and public health.[3]

›› ACT shouldn't yet come into widespread use because its use has not been adequately studied in pregnancy ‹‹

Although there need to be additional studies in pregnant women of the risks of using these drugs in pregnancies, even inadvertently, their use needs to be weighed against the risks of using older treatments or nothing at all. *Plasmodium falciparum* malaria can be particularly dangerous to mother and foetus during pregnancy,[7] so it is important that work continue toward offering expectant mothers the best possible option. There is particularly a paucity of clinical data on the effects of artemisinin derivatives on women who are in the first trimester of pregnancy, but unfortunately the same problem plagues the use of older treatments such as SP. However, based on animal studies and on the clinical data that does exist (including controlled trials in Asia and Africa which included hundreds of pregnant women among 15,000 participants[8]), the World Health Organization has already given the green light for use of artemisinin and its derivatives in the second and third trimesters.[9] Considering the available data, WHO experts have wisely recommended that artemisinin derivatives not be used during the first trimester of pregnancy, if there is an effective alternative. The same recommendation exists for SP.[10] Other current options include chloroquine in the few places where resistance is not a problem, and quinine, which is effective but difficult to use and has significant side-effects. The bottom line is that there is no reason to withhold ACT from the *general population* because of concerns about use in pregnancy.

arguments

ACT is "not ready for prime time."

Dennis Carroll, USAID

"State of the art is fine, but poor people tend not to be able to afford it..."

US official, Nairobi, Kenya

» It is better to use a less effective treatment that can be given in one dose than to expect people to comply with three days of ACT «

In a presentation at a Roll Back Malaria partners meeting in February 2002, the US Centers for Disease Control (CDC) urged African governments to be conservative when considering changing their malaria policy – whenever possible, to "leave it alone."[11] The CDC presented a schema indicating that malaria programme effectiveness would be higher with a single-dose drug that was only 50% effective rather than a three-day treatment that was 100% effective, essentially promoting SP monotherapy in areas where resistance had already developed. The CDC based its argument on an assumption that about 70% of people would not complete a multi-day treatment course. Simply put, the argument states that, since people will not take a three-day course, lives can be saved by offering a less effective one-time treatment.

As health professionals, MSF teams agree with CDC that compliance is a real challenge. For this reason we call on the international community to support endemic countries to improve compliance. But let's not use this as an alibi to continue giving older, less expensive, less effective medicines.

In KwaZulu Natal, South Africa, an ongoing evaluation of the combination ACT/DDT project in place since February 2001 has already suggested that compliance to the three-day ACT regimen has had reasonable success and can, with continued support, be sustained.[12] In a survey conducted in 2001 of about 2,500 households in KwaZulu Natal, 95% of recent cases self-reported completing their treatment.[13] (See page 15 for more on the KwaZulu Natal program.)

The important issue is maximizing compliance to ACT treatment. This means, among other things, training health workers, improving packaging of medicines and offering then for free or at affordable prices, and improving patient education and information. In the long term, it also means developing fixed-dose combinations.

"In poor countries like ours, children have only one chance. They struggle just to visit a health service, and if they get the wrong drug the first time, they are found dead."

Dr. Fred Binka, professor of epidemiology, University of Ghana

*Who is producing ACT now? **

European producers

Novartis, *a company based in Switzerland, sells a fixed-dose ACT combination (artemether-lumefantrine), under the name Coartem™. A WHO programme "controls" the supply of a discounted version of this drug, at $2.40 per adult dose. Coartem is sold at about US$12 in private pharmacies in developing countries.*
Coartem™ challenge:
1) simplify the WHO process for obtaining access to discounted Coartem.
2) reduce the "public" and private prices

Sanofi-Synthélabo, *based in France, sells artesunate produced by the Chinese company Guilin under the trade name Arsumax on the African market. They have also had a blister of Arsumax and amodiaquine under development for more than a year, but have so far failed to produce any supply. In July 2002, Sanofi told MSF that they could fulfil large orders for this combination blister by December 2002, but they are now saying that large quantities will not be available until September 2003. The company has also failed to file necessary paperwork to the WHO pre-qualification unit.*
Sanofi ACT challenge:
1) stop aggressively marketing the stand-alone artesunate product and
2) begin marketing the combination blister in needed quantities at an affordable price

Mepha *(based in Switzerland) has developed a combination blister of artesunate and mephloquine (for the Asian market) and is currently developing a combination blister of artesunate and amodiaquine for the African market.*

› Increasing quantities of raw material for and scaling up production of artemisinin-based combinations is not a technical challenge. What is missing is political will

Asian Producers

Indian producers

Several Indian companies are in the process of developing ACT blisters. They include Ipca, Medicamen (in collaboration with Danikapharma/Mission Pharma) and Cipla.
Indian producer challenges:
1) meet WHO, UNICEF and MSF quality requirements and
2) scale up production of artesunate in combination blister packs

Vietnamese and Chinese producers

Along with the Chinese, the Vietnamese are currently the leading extractors and synthesizers of artemisinin derivative raw materials. In Vietnam, several of these raw material producers are investing in meeting international standards for the manufacturing of tablets and will likely offer cheaper finished products by 2004. In China, the Guilin factory is the only one producing artesunate tablets. These tablets can only be purchased by non-profit institutions and governments for Africa (the private market is by contract covered by Sanofi).

African producers

African producers will also be part of the solution. For example, the Kenyan pharmaceutical company Cosmos has already started production of artemisinin derivative, and the Artemesia plant is now being grown in Tanzania. Other African companies are likely to follow suit in the near future.

**This is a non-exhaustive list of current producers of ACT*

The future of artemisinins

How to protect artemisinins

Large scale use of chloroquine and SP throughout much of Africa has led to rising levels of resistance. Isn't it reasonable to believe that artemisinin drugs will travel the same path? If they are used alone, there is a high risk of this. That's why the World Health Organization is clearly recommending the use of combinations containing artemisinin drugs, rather than artemisinins alone. Using artemisinins in combination with another effective antimalarial will help protect them against resistance. Conversely, since there are so few other drugs that still work, it makes sense to use them along with artemisinins to increase their longevity.

When resistance to the companion drug is still very low, it is the ideal time to introduce ACT, as treatment outcomes will be better and the life of the companion drug will be prolonged. For example, in Tanzania and Southern Sudan where resistance to SP is still quite low, it makes sense to begin combining SP with artesunate as soon as possible.

Artemisinin derivatives are already widely available as single drugs (not as part of combinations) in private pharmacies in many parts of Africa for people who can afford them. This availability in monotherapy invites the development of resistance. The availability of ACT in public facilities would both set a treatment standard and reduce the inappropriate use of artemisinin derivative monotherapy by individuals who are not currently being served by the public system.

What next in R&D

Blister packs of artesunate + SP and artesunate + amodiaquine to facilitate artemisinin-based combination treatment are expected in the short term (2003).

The future availability of ACT in fixed-dose combinations (FDCs) will further increase their ease of use. MSF is supporting the Drugs for Neglected Diseases Initiative (DNDi) in developing FDCs of artesunate/amodiaquine and artesunate/mefloquine, which should become available in 2005.

Several companies are also working on the development of artemisinin-based FDCs. Chinese company Holleykin is developing a dihydroartemisinin/piperaquine fixed dose combination (also known as Artekin), which should be available by 2005. Medicines for Malaria Venture, a non-profit foundation developing malaria drugs, and GlaxoSmithKline have been collaborating on the development of artesunate/LapDap, which should be available in 2006, and the Korean company Shin Poong and TDR are also expected to make available a fixed dose combination of artesunate/pyronaridine in 2006.

Synthetic versions of artemisinin derivatives are also an important element of ACT development, as they will eliminate the labour-intensive process of plant cultivation and extraction. They are likely to make up a major part of the next phase of antimalarial drug development. For example, the Medicines for Malaria Venture is planning to develop synthetic peroxides with a group of university researchers and artemisone with the pharmaceutical company Bayer. These products could become available by the end of the decade.

From past lessons learnt in the malaria field, we know that no drugs last forever, and increased levels of research are urgently needed to develop brand new drugs for malaria treatment. Unfortunately, few major multinational pharmaceutical companies have ongoing malaria drug development projects, and the non-profit sector has so far been handicapped by insufficient financing. For instance, the Medicines for Malaria Venture claims that the biggest limiting factor for its work is lack of funds. As a result, no new chemical entities against malaria are likely to become available in the next ten years. Political and financial support for research and development of antimalarial drugs is therefore critical.

Using the "non-compliance" argument to prevent widespread implementation of the WHO-recommended treatment is a deadly double-standard. ›

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"If it [malaria treatment] costs more, the increased cost must be weighed against the broader social costs. If we had not changed [malaria treatment policy] it would have caused a societal vicious circle: malaria would have increased, people would have died, the media would have reported, tourism would have gone down, there would have been less money in the system. There would be less money for health services. The economy is linked with malaria."

Senior health official, KwaZulu Natal
In the Southeast African Combination Antimalarial Therapy Evaluation, February 2002

"People keep bringing up the fact that ACTs are them. But what would you rather do - waste mon or fund a more expensive treatment that will save

© Sebastião Salgado/ Amazonas Images

Restocking the shelf

The idea is a simple one: restock Africa with a malaria medicine that works.

- *The World Health Organization must push for implementation of its own recommendation to switch to ACT*
- *Donors must stop wasting their money funding drugs that don't work and help fund efforts of endemic countries to make the switch to ACT*
- *Endemic countries need to back up their will to improve malaria control with increased budget allocations*
- *ACT must be provided to individuals free of charge, or at an affordable price*
- *International agencies and donors must provide technical support to facilitate both treatment implementation and upgrading international and domestic drug suppliers willing to produce ACT (with technology transfer and technical assistance to enhance production standards)*
- *UNICEF, WHO procurement and the Global Fund for AIDS, Tuberculosis and Malaria must pool needs and make large orders to prime the drug production pump and bring down prices*

expensive, as if it were a reason not to start using
ey on old cheap drugs that you know don't work
lives?"

Nick White
Chairman, Wellcome Trust Southeast Asian Tropical Medicine Research Units and
Professor of Tropical Medicine, Mahidol and Oxford Universities

- *International and/or regional pre-qualification needs to be augmented to assist countries in identifying quality drug sources*
- *Concerned parties must undertake operational research to improve use of current tools*
- *Research & development for new drugs, new formulations of existing drugs and improved diagnostic tools must be placed high on the agenda and implemented through government-supported research or non-profit initiatives such as the Medicines for Malaria Venture*

We need to implement ACT today.

We need to ACT NOW.

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