Changing national malaria treatment protocols in Africa :
What is the cost and who will pay?

Campaign for Access to Essential Medicines

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Case studies: Burundi, Kenya, Rwanda, Tanzania and Uganda

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I. Executive Summary

Early diagnosis and prompt treatment is a principal component of the global strategy to control malaria[1]. But many countries still include ineffective drugs in their national malaria treatment protocols. Today, an urgent challenge faces health ministries in many African countries: increasingly high levels of resistance to the former drugs of choice – chloroquine and sulphadoxine-pyrimethamine (SP, also known by its brand name Fansidar®) – are causing increasing rates of mortality, particularly among children.

The increasing evidence of high levels of resistance have led managers of national malaria programmes to rethink protocols. Most agree with the prevailing thinking that the best first-line treatment would be to use combinations containing artemisinin derivatives. However, many proposed new malaria policies do not reflect this growing consensus. In fact, many countries are contemplating switching to alternative monotherapies or combinations without artemisinin derivatives, and in some cases, this is supported by aid agencies. We believe that people have a right to effective antimalarial treatment, and that many countries would switch to highly effective drugs if financial resources were available and if continued supplies of affordable drugs were guaranteed.

The following are key criteria to consider when changing national treatment protocols:

1. Efficacy and safety of the proposed new protocols.
2. Potential compliance to treatment, which includes ease of use and the ability to convince caregivers and patients of the effectiveness and benefit of the new treatment.
3. Possibility of forestalling resistance to existing and new drugs.
4. Financial burden of change for the health system, including both direct cost of more expensive drugs and indirect costs such as retraining health workers.

The first three support a transition towards large-scale introduction of artemisinin-containing combinations. However, in the absence of resources necessary to make the change, the medically sound choice is likely to be subverted by the fourth criterion.

Decisions regarding protocol change will have long-term implications both for the hundreds of millions of people suffering from malaria, and physicians' future ability to treat life-threatening cases of the disease. For this reason, we conducted an analysis to estimate the cost of changing national protocols and the financial assistance that would be required to assist African countries unable to shoulder the entire burden of this change.

We chose to concentrate our analysis on five countries that are facing high levels of resistance and increasing morbidity and mortality: Kenya, Rwanda, Tanzania, Uganda (members of the East African Network for Monitoring Antimalarial Treatment EANMAT), and Burundi. The situation in these countries is such that they will soon be required to change their treatment policies. However, it is important to note that several other African countries face similar challenges.

Methodology

We looked at the supplementary costs of using an artemisinin-containing combination rather than a cheaper, sub-optimal combination (e.g. amodiaquine + SP). Potential need was estimated using the number of cases of uncomplicated malaria reported by the national health information system during a "normal" year without a major epidemic. Age distribution of malaria was used to quantify the need for drugs by adapting the protocol to each age group. When not available, figures were estimated from existing documentation and discussions with experts.

Results

Amodiaquine + artesunate is an effective and well tolerated combination which could be implemented in these five countries. In other regions, other combinations may be more appropriate. Using current drug prices, the supplementary cost of using the optimal amodiaquine + artesunate combination rather than the mid-term sub-optimal amodiaquine + SP is US$1.05 per patient. It is estimated that, with a large increase in demand, the price of the amodiaquine + artesunate combination could decrease by US$0.70 by 2004, bringing the supplementary cost of using this combination down to US$0.35.

The total additional cost of using an artemisinin-containing combination was calculated for each country. For Rwanda, which has an estimated 1.2 million cases of malaria per year, the additional cost would be US$945,000 per year. For Tanzania, which has an estimated 8.6 million cases per year, this cost would be US$6.4 million per year. The five countries have an estimated total of 25.3 million cases of malaria every year. Therefore, at today's prices, the total additional cost of using optimal treatment would be US$19.1 million per year. This amount could decrease by two thirds if the price of the combination were to come down as anticipated above. This analysis does not include the cost of changing protocols because these costs are already budgeted by the five countries. All are in any case planning to change their malaria treatment protocol; the only unanswered question is what combination they will change to.

Conclusions

It is governments' responsibility to change malaria protocols in order to provide effective treatment for patients in need. When considered in the context of national health budgets and current donor aid, it is financially feasible to move quickly toward adoption of artemisinin-containing combinations where medically indicated.

Although these figures may appear high to managers of malaria programmes, national governments should be able to make this critical change with varying amounts of international support. The fight against the leading killer of children in Africa is worthy of such an investment, and we have reason to believe that these estimated costs will decrease over time as more producers are validated and competition is encouraged. However, given the economic situation of these countries, support from international donors will be key.

II. *Malaria: morbidity, mortality and drug resistance*

Every year, there are an estimated 300 to 500 million cases of malaria in more than 90 countries. Ninety percent of cases occur in Africa among the world's poorest people. Of the four species of malaria, *Plasmodium falciparum* is responsible for most deaths – 1.5 to 2 million a year, ninety percent of which are African children[2]. Malaria remains the first cause of death for children under five in Africa and mortality is rising. Children are more vulnerable to the disease than adults because their immunity is less developed.

According to public health experts, there are more people suffering from malaria today than ever before. This is due to several factors: environmental changes, population movements and displacements, weakened health systems, insecticide resistance, and increasing drug resistance.

The emergence of drug-resistant *P. falciparum* has been a major contributor to the observed increase in malaria cases and deaths[3]. In Africa, according to Snow et al., "there is mounting evidence that mortality has increased significantly, coinciding with the rise in treatment failure with chloroquine"[4]. Several studies have confirmed this trend. In Senegal, data from sentinel demographic surveillance systems indicate that, among populations where low levels of malaria mortality had previously been achieved by means of effective health care delivery, child mortality attributable to malaria has increased by as much as six-fold in the last twelve years. This increase in mortality can be correlated to increases in levels of chloroquine resistance. Hospital studies in various African countries have documented a two- to three-fold increase in malaria deaths and hospital admissions for severe malaria, an increase which is also related in time with the emergence of chloroquine resistance[5].

Furthermore, there has been a striking increase in the number of severe malaria epidemics in Africa. The October 2000-March 2001 epidemic in Burundi was responsible for an estimated 2.9 million cases. A retrospective study showed that in three provinces with an estimated population of 1.3 million the epidemic killed 12,780[*] people from September 2000 to March 2001[6].

The epidemiology of the disease – including patterns of transmission, drug resistance and mosquito behaviour – varies greatly from one place to another. Responses must therefore be tailored to each specific situation and, although several combinations are highly effective everywhere, choice of treatment will depend on the type and level of resistance in a given place. In several West African countries for instance, resistance to SP has not yet developed and it may therefore still be possible to delay resistance and extend the usefulness of SP by combining it with artemisinin derivatives.

Chloroquine was first introduced in the 1950s – resistance emerged and spread rapidly during the 1970s, especially in Southeast Asia. In response, SP was widely introduced, but resistance emerged within four or five years, much faster than for chloroquine. However, after introduction of artemisinin combinations (e.g. mefloquine + artemisinin combination in Thailand and Cambodia), a reduction of the incidence of *P. falciparum* was observed[7]. This positive result served as an incentive to promote artemisinin-containing combinations to fight parasite resistance in Africa.

One of the key questions that is currently being addressed by health authorities is: at which level of resistance should national treatment protocols be changed? Ideally, treatment failure rates should be less than 5%, and this is achievable everywhere in the world using the available combinations. Experts convened by WHO have agreed on a methodology to assess resistance and have defined four different thresholds[8]:

1. a level of treatment failure below 5% is considered a "grace period";
2. treatment failure between 6 and 15% represents a warning period;

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[*] This figure was estimated from the number of deaths by fever. The confidence interval was 9,115-18,959.

3. when treatment failure rises to between 16 and 24%, activities to initiate change should start;
4. when treatment failure reaches 25% or above, change is required.

It is important that a consensus on the choice of a new treatment protocol be reached ahead of the time when protocols need to be changed, so that the process can be completed within the shortest period of time possible once it is required.

III. Growing consensus among experts on how to tackle malaria

There is growing consensus among international experts and WHO regarding effective strategies to address rising mortality and morbidity. The following are considered essential elements to include in plans to tackle malaria:

1. *Wider implementation of prevention and targeted prophylaxis*

Treatment and prevention strategies must be combined to maximise impact on the disease. In some populations, especially pregnant women, avoiding disease manifestation by prophylaxis or intermittent treatment is an important objective. In addition, house spraying to reduce mosquito populations in areas of unstable malaria transmission remains an important component of malaria prevention[9]. Use of insecticide-treated bednets (ITNs) has also been shown to be an effective strategy. A Cochrane review of eighteen trials showed that ITNs reduce mortality by around twenty percent in Africa, and that the lives of six children are saved for every thousand protected[10]. WHO and Roll Back Malaria are strongly advocating widespread introduction and sustained use of ITNs.

However, obtaining these reported results within large-scale programmes is more problematic. Effectiveness outside trial conditions has yet to be confirmed, as there are many barriers to scaling up programmes: cultural, behavioural, logistical, supply, and economic issues are at stake. For instance, annual re-impregnation of each bednet is still necessary. For Kenya, a minimum of US$100 million would have to be invested in the next five years to reach the national programme objective of 60% bednet coverage of the at-risk population, with at least 25% of the nets regularly treated with insecticide[11].

2. *Increased use of biological rather than clinical diagnosis*

There is also growing consensus that, wherever possible, it is best to confirm diagnosis using biological tests rather than basing diagnosis on clinical symptoms alone. Clinical diagnosis was actively promoted at the time when malaria treatments were cheap, safe and easy to use, and biological diagnosis was considered too complex and costly. However, it is now widely recognised that approximately half the people who present with fever and are treated for malaria in Africa may in fact not be infected with the parasite. In addition to increased drug costs, an unintended consequence of treating patients based on clinical diagnosis only is an accelerated rate of resistance. It is essential that the use of biological diagnosis be expanded, both to preserve new treatments and to reduce unnecessary costs associated with overuse of drug therapy,.

There are currently two principal ways of establishing biological diagnosis of malaria. The classical method, laboratory testing, involves microscopic examination of Giemsa-stained thick and thin blood films by trained lab technicians. Using this method, it is possible to measure parasite load and differentiate between different species of parasite. However, it requires specialised equipment and highly trained staff. One study estimated the per patient cost of this type of diagnostic test at between US$0.12 and 0.40, but the end cost to the patient is likely to be higher[12].

An alternative method is rapid diagnostic testing using simple immunochromatographic tests (ICT): a dipstick is immersed in a drop of blood mixed with a reagent; the appearance of a dark band on the dipstick indicates presence of parasite. Dipstick tests increase the speed of diagnosis, and are easier to use in resource-poor settings since no equipment is needed and only minimal health personnel training is required. However they do have limitations: some tests remain positive despite parasite clearance, they cannot quantify parasitaemia, and they may not diagnose certain species of malaria.

In order to increase the use of biological diagnosis, laboratory capacities of East African countries will need to be strengthened, at least in strategic places where large numbers of people can be monitored, such as capitals and large urban areas. Rapid diagnostic tests can immediately play a role where there is no access to lab tests. However, if they are to be more widely used, it will be necessary for their price to come down, and for additional research to be conducted to improve their performance. The minimum per patient cost of a rapid test is US$0.50. But it is important to note that even at the current price, the cost saving of using a diagnostic test is US$0.80 per adult (treating children is less expensive, so the saving would also be less). Assuming that half the patients currently treated don't actually have malaria, the potential saving could be significant. This issue requires further study. Nevertheless, in areas of low and middle transmission, rapid tests are especially useful and appropriate and should be actively promoted.

3. *Artemisinin-containing combinations used as first-line treatment*

The prevailing thinking on malaria treatment has been influenced by strategies deployed to treat leprosy, AIDS and TB which use multiple drug treatments to prevent the emergence of resistance and increase efficacy. By hitting different biochemical targets of the malaria parasite, drug combinations are more effective than monotherapies, protect each individual drug from the development of resistance and allow shorter treatment courses. Theoretically, based on current estimates of mutation frequencies, only one parasite in every 10^{12} would develop simultaneous resistance to two drugs[8].

In the case of malaria, most experts agree that the best current treatment solution is to use artemisinin-containing combinations. Artemisinin derivatives have attributes that make them especially effective: they are fast-acting, highly potent, very well tolerated and complementary to other classes of treatment.

When using artemisinin-containing combinations, the parasite load is first dramatically reduced by artesunate. After three days of treatment, the remaining parasites are then exposed to maximum concentration of the more slowly eliminated second drug, which substantially decreases the risk that strains with reduced sensitivity to this drug will emerge[8]. Clinical trials have demonstrated the efficacy of artemisinin-containing combinations and, to date, no resistance has been reported anywhere. Furthermore, because they prevent transmission, they reduce the incidence of malaria in areas of low endemicity. A recent WHO report stated that "based on available safety and efficacy data the following therapeutic options are available now and have potential for deployment if costs were not an issue: artemether/lumefantrine (co-artemether, also known by its brand name Coartem®), artesunate + amodiaquine, artesunate + SP where SP efficacy remains high. SP + amodiaquine in areas where efficacy of both amodiaquine and SP remain high. (mainly limited to West Africa)". Other treatment possibilities, such as lapdap, mefloquine and Malarone, are not currently included in WHO recommendations.

4. *Need for additional research and development (R&D).*

Despite the high potential of artemisinin-containing combinations, they are by no means a miracle cure. In general, a very limited number of drugs are currently effective against malaria. There is therefore an urgent need for operational research (effectiveness of treatment, improving adherence, etc.) as well as drug development. In addition to developing new treatments, further development of artemisinin

derivatives is also needed to increase the drug's shelf life, which is currently between two and three years.

Coartem®, a co-formulation of artemether and lumefantrine developed by Novartis, is currently the only fixed dose artemisin-containing combination. To address the need for other fixed dose treatments, MSF is working with WHO's Special Programme for Research and Training in Tropical Diseases (TDR) and other partners to support the work of developing co-formulations of amodiaquine/artesunate and mefloquine/artesunate. In the short term, it will be useful to develop a blister pack presentation of the amodiaquine + artesunate combination.

The extent of the neglect of malaria drug development is dramatic. In the last twenty years, other than Coartem®, not one novel antimalarial drug has been developed. This is partly due to the fact that malaria patients, especially those in poor countries, do not represent a high potential market. A 1996 report showed that an average of US$ 42 was spent on research for every malaria death, compared to US$3,270 for every HIV/AIDS-related death[13]. No long-term solution will be found unless research and development for new malaria drugs is increased. This will call for the active involvement of governments. The same will be required if existing diagnostics are to be improved and new ones are to be developed. Recently, the level of activity for malaria treatment development has begun to increase. One noteworthy development was the creation of the Medicines for Malaria Venture (MMV), a public private partnership devoted to the development of malaria drugs.

Although a vaccine would be the ultimate solution, progress will also not be made without a focused, well-funded vaccine research development effort. According to experts, a vaccine could be available ten years from now at the earliest.

IV East African Network for Monitoring Antimalarial Treatment Countries and Burundi: current situation and policy

Burundi, Rwanda, Kenya, Tanzania and Uganda are good examples of the challenges faced by countries with both high incidences of malaria and high rates of resistance to chloroquine and SP. All except Burundi are members of a regional malaria network called East African Network for Monitoring Antimalarial Treatment (EANMAT) and are planning to change their national treatment protocols shortly because of high levels of resistance to chloroquine and SP.

Incidence of malaria and resistance levels

To determine the magnitude of the problem and estimate need in these five countries, we looked at the number of malaria cases and levels of resistance to chloroquine and SP. In countries where these figures were available, e.g. Rwanda and Burundi, we used the number of cases of uncomplicated malaria reported by the national health information system during a "normal" year without a major epidemic. This number includes cases registered in public health facilities and those registered from the private sector. In the countries where these figures were partially available, they were estimated from a variety of different sources (see annex 1). The accuracy of these figures varies considerably from country to country. In some cases, numbers may be overestimated, where simple fevers were recorded as malaria cases because no confirming lab test was conducted; on the other hand, in some cases are under-estimated, because of limitations in reporting.

	Burundi[14]	**Kenya**[15]	**Rwanda**[16]	**Tanzania**[17]	**Uganda**[18]
Total population	6.5 million	30 million	7.2 million	32.8 million	21.1 million
Estimated number of malaria cases	2 million	8.2 million	1.2 million	8.6 million	5.3 million
Resistance to chloroquine	50-90%	66-87%	40%	28% - 72%	10-80%
Resistance to SP	13-63%	27-40%	16-45%	15-34%	11-60%

Table 1. Estimated resistance to traditional malaria drugs in the five countries.

Current national treatment policy

Due to high levels of resistance, all five countries have abandoned chloroquine treatment in their national policy. As a stop-gap measure, they have recently changed their protocols to sulphadoxine-pyrimethamine (SP) monotherapy as first-line treatment (in association with chloroquine for Uganda). But the choice of a replacement for chloroquine was dictated primarily by economic considerations[20]. Considering the high levels of existing resistance to SP, the consequences of the current policy are likely to be:

1. *Continued increases in morbidity and mortality*. As experts at a WHO meeting summarised in April 2001, "increasing resistance to chloroquine and SP will probably lead to an increase in malaria morbidity and mortality, particularly in children. Urgent action is needed to replace antimalarial drugs which have become, or are rapidly becoming ineffective".[13]

2. *Decreased faith in the public health system due to poor efficacy of treatment*. This loss of confidence may also result in diminished use of public health facilities for other health needs.

3. *Rapid increase in levels of resistance to SP*. According to a recent report examining the EANMAT experience, "introduction of SP as a replacement for chloroquine in East and Central Africa is a process that is characterised by the rapid selection and spread of parasite resistance to SP"[19].

Prof. Mutabingwu, the Chairman of the East African Network for Monitoring Antimalarial Treatment concludes:

> *"The rise in SP resistance is evident at sentinel sites in the region that have conducted repeat tests. After only three years of SP use, Kenya will soon have to change from SP to a more effective treatment… the situation in Kenya represents a strong argument for the use of antimalarial drugs in combination to delay resistance".*[19]

The health ministries of these countries are aware of the drawbacks of SP monotherapy and are therefore moving quickly toward introduction of combinations. However, because of the higher cost of artemisinin derivatives, they are contemplating regimens that do not contain this class of drugs. Once again, financial considerations are taking precedence over medically preferable choices.

Some countries are considering amodiaquine + SP combinations on a mid-term basis. The regional experts are aware that, given existing resistance to SP, using this combination is for many equivalent to

treating with amodiaquine monotherapy. To make matters worse, there is already evidence of some resistance to amodiaquine in the East African region. Using the sub-optimal combination of amodiaquine + SP is therefore likely to rapidly render both drugs useless in a given population. To avoid this outcome, the previously mentioned expert meeting advised the following: "the best candidates for combination therapy will be novel drugs that have not been previously used in monotherapy, have no demonstrable parasite resistance, and are not going to be used for monotherapy"[13].

In short, stop-gap mid-term strategies are ineffective, time-consuming, costly, and simply delay tougher decisions. Experience has shown that full implementation of a new malaria protocol takes at least two to three years, so it is imperative that the best long-term decisions are made in the coming months.

It is important to take into account that cultivation of the artemisinin plant and production of the drug takes around a year and a half. Considering this extensive timelag, it is essential to forecast needs and make advance orders. It is therefore critical for ministries of health and donors to commit funds rapidly so that suppliers can start the lengthy process of increasing production. Given the problems of shelf life and forecasting for increased production, it may be useful for an organisation such as UNICEF to be involved in management of drug supply.

Since it is primarily lack of funds that are forcing sub-optimal clinical decisions, the only way to stop widespread introduction of ineffective treatment is to find the resources to pay for more effective choices. Below is an analysis of the incremental costs that would be incurred between sub-optimal and effective treatment choices.

V. How much more would effective treatment cost?

We looked at the supplementary costs of using an artemisinin-containing combination rather than a cheaper, sub-optimal combination (e.g. amodiaquine + SP). Two artemisinin-containing combinations, amodiaquine + artesunate and artemether/lumefantrine, are currently considered the best options for the East African region[20]. We used the amodiaquine + artesunate combination as it is an effective and well tolerated combination which could be implemented in the five countries and is less expensive than artemether/lumefantrine. We acknowledge that in other regions other combinations may be more appropriate. As mentioned above, need was calculated using estimated number of cases. Since this analysis is based primarily on public health services figures, it represents the best available estimate of the number of patients treated for malaria in those facilities, and therefore the financial burden of malaria treatment for Ministries of Health (MOH).

Age distribution of malaria was used to quantify the need for drugs by adapting the protocol to each age group. When not available, figures were estimated from existing documentation and discussion with experts (see annex 1).

Cost of protocol change on a per adult patient basis

Currently, artesunate is by far the most expensive component of the proposed optimal regimen, amodiaquine + artesunate. However, since artesunate is not under patent, production could in principle be taken up by any manufacturer of generic drugs. For this reason, the price of artesunate is likely to decrease in the future when larger quantities of this drug are in demand.

MSF has identified artesunate manufacturers in China, Belgium, Switzerland, India, Korea and Vietnam. These producers are primarily using raw material from China and to a lesser extent Vietnam. Current price offers for the 600 mg artesunate dose necessary in the drug combination amodiaquine + artesunate range from US$0.63 to US$1.50 (see annex 2). Given this wide range of potential prices, we

chose to use the mid-range price of US$1.15 per adult dose to make a conservative analysis of needed funds. The cost of amodiaquine is US$0.15 per dose. We therefore calculated the cost of the combination amodiaquine + artesunate to be US$1.30 per adult treatment.

In addition, based on current price trends and historical experience, we estimate that the price of artesunate tablets will decrease significantly in the next few years. Once artesunate is widely used in Africa, large-scale production is likely to decrease the high production costs. We estimate that, by 2004, the cost of artesunate will be US$0.50 per adult treatment (600 mg dose), and the cost of the amodiaquine + artesunate combination will be US$0.60. In Vietnam, the price of production is almost at this level today, and historical experience with vaccines, antivirals and contraceptives shows that, when purchasing is done in a coordinated fashion and/or competition increases, prices drop dramatically.

One challenge faced by African health ministries is that registration of these products will likely be difficult and slow. WHO could play an active role in preparing and facilitating this process by setting up a pre-qualification system for malaria similar to the one being developed for AIDS drugs (validating the conformity of manufacture using international standards).

	AQ + SP* (proposed mid-term solution) in US$ per adult treatment	AQ + AS** (proposed optimal solution) in US$ per adult treatment	Difference between mid-term and optimal solutions
Current cost (2002)	0.25[21]	1.30	1.05
Target cost (2004)	0.25?	0.60	0.35

* amodiaquine + SP
** amodiaquine + artesunate

Table 2. Per patient costs – proposed mid-term versus optimal treatment prices.

The above table shows, on an individual patient basis, the price implications of using the type of treatment regimen that is currently being proposed in the five East African countries versus the optimal artemisinin-containing combination. The table shows that, at the price available today, the amodiaquine + artesunate combination would cost US$1.05 more per adult patient than the proposed mid-term sub-optimal of amodiaquine + SP.

As mentioned above, we estimate that the price of artesunate will likely decrease in coming years. We estimate that, by 2004, the additional cost of using the optimal rather than the sub-optimal combination will have decreased by two thirds, from US$1.05 to US$0.35.

Total cost of protocol change on a national level

The financial burden of treatment protocol change for the Ministry of Health was calculated using the number of malaria cases and cost of treatment according to age distribution. Estimates were made where exact data were not available. Cost estimates were made on the basis of a difference of US$1.05 between the cost of amodiaquine + artesunate and amodiaquine + SP (see annex 1 for details of calculations).

Country	Estimated number of malaria cases per year	Estimated supplementary cost of using AQ+AS in US$ per year
Burundi	2 million	1,617,000
Kenya	8.2 million	6,135,000
Rwanda	1.2 million	945,000
Tanzania	8.6 million	6,426,000
Uganda	5.3 million	4,007,000
Five countries combined in 2002	25.3 million	19,130,000
Five countries combined 2004	Assumed unchanged	6,300,000

Table 3. Estimated cost difference between sub-optimal and optimal treatment protocol at country level.

Table 3 above shows the supplementary cost for each country of using the optimal treatment regimen rather than the currently proposed mid-term regimen. This ranges from US$945,000 for Rwanda to US$6,426,000 for Tanzania. The total extra cost of adopting optimal treatment regimens for all five countries is a little over US$19 million. As mentioned previously, this cost will likely decrease over time as more producers are validated and competition is encouraged – our projection is that, by 2004, supplementary costs will decrease by two thirds to US$6.3 million for the five countries. In time, artemisinin-containing combination therapy will therefore become more accessible to developing countries, and the burden on external donors will be decreased.

These additional funds should be provided with a view to increasing access to treatment for all patients. This means that if patients are paying for the drugs, prices should be subsidised at the point of purchase to ensure that the increased price of the new treatment does not prevent them from accessing the drugs.

The cost of changing would be considerably higher with Coartem® that is priced at US$2.40 for an adult dose[†]. The total supplementary cost of introduction of this drug in the five countries would therefore be much higher, at US$39.2 million[‡]. Given that Coartem® is patented until 2010, it is hard to predict whether the price of this drug will come down in the near future.

Although US$19 million worth of additional funds will be needed on a regional basis, this investment will have multiple benefits, including saved lives of children and adults; decrease in visits to health centres, hospital stays and lost productivity; avoided expense of ineffective and often repeated treatment; and the ultimate need for more expensive treatment using quinine, mefloquine or co-artemether. Once this treatment is introduced, a decrease in incidence can be expected, especially in the very significant number of cases occurring outside high transmission regions.

[†] special deal arranged by WHO
[‡] Supplementary cost for Burundi, US$3,311,000; for Kenya, US$12,560,000; for Rwanda, US$1,935,000; for Tanzania, US$13,158,000; for Uganda, US$ 8,205,000.

In other words, less expensive options have hidden costs to the healthcare system and national budgets. If no action is taken on the national level, experience shows that people will self-treat with all available drugs, and in particular are likely to use artesunate in monotherapy. This is of special concern because artesunate monotherapy is indicated for seven days, and it is improbable that self-medicating patients will take the drug for the entire duration. Artesunate may therefore quickly be rendered useless as resistance rates rise.

International donors to fill the gap?

The cost to each country of changing treatment protocol ranges up to several million dollars. Given that Rwanda's health budget is US$10 million, and that the Kenyan Ministry of Health's budget for essential drugs is just over US$10 million, there is an obvious need for financial assistance to these countries to cover costs related to protocol changes.

The cost referred to above is the main cost incurred, and must be added to the one-time charges of changing protocols, including development and production of guidelines, training of public and private health workers, and running public education campaigns[§]. However, it is important to note that all five countries in this analysis are already considering changing to combination therapy and therefore will in any case incur protocol change costs. This is why we do not include these costs in our calculations.

Malaria is currently the leading killer of African children, and making the change to artemisinin-containing combinations will help reduce the toll of this disease. Malaria is also one of the three priority diseases that the international community has committed to fight. The Global Fund to fight AIDS, tuberculosis and malaria, which was set up to support developing countries fight against these diseases, estimated need at US$8 billion per year. So far, wealthy countries have pledged only US$1.9 billion. While WHO advocates for major investment in the health of developing countries in order to support their long-term development, donors have also remained quiet.[22]. Lack of funds means that today many African countries are on the verge of switching to sub-optimal national malaria protocols. The needed treatment is already available in Africa, but only at high prices in private pharmacies. Foreign donors can play a crucial role in overcoming this inequity. The time for action is now. With the help of international donors, ministries of health in Rwanda, Burundi, Kenya, Tanzania, Uganda and other African countries will be able to make the medically recommended choice.

VII. Conclusions/Recommendations: the case for immediate implementation of effective national protocols:

1. When considering changing national treatment protocols, it is essential that financial considerations based on costs of drug purchase do not lead to sub-optimal medical choices. Effective drugs that can save lives are available and must be included in national protocols. Other "transition" strategies are short-sighted and merely postpone the necessary switch to more effective treatment. They will also lead to increased incidence of disease and drug resistance.

2. The so-called "transition" strategy proposed by several countries may in fact remain in place for longer than expected, as protocol change is a difficult, expensive and painful process which cannot be repeated every few years. It will also be more expensive in the long-term when it becomes essential to switch to more expensive drugs such as quinine, mefloquine or co-artemether.

3. Developing countries should not be forced to cope with the financial burden of improving malaria treatment on their own. Malaria is a growing worldwide crisis and international aid

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[§] As a frame of reference, in Tanzania, the cost of changing from chloroquine to sulphadoxine-pyrimethamine (excluding the cost of drugs) was estimated at US$424,000 (Goodman C, EANMAT newsletter n°7, p.6).

should be forthcoming to help implement practical solutions. This analysis shows that change would be affordable with help from international donors.

4. Historical evidence in other therapeutic areas shows that prices of procuring artemisinin-containing combinations are likely to decrease over time.

5. International leaders must follow up on their political rhetoric and make available promised resources. There is great urgency in the case of malaria, and moderate investment can concretely improve treatment and save lives – it is a chance to transform words into actions. Furthermore, considering that international aid covers a significant proportion of the health budget of some developing countries, donors have an ethical responsibility to ensure that interventions are medically appropriate. WHO should work proactively to support the ministries of health in developing countries to adopt effective malaria protocols.

6. Antimalarials produced in Asia should be made available in Africa as soon as possible. UN organisations have a role to play: WHO should expand the existing AIDS drug pre-qualification system to malaria and UNICEF can directly support procurement and distribution.

7. Investment is needed for immediate development of co-formulations that can improve compliance and ease new protocol implementation.

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

9. In the long term, a considerable increase in research and development for malaria treatment is also necessary. Medicines for Malaria Venture (MMV) and other research initiatives should be actively supported.

Annex 1. Calculation of the incremental additional cost of changing to an artemisinin-containing combination versus a sub-optimal combination.

The dose given to each patient depends on his/her age. Patients under one year of age receive a quarter of the adult treatment dose. Patients aged 1-4 years receive half a dose. Those aged 5-15 years receive a three quarter dose, and adults receive a full dose.

BURUNDI

In Burundi, 2 million cases occur in a "normal" year (2000 and 2001 were hit by particularly severe epidemics). According to MSF estimates, one third of malaria patients are under five years of age (10% below one and 23% 1-5), 16% are 5-15 years of age and 51% are adults. Therefore, the total cost of change would be:
2 million x (0.1x0.25 + 0.23x0.5 + 0.16x0.75 + 0.51x1) x 1.05 = US$1,617,000.

KENYA

In Kenya, around 4.5 million cases per year were reported from 1996 to 1999[**]. However, the average report rate by health facilities varied from 33.8 to 39.3% during this period (a number of facilities which were not reporting are located in endemic areas), so this figure is unlikely to be accurate. Instead, we used an estimate of 8.2 million malaria outpatient diagnoses made in government facilities every year[††]. The distribution per age group was estimated as: 45% under five years (10% under one, and 35% from 1-5); 15% from 5-15; and 40% adults[‡‡]. The total cost would then be: 8.2 million x (0.1x0.25 + 0.35x0.5 + 0.15x0.75 + 0.4x1) x 1.05= US$6,135,000.

RWANDA

In Rwanda, 1.2 million cases of malaria are treated over the course of a usual year. 13% of patients are under 1 year of age; 15% are 5-15 years; and 50% are over 15 years old. The total annual cost of using the more effective and sustainable combination would therefore be:
1.2 million x (0.13x0.25 + 0.21x0.5 + 0.15x0.75 + 0.5x1) x 1.05 = US$945,000.

TANZANIA

In 1997, 1,131,000 cases of malaria were reported in Tanzania. According to Tanzania's country profile, the health facility response rate in 1997 was 13.2%[§§]. Given that malaria is endemic in almost the entire country, the number of cases can be estimated by extrapolating to a 100% reporting rate. The estimate is 8.56 million cases. The population at risk of endemic malaria in Tanzania is estimated to be 28 million, as compared to 17.7 million in Uganda. The estimate of 8.5 million cases for Tanzania is therefore consistent with the 5.3 million cases in Uganda. The epidemiology of malaria being similar to Uganda, we used the same age distribution for calculation. The total cost was therefore estimated to be:
8.5 million x (0.09x0.25 + 0.35x0.5 + 0.15x0.75 + 0.41x1) x 1.05 = US$6,426,000

UGANDA

As national data were not available, existing figures of cases reported by public facilities were collected, taking into account the number of reports received in each district as well as the average health unit reporting per district (i.e. the number of monthly reports received per year). The number of

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[**] Health Management information System Report for 1996-1999, April 2001
[††] National Malaria Strategy 200-2010, Division of Malaria Control, MOH Kenya, March 2001
[‡‡] Personal communication with Dr Snow, 2002.
[§§] RBM website

cases was estimated by district and consolidated nationally. The estimated number of malaria cases was 5.3 million. Basic age distribution data were available: 44% under 5 and 56% over 5. Taking into account the demographic distribution in Uganda (UN data), the total annual cost was calculated as: 5.3 million (0.09x0.25) + (0.35x0.5) + (0.15x0.75) + (0.41x1) x 1.05 = US$<u>4,007,000</u>.

Annex 2. Selection of lowest recent price offers for artesunate treatment.

Pharmaceutical Company	Recipient	Country	Price offer for one adult treatment (600mg dose)
Mepha	Offer to MSF, 2001	Switzerland	US$1.40
Mediplantex	Offer to WHO, 2000	Viet Nam	US$0.63
Guilin	Offer to non-profit institutions, 2001	China	US$1.00
Sanofi	Offer to MSF, 2001	France	US$1.30

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[14] Burundi data sources and further details: number of cases of malaria (MOH 1999); resistance to chloroquine: 50-90% according to location, often higher than 60% (Epicentre and MOH data); resistance to SP: 13-63%, often higher than 40% (Epicentre and MOH data).

[15] Kenya data sources: chloroquine resistance (MOH); SP resistance (EANMAT newsletter no.9). Details: resistance to chloroquine: Bondo: 79%, Kisumu: 87%, Kwale:66%, Nandi:78%; resistance to SP: Kibwezi: 29%, Bondo: 27% Kisumu: 40%.

[16] Rwanda data sources: chloroquine resistance (WHO report 11/01, footnote 7 p.36); SP resistance (EANMAT newsletter no.9). Details: resistance to SP: Rwaza: 16%, Rukara: 45%

[17] Tanzania data sources: chloroquine resistance (WHO report 11/01, ibid p.37); SP resistance (EANMAT newsletter no.9). Details: resistance to SP: Mlimba: 15%, Kyela : 17%, Mkuzi : 34%.

[18] Uganda data sources: chloroquine resistance 10-60% (MOH data); chloroquine resistance 80% and SP resistance 60% in Mbarara (Epicentre,2000, unpublished result); SP resistance in Jinja and Rukungiri (EANMAT newsletter no.9). Details: resistance to SP: Jinja: 11%, Rukungiri: 19%, Mbarara: 60.1%.

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