Theme Papers

Combination therapy for malaria in Africa: hype or hope?

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The development of resistance to drugs poses one of the greatest threats to malaria control. In Africa, the efficacy of readily affordable antimalarial drugs is declining rapidly, while highly efficacious drugs tend to be too expensive. Cost-effective strategies are needed to extend the useful life spans of antimalarial drugs. Observations in South-East Asia on combination therapy with artemisinin derivatives and mefloquine indicate that the development of resistance to both components is slowed down. This suggests the possibility of a solution to the problem of drug resistance in Africa, where, however, there are major obstacles in the way of deploying combination therapy effectively. The rates of transmission are relatively high, a large proportion of asymptomatic infection occurs in semi-immune persons, the use of drugs is frequently inappropriate and ill-informed, there is a general lack of laboratory diagnoses, and public health systems in sub-Saharan Africa are generally weak. Furthermore, the cost of combination therapy is comparatively high. We review combination therapy as used in South-East Asia and outline the problems that have to be overcome in order to adopt it successfully in sub-Saharan Africa.

Keywords: malaria, drug therapy, transmission; drug combinations; antimalarials, pharmacology; drug resistance; forecasting; cross-cultural comparison.

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Introduction

The African Region has the largest number of people exposed to stable malaria transmission and the greatest burden of malaria morbidity and mortality in the world (*1*, *2*). The problems associated with malaria treatment in Africa can be expected to increase the rates of severe illness and death substantially. This may already have occurred in Senegal (*3*). These problems can also be expected to contribute to epidemics and to the expansion of the disease into previously malaria-free areas (*1*, *4*, *5*). Several countries have already abandoned chloroquine (CQ) in favour of sulfadoxine/pyrimethamine (SP) because of worsening CQ resistance, and more are considering the revision of treatment guidelines. This process has improved malaria treatment and in some settings has resulted in noticeable declines in rates of severe illness and malaria-related mortality (P. Kazembe, personal communication). However, the resistance of the malaria parasite to SP is growing and there is no obvious affordable alternative (*6*).

There is an urgent need to make efficacious and affordable therapy available in regimens that encourage compliance by patients and providers. Decisions made now about antimalarial therapy in Africa will affect future options. The inappropriate use of the limited and shrinking pharmacopoeia of affordable and effective antimalarial drugs should not be allowed to continue. New therapeutic strategies, a better understanding of the mechanisms of resistance, improved drug utilization, and new partnerships to tackle cost barriers should all be brought into play.

The situation is exacerbated by generally poor access to health care, chronic underfunding of public health services, and deficient training of health workers, who are inadequately motivated, equipped and supported (*7*). The newer antimalarials tend to be more expensive than African economies can bear (*8*). These factors add up to a malaria disaster (*9*).

Recent observations in South-East Asia, especially on Thailand's borders with Cambodia and Myanmar, suggest that a highly efficacious combination therapy, including the use of an artemisinin derivative, has halted a rapid decline in the efficacy of mefloquine (MQ) and may have reduced overall malaria transmission (*10–12*). These observations have led to a plea for rapid deployment of this strategy in other malarious areas, especially sub-

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Saharan Africa. There is even an implication that the use of single agents is unethical (*13*).

The experience in South-East Asia offers much hope for Africa. However, the extrapolation of observations from a specific epidemiological context to an entire continent with very different malaria epidemiology is problematic and may offer false prospects. Several current studies impinge on outstanding issues and questions concerning the applicability of combination therapy strategies in Africa (P. Olliaro, personal communication; *14*). When the results become available it will be important to maintain a clear understanding of these issues and their implications for the ultimate success of combination therapy in Africa. We describe these issues, review the current state of knowledge about them, consider the potential limitations of combination therapy, and identify some of the problems that must be overcome if the continent is to benefit from it.

The logic of combination therapy

The basic tenet of combination therapy is that the probability of resistance developing simultaneously to two chemotherapeutic agents with independent mechanisms of action is extremely low, of the order of once in 10^{12} treatments. This frequency is the product of the probabilities of the acquisition of a resistant mutation to each drug multiplied by the number of parasites in a typical infection (*12*).

Some studies have examined the efficacy of drug combinations not containing artemisinin derivatives, including SP combined with MQ (MSP)[a](*15*) and SP combined with CQ (*16*). Newer fixed combination drugs, some using an artemisinin component, are being developed or marketed. They include chlorproguanil/dapsone (Lap Dap), Malarone (atovaquone + proguanil), and co-artemether (lumefantrine + artemether) (*17*, *18*).

The effect of combination therapy is enhanced by the inclusion of an artemisinin derivative. Artemisinin antimalarials decrease parasite density more rapidly than other antimalarial drugs (*19*). When used alone, the short half-life of the artemisinin derivatives minimizes the period of parasite exposure to subtherapeutic blood levels. In combination with another drug with a longer half-life, the short half-life and rapid parasite clearance time of artemisinin derivatives mean that many fewer parasites are exposed to the companion drug alone after elimination of the artemisinin component. Furthermore, exposure occurs when blood levels of the drug close to the maximum are still present (*12*). Another benefit of artemisinin combinations is the 90% reduction in gametocyte levels in treated patients (*10*). These characteristics minimize the probability that a resistant mutant will survive therapy and may also reduce overall malaria transmission rates.

[a] The use of trade names is for identification only and does not imply endorsement by the United States Public Health Service or the United States Department of Health and Human Services.

Evidence of success in combination therapy in Thailand

In Thailand, CQ was replaced by SP monotherapy as the first-line therapy for uncomplicated malaria in 1973. Because of rapidly declining SP efficacy, MSP was introduced during 1984 in the Thai-Cambodian border refugee camps and in 1985 its use was extended to the whole of Thailand (Thimasarn, personal communication; *20*). By 1989, *in vivo* tests and confirmatory *in vitro* tests with MQ at 15 mg/kg showed that cure rates in specific areas of Thailand had dropped from about 95% in 1985 to about 50% (*21*). Because of these low cure rates and the failure of MQ at 25mg/kg to prolong higher efficacy substantially, the use of MQ plus three days of artesunate (MQA_3) was adopted in these areas in 1994–96. This restored the cure rates to 90–95% (Thimasarn, personal communication; *20*).

In the Karen refugee camps in Tak Province, Thailand, along the north-western border with Myanmar, MQA_3 was introduced as the treatment of choice in mid-1994 (*11*). In 1994, MQ monotherapy at 25 mg/kg had a failure rate of 31%, whereas that for MQA_3 was 2% (*22*). Subsequent monitoring of the efficacy of this combination showed that failure rates stabilized over the period 1993–95 (*11*). It has been suggested that combination therapy has allowed the efficacy of MQ itself to stabilize or even recover by eliminating indigenous MQ-resistant parasites from circulation, with illness being caused by imported susceptible parasites (*20*).

In the Karen refugee camps the effect of MQA_3 on malaria transmission has been carefully investigated. Since 1986 there has been a gradual decline in the incidence of *falciparum* malaria (to an average of 0.4 *falciparum* infections per person per year in 1994) (*10*). The mean monthly incidence of malaria during this period was 3.37%. After the introduction of MQA_3 combination therapy the mean monthly incidence dropped to 1.58% (*10*). Additionally, combination therapy reduced gametocytaemia eightfold among patients with primary infections and by a factor of 18 among those with recrudescent infections following MQ, quinine or halofantrine treatment (*10*).

Extrapolating from Tak Province, Thailand, to the rest of South-East Asia

The experience in this area of Thailand suggests that combination therapy offers a solution to the problem of drug resistance. However, wider observations in South-East Asia may contribute to a better understanding of both the potential and the limitations of this strategy. The following four points in particular should be borne in mind.

The rapid development of antimalarial drug resistance is not an inevitable result of monotherapy. South-East Asia has an extremely variable distribution of drug resistance; while some areas have

high rates of resistance to multiple drugs, elsewhere there is still high sensitivity even to CQ (*23*). In Thailand's Kanchanaburi Province, which is contiguous with Tak Province, MQ monotherapy has been used for 14 years and its *in vivo* efficacy has declined little or not at all (Thai Ministry of Public Health surveillance data, unpublished). On the eastern border of Thailand there are areas with multidrug resistance near others in which such resistance does not occur.

There are clearly other factors, most of them poorly understood, which contribute to the development of resistance to given antimalarials. It is also evident that the use of combination therapy may not be essential in all areas. In 1997 a meeting of malaria experts from the South-East Asia Region recommended that the combination of artesunate and MQ be used only in areas where MQ-resistant parasites were present and that CQ, SP or MQ monotherapy be continued in areas where these drugs remained effective (*23*). Although the experts recognized the increasing evidence in support of the more widespread use of combination therapy with artesunate and MQ, they did not feel that there were sufficient grounds for making a more generalized recommendation in its favour (*23*). Thailand's current policy restricts the use of artesunate + MQ for first-line treatment to certain parts of the country's borders with Cambodia and Myanmar (*24*).

The use of drugs in combination does not necessarily prevent the development of resistance. The risk of resistance developing is believed to be much lower if drugs with short half-lives are used than if ones with longer half-lives are employed. Until recently, no naturally occurring resistance to an artemisinin compound had been reported (*13*). However, a recent study in Thailand compared *P. falciparum* isolates from the Cambodia and Myanmar border areas, where artemisinin-containing combination therapy had been used extensively, with isolates from southern Thailand, where MQ monotherapy remained generally effective and artemisinin drugs were used infrequently (*24*). The isolates from the border areas had lower responses to artesunate and artemisinin *in vitro* than those from southern Thailand, suggesting a drift towards reduced sensitivity. This could happen because of uncontrolled and inappropriate use of artemisinin monotherapy outside the formal sector. However, the declines suggest that the strategy is vulnerable to drug use in communities and in the private sector.

The use of drugs with a short half-life does not necessarily prevent the development of resistance. Studies conducted in southern Yunnan Province, China, where monotherapy with artemisinin has been available since the mid-1980s, also suggest declining sensitivity to artemisinin and its derivatives (*25*). Similarly, recent *in vitro* studies in areas of high transmission in southern Viet Nam indicate declining sensitivity to artemisinin (A. Schapira, personal communication). The current national antimalarial treatment guidelines for Viet Nam recommend a wide range of therapeutic options, including five-day monotherapy with artemisinin or artesunate for the treatment of cases of probable uncomplicated malaria when laboratory diagnosis is unavailable (*26*). The use of MQ alone or combined with artesunate is limited by high cost and, especially in the south, by patients' preferences. Artemisinin drugs available in the private sector are typically sold for monotherapy, often in incorrect doses (Le Dinh Cong, personal communication; Bloland, personal observations; *27*).

The cause and effect relationship between the use of artemisinin derivatives in combination with MQ and declines in malaria transmission is not clear. To ascribe overall declines in malaria transmission in Thailand and elsewhere in South-East Asia to the deployment of artesunate-MQ combination therapy is an oversimplification. Several other factors have been at work in the same period of time. Deforestation in areas of former intense *Anopheles dirus* transmission has greatly reduced the incidence of malaria in large areas of Cambodia and Thailand. For several decades the transmission of malaria on Thailand's borders with Cambodia and Myanmar has been influenced by political actions and the consequent limitations on or increases in population movement into and out of forested areas (*24*). In Viet Nam, concurrent implementation of other malaria control activities and a general improvement in the country's economy may also be responsible for declines in malaria since the early 1990s (*28*). In Viet Nam the major reduction in mortality followed the introduction of artemisinin monotherapy rather than combination therapy. Dramatic reductions in malaria incidence have occurred in areas where dedicated diagnostic and treatment facilities have provided access to rapid treatment, even with an artemisinin derivative used for monotherapy.

Extrapolating from South-East Asia to Africa

Consideration of the practicalities of implementing combination therapy in Africa raises various concerns, many of which are not unique to Africa or to combination therapy. Furthermore, several of the non-economic challenges to malaria therapy in Africa would be the same for any monotherapy or combination therapy. Nonetheless, it is imperative to examine all these challenges because of the magnitude of the malaria problem, the struggling economies, and the inadequate public health infrastructure in much of Africa.

Drug choice

It is not obvious which drug combination is best for use in Africa. The choice of the second component may well affect the expected effectiveness of a combination therapy approach. Important factors include cost, ease of administration, acceptability, relative elimination times and current levels of

resistance to the partner drug. Because of the high price of MQ (US$ 3 for an adult dose at 25 mg/kg) (*29*) and because CQ and SP, which are less expensive ($ 0.10 for an adult dose), still retain some efficacy, discussions of combination therapy for Africa have focused on the use of CQ or amodiaquine plus artesunate in areas where CQ resistance is relatively low and of SP plus artesunate in areas where CQ resistance is high (Piero Olliaro, personal communication).

While the probability of simultaneous emergence of resistance *de novo* to two drugs may be of the order of once in 10^{12} treatments, the calculations have to be modified if resistance to one of the components of the combination already exists. Instead of focusing only on the emergence of resistance, it is necessary to consider the perpetuation and spread of pre-existing resistance. Since the combination of artesunate with MQ in Thailand apparently restored the efficacy of malaria treatment at a time when MQ monotherapy failure rates had already risen to 50%, it may be that combination therapy could still be highly effective in inhibiting resistance, notwithstanding pre-existing resistance in the parasite population. This would be highly relevant to the situation in Africa, where CQ resistance is widespread and some SP resistance is present in the eastern and southern regions.

The mechanism of development of resistance to the companion drug to an artemisinin derivative may affect the success of the combination. If the mutations required for resistance to the companion drug are more readily generated (i.e. if single-locus mutations are required instead of multiple-locus mutations), more rapidly spread, or more genetically stable within the parasite population (i.e. if there is no selective disadvantage associated with maintaining those mutations), the resistance to the companion drug may continue despite combination with an artemisinin compound.

While *de novo* emergence of resistance may occur at some point, importation may be a significant factor contributing to the emergence of resistance in a new geographical area (*30*, *31*). Human mobility makes it possible for the importation of resistant parasites to occur at rates far greater than 1 in 10^{12}, and importation has been implicated in the emergence or intensification of resistance in some areas outside Africa (*5*, *31*, *32*). Unless a very high proportion of infections is exposed to combination therapy as opposed to monotherapy, resistant parasites could easily be introduced and maintained in a population, eventually threatening the efficacy of the combination.

There is a suggestion that the activity of artemisinin and MQ are not independent: the benefits observed with artemisinin/MQ combinations may not be realized when a drug other than MQ is used. Recent *in vitro* data suggested that an artesunate/MQ combination had synergistic action, whereas artesunate/pyrimethamine was mildly antagonistic and artesunate/CQ could be either, depending on the parasite isolate tested (*33*). There is also evidence of a potential for cross-resistance between MQ and artemisinins (*24*). While it is not clear that the synergy, antagonism or potential for cross-resistance has any clinical or practical relevance, further questions arise about the most appropriate drug to combine with artesunate. What limits are there to extrapolating observations derived specifically from a combination of MQ and artesunate?

Use of combination therapy in areas of moderate to intense transmission

There is a marked difference in the intensity of transmission between South-East Asia, especially those areas where combination therapy has been studied most, and sub-Saharan Africa. The intensity of transmission is often characterized in terms of the entomological inoculation rate (EIR), expressed as the number of infective mosquito bites per person per time period (*34*).

The intensity of malaria transmission varies greatly in Asia, and foci of intense transmission can be found, but Asia is generally considered to have low transmission rates (*35*, *36*). The EIR in the Karen refugee camps in Tak Province, Thailand, has been estimated to be 0.3 infective bites per year; children aged 2–15 years experience an average of one *falciparum* infection every 2 to 3 years (*37*). In 1994, overall infection rates in this area were estimated to be 0.4 infections per person per year (*10*).

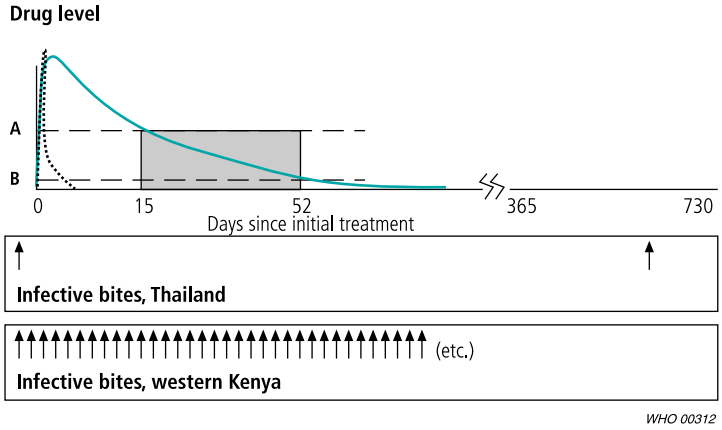
Transmission rates also vary widely in sub-Saharan Africa. However, a greater proportion of the population lives in areas where transmission is far more intense than is typical in South-East Asia. The EIR ranges from <1 infective bite per year in highly seasonal areas in the Sahel (*38*, *39*), to 200–300 infective bites per person per year in western Kenya (*40*), and to 1000 per person per year in the United Republic of Tanzania (*41*).

It is estimated that 466 million people live in areas of sub-Saharan Africa where malaria is endemic, and fairly conservative estimates of the rate of clinical infections by age group suggest that nearly 208 million clinical cases of malaria occurred in Africa in 1995. An additional 13 million clinical infections were thought to occur among an estimated 54 million people living in areas subject to epidemics of malaria (*2*).

The high transmission rates, the large populations at risk and the large burden of illness are relevant to the applicability of combination therapy in Africa.

Impact of combinations of drugs with mismatched half-lives. The probability that a given malaria patient will be re-exposed to malaria shortly after treatment and at a time when blood drug levels might still be within the range exerting selective pressure for resistance (i.e. high enough to kill most sensitive parasites but too low to kill resistant ones) is far greater in areas of intense malaria transmission (Fig. 1). For SP the period of greatest selective pressure on parasites has been estimated to be 15–52 days after treatment (*42*).

Fig. 1. **Simplified schematic representation of pharmacokinetic profile of combination therapy.** Solid curve: sulfadoxine/pyrimethamine (SP). Dashed curve: artesunate. Horizontal line A represents the minimal synergistic SP level required to kill pyrimethamine-resistant strains of *Plasmodium falciparum*; horizontal line B represents the minimal synergistic SP level required to kill pyrimethamine-sensitive strains. The grey area represents the resistance selection period (*42*). Arrows represent typical frequency of infective bites in Thailand (top row: 0.3 infective bites per year) and western Kenya (bottom row: 200 to 300 infective bites per year), and illustrate the likelihood of exposing newly infecting parasites to selective levels of SP.



In Kilifi, Kenya, where the EIR is in the range 0.01–0.09 infective bites per person per night (*43*), 46% of reinfections among SP-treated patients occurred during this period (*42*). In areas such as Tanzania, with an estimated EIR range of 1–2.7 infective bites per person per night, the exposure of parasites to potentially selective levels of SP is unavoidable. In comparison, in north-western Thailand, where the EIR was 0.3 infective bites per person per *year*, the exposure of parasites to selective levels of MQ was highly unlikely, even though, on the basis of plasma half-lives, the period of selective pressure for MQ ($t_{1/2}$ approximately 336–432 hours (*44*, *45*) might be expected to be longer than that for SP ($t_{1/2}$ for pyrimethamine approximately 81–95.5 hours; $t_{1/2}$ for sulfadoxine 116–184 hours) (*42*).

Experience with drug combinations in which half-lives were mismatched, such as the combination of MQ with SP, has long been a cause for concern among malariologists (*19*, *46*). In contrast to SP or MQ, artesunate has a period of selective pressure of the order of a few hours (*13*). While the combination would confer some degree of protection on the artesunate component, artesunate would have been completely eliminated by the time SP or MQ drug levels reached their period of maximum selective pressure, as defined above, leaving them completely unprotected in return. Consequently, the combination of an artemisinin derivative and another drug with a short half-life, such as chlorproguanil–dapsone, might be particularly desirable.

There are two post-treatment opportunities for drug-resistant mutants to be selected. The first occurs when parasites from the initially infecting population survive the antimalarial action of the drug or drugs used for treatment. The second is when new broods of parasites are exposed to suboptimal drug levels during the drug elimination phase. It is unclear which of these is more important for the development, spread and intensification of drug resistance. Studies of recrudescent infections show that surviving parasites have a much greater level of resistance *in vitro* than pretreatment parasites and that patients with recrudescent infections have a greater risk of a failed second round of treatment with the same drug (*47*, *48*). However, work done in Kenya with SP suggests that post-treatment exposure of new parasites also exerts a powerful selective force (*42*). This becomes a critical consideration in respect of the impact of combination therapy at the population level in areas of moderate to intense malaria transmission.

Relation between transmission intensity and emergence of resistance. There is no clear understanding of the relation between transmission intensity and the development of drug resistance. It has been variously suggested that resistance is more likely in low-transmission environments (*49*, *50*), in high-transmission environments (*51–53*), or in either low-transmission or high-transmission environments but not in intermediate transmission environments (*54*, *55*).

The relation between the intensity of transmission and the genetic structure of the parasite is evidently complex and subject to other confounding/contributing factors such as overall drug pressure, clone multiplicity and behavioural factors that affect appropriate and complete drug use (*30*, *51*, *55–58*). As explained below, there are reasons to believe that these factors play a significant role in facilitating the development of resistance in areas of intense malaria transmission.

In South-East Asia the strategy has been applied by a publicly funded, well-trained and supervised service in which access to antimalarial drugs is strictly controlled, all suspected cases are confirmed by microscopy and treatment is given free. It therefore seems reasonable to question the validity of using the experience from particular areas of very low transmission in South-East Asia as a model for predicting what will happen in areas of moderate or intense transmission in sub-Saharan Africa.

Relation between transmission intensity, acquired immunity and expression of clinical disease. Acquired immunity is generally greater in areas of intense transmission, creating a complex relationship between infection, illness and treatment.

In areas of very low or unstable seasonal transmission, either effective immunity does not develop in most people or any immunity that does develop wanes before a subsequent infection is experienced. Most infected people therefore become symptomatically ill. In north-western Thailand, for instance, it has been estimated that 87% of infected people become symptomatic, with no differences across age groups (*35*). In areas of high transmission, however, asymptomatic infections are common, and there is a strong age effect on the probability of experiencing clinical illness when infection is present, young children being at far greater risk than adults.

Among a cohort of children aged up to 14 years who were monitored over a number of years in rural western Kenya, where the EIR was approximately 200–300 infective bites per year (*40*), asymptomatic *falciparum* infections accounted for 57–92% of all *falciparum* infections diagnosed, depending on age group (Bloland, unpublished data; *59*). Infections associated with symptoms among older children and adults tend to be milder (*60*, *61*).

Infected individuals seek treatment only when they become symptomatic and the likelihood of treatment-seeking increases with the severity of symptoms. Under conditions of low transmission and well-deployed combination therapy there is a high probability of most infected people seeking some form of treatment, thus increasing the probability of most infections being treated with combination therapy (e.g. 90% in north-western Thailand). Under conditions of high transmission a much smaller proportion of infected people seek treatment, and fewer infections are covered, even by a well-functioning health system (e.g. only 10–50% in western Kenya). This gives resistant parasites an opportunity to increase in absolute numbers and spread within the population. Any patients receiving combination therapy would benefit from its high efficacy but the social benefit of delaying the development of drug resistance in the community might not be obtained.

Research on treatment and treatment-seeking behaviour in Africa has traditionally focused on under-five-year-olds and pregnant women, the usual high-risk groups. Comparatively little is known about treatment-seeking behaviour and drug use among older children and non-pregnant adults, who comprise the bulk of any population at risk of malaria infection. This large population of asymptomatic or minimally symptomatic individuals could not only contribute to the maintenance of intense malaria transmission by acting as significant sources of gametocytes (*62*) but could also perpetuate resistance through the inappropriate use of drugs.

Diagnosis of malaria

In the areas of South-East Asia where combination therapy has been used most widely, laboratory-based diagnosis in the public sector is the rule. In sub-Saharan Africa, however, laboratory diagnosis of malaria is the exception (*63*), and consequently there is significant overdiagnosis and treatment of fever as malaria (*64*, *65*). Attempts to improve the sensitivity and specificity of the clinical diagnosis of malaria have had only modest success (*66*). Some case management strategies that emphasize syndromic classification in an attempt to improve peripheral practice, e.g. the Integrated Management of Childhood Illness initiative, also tend to overdiagnose fever as malaria (*67*). Laboratory-based diagnosis, however, has been shown to reduce the use of antimalarial drugs (*68*).

Reliance on the clinical diagnosis of malaria, which may continue in sub-Saharan Africa for the foreseeable future, can be expected to contribute to the development and intensification of drug resistance in any strategy of malaria therapy, including combination therapy. The resulting overdiagnosis of malaria and the corresponding overuse of antimalarials can contribute to excessive drug pressure. Antimalarial drugs given to aparasitaemic individuals may contribute to selective drug pressure if the affected persons remain at high risk of subsequent exposure to malaria while drug levels are declining, as is likely to occur in areas of intense malaria transmission.

Drug use

People's perceptions of the etiology of illness and their subsequent reaction to illness, such as their treatment-seeking behaviour, their selection or acceptance of available treatment options and their adherence to recommended drug regimens, have a tremendous effect on the use of any antimalarial drug and play an important role in the effectiveness of a strategy of combination therapy in the prevention of resistance. Poor practices of drug use threaten combination therapy in two ways: inappropriate dosing provides increased opportunities for parasites to be exposed to suboptimal blood levels of either drug in the combination; and one or both components may continue to be given as monotherapy.

The use of antimalarial drugs at the community level can be the source of substantial drug pressure. Self-treatment in Africa is common: 12–94% of participants in various surveys have reported self-treatment of malaria (*69*). Among children with reported fever in Kenya and Togo, 60% and 83% respectively had been treated at home with an antimalarial drug (*70*, *71*). Malaria patients are often brought to a health clinic only after the failure of treatment at home (*72*). In western Kenya, between 49% and 74% of children enrolled in an antimalarial drug efficacy study based on the outpatient department of a rural health clinic already had measurable CQ in their urine (*73*).

In order to obtain the benefits of combination therapy and protect the component drugs, complete adherence to the full recommended dosing regimen is necessary. Long-duration regimens, complex dosing schemes, high cost, poor understanding of how or why to adhere to recommended regimens, and adverse reactions to treatment contribute to non-adherence. Perceptions of wellness can also affect adherence: if symptoms are relieved before a regimen is complete, treatment may be halted and the remaining drug may be saved for later use (*69*). Adherence to multiple day regimens of antimalarial drugs is poor. In Malawi, only 14% of children who received CQ treatment within two days of the onset of fever received a correct dose (*74*). Of children treated at home in Kenya and Togo, only 12% and 30% respectively received adequate CQ (*70*, *71*).

Improper drug use is common. Combination therapy, however, may be more vulnerable if the strategy requires several drugs to be taken together (coadministration) as opposed to having the component drugs together in a single tablet (coformulation). The higher cost to patients of combination therapy might lead to incorrect dosing or even monotherapy. The rapid alleviation of symptoms after treatment with artemisinin derivatives, which is the benefit most apparent to users, may in itself lead to truncated treatment regimens or artemisinin monotherapy (*22*, *75*).

The goal of slowing down the development of resistance by using combination therapy may be undermined by these economic and behavioural influences. Although the proper use of combination therapy may be enhanced by the use of blister packs, improved education of patients, subsidization of costs and coformulation, the incorrect use of antimalarial drugs can be expected to remain a challenge.

Private and public sector sources of malaria treatment

In sub-Saharan Africa the proportion of patients seeking malaria treatment outside the official health sector ranges from 12% to 82% (*69*). The private sector accounts for 40–60% of all antimalarials distributed, and unofficial sources, such as street sellers and market stalls, account for as much as 25% (*8*). Clearly, if the successful implementation of combination therapy as a strategy for inhibiting drug resistance and decreasing transmission depends partly on exposing a high proportion of *falciparum* infections to the therapy, both the public and the private sectors should be involved, including as many unofficial sources as possible. Otherwise, the majority of infections would be missed and there would be a risk of compromising the effectiveness and success of the strategy.

The dominant role of the private sector in providing malaria therapy in Africa poses three challenges to the effectiveness of combination therapy: poor prescription practices, the continued provision of almost all the possible companion drugs as monotherapy, and the sale of drugs of poor quality. Malaria treatment in the private sector is often characterized by poor advice and improper dosing by drug sellers (*8*, *76–78*). This reflects a willingness or an economic necessity on the part of the seller to distribute inadequate amounts of drugs, and, frequently, an inability or unwillingness on the part of the buyer to pay for a complete course of treatment (*8*). While this situation can be modified to some extent through training or creative packaging (*76*, *79*), there is a high likelihood that drugs will continue to be misused in the commercial sector.

Market forces can be expected to influence which drugs are available in the commercial sector. Access may be limited through attempts to regulate availability, for instance by limiting the type or number of outlets that can sell a given drug or by requiring a physician's prescription. However, this strategy often fails when regulatory systems are weak, and can even increase demand in the community for a drug and encourage the private sector to meet the demand (*8*). Where combination therapy is co-administered rather than coformulated the components are highly likely to be sold singly, especially if consumers link rapid relief of symptoms to one component drug but not the other.

Drugs of poor quality, including artemisinins, contribute to drug pressure while failing to provide successful malaria treatment. A survey of antimalarials and other drugs on sale in Nigeria found that 36% of samples were substandard and that most of these came from unofficial outlets. While some samples contained no active ingredient, most had an active ingredient in an inadequate amount (*80*).

Economics of combination therapy for malaria

Combination therapy costs substantially more than either CQ or SP. A paediatric treatment dose of combination therapy for a child weighing 7.5 kg costs $ 0.48, whereas the equivalent costs of monotherapy with CQ and SP are $ 0.013 and $ 0.017 respectively (*29*).

The appropriate use of antimalarial drugs should be maximized in order to increase the likelihood of realizing all the potential benefits of combination therapy. Because of the need for strict control over the use of antimalarials, this probably requires expensive complementary measures such as strengthening and enforcing pharmaceutical regulations, improving the training of health workers, introducing packaging that will encourage adherence, and improving the education of consumers and drug providers. Market forces and the need for public financing can be expected to present obstacles to the widespread implementation of combination therapy in sub-Saharan Africa, even if it proves to be cost-effective in terms of therapeutic efficacy, delay in the development of resistance or reduced transmission.

The cost of antimalarial drugs is one of the complex array of factors determining the market for malaria therapy locally, nationally and internationally (*8*). The private sector can be expected to continue producing and successfully selling antimalarial drugs, including artemisinin products, as monotherapies. It is already beginning to offer combination therapy in the form of products like co-artemether, a coformulation of lumefantrine and artemether (P. Ringwald, personal communication). The successful implementation and use of combination therapy will probably require strict and effective guidance of private sector markets. The international public health community, however, is inexperienced in providing such guidance and influencing markets.

Children aged under 5 years may experience five or six febrile episodes a year. Febrile illnesses are nearly always treated presumptively as malaria. The provision of antimalarials for the management of fever at home and the intermittent presumptive treatment of

pregnant women are increasingly discussed as important components of malaria control strategies. Meeting these needs as well as any other public sector use of combination therapy for malaria would greatly exceed the per capita public resources available for health. Furthermore, facilitating the appropriate use of combination therapy in the private sector and ensuring equitable access to treatment would require a substantial reduction in the cost presented to the consumer, implying a need for subsidies.

The need for public financing of combination therapy raises a number of difficult questions. In much of Africa, combination therapy offers no overwhelming additional therapeutic benefit in the short term; the use of SP, MQ, quinine and other monotherapies generally retains high efficacy, as would artemisinin monotherapy. In the current sub-Saharan context, combination therapy offers the potential of longer-lasting therapeutic efficacy for each of the antimalarials in question; another potential benefit, deriving from the artemisinin component, is that of diminished transmission through a reduction in the prevalence of gametocytes. Neither of these benefits would be perceptible to patients, carers, providers or consumers. Private financing cannot be expected to support the considerable added cost of providing an almost exclusively public good, except in the unlikely situation where combination therapy is the only malaria treatment available. A clear demonstration that the benefits of combination therapy are attainable in sub-Saharan Africa is needed before difficult decisions can be made on the use of limited public resources.

Conclusion

At present there is no clear answer to the question of whether combination therapy is hype or hope for sub-Saharan Africa. Combination therapy appears to offer a highly effective treatment of malaria and, at the individual level, may reduce the likelihood of resistant parasites being selected and transmitted. However, without further investigation it is impossible to be sure that the development of resistance would be inhibited and that transmission would be reduced on a population basis, especially in the complex environment with which we are concerned.

There is huge scope for reducing the number of deaths by using appropriate drugs correctly, and this should be a priority in malaria control. Decisions about formulating and implementing better treatment policies are urgently required. A more comprehensive information-gathering and operational research strategy should be initiated immediately in order to make rational decisions as soon as possible on the appropriateness of deploying combination therapy. Important questions should be tackled simultaneously rather than sequentially. Meanwhile, those responsible for the financial resources necessary for the implementation of any drug strategy that replaces CQ and SP in Africa, including that of combination therapy, should calculate the overall costs and try to assess the level of commitment to it over the long term. ■

Résumé

Traitements antipaludiques associés en Afrique : faut-il y croire ?

La pharmacorésistance constitue l'une des plus grandes menaces pour la lutte antipaludique. En Afrique, l'éventail des antipaludiques efficaces et bon marché se rétrécit et la situation est exacerbée du fait d'un accès généralement difficile aux soins de santé, d'une absence chronique de financement de la santé publique et de l'insuffisance de la formation et de la motivation des agents de santé ainsi que des moyens et du soutien sur lesquels ils peuvent compter. Le coût des nouveaux antipaludiques a tendance à être plus élevé que celui que les économies africaines peuvent supporter. Il est urgent de ralentir le développement de la résistance et de veiller à fournir dans le futur un traitement antipaludique efficace.

Le fait d'avoir conscience de la situation explique la réponse enthousiaste apportée aux observations faites récemment en Asie du Sud-Est, surtout dans les régions situées de part et d'autre des frontières qui séparent la Thaïlande du Cambodge et du Myanmar, indiquant qu'un traitement associé par les dérivés de l'artémisinine et la méfloquine offre une solution possible au problème de la pharmacorésistance. Il a été avancé que ces traitements associés pouvaient améliorer l'efficacité thérapeutique, diminuer la transmission en abaissant la gamétocytémie et ralentir l'apparition d'une résistance à l'un ou l'autre des médicaments de cette association.

Le présent article fait le bilan de l'expérience que l'on a du traitement associé en Asie du Sud-Est et expose les obstacles auxquels sa mise en œuvre se heurte en Afrique subsaharienne. Les taux de transmission plus élevés, la proportion importante d'infestations asymptomatiques chez les sujets semi-immuns, l'usage souvent inapproprié des médicaments, l'absence générale de diagnostic du paludisme au laboratoire, la défaillance quasi totale des systèmes de santé publique et un coût sensiblement plus élevé des traitements associés constituent les principales difficultés rencontrées pour mettre en œuvre ces derniers de façon efficace.

Pour pouvoir prendre rapidement les décisions qui s'imposent concernant les futurs traitements antipaludiques en Afrique, il conviendrait de mettre en œuvre de nouvelles stratégies thérapeutiques, de mieux comprendre la nature et les mécanismes de la résistance, d'adopter de nouvelles façons de procéder pour améliorer l'usage et l'observance des traitements et de mettre en place de nouveaux partenariats afin d'aborder les problèmes posés par le coût élevé de ces traitements.

Resumen

Terapia combinada contra el paludismo en África: ¿está justificado el optimismo?

La farmacorresistencia es uno de los mayores peligros que amenazan a la lucha antipalúdica. En África, la progresiva reducción del arsenal de medicamentos antipalúdicos asequibles y eficaces se ve agravada por el generalmente escaso acceso a la atención sanitaria, por una falta crónica de fondos para la salud pública y por el hecho de que los agentes de salud no cuentan con la formación, la motivación, el equipo y el apoyo necesarios. Los antipalúdicos más recientes suelen ser también más caros de lo que las economías de África pueden permitirse. Hay que actuar cuanto antes para frenar el desarrollo de resistencia y asegurar el futuro suministro de tratamiento antipalúdico eficaz.

La conciencia de la gravedad de la situación explica la favorable respuesta con que ha sido acogida la reciente observación, realizada en Asia sudoriental, sobre todo a lo largo de la frontera de Tailandia con Camboya y Myanmar, de que la terapia combinada con derivados de la artemisinina y con mefloquina es una posible solución al problema de la farmacorresistencia. Se ha sugerido que la terapia combinada puede mejorar la eficacia terapéutica, disminuir la transmisión reduciendo la gametocitemia, y frenar el desarrollo de resistencia a cualquiera de los fármacos combinados.

En el presente artículo se examina la experiencia adquirida con la terapia combinada en Asia sudoriental y se describen los obstáculos con que tropieza su aplicación en el África subsahariana. Las mayores tasas de transmisión, la alta proporción de infecciones asintomáticas en personas semiinmunizadas, el uso con frecuencia inapropiado y sin información suficiente de los medicamentos, la falta general de medios de diagnóstico de laboratorio del paludismo, la precariedad general de los sistemas de salud pública y el costo considerablemente mayor de la terapia combinada son graves obstáculos para el despliegue eficaz de esa terapia.

Para poder tomar urgentemente decisiones respecto al futuro del tratamiento antipalúdico en África, es deseable poner en marcha nuevas estrategias terapéuticas, conocer mejor los mecanismos de resistencia, idear nuevas alternativas para mejorar el uso y la observancia del tratamiento, y forjar nuevas alianzas que permitan superar la barrera que representan los altos costos.

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