WHO/CDS/RBM/2001.35
Distribution: General
Original: English

ANTIMALARIAL DRUG COMBINATION THERAPY

Report of a WHO Technical Consultation

4 – 5 April 2001

World Health Organization

ANTIMALARIAL DRUG COMBINATION THERAPY

Report of a WHO Technical Consultation

World Health Organization, Geneva

WHO, 2001

Text editor: M. Geyer

Layout and production: Graficim

The authors wish to recognise the contributions made to the writing of this report at country level by Ministries of Health and other partners, Regional Offices of WHO, and at a global level by mission reports, partners and the RBM team.

Roll Back Malaria
World Health Organization
20 Avenue Appia,
CH-1211 Geneva 27, Switzerland
Tel: +41 (22) 791 3606, Fax: +41 (22) 791 4824,
E-mail: rbm@who.int Web site: http://www.rbm.who.int/

WHO/CDS/RBM/2001.35

CONTENTS

ABBREVIATIONS

ACT	artemisinin-based combination therapy
AIDS	acquired immunodeficiency syndrome
AQ	amodiaquine
CQ	chloroquine
CT	combination therapy
DHA	dihydroartemisinin
DRAs	drug regulatory authorities
G6PD	glucose-6-phosphate dehydrogenase
GMP	good manufacturing practice
HIV	human immuno-deficiency virus
P. falciparum	*Plasmodium falciparum*
P. vivax	*Plasmodium vivax*
RBM	Roll Back Malaria
SP	sulfadoxine-pyrimethamine
TDR	Special programme for Research and Training in Tropical Diseases
WHO	World Health Organization

INTRODUCTION

A WHO Technical Consultation on Antimalarial Combination Therapy was held in Geneva, Switzerland on 4 and 5 April 2001. Participants reflected a wide range of expertise in the development and use of antimalarial drugs (Annex 1).

Early diagnosis and prompt treatment is one of the principal technical components of the global strategy to control malaria (1). The effectiveness of this intervention is highly dependent on antimalarial drugs, which should not only be safe and effective, but also available, affordable and acceptable to the population at risk. The rational use of an effective antimalarial drug not only reduces the risk of severe disease and death and shortens the duration of the illness, but also contributes to slowing down the development of the parasite's resistance to antimalarial drugs. The emergence and rapid spread of *P. falciparum* resistance to commonly used antimalarial drugs poses a serious challenge to the effectiveness of early diagnosis and prompt treatment as a priority strategy within current malaria control efforts (2-4).

In November 2000, an Informal Consultation on the Use of Antimalarial Drugs was convened by WHO in Geneva. This meeting reviewed and updated recommendations on the use of antimalarial drugs for chemoprophylaxis and treatment, based on the information available. The meeting acknowledged the limited number of treatment options that are available to countries to improve their treatment policies. This is of particular concern in areas of highest resource constraints such as sub-Saharan Africa where a lack of resources has contributed to the continued use of drugs whose effectiveness have been compromised by drug resistance. The potential value of malaria therapy using combinations of drugs (5-9) was identified as a strategic and viable option in improving efficacy, and delaying development and selection of resistant parasites. However, the systematic review of existing data on combination therapy for malaria and identification of specific candidate drugs, especially for Africa, was beyond the scope of the November meeting.

Thus, in view of this recognition of the role of combination therapy, RBM considered it timely to convene a technical consultation to:

- review current evidence on combination therapy with antimalarial drugs
- recommend the minimal criteria for selection and use of combination therapies of antimalarial drugs in different epidemiological settings
- select appropriate combinations for use, particularly in African countries
- identify priority research, product development and production needs to facilitate the implementation of antimalarial combination therapies.

The technical consultation took the form of presentations based on working papers and plenary discussions, on the basis of which specific conclusions and recommendations were agreed. The proceedings of the meeting and working papers form the basis of this report.

1. COMBINATION THERAPY IN THE CONTEXT OF TREATMENT POLICY

A national antimalarial treatment policy is a set of recommendations and regulations concerning the availability and rational use of antimalarial drugs in a country (10). The policy should provide decision-makers with evidence-based recommendations in addition to giving health workers clear guidelines for providing early diagnosis and prompt treatment appropriate to the local context.

1.1 Purpose of drug policy

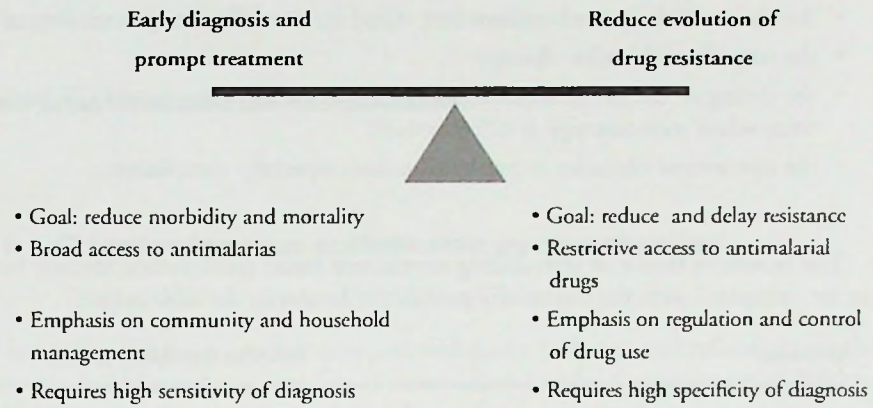
The objective of a national antimalarial treatment policy is to enable the population at risk of malaria infection to have access to safe, good quality, effective, affordable and acceptable antimalarial drugs, in order to:

- ensure a rapid and long lasting clinical cure for individual malaria patients
- prevent progression of uncomplicated malaria to severe disease and death
- shorten clinical episodes of malaria and reduce the occurrence of malaria-associated anaemia in populations residing in areas of high malaria transmission
- reduce consequences of placental malaria infection and maternal malaria-associated anaemia through chemoprophylaxis or preventive intermittent treatment during pregnancy
- delay the development and spread of resistance to antimalarial drugs.

One key challenge facing antimalarial treatment policy development is achieving a balance between two essential, but at times competing, principles: ensuring prompt treatment of malaria and ensuring that antimalarial drugs have a maximum useful therapeutic life (figure 1.). These two essential parts should however be compliementary. Ensuring adequate regulation and control of drug use should allow for equity and rational use of antimalarial drugs with the resultant reduction in mortality and at the same time reduce or delay drug resistance by the parasites.

An effective first-line antimalarial treatment would have a greater impact on reducing malaria mortality than merely improving second-line treatment or the management of severe malaria. Therefore, combination therapies must be available and affordable to communities for use in the first-line treatment of malaria.

Figure 1. Balance between (1) provision of early diagnosis and prompt treatment, and (2) minimising the development of antimalarial drug resistance



1.2 Combination therapy with antimalarial drugs

The concept of combination therapy is based on the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination.

Combination therapy (CT) with antimalarial drugs is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite. In the context of this definition, multiple-drug therapies that include a non-antimalarial drug to enhance the antimalarial effect of a blood schizontocidal drug are not considered combination therapy. Similarly, certain antimalarial drugs that fit the criteria of synergistic fixed-dose combinations are operationally considered as single products in that neither of the individual components would be given alone for antimalarial therapy. An example is sulfadoxine-pyrimethamine.

Rationale for the use of combination therapy in Africa

It is currently estimated that 90% of global episodes of clinical malaria and 90% of global malaria mortality occur in sub-Saharan Africa. Malaria control efforts in the region have been greatly affected by the emergence and spread of chloroquine resistance. This was first recorded in 1979 in East Africa, but has now been reported from almost all malaria endemic countries of Africa (11). Sulfadoxine-pyrimethamine (SP) was, until recently, seen as the obvious successor to chloroquine. However, resistance to SP is developing quickly even with its current use (12, 13), thus reducing the useful therapeutic life of this drug.

Artemisinin-based combination therapies have been shown to improve treatment efficacy and also contain drug resistance in South-East Asia (14, 15, 16).

However, major challenges exist in the deployment and use of antimalarial drug combination therapies, particularly in Africa. These include:

- the choice of drug combinations best suited for the different epidemiological situations
- the cost of combination therapy
- the timing of the introduction of combination therapy (e.g. should CT be deployed in areas where monotherapy is still effective?)
- the operational obstacles to implementation, especially compliance.

The factors in favour of introducing artemisinin based combination therapy in the Africa region are compared with the potentially prohibitive factors in the table below.

In favour	Potential prohibitive factors
• Current inadequacy of first-line treatments in many countries, including possible hidden burden from malaria and chronic anaemia	• Potential misuse of artemisinin derivatives, risking their value in treatment of severe malaria
• High efficacy of artemisinin derivatives in rapid clearance of symptoms and parasites	• Limited knowledge and use of combination therapies with or without artemisinin derivatives
• No documented resistance to artemisinin and its derivatives at present	• Problems of adherence to co-administered (non-fixed) combinations, particularly at the household level
• Possible delay or slowing of spread of resistance to available effective and affordable antimalarial drugs, if included in combination therapy	• Lack of evidence of its effectiveness in delaying development of resistance in areas of high transmission
• Potential for transmission reduction due to the effect of artemisinin derivatives on gametocyte carriage rate (applicable to areas with low or moderate malaria transmission)	• Higher cost of artemisinin derivatives
	• Effort and cost of changing treatment policy

The costs of antimalarial combination therapies are over ten times more expensive than those of the traditional drugs currently used in Africa as monotherapy. Thus a change to and implementation of combination therapy would involve higher direct and indirect costs to health services, necessitating substantial financial support through sustained international public/private support, as these higher costs would be out of reach for many developing nations, especially in sub-Saharan Africa.

Although combination therapy is accepted as the rational approach to case management in Africa, current evidence of its effectiveness within the region is limited. There is also little or no information on the safety and efficacy of combination treatment in pregnant women and young children, which are specific high-risk groups in Africa. Carefully planned operational research studies to address these challenges should be part of the implementation process of combination therapy in the region. A regional or sub-regional approach to the introduction of antimalarial drug combinations is recommended. This will facilitate the sharing of information and expertise among countries.

2. ANTIMALARIAL THERAPY COMBINATION DRUGS

2.1 Non-artemisinin based combinations

2.1.1 Chloroquine plus sulfadoxine-pyrimethamine

Chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) are antimalarial drugs that are used frequently in Africa either as first-line or second-line drug for the treatment of *P. falciparum* malaria. CQ is a 4-aminoquinoline while SP is a fixed-dose combination of two antifolate compounds. These are blood schizontocidal drugs active against *P. falciparum* with no reported cross-resistance. In Africa *P. falciparum* resistance to CQ has increasingly spread and intensified since it was first documented in 1979. Similarly, *P. falciparum* resistance to SP has also increased since the late 1980s, particularly in East Africa where it has been used on a larger scale as first-line drug (12, 13, 17). Resistance to SP is also demonstrable in parts of West Africa (18).

Several physicians in Africa are already practising the combined use of CQ+SP for the treatment of *P. falciparum* infection in individual patient care, and national health authorities have deployed the use of the combination in some countries (e.g. Ethiopia) where both *P. falciparum* and *P. vivax* are common.

The pharmacokinetic properties of CQ and SP have, individually, been extensively studied (19, 20). CQ and SP have reasonably similar pharmacokinetic profiles, with varied modes of action on different biochemical targets in the parasite and are therefore technically suitable candidates for combination therapy. However, as there is no published information on the *in vitro* pharmacodynamic interactions of the combination it is not known whether their activities are synergistic, antagonistic or additive (*Warhurst D., personal communication*).

In areas with high levels of *P. falciparum* resistance to CQ and moderate resistance to SP, the combination of CQ+SP would not be expected to achieve significantly better cure rates than SP alone. Moreover, it is unlikely that the use of CQ+SP would retard the development and selection of resistance to SP.

Despite parasite resistance, CQ still effects a significant anti-inflammatory action through modulation of the cytokine pathway, and thereby the use of CQ+SP may achieve a more rapid resolution of symptoms than treatment with SP alone.

Studies in The Gambia (21) and Papua New Guinea (22) which compare the efficacy and safety of CQ+SP to that of SP alone, show that the efficacy of the combination is dependant on the levels of resistance to the individual components. The combination has been in use in Vanuatu since 1994, and there has not been any recorded malaria mortality since 1996, though this reduction cannot be entirely attributed to the use of the combination (*Schapira A., personal communication*). The combination of CQ+SP has also been a standard first-line treatment in peninsular Malaysia since 1997, and in Papua New Guinea since 2000, both of which are areas with *P. falciparum* and *P. vivax* infections.

Overall, the available evidence has shown that the CQ+SP combination is unlikely to have a significant advantage over SP alone in areas of predominant *P. falciparum* transmission with high levels of resistance to CQ. Since this reflects the current situation in most of sub-Saharan Africa, a change to this combination as a first-line treatment policy is unlikely to give any significant useful long-term advantage.

2.1.2 Amodiaquine plus sulfadoxine-pyrimethamine

Amodiaquine (AQ) is a 4-aminoquinoline similar in structure and activity to chloroquine. Like chloroquine, it also has antipyretic and anti-inflammatory properties.

A recent review of studies on the treatment of uncomplicated falciparum malaria conducted over the past ten years in Africa showed a higher therapeutic efficacy of amodiaquine over chloroquine, with a tendency towards faster clinical recovery. This difference was also observed in areas with mild to moderate parasite resistance to chloroquine (23, 24).

The global use of amodiaquine has declined owing to reports of severe adverse reactions following its use for chemoprophylaxis of malaria (25-27). Most of the reported severe adverse events were in male patients over 40 years of age (26, 28, 29). However, some countries have continued to use AQ in the therapeutic management of uncomplicated malaria and there have been no reports of severe adverse events following its use in malaria treatment.

AQ and SP have reasonably similar pharmacokinetic profiles, with varied modes of action on different biochemical targets in the parasite and are therefore technically suitable candidates for combination therapy.

There are presently three published studies on the efficacy and safety of AQ+SP compared to AQ alone. All date back to the 1980s. One was undertaken in China (30), and the other two in Mozambique (31, 32). In a meta-analysis of these studies, parasite clearance rates at 28 days tended to favour AQ+SP (33). A recent trial in Uganda (*Kamya M., et al. unpublished*), showed a higher rate of clinical and parasitological cure with AQ+SP than with SP alone. However, the combination was no more effective than AQ alone, which still had an efficacy of 95% when used as monotherapy. The safety data obtained in these clinical trials were limited, but did not suggest that adverse reactions of AQ were increased by the co-administration of SP.

In some countries in West and Central Africa, where levels of resistance to AQ are generally less than those of CQ (23), a change to AQ+SP would probably be a more cost effective option with a longer useful therapeutic life than a change to monotherapy with SP. However, there are still some concerns over the safety of AQ for widespread unsupervised repeated treatment of malaria. More data on safety, including its use during pregnancy, is required.

2.1.3 Atovaquone-proguanil (Malarone™, GlaxoWellcome)

This is a fixed-dose combination of atovaquone (a naphthoquinone derivative) and proguanil. It is available as film-coated tablets in adult and paediatric formulations. Though atovaquone has antimalarial activity, when used alone recrudescence of parasitaemia occurs in one-third of patients with *P. falciparum* infection (34). However, in combination with proguanil hydrochloride a synergistic effect is seen. Atovaquone-proguanil is highly efficacious against *P. falciparum*, including strains that are resistant to chloroquine and mefloquine, with cure rates of 94-100% (34-37).

The pharmacokinetic profile and toxicology of Malarone™ have been documented (38, 39). While the available efficacy and safety data for Malarone™ treatment are encouraging, the high cost and restricted availability limit its potential as a suitable option for combination therapy. The manufacturer does not envisage active commercialization of the drug in malaria endemic countries. Instead, a Malarone™ Donation Program has been launched by Glaxo Wellcome with a proposed global donation of one million treatment courses for the management of uncomplicated malaria treatment failures (35, 40). This program has begun at several sites in Kenya and Uganda. Under the guidelines of the Donation Program, use of the drug is to be restricted to patients with confirmed *P. falciparum* malaria who fail to respond ro treatment with current first-line and second-line drugs.

The use of Malarone™ in children with severe anaemia in whom oral medication is possible is currently being investigated in Zambia. Malarone™ co-administered with artesunate has also been evaluated in Thailand (*White N., personal communication*). The safety and efficacy of Malarone™ in the management of malaria during pregnancy is being researched by WHO.

Current contra-indications include hypersensitivity to atovaquone or proguanil or presence of renal insufficiency. In view of a paucity of appropriate safety and efficacy data, its use is not recommended in young children with a body weight of less than 11 kg, in pregnant women, and in breastfeeding women.

2.1.4 Mefloquine-sulfadoxine-pyrimethamine (Fansimef™, Roche)

The combination of mefloquine-sulfadoxine-pyrimethamine (MSP) was developed for therapeutic use on the basis of the observation that its components display at least additive activity and that their combination might delay the emergence of parasite resistance (19). There is no pharmacokinetic interaction between the components, with profiles of mefloquine and SP corresponding to those obtained with equal doses of the individual components. The long elimination half-life of mefloquine (= 20 days in adults) is an advantage for single dose treatment, but a disadvantage in areas with intensive malaria transmission where the residual drug level for a long duration is likely to exert high selection pressure on the parasite population (41).

Contrary to theoretical postulations, the use of MSP as a first-line treatment for uncomplicated *P. falciparum* infections in Thailand was associated with a rapid development of resistance to mefloquine on the Thai-Cambodian border (42, 43). It is thought that this was caused by residual, post-therapeutic drug blood levels in individuals who returned to areas with

intensive malaria transmission and contracted new infections (44) rather than by the relatively low 15 mg/kg dose of mefloquine in the combination (45). Other contributory factors included the already existing resistance to SP in Thailand (46) as well as the concomitant use of mefloquine with lesser bioavailability than that in MSP as monotherapy. The poor match between the half-lives of mefloquine and SP (47) could also have affected the therapeutic useful life of the MSP as the mutual protection of the drugs relates only to the therapeutic phase, i.e. the treatment of the current infection.

As a result, MSP has not been recommended for general use by malaria control programmes for either prophylaxis or treatment since 1990 because of concerns about the risk of severe adverse reactions to the combination.

2.1.5 Quinine plus Tetracycline or Doxycycline

In areas with decreasing susceptibility of *P. falciparum* to quinine where a seven-day course of quinine is not fully curative, the addition of the relatively slow-acting drug tetracycline ensures a high cure rate (48). Co-administration of quinine plus tetracycline has been employed in the treatment of uncomplicated *falciparum* malaria since the late 1970s.

Doxycycline, derived from oxytetracycline, has an identical spectrum of activity as tetracycline and is currently also being used in combination with quinine. Doxycycline is more completely absorbed, more lipid-soluble and more stable, and less likely to transform to a toxic product. It also has a longer plasma half-life than tetracycline. Since the costs of tetracycline and doxycycline are equivalent, the once daily regimen of doxycycline offers considerable operational advantages over tetracycline, which must be administered four times daily.

The practical constraints with the combined treatment of quinine and tetracyclines relate mainly to patient adherence and safety. Patient adherence is strongly influenced by adverse reactions to quinine and the cumbersome nature of the drug regimen that requires eight-hourly doses of quinine for three to seven days, and six-hourly doses of tetracycline for seven days (in total 37 to 49 drug doses). The regimen can be considerably simplified by the once daily use of doxycycline instead of tetracycline. Tetracycline and doxycycline are contra-indicated in pregnant women, breastfeeding women and children less than eight years of age.

As a result of the above, it is difficult to recommend quinine plus tetracyclines as a first-line treatment for uncomplicated malaria. However, quinine plus doxycycline (preferably) could be considered as an option for treating patients who have failed to respond to first-line and/or second-line treatment and are still able to take oral medication.

2.2 Artemisinin-based combinations

The advantages of artemisinin based combination therapy (ACT) relate to the unique properties and mode of action of the artemisinin component, which include the following:

- rapid substantial reduction of the parasite biomass
- rapid resolution of clinical symptoms
- effective action against multidrug-resistant *P. falciparum*
- reduction of gametocyte carriage, which may reduce transmission of resistant alleles (in areas with low or moderate malaria transmission)
- no parasite resistance documented as yet with the use of artemisinin and its derivatives
- few reported adverse clinical effects, however pre-clinical toxicology data on artemisinin derivatives are limited.

Artemisinin (qinghaosu), artesunate, artemether and dihydroartemisinin have all been used in combination with other antimalarial drugs for the treatment of malaria (49). Of all of these drugs artesunate has the most documented clinical information.

Pre-clinical studies have shown that artemisinin and its derivatives do not exhibit mutagenic or teratogenic activity. However, the drugs have caused fetal resorption in rodents at relatively low doses of > 10 mg/kg, when given after the sixth day of gestation (50). Reports on the use of these drugs in humans during pregnancy are limited (51, 52). Thus, because of the effects in rodents and the very limited data in humans, the artemisinin derivatives are not currently recommended for use in the first trimester of pregnancy (53).

Due to the very short half-life of artemisinin derivatives, their use as monotherapy requires a multiple dose regimen of seven days duration. Combination of one of these drugs with a longer half-life "partner" antimalarial drug allows a reduction in the duration of artemisinin treatment, while at the same time enhancing efficacy and reducing the likelihood of resistance development to the partner drug.

Artesunate used in combination therapy have been shown to delay the development of resistance to its partner drug (mefloquine) in low malaria transmission areas in South-East Asia (9, 54-56). The effect on resistance development in areas of high malaria transmission remains to be determined. In most of the ACT currently in use or being evaluated, the partner drug is eliminated slowly, and remains unprotected once the artemisinin compound has been eliminated from the body, thus exposing sub-therapeutic blood levels to new infections. The implications of this pharmacokinetic mismatch in ACT are not clear at present, particularly in areas of high malaria transmission.

Because artemisinin compounds are derived from plant extracts and at least a two-year lead-time is needed to cultivate the plants, the supply of raw materials may become a substantial problem and may slow the deployment of ACT.

2.2.1 Artesunate plus chloroquine

Efficacy and safety of the combination of artesunate plus chloroquine have been evaluated in three randomized double-blind, placebo-controlled clinical trials conducted in Burkina Faso, Côte d'Ivoire and Sao Tome and Principe. The combination was well tolerated with no untoward adverse reactions. However, preliminary results available from Burkina Faso and Sao Tome and Principe showed very high chloroquine failure rates (>60%) and sub-optimal efficacy of the

combination with less than 85% parasitological cure rate on Day 14 in intent-to-treat analysis. Similar results were obtained from the Côte d'Ivoire study (*Olliaro P., personal communication*). Based on these findings, artesunate + CQ does not appear to be a viable option in areas with pre-existing moderate to high levels of *P. falciparum* resistance to CQ.

2.2.2 Artesunate plus amodiaquine

The efficacy and safety of artesunate plus amodiaquine have been evaluated in three randomized, double-blind placebo-controlled clinical trials conducted in Gabon, Kenya and Senegal. The combination was efficacious and well tolerated. The level of efficacy coincides with low levels of AQ resistance in the study sites. The 14 day parasitological cure rate of the combination was >90% in intent-to-treat analysis at all sites. (*Olliaro P., personal communication*).

Artesunate plus amodiaquine appears to be a viable option particularly in areas where CQ efficacy is already compromised. However, continued monitoring of resistance to AQ and the impact of AQ resistance on the effectiveness of the combination would need to be carefully monitored.

2.2.3 Artesunate plus sulfadoxine-pyrimethamine

The efficacy and safety of SP plus artesunate have been evaluated in three randomized, double-blind, placebo-controlled clinical trials in The Gambia (57), Kenya and Uganda. This combination was very well tolerated and, as with CQ and AQ combinations with artesunate, the therapeutic efficacy was dependent on the level of pre-existing resistance to the partner drug. These studies also evaluated the efficacy of SP combined with two different dose regimens of artesunate: either a single day or a three-day regimen of artesunate. The three-day regimen of artesunate was more efficacious than the one-day regimen (*Olliaro P., personal communication*). The increasing levels of resistance to SP will limit the use of artesunate + SP, particularly in the eastern parts of Africa. However, it may still be a viable option for some countries of West Africa and other areas where SP efficacy is not yet compromised by resistance.

2.2.4 Artesunate plus mefloquine

The co-administration of artesunate plus mefloquine have been in use for many years in parts of Thailand and has become the first-line treatment in several parts of South-East Asia (54-56). Dose regimens have ranged from a single dose of artemisinin (or its derivative) plus mefloquine (15mg/kg, single dose), to the currently recommended regimen of artesunate (4mg/kg once daily) for three days plus mefloquine (25mg base/kg) given as a split dose of 15mg/kg on Day 2 and 10mg/kg on Day 3.

Adverse reactions reported with the use of mefloquine included severe adverse neuropsychiatric effects, a few cases of cardiotoxic effects (58-60) and incidents of vomiting in young children (which is reduced by dividing the dose of 25mg/kg and administering it over 2 days (61)). It has also been shown that using the high dose mefloquine in combination with artesunate results in less adverse reactions than the use of mefloquine alone, probably because of the delayed administration of mefloquine, i.e. after the symptoms of malaria have been curbed by artesunate (61).

The combination of artesunate plus mefloquine is not considered a viable option for use as first-line therapy in Africa. There is concern that the long half-life of mefloquine may lead to the selection of resistant parasites in areas of intense transmission. Furthermore, there are also concerns of a possible increase of mefloquine related adverse reactions when used unsupervised on a large scale for treatment of malaria.

Trials in Thailand have established the superiority of a three-day over a single-day treatment of artesunate when used in combination with mefloquine. Thus a single-day artesunate plus mefloquine treatment is not recommended for use even in the acute phase of a complex emergency or during malaria epidemics. An alternative regimen of 8mg/kg mefloquine daily for three days would facilitate the combination of mefloquine and artesunate in a blister pack or the production of a fixed dosage formulation. However, this latter regimen of mefloquine has not yet been evaluated.

2.2.5 Artemether-lumefantrine (Coartem™, Riamet™ Novartis)

This is a co-formulation of artemether and lumefantrine (an aryl alcohol related to quinine, mefloquine and halofantrine), for which a total of 16 clinical trials with more than 3000 patients, including children <5years of age, have been carried out in Europe, South-East Asia and Africa. This combination has proved as effective, and better tolerated, as artesunate plus mefloquine in the treatment of multi-drug resistant *P. falciparum* when given as a six-dose regimen over three days (62). In areas of intense transmission with high background malaria immunity, a four-dose regimen has performed well, but in non-immune populations (mainly in South-East Asia) the four-dose regimen has resulted in failure rates of approximately 20%. This failure rate was reduced to less than 5% by increasing the dose to a six-dose regimen (63-66). There are as yet no serious adverse reactions documented, and studies show no indication of cardiotoxicity (67). However, the drug is not recommended for use in pregnancy and lactating women, as safety for use in these groups has not yet been established. Post-market surveillance and Phase IV studies also need to be undertaken for Coartem™.

Artemether-lumefantrine is the most viable artemisinin combination treatment available at the moment (though it is not recommended for pregnant women and breastfeeding mothers), because in addition to its efficacy, safety and tolerance profile, it is available as a fixed-dose formulation, increasing the likelihood of patient compliance with the drug regimen.

2.3 Combinations in the pipeline

It is possible that some of the antimalarial combination drugs currently under development will prove to be highly efficacious, safe and well-tolerated, with a potential for widespread use at prices affordable in most of the world. It should be noted that some of the components of these combinations will be "new chemical entities" that have not been used as monotherapy for the management of malaria. Resistance to these new combinations may therefore be slower to develop.

2.3.1 Piperaquine-dihydroartemisinin-trimethoprim (Artecom™) and Artecom™ plus primaquine (CV8™)

The co-formulation of piperaquine-dihydroartmesinin-trimethoprim, called Artecom,™ by its Chinese producers, and the co-administration of Artecom with primaquine, called CV8™ (CV = China-Viet Nam), are the result of initial animal model work at the Guangzhou Institute of Traditional Medicine in China. Clinical studies have been carried out mainly in multi-drug resistant areas of Viet Nam.

Though no pharmacokinetic data exist for Artecom™, some data exists for the individual components of the combination. Animal toxicology studies indicate additive toxicity of the combination components. A study of the effects of the combination on the behaviour of mice indicated a sedative effect at 10 times the curative dose, but not at the normal dose. In beagle dogs, no cardiovascular (including ECG) or respiratory system effects were demonstrated. No data on mutagenicity or teratogenicity of the combination are available (*Hien T., personal communication*).

Trials with Artecom™, plus primaquine (CV8™), using a three-day regimen in patients over seven years old in southern and central Viet Nam from 1993 to 1998, gave an efficacy consistently above 93% in 28-day tests even in multi-drug resistant areas. This has also been documented in Hainan (China), in areas where there is piperaquine resistance. (*Hien T., personal communication*).

No serious adverse events have been observed in any of the documented human studies. The main adverse reactions have been nausea and vomiting, which were due to piperaquine and are dose-related. Sinus bradycardia was also reported in one clinical study and should be looked for in future Phase III trials. There are no data on children under 7 years, pregnant women or on drug excretion in breast milk.

Viet Nam has decided to maintain primaquine in the combination tablet, which, according to Guangzhou investigators, is for its gametocytocidal effect. However, dihydroartemisinin (DHA), which is a component of Artecom™, has similar (though less marked) effects, thus reducing the rationale for primaquine. The primaquine dosage is 40 mg administered over three days. It is uncertain whether this low dosage causes adverse reactions in G6PD deficient individuals.

Before Artecom™ can be registered internationally and incorporated into treatment policies for uncomplicated malaria, it will be necessary to obtain more detailed pre-clinical toxicology data

in animals, and clinical data on efficacy, safety and tolerability in young children and in pregnant women. This could be achieved in a relatively short period with multi-center collaborative studies, and, with positive results, Artecom™ could be a viable combination drug for widespread use, with the price of a full adult dose currently quoted at around US$1.20.

It is encouraging that the combination is highly efficacious in Viet Nam in an area with multi-drug resistance, and also in areas of Hainan in areas with piperaquine resistance. However, the long half-life of piperaquine is of concern in relation to potential development of resistance in areas of intense malaria transmission.

2.3.2 Pyronaridine plus artesunate

Pyronaridine (an acridine-type Mannich base) co-formulated with artesunate. There are no pharmacokinetic data on the combination, though studies of pyronaridine alone have been made, albeit on a limited scale. The toxicity profile of pyronaridine is comparable to that of chloroquine, but at high doses mutagenicity and fetal resorption in rats have been observed (20).

A study in Hainan (an area with *P. falciparum* resistance to pyronaridine due to the earlier widespread use of the drug), showed a clinical response rate of 100% with the combination on a regimen of pyronaridine (400mg) plus dihydroartemisinin (DHA) (100mg) daily for 2 days (*Liu Dequan, personal communication*). A dosage regimen of pyronaridine (400mg) in combination with artemether (150mg) or artesunate (150mg) daily x 2, gave a clinical efficacy of 100% (68). There are no data in children under five years, pregnant women or on drug excretion in breast milk.

2.3.3 Naphthoquine plus dihydroartemisinin

Naphthoquine and dihydroartemisinin (DHA) have been co-formulated for trial purposes. Presently, the exact ratio of the components is still classified. Though information on the toxicology, pharmacokinetics and safety is very limited, interest in this product has arisen due to the results of a few preliminary clinical studies that indicated a cure rate of 100% obtainable with a two-dose one-day regimen. Li Guangqian, in a comparative study in 1999, obtained a clinical efficacy of 100% compared to 80% using a five-day course of artesunate (69). Clinical data of this product are of great interest, but the lack of pre-clinical data, especially toxicology data on naphthoquine, makes it difficult to determine the potential future status of this product.

2.3.4 Chlorproguanil-dapsone plus artesunate (CDA™ or Lapdap plus™)

The final product of CDA™ will be a fixed-ratio co-formulation of chlorproguanil-dapsone (Lapdap™) and artesunate. While data exist for Lapdap™ and artesunate individually, there are no data yet on CDA™. However, initial toxicology work is under way, while other studies due to start soon include Phase I pharmacokinetic work, Phase II artesunate dose-finding studies and Phase III safety and efficacy studies in adults. Safety and efficacy data is also required in young children, pregnant women and breastfeeding mothers.

Lapdap™ is entering its final phase of development and is expected to be available in some African countries in 2002 already for use as monotherapy. While CDA™ provides a potential combination option, there are concerns that the deployment of Lapdap™ as monotherapy for widespread use could affect the useful therapeutic life of CDA™. Thus, the deployment of Lapdap™ as monotherapy is not recommended in Africa in order to prevent a possible compromise of the useful therapeutic life of CDA™. There is also an added advantage of using a combination partner that would not have been deployed previously as monotherapy.

3. Implementation issues

3.1 Criteria for selection of combinations of antimalarial drugs

A set of criteria to assist in determining the relative merits of various combination therapy antimalarial drugs for different epidemiological conditions has been proposed (Annex 2). These criteria form the parameters of a framework to guide the choice and selection of antimalarial combination drugs. Although a scoring system is part of this set of criteria, the scores and weights are arbitrary and secondary to the process of identifying the key determinants highlighted by these criteria. The scores generated from these criteria are not intended to be strictly applied, but rather provide a means of guiding comparisons of different combination therapies. The major criteria in order of significance are:

1. Therapeutic efficacy of the combination, irrespective of the efficacy of the individual components;
2. Safety of the drugs in combination, especially amongst high risk groups;
3. Potential for widespread use of the combination at all levels of the health care system, including its use for home management;
4. Potential for consumer compliance;
5. Cost effectiveness;
6. Potential to delay or prevent development of resistance;
7. Other factors including product availability, production capacity and potential for widespread use at a sub-regional level.

3.1.1 Therapeutic efficacy

The therapeutic efficacy of the combination product is the most important criterion. This compares the combinations in terms of clinical and parasitological cure, and the rapidity of clinical recovery. Therapeutic efficacy (clinical cure) is currently proposed to guide the process of changing antimalarial treatment policy in the African region (70). This could also be applied to the antimalarial combination drugs. Parasitological cure rate is also very important as this has been closely linked to the development of resistance by the parasites. The level of parasite resistance to a single drug at which point it is no longer considered useful as component of a combination therapy is not yet defined. It is generally accepted that the lower the level of resistance, the higher the chances that the combination drug will have a longer useful therapeutic life. Thus the best candidates for CT 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.

3.1.2 Safety

The primary safety concern of combination products is the possibility of additive or synergistic adverse interactions between the components. These interactions can take the form of:

- chemical interactions which can decrease efficacy, increase toxicity and diminish the shelf life of the product;
- biological interactions with an additive or synergistic effect on adverse reactions; and
- pharmacokinetic interactions with an influence of one component on the absorption, distribution, biotransformation or elimination of the second component, with either a resultant increased or decreased potential for toxicity.

It is essential to establish the toxicology profile in animal studies prior to evaluation of safety in the general human population. Safety profile is particularly required in special risk groups such as pregnant women, children under the age of 5 years, lactating women (excretion of product in breast milk and its effect on the child) and in people with HIV/AIDS.

3.1.3 Consumer acceptability

Patients' acceptance of any treatment strategy is a function of both the true characteristics of a drug (efficacy, half-life and side effects) and the consumers' perceived characteristics (e.g. product presentation - taste, colour, etc.).

Other factors also influencing acceptance include the reputation of the drug or drug combination, its capacity to induce rapid onset of symptomatic relief (antipyretic), irrespective of the rate of elimination of parasites, with minimal side effects.

3.1.4 Consumer compliance

The acceptance of new treatment may also be influenced by the complexity of the dose regimen. Co-formulation, appropriate packaging, simplified dosage schedules and reduced treatment duration will positively influence patients' compliance to therapy.

3.1.5 Costs and cost effectiveness

Policy change and implementation of a combination therapy strategy results in direct and indirect costs to health services. Balancing these costs against those associated with the consequence of not changing treatment policy (which may include the further costs resulting from treatment failure and re-treatment, treating infections that progress to severe disease, in addition to loss of productivity and mortality) is required to understand the economic implications of a treatment policy change.

Because of the increased cost and complexity inherent in most, if not all, combination therapy strategies, the success of combination therapy will depend more heavily on the presence of a functional health system with greater requirement for infrastructure, equipment and manpower development. There are, however, some examples to suggest that a highly effective treatment provided in a simple-to-use way could still produce benefits even in situations with weak health systems (*Foster S., personal communication*).

Increasingly, an effective drug supply system for the distribution of antimalarial drugs is considered an effective mix of public and private (profit and non-profit) involvement in the areas of procurement, storage and transport services as well as in dispensing the medication to the patient.

The criterion of cost-effectiveness has been difficult to apply in most regulatory systems. However, with the increasing use of various tools of pharmaco-economics, a number of countries are starting to explore the possibility of incorporating cost-effectiveness with other traditional markers (safety, efficacy and quality) in assessing products. WHO expertise and support in this area will be valuable.

3.1.6 Potential to delay or prevent development of resistance

Based on different pharmacokinetic and pharmacodynamic properties, the potential ability of the combination to delay development of resistance against each component of the combination is associated with:

1. Optimal compatible half-life of the combination components
2. Mode of action (Synergistic or additive)
3. Gametocytocidal activity - ability to reduce transmission of resistant strains

3.2 Technical requirements and processes for introducing combination therapy

The regulation and control of medicines at the national level takes place in the context of the national drug policy and the prevailing legal framework. The legal framework constitutes enacted legislation, principal acts and enabling regulations and guidelines.

The two core functions of the national Drug Regulatory Authorities (DRAs) are:

- Drug registration; and
- Regulatory control and quality assurance of pharmaceutical products, including surveillance of drug distribution channels and information control.

3.2.1 Drug registration

Drug registration is the first component in ensuring the quality of drugs available in the market and is one of the main responsibilities of national DRAs. Most countries are already undertaking the exercise of registering drugs based on criteria of safety, efficacy, quality and, in some cases, access needs.

With the introduction of new antimalarial drugs, including innovative combinations of already existing drugs, drug registration and marketing authorization will be critical. The co-administration of drugs already registered individually for monotherapy may not require any special regulatory action. However, co-packaging of such drugs could require the justification of need in addition to a demonstration of safety. It would also be necessary to develop new package inserts. Co-formulation of combination drugs would also require a full regulatory process, necessitating the establishment of a regulatory dossier. This technical documentation for the dossier should contain administrative details, formula, chemistry and pharmacy, pharmacology and toxicology, labelling, package insert and storage conditions of the product.

3.2.2 Regulatory control and quality assurance

DRAs are also responsible for ensuring that drug information and promotional materials meet the standards and ethical criteria of drug promotion.

It is critical that all antimalarial drugs deployed are of good quality and are efficacious. In order to ensure that the antimalarial drugs available in the market are of the desired quality specifications, countries need to have competent pharmaceutical inspection programmes, backed by well-equipped and functional national drug quality control laboratories. Rapid quality assessment tools, such as the *mini-lab* can supplement the testing of drugs at points of entry and in peripheral settings.

Practical measures are needed to strengthen regulatory control to assure drug quality and combat counterfeit drugs likely to be a major threat with the introduction of, and expected high

demand for, more expensive combination antimalarial drugs. DRAs should approach overall quality assurance by combining inspection of pharmaceutical manufacturing plants with regard to GMP, as well as ensuring that the pharmaceutical products available on the market meet the prescribed quality specifications. It should be noted that DRAs have varying capacities for GMP inspection. In most of sub-Saharan Africa, this area of pharmaceutical regulation is not appropriately developed and there may be a benefit in taking sub-regional approaches to building capacities in these areas.

The DRAs regulation of public and private drug distribution channels through issuing of licenses and permits should be strengthened. These distribution channels include wholesale and retail pharmacies, hospitals and clinics where large amounts of medicines are dispensed.

3.3 Industrial partnerships and their roles

Collaboration with the industrial private sector is vital in Research and Development, and in the production of combination therapy drugs. Examples of already existing collaboration include:

- Collection of post-marketing surveillance data (e.g. Novartis and Coartem™);
- Development and registration of new product (e.g. GlaxoSmithkline and CD/CDA™; Shin Poong and Pyronaridine plus artesunate);
- Co-sponsoring of post-registration development work by WHO and MSF (e.g. GMP artesunate + SP co-packaged blisters packs with IDA); and
- Local public and private partnerships (e.g. development of Artecom™ and CV8™ by local private investors in Viet Nam and China; Sanofi-synthelabo providing artesunate for TDR trials in Africa).

Private and public partnerships could assist in facilitating appropriate regulatory assessments necessary for combining existing antimalarial drugs. By involving research institutions that are able to generate pre-clinical and clinical data, and by ensuring the production of drugs according to international GMP standards, an active partnership with the manufacturer at planning stages of development process would clearly benefit the process. Negotiations could be made to compensate public sector financing with "preferential pricing".

One issue of particular interest to WHO is improving estimates of needs for drug production and market forecasting through collaboration with the private sector. Also, the potential for public-private partnership in promoting access to effective CT should be more actively explored.

A projected timeline of the availability of new antimalarial combination drugs for treatment policy is shown in Annex 3.

4. Conclusions and recommendations

Overview

The conclusions and recommendations of the meeting strongly endorse the potential of combination therapy for use in Africa. Appropriate national and regional based studies should be initiated with all possible speed to assess their potential for incorporation into National Policies in preference to monotherapy. There are however two practical caveats:

- There is limited clinical experience for many of the combinations being considered. It is acknowledged that full safety and efficacy needs to be demonstrated on a case by case basis involving appropriate prospective studies, including where necessary regulatory and Phase IV studies, and appropriate surveillance, particularly of adverse events
- It is acknowledged that in the case of artemisinin-based combinations the cost of treatment will increase significantly over traditional monotherapies such as chloroquine or SP (by a factor of up to 10-fold). In countries where healthcare systems cannot afford the introduction of combination therapies other alternatives may need to be considered.

These caveats epitomise the dilemma facing many national malaria control programmes. Increased global funding will be required to facilitate the appropriate exploration of use, and purchase, of optimal antimalarial drugs. Failure to assure increased funding for antimalarials will provide a major obstacle for many countries in Africa in moving to combination therapy.

Specific Points

- Increasing resistance to chloroquine and sulfadoxine/pyrimethamine will probably lead to an increase of malaria morbidity and mortality, particularly in children, and urgent action is needed to replace antimalarial drugs which have become, or are rapidly becoming, ineffective.
- Combination therapies preferably using "novel" antimalarial drugs with different modes of action is the way forward for improving therapeutic efficacy and delaying development of resistance in antimalarial chemotherapy.
- Artemisinin-based combinations have several distinct advantages in that they produce rapid clinical and parasitological cure, there is as yet no documented parasite resistance, they reduce gametocyte carriage rate, and are generally well tolerated.
- Based on available safety and efficacy data, the following therapeutic options are available now and have potential for deployment (in prioritized order) if costs were not an issue:
  i. artemether-lumefantrine (Coartem™)
  ii. artesunate (3 days) plus amodiaquine
  iii. artesunate (3days) plus SP in areas where SP efficacy remains high
  iv. SP plus amodiaquine in areas where efficacy of both amodiaquine and SP remain high. This is mainly limited to countries in West Africa.
- These combination options need continued documentation of safety and efficacy as part of any potential implementation process, especially among very young children, pregnant women, and breastfeeding mothers and their babies.
- Artemisinin-based combination therapies are at an early stage in Africa and there is a need for extensive Phase IV studies and post-marketing surveillance.

- Other artemisinin-based combination therapies in the pipeline are recommended for accelerated development, particularly piperaquine-DHA combination (Artecom™, CV8™), Lapdap-artesunate and pyronaridine-artesunate.
- Options that are not recommended for policy at this time include:
  i. chloroquine-based combinations (CQ + SP and CQ + artesunate)
  ii. one-day treatment of artesunate + SP
  iii. mefloquine-based combinations (e.g. mefloquine plus artesunate) in areas of high malaria transmission
  iv. one-day treatment of artesunate plus mefloquine in the acute phase of a complex emergency or malaria epidemics
- The lack of safe and effective preventive therapies for use in pregnancy in SP resistant high transmission areas and in epidemic situations was noted. This issue needs to be addressed urgently.

References

1. *A global strategy for malaria control*, Geneva, World Health Organization: Geneva, 1993.
2. Bloland PB *et al.* Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. *Journal of Infectious Diseases*, 1993, **167**(4):932–937.
3. Bloland PB and Ettling M. Making malaria treatment policy in the face of drug resistance. *Annals of Tropical Medicine and Parasitology*, 1999, **93**(1): 5-23.
4. Marsh K. *et al.* Malaria disaster in Africa. *Lancet*, 1998, **352**: 924.
5. White N. Antimalarial drug resistance and combination therapy. *Philosophical transactions of the Royal Society of London*, 1999, B (354): 739 -749.
6. White NJ. Averting a malaria disaster. *Lancet*, 1999, **353:** 1965 - 1967.
7. White NJ. Preventing antimalarial drug resistance through combinations. *Drug resistance updates*, 1998, **1:** 3-9.
8. *The use of artemisinin and its derivatives as antimalarial drugs*: report of a joint CTD/DMP/TDR Informal Consultation. Geneva, World Health Organization, 1998, WHO/MAL/98.1086.
9. Price RN. *et al.* Effects of artemisinin derivatives on malaria transmissibility. *Lancet*, 1996, **347:** 1654-1658.
10. *Antimalarial drug policies: data requirements, treatment of uncomplicated malaria and the management of malaria in pregnancy*. Geneva, WHO/MAL/94.1070
11. *The use of essential drugs*, Geneva, World Health Organization 2000 (WHO Technical Report Series No. 895)
12. Ogutu RB *et al.* The efficacy of pyrimethamine-sulphadoxine resistance of *Plasmodium falciparum* malaria in Kenyan children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, **94:**83-84
13. Trigg JK *et al.* Resistance to pyrimethamine-sulfadoxine in *Plasmodium falciparum* in 12 villages in north east Tanzania and a test of chlorproguanil-dapsone. *Acta Tropica*, 1997, **63:**185-189.
14. Peters W. The prevention of antimalarial drug resistance. *Pharmacology and Therapeutics*, 1990, **47:** 497-508.
15. White N. Delaying antimalarial drug resistance with combination therapy. *Parassitologia*, 1999, **41:** 301-308.
16. White NJ and Olliaro PL. Strategies for prevention of antimalarial drug resistance: rationale for combination therapy for malaria. *Parasitology Today*, 1996, **12:** 399-401.
17. Ronn AM. *et al.* High level of resistance of *Plasmodium falciparum* to sulfadoxine-pyrimethamine in children in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1996, **90**(2):179-181.
18. Onyiorah E. *et al.* Early clinical failures after pyrimethamine-sulfadoxine treatment of uncomplicated malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1996, **90:**307-308.
19. *Advances in malaria chemotherapy. Report of a WHO Scientific group*. Geneva, World Health Organization, 1984 (WHO Technical Report Series No. 711).
20. *Practical chemotherapy of malaria. Report of a WHO Scientific Group*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 805).
21. Bojang KA. *et al.* A trial of Fansidar™ plus chloroquine or Fansidar alone for the treatment of uncomplicated malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1998, **92:**73-76.
22. Darlow B. *et al.* Sulfadoxine-pyrimethamine for treatment of acute malaria in children in Papua New Guinea. *American Journal of Tropical Medicine and Hygiene*, 1982, **31:**1-9.
23. Olliaro P. *et al.* Systematic review of amodiaquine treatment in uncomplicated malaria, *Lancet*, 1996, **348:**1196-1201.
24. Brasseur P. *et al.* Amodiaquine remains effective for treating uncomplicated malaria in west and central Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1999, **93**(6):645-650.

25. Hatton CS. *et al.* Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet*, 1986, **1:**411-414.

26. Neftel KA. *et al.* Amodiaquine induced agranulocytosis and liver damage. *British Medical Journal*, 1986, **292:**721-723.

27. Winstanley PA. *et al.* The disposition of amodiaquine in Zambians and Nigerians with malaria. *British Journal of Clinical Pharmacology*, 1990, **29**(6):695-701.

28. Rovieux B. *et al.* Amodiaquine induced agranulocytosis. *British Journal of Haematology*, 1989, **71:** 7-11.

29. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine-sulphadoxine, pyrimethamine-dapsone and to amodiaquine in Britain. *Journal of the Royal Society of Medicine*, 1990, **83**(2)82-85.

30. Huang Q. *et al.* Effectiveness of amodiaquine, sulfadoxine-pyrimethamine, and combinations of these drugs for treating chloroquine-resistant falciparum malaria in Hainan Island, China. *Bulletin of the World Health Organization*, 1988, **66:** 353-358.

31. Schapira A, Schwalbach JFL. Evaluation of four therapeutic regimens for falciparum malaria in Mozambique. *Bulletin of the World Health Organization*, 1988, **66:** 219-226.

32. Dinis DV, Schapira A. Comparative study of the efficacy and side-effects of two therapeutic regimens against chloroquine-resistant falciparum malaria in Maputo, Mozambique. *Bulletin de la Société de Pathologie Exotique*, 1990, **83:** 521-528.

33. McIntosh HM, Greenwood BM. Chloroquine or amodiaquine combined with sulphadoxine-pyrimethamine as a treatment for uncomplicated malaria: A systematic review. *Annals of Tropical Medicine and Parasitology*, 1998, **98:** 265-270.

34. Looareesuwan S. *et al.* Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *American Journal of Tropical Medicine and Hygiene*, 1996, **54**(1): 62-66.

35. Radloff PD. *et al.* Atovaquone and proguanil for *Plasmodium falciparum* malaria. *Lancet*, 1996, 347:1511-1514.

36. Anabwani G. *et al.* Combination of atovaquone and proguanil hydrochloride vs. halofantrine for the treatment of *Plasmodium falciparum* malaria in childen. *Paedriatric Infectious Diseases Journal*, 1999, **18**(5):456-461.

37. Looareesuwan S. *et al.* Efficacy and safety of atovaquone/proguanil compared with mefloquine treatment of acute *Plasmodium falciparum* malaria in Thailand. *American Journal of Tropical Medicine and Hygiene*, 1999, **60**(4): 526-532.

38. Gillotin C. *et al.* Lack of pharmacokinetic interaction between atovaquone and proguanil. *European Journal of Clinical Pharmacology*, 1999, **55**(4): 311-315.

39. Sabchareon A. *et al.* Efficacy and pharmacokinetics of atovaquone and proguanil in children with multidrug-resistant *Plasmodium falciparum* malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene 1998*, **92**(2): 201 -206.

40. Bloland PB. *et al.* Malarone donation program in Africa. *Lancet*, 1997, **350:** 1624-1625.

41. Watkins WM, Mosobo M. Treatment of *Plasmodium falciparum* malaria with pyrimethamine-sulfadoxine: selective pressure for resistance is a function of long elimination half-life. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, **87:** 75 - 78.

42. White NJ. Antimalarial drug resistance: the pace quickens. *Journal of Antimicrobial Chemotherapy*, 1992, **30:** 571-585.

43. Nosten F. *et al.* Mefloquine-resistant falciparum malaria on the Thai-Burmese border. *Lancet*, 1991, **337:**1140-1143.

44. Wernsdorfer WH. *et al.* A symposium on containment of mefloquine-resistant falciparum malaria in Southeast Asia, with special reference to border malaria. *Southeast Asian Journal of Tropical Medicine and Public Health*, 1994, **25:**11-18.

45. White NJ. Drug resistance in malaria. *British Medical Bulletin*, 1998, **54**(3):703-715.

46. Riekmann K. *et al.* Response of *Plasmodium falciparum* infections to pyrimethamine-sulphadoxine in Thailand. *American Journal of Tropical Medicine and Hygiene*, 1987, **37:** 211-216.

47. White NJ. Combination treatment for falciparum prophylaxis. *Lancet*, 1987, **1:**680-681.

48. Looareesuwan S. *et al.* Randomised trials of mefloquine-tetracycline and quinine-tetracycline for acute uncomplicated falciparum malaria. *Acta Tropica*, 1994, **57:**47-53.

49. Hien TT. An overview of the clinical use of artemisinin and its derivatives in the treatment of falciparum malaria in Viet Nam. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, **88**(Suppl. 1):S7-S8.

50. Qinghaosu ACC. Antimalarial studies on qinghaosu. *Chinese Medical Journal*, 1979, **92:**811-816.

51. Li GQ. *et al.* Clinical trials of artemisinin and its derivatives in the treatment of malaria in China. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, **88** (Suppl. 1):S5-S6.

52. Wang TY. Follow-up observation on the therapeutic effects and remote reactions of artemisinin (qinghaosu) and artemether in treating malaria in pregnant women. *Journal of Traditional Chinese Medicine*, 1989, **9**(1):28-30.

53. McGready R. *et al.* Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1998, **92:**430-433.

54. *The use of artemisinin and its derivatives as antimalarial drugs: report of a joint CTD/DMP/TDR Informal Consultation.* Geneva, World Health Organization, 1998 WHO/MAL/ 98.1086.

55. White NJ. Minireview: assessment of the pharmacodynamic properties of antimalarial drugs *in vivo*. *Antimicrobial Agents and Chemotherapy*, 1997, **41**(7):1413-1422.

56. *WHO Informal Consultation on the neurological investigations required for patients treated with artemisinin compounds and derivatives.* Geneva, World Health Organization, 1998.

57. von Seidlein L. *et al.* Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial, *Lancet*, 2000, **355:** 352-357

58. Havaldar PV, Mogale KD. Mefloquine induced psychosis. *Paediatric Infectious Diseases Journal*, 2000, **19:**166-167.

59. Potasman I. *et al.* Neuropsychiatric problems in 2,500 long-term travellers to the tropics. *Journal of Travel Medicine*, 2000, 7(1):5-9.

60. Ekue JMK. *et al.* A double blind comparative clinical trial of mefloquine and chloroquine in symptomatic falciparum malaria. *Bulletin of the World Health Organization*, 1983, **61:**713-718.61.

61. ter Kuile FO. *et al.* Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bulletin of the World Health Organization*, 1995, **73**(5): 631-642.

62. Tamariya P. *et al. In vitro* sensitivity of *Plasmodum falciparum* and clinical response to lumefantrine (benflumetol) and artemether. B*ritish Journal of Clinical Pharmacology*, 2000, **49**(5):437-444.

63. Looareesuwan S *et al.* A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute *Plasmodium falciparum* malaria in Thailand. *American Journal of Tropical Medicine and Hygiene*, 1999, **60**(2):238-243.

64. van Vugt M *et al.* Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria. *Antimicrobial Agents and Chemotherapy*, 1998, **42**(1):135-139.

65. von Seidlein L *et al.* Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. *Journal of Infectious Diseases*, 1997, **176**(4):1113-1116.

66. Novartis. *A randomised, double-blind, parallel group trial comparing efficacy, safety and pharmacokinetics of the standard schedule (4 _ 4 tablets over 48 hours) with two higher dose schedules of co-artemether in the treatment of acute Plasmodium falciparum malaria in adults and children in Thailand.* Basle, Novartis Pharma AG, 1997.

67. van Vugt M *et al.* No evidence of cardiotoxicity during antimalarial treatment with artemether-lumefantrine. *American Journal of Tropical Medicine and Hygiene*, 1999, **61**(6):964-967.

68. Chen Chang *et al. Second International Conference on Tropical Medicin, Sanya, China, 1999, (unpublished abstract)*

69. Li Guangqian. *Second International Meeting on Tropical Medicine, Sanya, China 1999 (unpublishedd abstract)*

70. *Framework for developing, implementing and updating antimalarial treatment policy in Africa. A guide for country malaria control programme*. Harare, WHO/AFRO 2000.

Annex 1

List of participants

Technical advisers[1]

- Professor Pierre Ambroise-Thomas, Interactions Cellulaires Parasite-Hôte (ICPH) ER CNRS 2014 Faculté de Médécine, Université Joseph Fourier, 38043, Grenoble, France
- Dr Fred Binka, School of Public Health, University of Ghana, Accra, Ghana
- Dr Peter Bloland, Malaria Epidemiology Branch, Division of Parasitic Diseases, National Center for Infectious Diseases, CDC, Georgia, USA (*Rapporteur*)
- Dr Dennis Carroll, Senior Public Health Adviser, Office of Health and Nutrition, U.S. Agency for International Development, Washington DC, USA
- Dr Susan Foster, Chair, Dept. of International Health, Boston University School of Public Health, Boston, USA
- Professor Oumar Gaye, Parasitology Service, Faculty of Medicine, C.A. Diop University, Dakar, Senegal
- Professor Brian Greenwood, Department of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK *(Chairman)*
- Dr Andrew Kitua, Director-General, National Institute for Medical Research, Dar-es-Salaam, United Republic of Tanzania
- Dr Jacques Le Bras, Centre National de Référence de la Chimiosensibilité du Paludisme, Hôpital Bichat Claude Bernard, 75018, Paris, France
- Ms Gugu Mahlangu, Director-Medicines Control, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe
- Dr Sylvia Meek, Head, Malaria Consortium, London School of Hygiene and Tropical Medicine, London, UK.
- Dr Robert Ridley, Chief Scientific Officer, Medicines for Malaria Venture (MMV), Geneva, Switzerland
- Dr Alistair Robb, Senior Public Health Specialist, Health and Population Department, Department for International Development, London, UK.
- Professor Lateef Salako, Chief Executive, Federal Vaccine Production Laboratory, Yaba, Lagos, Nigeria (*co-Chairman*)
- Dr Richard Steketee, Division of Parasitic Diseases, National Center for Infectious Diseases, CDC, Atlanta, GA, USA
- Dr William Watkins, Senior Research Fellow, Department of Pharmacology & Therapeutics, University of Liverpool, Liverpool, UK
- Dr Wilson Were, Resident Paediatrician, Rubaga Hospital, Kampala, Uganda
- Professor Walther Wernsdorfer, Department of Specific Prophylaxis and Tropical Medicine, University of Vienna, Vienna, Austria
- Professor Nicholas White, Faculty of Tropical Diseases, Mahidol University, Bangkok, Thailand
- Professor Jack Wirima, Mwaiwathu PVT Hospital, Blantyre, Malawi

[1] All participants completed declaration of interest forms prior to the meeting.

WHO Secretariat

Regional Advisers

- Dr Keith Carter, Regional Adviser - Malaria, WHO Regional Office for the Americas, Pan American Sanitary Bureau, Washington, DC, USA
- Dr Yao Kassankogno, Regional Adviser - Malaria, WHO Regional Office for Africa, Parirenyatwa Hospital, Harare, Zimbabwe
- Dr Allan Schapira, Regional Adviser - Malaria, WHO Regional Office for Western Pacific, Manila, Philippines
- Dr Vinod Sharma, WHO Regional Office for South-East Asia, New Delhi, India
- Dr Tom Sukwa, Malaria Drug Policy, WHO Regional Office for Africa, Parirenyatwa Hospital, Harare, Zimbabwe

WHO Headquarters, Geneva, Switzerland

- Mr David Alnwick, Project Manager, Roll Back Malaria
- Dr Andrea Bosman, Roll Back Malaria
- Dr Kabir Cham, Roll Bank Malaria
- Dr Jane Crawley, Roll Back Malaria
- Dr Charles Delacollette, Roll Back Malaria
- Dr Elisabeth Feller-Dansokho, Roll Back Malaria
- Dr Win Gutteridge, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases/Product Research and Development
- Dr Jane Kengeya-Kayondo, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases/Intervention Development and Evaluation
- Dr Kamini Mendis, Roll Back Malaria
- Dr Bernard Nahlen, Roll Back Malaria
- Dr Piero Olliaro, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases/Intervention Development and Evaluation
- Dr Peter Olumese, Roll Back Malaria (*Secretary*)
- Dr Clive Ondari, Essential Drugs and Medicines Policy/Drug Action Programme
- Dr Aafje Rietveld, Roll Back Malaria
- Dr Jean Rigal, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases/Intervention Development and Evaluation
- Dr Robert Taylor, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases/Intervention Development and Evaluation
- Dr Awash Teklehaimanot, Technical Co-ordinator, Roll Back Malaria

Annex 2

MATRIX FOR COMPARING ANTIMALARIAL COMBINATION THERAPIES

A proposed scoring system by which various combinations can be compared is presented below. This is a framework for guiding the process of selection of antimalarial combination drugs. The scores and weights attached to this set of criteria are arbitrary and secondary to the process of evaluating the various issues highlighted by these criteria. The scores generated are not intended to be strictly applied but rather provide a means of objectively comparing different drug combinations across an arbitrary set of scales. (Note: a lower score is better for each of the individual categories and therefore for the overall score).

The groupings of the criteria in order of significance are as follows:

A. Therapeutic efficacy

Based on the AFRO recommended guideline for antimalarial treatment policy change (70), efficacy of the combination (irrespective of the efficacy of the individual components) is scored as:

Treatment failure < 5% = 1; 6%- 15%=2; 16 - 24% = 3 and > 25% = 4

B. Clinical Safety

Based on "safety for clinical use" in different risk groups (score each group):

1. All age groups
2. Children under 5 years of age
3. Infants
4. Pregnant women
5. Breastfeeding mothers
6. People living with HIV/AIDS

Recommended for clinical use = 1; Not recommended for clinical use = 2

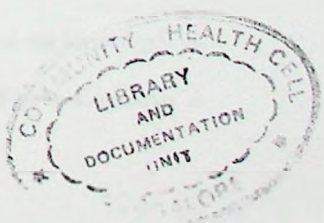
C. Potential for widespread use in different health care settings

Any special training or facility support (diagnosis, drug storage and delivery etc) needed for deployment of the combination at different health care delivery levels:

a. Community/home management

b. Clinics/Health centres

c. Hospitals



Ability to use at all levels = 1, Other levels except community/home management = 2, Hospitals alone = 3.

D. Potential for consumer compliance

Based on product factors that can influence consumer acceptance and use:

a. **Product formulation:** *Co-formulation = 1; Co-administration = 2*

b. **Dosage schedule:** *Number of daily dose multiplied by the duration of treatment dose*

c. **Consumer acceptability:** *Acceptable = 1; score increases to a maximum of 4 with reducing acceptability based on factors such as side effects, taste, colour, number of tablets per dose, etc.*

d. **Dosage formulation:** *adult and paediatric = 1, adult only = 2*

E. Cost and cost effectiveness

A measure of cost per clinical outcome (clinical cure and/or radical cure)

F. Potential to delay parasite resistance to the combination

Based on different pharmacokinetic and pharmacodynamic properties, the potential ability of the combination to delay development of resistance against each component of the combination is scored:

1. Optimal compatible half-life of the combination components

   Compatible half-lives = 1; Non-compatible half lives = 2

2. Mode of action

   Synergistic=1; additive action = 2; antagonistic activity = 3

3. Gametocytocidal activity - ability to reduce transmission of resistant strains

   Gametocytocidal activity =1; No gametocytocidal activity = 2

G. Product availability

1. Production capability:

   a. Reliable production source (GMP standards): Yes =1; No = 2

   b. Reliable production capacity: Yes =1; No = 2

2. Local availability:

   a. Registered for use: Yes =1; No = 2

   b. available at affordable cost for wide spread use: Yes =1; No = 2

H. Potential for wide geographical application

This is an assessment for potential wide-spread regional/sub-regional use of the product based on a combination of factors like:

- regional efficacy profile
- regulatory status and production capacity
- cost effectiveness.

Potential for wide spread use = 1; Limited application = 2

It may not be possible to measure some important access issues, e.g. inter-country collaboration, structure of health system and facilities, etc.

Combination therapy comparative matrix

Criteria	Drug A	Drug B	Drug C	Drug D
A. Therapeutic efficacy of the combination				
a. Efficacy studies				
b. Comparative efficacy studies				
B. Clinical safety				
a. All age groups				
b. Children under 5 years				
c. Infants				
d. Pregnant women				
e. Breastfeeding mothers				
f. People living with HIV/AIDS				
C. Potential for widespread use in different health care settings				
a. Community/home management				
b. Clinics/health centres				
c. Hospitals				
D. Potential for consumer acceptability and compliance				
a. Product formulation				
b. Dosage schedule				
c. Acceptability				
d. Dosage formulation (adult/paediatric)				
E. Cost and cost effectiveness				
F. Potential to delay drug resistance				
a. Compatible half-life				
b. Mode of action				
c. Gametocytocidal activities				
G. Availability				
a. Reliable production source				
b. Adequate production capacity				
Local availability				
a. Registered				
b. Available at affordable cost				
H. Potential for wide geographical application				
Regional spread of application				

Annex 3

Projected time line for the availability of new combination drugs

(Additional time would be needed for registration process and potentially for Phase IV studies prior to wide-scale policy implementation).

2001:	Amodiaquine plus artesunate **co-administration**
	SP plus artesunate **co-administration**
	Amodiaquine plus SP **co-administration**
	Chlorproguanil-dapsone plus artesunate **co-administration**
2002-2003:	Amodiaquine-artesunate **co-formulated**
2004-2005:	Chlorproguanil-dapsone-artesunate **co-formulated**
	Pyronaridine-artesunate **co-formulated**
	DHA-piperaquine (+/- trimethoprim +/- primaquine) **co-formulated**

Annex 4

Possible scenarios for policy change from chloroquine first-line therapy to combination therapy

1. Chloroquine directly to a "durable long-term" combination therapy strategy (ACT).
2. Chloroquine first to an interim strategy then to a "durable long-term" combination therapy strategy.
3. Chloroquine with or without an interim strategy to a tiered treatment system:
   a. One drug strategy for community use and a second for facility use
   b. One drug strategy for general treatment and a second for use among pregnant women.

Notes:

1. For countries not requiring an urgent replacement of chloroquine, option 1 would be advised as soon as possible to prevent the development of resistance to other antimalarial drugs used as monotherapy, e.g. areas of West Africa would most likely be included in this category.
2. Many countries in eastern and southern Africa have, by default, already adopted what could be considered an interim strategy involving SP as first-line therapy (Malawi, Kenya, Tanzania, some provinces of South Africa, Botswana, etc). A subsequent change would be to a "durable"combination therapy strategy (ideally not including a component drug that has been in wide spread use).
3. Countries in urgent need of changing away from chloroquine are in a difficult position. Although some combination therapies are now available (or will be in the very near future), none except mefloquine plus artesunate have sufficient safety and efficacy data from areas of low to moderate transmission to eliminate most doubts about use on a very large scale. However, mefloquine is currently not recommended for use in areas of intense transmission making mefloquine plus artesunate not an option in these areas.

   Combination therapy's viability as a policy option in the short term is dependent on the speedy compilation of safety data that would be required for registration in a given country.
4. Those countries adopting an interim strategy should consider including a combination therapy drug into their treatment policy as a second-line treatment even if combination therapy is not used for first-line treatment. This would offer an opportunity to gain clinical and operational experience with the drug before it is adopted as a first-line treatment.
5. Malaria prevention and treatment during pregnancy deserves urgent attention. One possibility would be to reserve SP for use only as preventive intermittent treatment in pregnancy until such time as safe and efficacious alternative drugs for use in pregnancy can be identified. In the immediate future, combination therapy options not including SP for first-line treatment of non-pregnant individuals is limited to amodiaquine plus artesunate, or artemether-lumefantrine.

Roll Back Malaria, World Health Organization, 20, avenue Appia
CH-1211 Geneva 27, Switzerland Tel: (41) 22 791 2891, Fax: (41) 22 791 4824
E-mail: rbm@who.int Web site: www.rbm.who.int/