

# Antimalarial drug combination chemotherapy in malaria case management in Tanzania: how did it come about?

Malaria is a major public health and socioeconomic problem in sub-Saharan Africa including Tanzania. Every year about one million deaths result as a direct consequence of infection with *Plasmodium falciparum*. In Tanzania the malaria situation is worsening every year, as malaria-related morbidity and mortality is increasing. This situation has been worsened by the development and widespread of *Plasmodium falciparum* resistance to chloroquine (CQ) and followed by loss of efficacy due to development of resistance against sulfadoxine-pyrimethamine (SP). Hence, this has severely compromised effective treatment and malaria control programs in most sub-Saharan countries including Tanzania. The aim is to review various literatures using google, medline/PubMed search and publications on the drawbacks that have led to most sub-Saharan countries, including Tanzania, phasing out both CQ and SP, which were effective and cheap/affordable first-line drugs for clinical management of uncomplicated malaria. However, despite drawbacks of resistance to SP, the drug is still used for intermittent presumptive prophylactic treatment for pregnant women and infants, and CQ for patients with sickle cell anemia in mainland Tanzania. Thus, early recognition/diagnosis and prompt effective treatment with recommended first-line antimalarials including the use of long-lasting insecticide treated nets remains the mainstay of malaria control strategies in Sub-Saharan Africa. Furthermore, there is a strong need for improved understanding on optimizing malaria treatment policies so as to prevent/minimize the development and spread of drug resistant malaria by improving compliance, drug quality, rational prescribing and rational use of antimalarial drugs in sub-Saharan countries.

**KEYWORDS:** amodiaquine ■ antimalarials ■ antiretrovirals ■ artemisinin-lumefantrine ■ chloroquine ■ combination therapy ■ malaria ■ sub-Saharan countries ■ sulfadoxine-pyrimethamine ■ Tanzania

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## Background & literature review

Malaria is a major public health and socioeconomic problem in sub-Saharan Africa including Tanzania. It is estimated that every year between 300 and 500 million clinical cases of malaria occur [1], and approximately one million deaths result as a direct consequence of infection with *Plasmodium falciparum* [2]. Malaria-related morbidity and mortality are more prevalent in children [3].

Furthermore, malaria infection during pregnancy is a major public health problem in tropical and subtropical regions throughout the world. Pregnant women constitute the second main adult risk group for malaria and 80% of deaths due to malaria in Africa occur in pregnant women and children under 5 years of age [101]. It is estimated that in Africa over 30 million women become pregnant annually and most of these women live in areas of stable malaria transmission [101].

Although human malaria is caused by four parasite species of *Plasmodium*, most infections and severe morbidity and mortality are caused by *P. falciparum*, which has been shown to be

common in pregnant than nonpregnant women and to have substantial adverse effects on pregnancy outcomes including low birth weight, fetal distress, premature labor, intrauterine growth retardation and an increased number of still births, miscarriages and neonatal deaths. Acute *P. falciparum* malaria during pregnancy is considered to be particularly dangerous, since the underlying anemia can be dramatically exacerbated by red blood cell destruction. However, malaria is commonly asymptomatic during pregnancy and is not always diagnosed. A clinical trial in Kenya reported that presumptive treatment of all pregnant women in endemic malarial areas with only two doses of sulfadoxine/pyrimethamine (SP) reduced the incidence of anemia among first-time mothers by 39% [2].

The malaria situation is deteriorating every year in Tanzania [4], as evidenced by widespread *P. falciparum* resistance to chloroquine (CQ) [5], loss of efficacy due to resistance against SP, and increasing malaria-related morbidity and mortality [102]. Resistance to CQ and SP has severely compromised effective treatment and malaria control programs in most sub-Saharan countries.

Furthermore, the role of HIV in the epidemiology of malaria in pregnancy needs to be considered as an estimated 27 million people are living with HIV/AIDS and 55% of all adult HIV infection is among women of reproductive age. There is also a geographical overlap between malaria and HIV, and 44% of the 43 sub-Saharan African countries with malaria have HIV seroprevalence of  $\geq 10\%$  among antenatal clinic (ANC) attendees [6,7].

Despite these drawbacks and the phasing out of both CQ and SP for clinical management of uncomplicated malaria, SP is still used for intermittent presumptive prophylactic treatment (PT) for pregnant women and infants in mainland Tanzania [6–9,103]. In endemic areas of Tanzania and other sub-Saharan countries, early diagnosis and prompt effective treatment including the use of long-lasting insecticide-treated bed nets (ITNs), remain the most effective malaria control strategies [10,11]. However, PT with SP and ITNs use must go hand in hand with early recognition and prompt effective case management of malaria in children and in pregnant women [104].

The WHO recommends that all endemic countries provide a package of interventions for prevention and management of malaria in pregnancy, which include:

- Diagnosis and treatment of all episodes of clinical disease and anemia;
- ITNs for prevention of mosquito bites and infection;
- IPT with SP.

Intermittent preventive treatment with SP is recommended for prevention of infection in pregnancy to complement treatment of clinical disease and use of long-lasting ITNs [103]. Under this strategy, all pregnant women at risk of *P. falciparum* infection in sub-Saharan Africa with stable malaria transmission should receive at least two doses of SP for IPT at the first and second regularly scheduled ANC visits. In areas where greater than 10% of pregnant women are infected with HIV, a third dose should be given at the last scheduled ANC visit. The WHO advocates that SP for IPT should be taken under direct observation at the ANC visit [103].

Thus, there is a strong need for improved understanding of how to optimize malaria treatment policies to prevent/minimize development and spread of drug-resistant malaria, including monitoring adverse drug interactions in co-infections like malaria and HIV [12,13,101]. Furthermore, there is a strong need for improving healthcare including the performance of

healthcare providers, so that they can they can make the correct diagnosis and provide the correct treatment. This should be accompanied with regular evaluations of various diagnostic tests [14]. Furthermore, the training and education of mothers of children under 5 years of age to recognize fevers and to report this to formal health facilities where they can get prompt treatment as early as possible would be beneficial. Education on adherence to prescribed medications is also required, as irrational use of any drugs including antimalarials promotes development and spread of drug-resistant malaria, and prolongs the duration of illness or could lead to worsening of the condition and ultimately death [15–18].

Routine monitoring of drug resistance, blood concentrations and side effects related to any newly introduced antimalarial drugs such as artemisinin–lumefantrine combination (ALU) therapy in Tanzania may be warranted, as drug failure and drug-related side effects may reduce compliance to medications. Additionally, information regarding the drug should be given so that they become aware of the anticipated rare side effects that may occur following antimalarial drug use. For example, SP was negatively perceived by consumers in Tanzania due to rumors about its side effects [19,20]. Lack of diagnostic equipment such as light microscopes and other reagents for confirmation of malaria diagnosis in formal healthcare facilities (i.e., dispensaries and health centers) has been reported and continues to be a problem in Tanzania [14,15].

Although Tanzania has well-organized primary healthcare services, access to health services is limited in most Sub-Saharan countries, and the majority of children under 5 years are reported to die at home [3,21]. Most fever episodes are first recognized and responded to in homes by caregivers [22–24]. There is a need to train mothers/guardians to recognize signs and symptoms and to promptly seek care or correctly administer first aid medicine. Therefore, healthcare services should be made available close to homes, in order to save the lives of many vulnerable sick children. Global initiatives have been proposed and an integrated management of childhood illnesses (C-IMCI) has been started, which aims at improving home care and care-seeking behavior. A good example of how training of mothers to correctly administer CQ to sick children with fever has reduced deaths in children under 5 is Ethiopia where deaths were reduced by 40% [25,26].

Presumptive treatment of malaria has been shown to reduce the risk of the disease condition worsening [27]. This was achieved using trained

community volunteers as drug distributors and suppliers of drugs to neighbors when drugs were needed. Thus, ensuring rural people have prompt access to antimalarial drugs is important and advantageous. However, inadequate administration of antimalarials to children in homes through self-treatment has been reported as an irrational rampant practice in Tanzania and other sub-Saharan countries [15,26,28–30]. Additionally, self-treatment practices with sub-therapeutic doses of antimalarial drugs favors and promotes the emergence and development of drug resistance. This practice has led to CQ, the cheapest and most affordable drug, losing its effectiveness in almost all malaria endemic countries in Africa and Asia. For example, in Tanzania resistance to SP occurred in less than 5 years after its introduction and after the phasing out of CQ in 2001, and was replaced by ALU in November 2006 as an artemesin-based combination therapy.

In most parts of Tanzania, malaria is endemic and has been reported to be the major cause of fevers; this association varies with season and age [31]. The prescribing of treatments based on fever or history of fever alone may result in over-diagnosis of malaria and overuse of antimalarials. Furthermore, it may cause delay in treating conditions or symptoms that mimic malaria such as pneumonia as it has been reported that clinical overlap between malaria and severe pneumonia exists in African children [31]. Thus, it is important to carefully consider history of fever as an aid to making other differential diagnoses to rule out other fever-related conditions.

Fever due to malaria has been reported to fluctuate and a child with clinical malaria may show normal temperatures on arrival at the healthcare facility [32,102]. This highlights the importance of carefully using a thermometer when measuring children's temperatures in order to assess malaria fever episodes. In malaria endemic areas, clinical features of malaria and pneumonia overlap [33]. Thus, clinicians in most healthcare facilities need to perform an adequate physical examination after getting a history of fever and cough by conducting a thorough chest examination (auscultation) in order to rule out other causes of fever that may be labeled as malaria.

Advocating community-based antimalarial and antibiotic use through self-treatment has both advantages and disadvantages. One disadvantage is that irrational use may promote development of drug resistance and toxicity if used in subtherapeutic doses and excessive doses, respectively [15]. There are Global Initiatives advocating home-based management of fevers in many African

countries using various specific health education interventions and prepackaged antimalarial drugs close to the people in rural communities, and the inclusion of prepacks of antibiotics in such settings or programs may be useful as the benefits outweighs the risks if mothers can be properly trained as evidenced in other African studies [25,26].

Home-based care promotes prompt treatment by reducing the lag time between perception of an illness and administration of an antimalarial [34]. It avoids treatment delays associated with a lack of transportation or inability to pay for transportation to the health facility, as well as the time constraints incurred by the family. In Togo rural communities, 97% of the children treated at home received an antimalarial drug on the first day of their fever [35].

In Tanzania, ALU is the first-line and amodiaquine the second-line drug for treating uncomplicated malaria. Amodiaquine, owing to its low cost and effectiveness against CQ-resistant *P. falciparum*, is now being used as second-line treatment in mainland Tanzania. Zanzibar was one of the first countries in sub-Saharan Africa to officially propose the intention of re-introducing this antimalarial drug in 2002, in the form of a combination with an artemisinin derivative, artesunate [36]. Observations of some degree of cross-resistance between amodiaquine and CQ have been documented [36], and a high degree of CQ resistance was seen in Zanzibar [37]. It is anticipated that amodiaquine resistance might exist in mainland Tanzania, and the question of how long resistance to amodiaquine can be prevented by its combination with other antimalarials remains. Therefore, the current general pattern of amodiaquine resistance as well as ongoing changes in the sensitivities of malaria parasites needs to be closely and continually monitored. Even though fixed combinations exist on the market, they are unaffordable for people in developing countries.

In the absence of major new breakthroughs with regards to new drug combinations or an effective vaccine, the new concept in malaria control is to use existing drugs in combinations to possibly prolong their effectiveness [16]. Such combinations have been applied in south-east Asia successfully to control malaria using artemisinin-based combination therapy [17,18,37]. The hypothesis of using drug combination therapy is that drug combinations containing two or more components (active ingredients) with different modes of actions or half lives protect each other from development of resistance and simultaneously potentiate synergy, enhancing the efficacy and promoting compliance [38]. Artemisinin

derivatives exert a rapid and gametocytocidal effect against multidrug-resistant *P. falciparum*, which potentially reduces transmission of resistant alleles [17]. There is no established stable resistance against artemisinin derivatives to date.

The theoretical framework for the prevention of resistance is based largely on the rapid reduction of biomass of parasites, reducing the risks/chances for spontaneous parasite mutations to a minimum and thus reducing the potential for the selection of drug-resistant mutants [18]. This is the role of the artemisinin derivatives, while the longer acting partner drug SP or amodiaquine eliminates the remaining/semi-viable parasites, thus protecting against the emergence of artemisinin resistant strains. However, there is one complication of development of resistance with long elimination half-life drugs in highly endemic environments; during this period, these drugs with long half-lives contain residual drug concentrations, thus, if multiple reinoculations and reinfection occur in an individual, then malaria parasites may be anticipated and could potentially enhance further selection of resistant mutants. Owing to the the short half-life of monotherapy compounds, their use requires multiple daily doses over a period of 7 days. Thus, combining them with longer acting drugs allows for a reduction in treatment duration whilst simultaneously enhancing compliance, efficacy and reducing the likelihood of resistance development [39].

Malaria infection, especially in high endemic areas represents a unique opportunity to study community pharmacokinetics and pharmacodynamics including aspects such as selection of drug resistance *in vivo*, and this approach has been some proposed by researchers [40]. As such there is the possibility of quantitatively measuring biomass and drug pressure by determining parasite densities/total numbers of parasites and blood drug levels, respectively. Genetic markers identified in SP resistance have provided a useful tool for monitoring the dynamics of drug resistance selection or prevention. The markers are comprised of mutations in the *dhfr* gene (loci 16, 51, 59, 108 and 164), which codes for the target enzyme of pyrimethamine, and mutations in the *dhps* gene (loci 436, 540, 581 and 613), which codes for the target enzyme of sulfadoxine. Some studies suggest that with the increasing number of mutations on these loci the parasites become increasingly more resistant to SP [18,41,42].

Amodiaquine is a quinoline with partial cross-resistance that is known to occur with CQ. Hence the molecular markers for quinoline

resistance (*pfert* and *pfmdr*) may provide some basis for studying the evolution of amodiaquine resistance; however, more baseline studies on such possible associations are needed before their use in epidemiological studies. It is known that oral amodiaquine is quickly metabolized in the liver to desethylamodiaquine, which is a major and active antimalarial metabolite with a long half-life. Thus, attention should be given to both compounds based on their known pharmacokinetic and pharmacodynamic profiles and desethylamodiaquine needs to be studied for efficacy *in vitro*. Novel molecular markers should be used to search for resistance of both compounds in addition to *pfert* and *pfmdr*.

In conclusion, using artemisinin derivatives in combination with other antimalarials with longer half-lives is thought to be highly effective and considerably delays and prevents development of parasite resistance to the individual drugs. However, data are lacking on the relative protection against reinfection during the elimination period. Baseline data are urgently required prior to the implementation of future malaria guidelines in Tanzania and other sub-Saharan countries.

### Future perspective

Without improved understanding of malaria treatment policies, it will be difficult or even impossible to prevent/minimize the development and spread of drug-resistant malaria to new drugs and other drug combination therapies. Improving compliance, drug quality, rational prescribing and rational use of antimalarial drugs may help to prolong the shelf-lives of future drugs. At present most sub-Saharan countries, including Tanzania, have moved to combination therapies, which are expensive. Thus, if resistance develops against these combination drugs, developing countries will have no option but to continue to use more and more expensive antimalarial combination therapies. Considering the lack of funds governments have this could be a catastrophe for poor malaria endemic countries.

### Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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## Executive summary

- Malaria is a major public health problem and a disease that kills children under 5 years of age in sub-Saharan Africa.
- Annually about one million deaths result from malaria, and malaria-related morbidity and mortality are increasing.
- This situation has been worsened by the development of resistance to most cheap and affordable antimalarial monotherapies such as chloroquine and sulfadoxine-pyrimethamine (SP).
- This has severely compromised effective treatment and malaria control programs.
- Drawbacks have led to the phasing out of both chloroquine and SP.
- Despite resistance to SP, the drug is still used for intermittent presumptive prophylactic treatment for pregnant women and infants.
- Thus, early diagnosis and prompt treatment with effective first-line antimalarial drug combinations such as artemisinin-based combination therapy and the use of long insecticide-treated nets remains the mainstay of malaria control strategies in sub-Saharan Africa.

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