

# The role of antimalarial treatment in the elimination of malaria

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## Abstract

With declining transmission of malaria in several regions of the world and renewed interest in the elimination of malaria, strategies for malaria control using antimalarial drugs are being revisited. Drug-based strategies to reduce transmission of malaria need to target the asymptomatic carriers of infection. Drugs that are effective against gametocytes are few in number, but it may be possible to reduce gametocyte production by killing the asexual stages, for which more drugs are available. Drugs for use in large-scale programmes must be safe and tolerable. Strategies include improving access to treatment for malaria with an efficacious drug, intermittent-treatment programmes, and mass drug administration, with and without screening for malaria. Recent proposals have targeted high-risk groups for interventions. None of the strategies has been rigorously tested with appropriate control groups for comparison. Because of the lack of field evidence, modelling has been used. Models have shown, first, that for long-lasting effects, drug administration programmes should be linked with vector control, and second, that if elimination is the aim, programmes are likely to be more successful when applied to smaller populations of a few thousand or less. In order to sustain the gains following the scaling up of vector control and use of artemisinin combination therapies (ACTs), strategies that use antimalarials effectively need to be devised and evidence generated for the most cost-efficient way forward.

**Keywords:** Africa, Asia, drugs, elimination, malaria, mass drug administration, screening and treatment, transmission

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## Background

In recent years, a declining trend for malaria transmission has been observed in sub-Saharan Africa and worldwide [1–3]. In some part, this decline in reported malaria is attributable to improved diagnostic testing by the use of parasitological confirmation of a case and a willingness to improve burden estimates by better defining the populations at risk. It has been noted that the start of the decline occurred in some areas before the widespread use of vector control methods and the advent of artemisinin combination therapy (ACT) [4]. Scaling up of the use of long-lasting insecticide-treated bed-nets, indoor residual spraying and ACTs has probably accelerated this downward trend [5,6]. Important

factors in the reduced transmission seen in many parts of the world have yet to be identified, but are likely to be associated with improved economic status. Many countries are currently aiming to eliminate malaria by using a variety of combinations of interventions. This article reviews the role of antimalarial treatment of clinical cases, intermittent preventive treatment (IPT) and schemes of mass drug administration (MDA) in malaria elimination.

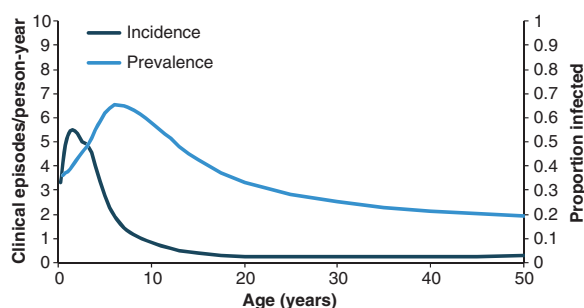
## Asymptomatic Carriage

The paradigm shift that needs to take place when consideration is being given to moving from malaria control to elimination is in understanding that malaria in endemic areas is an

asymptomatic infection among semi-immune populations. The classic symptoms of clinical malaria occur in those without substantial immunity. It is the semi-immune population, who carry asymptomatic infection, that are responsible for onward transmission, as they are more likely to remain untreated and carry parasites for a longer period. Therefore, in order to reduce malaria transmission, the asymptomatic parasite pool (the biomass of parasites carried by the population) needs to be targeted. Fig. 1 shows the age-specific incidence of clinical cases and the age-specific prevalence of asymptomatic carriage of malaria predicted by a model [7] in a high-transmission setting (entomological inoculation rate of 85 infectious bites per person-year). It shows that the burden of clinical disease is in the youngest age groups, whereas the burden of infection is in the older age groups. Gametocytes are the infective stage transmitted to mosquitoes and, in the case of *Plasmodium falciparum*, appear in peripheral blood about 2 weeks after asexual parasites are first detected. Current understanding of gametocyte biology suggests that gametocyte production is dependent on asexual parasite biomass [8]. In two malaria species, *Plasmodium vivax* and *Plasmodium ovale*, the addition of a dormant liver stage of the parasite introduces a further challenge for malaria elimination.

## Antimalarial Drug Delivery Strategies

Drug delivery methods that target the asymptomatic pool are currently not well developed. This is partly because the asymptomatic pool is not well defined. In areas of moderate and high endemicity in sub-Saharan Africa, the at-risk groups for clinical malaria are well defined and targeted. In these areas, malaria control and drug delivery are mainly focused on children under the age of 5 years and pregnant women, as these groups suffer the brunt of disease. However, these groups do not represent the major population groups har-



**FIG. 1.** Incidence of clinical disease and prevalence of infection by age in a population from a high endemic setting, entomological inoculation rate = 85 (estimated using a model [7]).

bouring the asymptomatic parasite pool. Below, we discuss strategies that might target the asymptomatic parasite pool.

The widespread use of an efficacious antimalarial for the treatment of malaria cases alone may have an effect on malaria transmission. Mboera and Magesa [9] showed trends of falling sporozoite rates in a highly endemic area in Tanzania when first chloroquine and then sulphadoxine–pyrimethamine were introduced, followed by rising sporozoite rates when resistance to the drugs developed. This phenomenon has also been reported in areas where ACTs have been introduced, although no rigorous investigation of the association between efficacious drugs and a reduction in transmission has taken place [5,10–12].

In the setting of massive overdiagnosis and overtreatment of malaria, as seen in much of the world because of the use of poorly sensitive clinical diagnosis and self-treatment, it is plausible that the asymptomatic pool is successfully targeted. We have theorized that, in the late 1990s, increasing access to treatment and gross overtreatment led to prophylaxis of a large proportion of the population at risk of malaria and resulted in falling transmission across East Africa. This was accomplished through the introduction of integrated management of childhood illness, improved public health education, and the habit of treating all febrile disease as malaria [4]. However, current treatment policy does not promote overtreatment with antimalarials, for sound reasons. First, the individual should be treated for the condition that they have, as there is an increased risk of mortality in those wrongly diagnosed as having malaria [13]. Second, owing to the poor sensitivity of clinical diagnosis and the resulting high numbers of false positives, it is not cost-effective to treat with expensive ACTs [14]. Third, health statistics generated from clinical diagnosis mislead control programmes with regard to the true burden of disease and the appropriate target of control measures.

Many alternative drug delivery strategies have been suggested by different sources. A list of strategies and their definitions is shown in Table 1, although this is not exhaustive. A selection of these strategies is outlined here to highlight the key issues. IPT consists of a full treatment dose of antimalarial being given to an asymptomatic individual, regardless of infection status, at an opportunistic time such as during a vaccination visit in the case of infants (IPTi), at the time of regular antenatal appointments in the case of pregnant women, and at calendar time-points in the case of children (IPTc). The majority of IPTc studies have been carried out in children <5 years of age. Only in the highest-transmission settings will this include the majority of asymptomatic carriers. However, if the age range is increased to include those 10 years of age or even older, it is conceivable that the strategy will reduce transmission significantly. Further

**TABLE 1.** Acronyms and definitions of strategies for mass drug administration

Acronym	Name	Definition
MDA	Mass drug administration	Simultaneous drug administration, without testing, to the total population of an island, country, region or district
TMDA	Targeted mass drug administration	Drug administration to all people living within a small high-risk area, without testing, such as the population surrounding a case
MSAT or MBS	Mass screening and treatment or mass blood survey	Screening of all persons irrespective of symptoms and treatment of positives only
FSAT	Focal screening and treatment	As MSAT, but in a localized area such as a household, neighbourhood, or village
MFT	Mass fever treatment	Treatment of all people with fever, irrespective of diagnosis
ACD or MSFAT	Active case detection or mass screening of fever and treatment	Screening of all people with fever and treatment of positives
IPT	Intermittent preventive treatment	Giving a full treatment dose of an antimalarial to an asymptomatic individual, regardless of infection status, at an opportunistic time
IPT <sub>i</sub>	Intermittent preventive treatment of malaria in infants	IPT of infants (under the age of 1 year) at times of vaccination
IPT <sub>p</sub>	Intermittent preventive treatment of malaria in pregnancy	IPT of pregnant women at times of antenatal visits
IPT <sub>c</sub> or SPC	Intermittent preventive treatment of malaria in children or seasonal prophylaxis in children	IPT of children at defined time periods during the malaria season in seasonal transmission sites. Usually applies to children under the age of 5 years

increasing the age for IPT makes this similar to MDA. The aim of MDA when it is used for elimination attempts is to clear parasites from the population for longer than the lifespan of a mosquito by including all of the population in a series of drug rounds.

Two studies of MDA have reported success in combination with vector control [15,16]. The first, by Kaneko *et al.* [15], used MDA on an island of fewer than 800 people and reported elimination of malaria. In the second study, of 17 villages in Cambodia, MDA given once, or in some cases repeated at day 42, to the entire population successfully reduced the parasite prevalence from 52.3% to 2.6% after 3 years [16]. As there were no control groups with which to assess temporal changes in transmission in these studies, no firm conclusions on the added benefit of MDA to vector control can be made, except that substantial decreases in transmission appear to be possible with this combination.

The emergence and spread of drug resistance is a feared consequence of MDA. This is more likely when indirect MDA methods are used, e.g. when antimalarials are added to salt at low concentrations. This has led to parasites being exposed to subtherapeutic concentrations of drug and the selection of drug-resistant parasites [17]. MDA applied directly with therapeutic concentrations of antimalarials has not been directly linked to the emergence of antimalarial resistance, but it is likely to significantly increase selection pressure on the parasite population [17]. Widespread use of antimalarials such as sulphadoxine–pyrimethamine in routine clinical practice appears to select resistant parasites [18]. One way to reduce the chance of selecting drug-resistant parasites is to use combination treatment [19]. The combination treatment should include a long-acting antimalarial to provide a period of prophylaxis [20], in order to reduce transmission and to protect the short-acting partner drug.

Side effects and adverse events are unwanted at an individual level, and may affect the acceptability and thus reduce the effectiveness of MDA. In the Cambodian trial [16], low

doses of primaquine were used in combination with dihydroartemisinin–piperaquine, and no adverse reactions were reported. Side effects in pregnancy, especially in the first trimester, when there is high risk of embryotoxicity, are a concern in MDA programmes. An MDA intervention in Gambia that investigated this association showed that, among women who received MDA (artemisinin–sulphadoxine–pyrimethamine), there was no increase in abnormalities in their infants [21]. Testing for pregnancy should be offered to women if their pregnancy status is in doubt, especially in the first trimester.

The logistics of carrying out an MDA programme are complex, especially in large countries. In particular, if there are large migrant or non-compliant communities, MDA can fail because of re-introduction of parasites or untreated foci remaining within the MDA area. Community involvement is essential for successful MDA interventions, as high coverage with drugs is needed over a period of several weeks. In Aneityum and Cambodia, the study teams achieved high compliance rates by working with the communities [16,22]. To be more effective, in addition to the required high coverage, MDA needs to be given within a short time and during the low-transmission season, when numbers of parasites are lowest. In order to obtain the maximum effect, it is probably necessary to incorporate vector control measures such as long-lasting insecticide-treated bed-nets and indoor residual spraying before implementing MDA [8]. Repeated rounds of MDA are likely to be necessary to achieve parasite clearance from the population and elimination of parasites from people who experience recrudescence following treatment. In Cambodia, villages that received two rounds of MDA had better parasite clearance than those that received one round [16], and in Aneityum, successful eradication was achieved only after seven rounds of MDA with multiple drugs over 9 weeks [22]. Thus, logistically, MDA is an intensive ordeal.

In order to reduce unnecessary risks, mass screening and treatment (MSAT) has been proposed. This adds a layer of

complexity to a programme by requiring that people be screened with a test for malaria and that only those who are positive receive treatment. This method relies on a sensitive diagnostic method, so that as many infected individuals as possible are detected. Unlike in MDA, prophylaxis is not given to those who are at risk but not infected or to those who are infected but carrying parasites at a density below the level of detection. Currently available screening methods for use in the field are microscopy and rapid diagnostic tests. Field-based methods for highly sensitive molecular tests are under development.

With better understanding of the micro-heterogeneity of malaria and the asymptomatic pool, more targeted approaches for drug delivery may become feasible. It is becoming clear that, even in areas of moderate transmission, malaria is a focal disease [23,24]. It also appears that there is overdispersion of malaria, a small proportion of the population being responsible for most of the transmission [25]. Thus, if these foci, or hot spots, where the high-transmission populations live, can be identified and treated, there may be a major impact on transmission, with reduced exposure to antimalarial drugs and improved quality and coverage of malaria control. Both screening and treatment and MDA are being investigated as tools for targeting foci, namely focal screening and treatment and targeted MDA.

## Drug Options for Malaria Elimination

In this section, we discuss the drugs that are available for MDA, both for the entire population and for high-risk groups, such as IPTi and IPTc. Any drug used for MDA must be extremely safe, acceptable, and efficacious. Safety is a major concern—a rare adverse event can lead to a significant number of cases when a drug is administered to a large population. In addition, only a small proportion of the population carrying parasites or who are at risk of infection would receive the benefits of treatment at the individual level, whereas a large proportion of the population, who are at low or no risk of malaria, would need to receive treatment in order for the benefits to be achieved at the population level. Drugs need to be well tolerated by and acceptable to communities in order to achieve high levels of coverage. The drug must be efficacious. According to the malaria eradication research agenda, the target drug profile for MDA should be as follows: a single dose, effective in eliminating asexual and sexual parasites in the blood stage, active against dormant liver stages in the case of *P. vivax*, and long-acting in order to prevent new infection [26]. We are some way from achieving this ideal.

Drugs that reduce gametocyte production or survival are key to reducing transmission. The 8-aminoquinolines primaquine and the closely related tafenoquine (under development) are the only two drugs that are effective against mature gametocytes. Primaquine, when given as a single dose between 30 mg base and 45 mg base, has good efficacy in reducing *P. falciparum* gametocyte density to levels below the level of detection by microscopy [27]. Primaquine also has an effect against hypnozoites, the dormant liver stage of *P. vivax* and *P. ovale*. However, courses need to be given for between 7 and 14 days to achieve this radical cure. The 8-aminoquinolines have not been widely adopted in malaria treatment, because of the adverse effect of haemolysis in individuals carrying the inherited red blood cell enzyme defect glucose-6-phosphate dehydrogenase deficiency. This condition is highly prevalent in communities that are at risk for malaria. Thus, primaquine use is generally confined to countries where the risk/benefit ratio is lowest, i.e. countries that are in pre-elimination and elimination mode, where the frequency of treatment is low. A recent review shows that several commonly used antimalarials—sulphadoxine–pyrimethamine, amodiaquine, and chloroquine—have some effect on immature *P. falciparum* gametocytes where resistance is limited, but that the artemisinin component in ACTs improves gametocidal activity by at least 50% [8]. Gametocytes of other *Plasmodium* species are metabolically active and are thus generally sensitive to drugs used to treat asexual infection [8].

There are several drugs available to treat asexual infection. Targeting the asymptomatic asexual infections would reduce gametocyte production and also reduce the number of early infections that become symptomatic. IPTi and IPTc in settings of moderate and high endemicity reduce the number of clinical episodes of malaria [28], primarily through prophylaxis [29,30]. This means that long-acting, safe, well-tolerated and efficacious drugs are needed to achieve the maximum benefit of IPT. Drugs that fit this description are few in number. Long-acting drugs to which there is little reported resistance are piperazine and mefloquine, whereas chloroquine, sulphadoxine–pyrimethamine and amodiaquine are limited geographically by increasing drug resistance. The drug combination used in Aneityum Island, Vanuatu in the 1980s [15] was chloroquine, sulphadoxine–pyrimethamine, and primaquine. However, the use of chloroquine is now seriously limited, because of the spread of drug resistance genes in most regions of the world. Artemisinin–sulphadoxine–pyrimethamine was investigated in Gambia as a tool for transmission blocking in 2000, but failed to show a lasting effect as compared with the control villages [17]. More recently, artemisinin–sulphadoxine–pyrimethamine showed

good efficacy in reducing gametocyte carriage in children in Tanzania, with a higher dose of artemisinin, but the addition of primaquine was associated with a high risk of haemolysis [31]. The Cambodian study of MDA, which had no control villages and applied concurrent vector control, appeared to show effectiveness at reducing parasitaemia to low levels in 17 villages by the use of dihydroartemisinin–piperaquine–primaquine, with no major side effects over 3 years [16]. The effects of dihydroartemisinin–piperaquine and artemeter–lumefantrine on gametocytes were compared in Kenya, and showed no difference at day 28 post-treatment [32]. There was no untreated control group in this study. Trials of IPTi and IPTc showed that mefloquine [33], artemisinin–sulphadoxine–pyrimethamine [34], artemisinin–amodiaquine [34], sulphadoxine–pyrimethamine–amodiaquine [35,36] and dihydroartemisinin–piperaquine [37–39] were efficacious in preventing cases of malaria, but no trial assessed their effect on gametocytes or transmission. Thus, currently, the best drug combinations for an elimination programme are likely to be multiple-day regimens with an artemisinin to kill immature gametocytes and asexual parasites, a long-acting antimalarial to kill asexual parasites and offer blood-stage prophylaxis, and primaquine to kill mature parasites. In Cambodia, where delayed clearance of parasites with artemisinin has been noted, atovaquone–proguanil is used for treatment. The use of atovaquone–proguanil in MDA for transmission reduction may be evaluated in this area.

## Modelling Interventions

Owing to the lack of comprehensive evidence on drug delivery strategies, modelling the effect of drug-based interventions may help to guide programmes. Models have focused on *P. falciparum*. Gametocytaemia and infectiousness of individuals after different types of treatment, such as artemisinin–sulphadoxine–pyrimethamine with and without primaquine [31], have been measured in the field, and these results can be used as model inputs [40]. However, there is still a need for detailed long-term follow-up of treated individuals to provide an accurate measurement of their infectiousness to mosquitoes over time. Models confirm that high coverage with effective case management has the potential to reduce transmission, as measured by both the prevalence and incidence of infection [41,42]. In areas of lower transmission, these effects could be large, approaching those of insecticide-treated nets [40]. However, where transmission levels are high, effective case management has a proportionately much smaller effect, owing to both a high rate of asymptomatic infection, and saturation of the infection in the population.

Nonetheless, good case management is predicted to have a large indirect impact on total disease burden, particularly that of severe disease. The role of effective case management in limiting malaria epidemics has also been shown to be important [43].

Models have explored the impact of the widespread use of the gametocytocidal drugs artemisinin (as part of combination therapy) and primaquine for case management [40,44]. ACTs are predicted to have a substantially larger impact on community-wide transmission than previous first-line treatments, such as chloroquine and sulphadoxine–pyrimethamine [40]. This effect is expected to be seen mainly in areas of low-to-moderate transmission; in areas of high transmission, a long-acting drug providing prophylaxis could reduce transmission more than a short-acting ACT. In a modelling case study, the use of ACT was able to explain the observed reduction in transmission following the widespread introduction of artesunate–mefloquine on the Thai–Myanmar border [44]. The additional impact of adding primaquine to treatment regimens has been estimated [44,45], and the impact is likely to be maximized if primaquine can be given about a week after the initial symptoms, to coincide with the appearance of mature gametocytes [44].

Modelling of MDA includes both MDA and MSAT interventions [7,45–47]. The predictions of all models agree with each other and with trial results, showing that mass treatment interventions used alone only temporarily reduce transmission unless they are repeated. This is because the vectors are still in place, and, remaining or imported parasites are therefore able to re-invade the population when blood drug levels decline. For this reason, the benefit of a one-off round of mass treatment in a high-transmission setting is likely to be negligible. However, the impact may last for a reasonably long time in areas of lower transmission where the rate of spread is slow; potentially 2 years or more if the slide prevalence is  $\leq 5\%$  [45]. Seasonal dynamics can be exploited to maximize the effects of mass treatment by treating in the dry season [45,46,48]. Repeated mass treatment, when combined with vector control, can dramatically reduce transmission, at least temporarily, and there is a chance of achieving elimination if sufficient coverage and a sufficient number of rounds are implemented. This probability of elimination can be examined with stochastic models [7,45,46]. These results are highly sensitive to population size: the probabilities of elimination being achieved through mass treatment are much lower in large populations that have overlapping mosquito populations. For example, five fortnightly rounds of MDA with 80% coverage were estimated to have  $>30\%$  probability of eliminating malaria in a population of 1000 with a baseline slide

prevalence of <8%, whereas the same intervention in a population of 10 000 had a close to zero probability of achieving elimination [45]. A model accurately reproduced the elimination of malaria in a small population on Aneityum, Vanuatu [49].

IPTi, although effective in reducing the clinical burden, is unlikely to reduce population-wide transmission, as such a small proportion of the population is treated. However, IPTc, which reaches a larger proportion of the infectious reservoir, could have a larger impact [50], particularly as the reservoir can be concentrated in older children.

## Conclusion

Strategies involving the use of drugs in elimination appear likely to be adopted in the near future where countries have successfully scaled up vector control. However, few strategies have been tested against transmission endpoints and with appropriate control groups. Logistically and ethically, it is likely that any large-scale treatment of asymptomatic infections will be targeted to areas of high risk or will include an element of testing before treatment to reduce the risks associated with MDA, such as side effects and resistance. As interest is renewed in the use of MDA, evidence of past and ongoing mass treatment strategies is being collated by the Cochrane Collaboration and others. Endemic countries are looking for guidance on this issue, and researchers need support in order to test strategies, such as MSAT, targeted MDA, or MDA in combination with IPTc, with careful selection of appropriate control groups. These studies should be carried out in different settings, including both *P. falciparum* and *P. vivax*, and on different continents.

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