# Does antimalarial mass drug administration increase or decrease the risk of resistance?

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**Summary**

All antimalarial drugs have eventually succumbed to resistance. There is a general belief that the more people that are exposed to an antimalarial drug, the more likely it is for resistance to emerge. Mass drug administration is therefore considered a potent cause of antimalarial drug resistance. However it is the total number of parasites exposed and their individual probabilities of survival and spread that determine the risk, *not* the number of people that contain them. In malaria endemic areas a substantial proportion of the community carries malaria parasites in their blood without being ill. Although there are many more people with asymptomatic than symptomatic malaria at any time their parasite burdens are several orders of magnitude lower, and their host-defence mechanisms have proved substantially more effective. Symptomatic infections with high parasite numbers the most likely source of resistance emergence. Effective mass treatment which reduces the number of symptomatic malaria cases reduces the overall parasite load in a population and so can reduce the threat of antimalarial resistance emerging and spreading in treated populations.

**Introduction**

It is widely considered that antimalarial drug resistance is encouraged by use of mass treatment (1-5). This has often reduced support for its use and sometimes prevented its deployment. Although inappropriate, badly executed or poorly accepted mass drug administration certainly can lead to resistance, effective mass treatment can prevent the emergence of resistance, and thereby protect the antimalarial drugs. The circumstances under which mass antimalarial drug treatment increases or decreases the risk of resistance are discussed.

Search strategy until May 2016: Articles in NLM PubMed and Embase were searched using the terms “malaria” AND “mass treatment” or “mass drug administration”

**Emergence and spread of antimalarial drug resistance**

There are two elements to the problem of antimalarial drug resistance; de-novo emergence and subsequent spread. Successful *emergence* of de-novo antimalarial drug resistance is a relatively rare event. Chloroquine resistance in *P. falciparum* may have arisen de-novo less than ten times in fifty years (6). De-novo resistance requires the formation and then successful multiplication of a usually single mutant malaria parasite to generate transmissible densities of gametocytes, and their successful transmission via anopheline mosquitoes to other vulnerable humans. This circumstance is most likely to arise when a patient with a high parasite burden, reflecting lack of adequate host-defence against the infecting parasites, receives an inadequate antimalarial dose (because of either

poor drug quality, underdosing, vomiting, poor absorption or unusual pharmacokinetics) (7). In the partially treated host the usually single mutant parasite must multiply successfully until it can generate transmissible densities of gametocytes (at least 8 generations). A newly emergent resistant malaria parasite is irrelevant epidemiologically unless it spreads to infect other people. Thus recrudescence is essential if de-novo antimalarial drug resistance is to spread. The s*pread* of resistance is encouraged by selection – the survival advantage of drug-resistant parasites over sensitive parasites. Preferential survival occurs when an acquired drug-resistant infection fails treatment, producing more transmissible gametocytes, whereas a drug- sensitive infection receiving the same treatment would be cured (8). Resistance may also increase the probability of generating transmissible densities of gametocytes from the primary infection (i.e without treatment failure) (8, 9). In addition selection of resistance to slowly eliminated drugs can occur when a human living in a malaria endemic area is infected with a drug-resistant parasite which emerges from the liver at a time (often referred to as a window of selection) when residual antimalarial drug concentrations are sufficient to eliminate sensitive but not resistant parasites (10). Selection in the drug's elimination phase amplifies existing resistance, but it is a relatively unlikely source of de-novo resistance because the number of parasites is one thousand to one hundred million times lower than in a symptomatic infection (7).

**Mass drug administration**

This refers to the administration of antimalarial drugs to an entire population in a malaria endemic area. The objective of MDA has usually been to eliminate malaria from the target population, or occasionally to control an epidemic (1-5, 11-20). MDA (sometimes now called targeted malaria treatment) has often been a controversial approach, and it is widely considered to lead to antimalarial drug resistance.

In the past mass primaquine administration was used extensively to eliminate vivax malaria (usually the long latency form in temperate zones). Without primaquine MDA will not eliminate *P. vivax* because relapses will not be prevented (15, 16). Today the more usual target of MDA is *P. falciparum* (13, 14, 18 -22). The majority of MDA recipients are healthy, but some have asymptomatic parasitaemia. The therapeutic objective is to clear all these healthy malaria parasite carriers from their blood stage infections and, by providing a period of post-treatment prophylaxis, to prevent reinfection for a period of time (usually at least one month) – or permanently (22). A full treatment dose is given usually, and repeated once or twice at monthly intervals. Healthy subjects with asymptomatic parasitaemia clear their infections more readily than patients who are ill for two main reasons. First the parasite densities are orders of magnitude lower (i.e. there are substantially less parasites to kill), and second the "immunity" which controlled the infection in the first place, and allowed persistence

of parasitaemia without illness, augments substantially the antimalarial drug effect. Immunity should also limit the density and thus transmission potential of any recurrent infection. This marked difference in therapeutic responses is very important as resistance selection is driven by parasite numbers and treatment failure (i.e. recrudescence or breakthrough reinfection).

*a) How MDA could select antimalarial drug resistance*

The emergence and spread of de-novo resistance requires treatment failure i.e. recrudescence (7). Recrudescence to generate transmissible densities of gametocytes following a full course of treatment in an asymptomatic individual is exceedingly unlikely. Even if an incomplete dose is taken this risk is relatively low as it would require effective regrowth of an infection which the host had *already* controlled without drugs.

Slow drug elimination is widely considered a risk factor for resistance selection (23, 24). As plasma concentrations decline slowly after antimalarial treatment they offer a window of selection within which a newly acquired resistant infection can establish whereas a sensitive infection cannot (10). Although this is a relatively rare cause of de-novo resistance, it is a potentially important cause of the *spread* of antimalarial drug resistance (10). It is particularly relevant to those individuals, such as young children, who have little or no malaria immunity and are more likely therefore to develop a transmissible infection if inoculated with malaria sporozoites. It is important to note that the window of selection offered by a series of mass treatments given at intervals shorter than that to the opening of the window of selection provides the same selection opportunity as a single treatment (Figure 1). For the same reason, and contrary to general opinion, continued chemoprophylaxis (adhered to correctly, and irrespective of duration) offers the same opportunity for resistance selection as a single treatment provided there is no high level resistance. This is because the only time that a resistant infection can become established in an individual, and eventually generate sufficient gametocytes to transmit malaria, is during the final elimination phase (after the last drug administration) (Figure 1). This emphasizes the importance of adherence in any MDA campaign, and thus the critical role of community engagement and understanding to minimize missed doses or incomplete treatments (21, 25).

These effective methods of mass drug administration in which therapeutic antimalarial drug concentrations are provided immediately can be contrasted with an approach promoted during the global malaria eradication effort sixty years ago called the Pinotti method (26). Antimalarial drugs (chloroquine or pyrimethamine) were then added to “table” salt. Everyone who used the medicated salt consumed the antimalarial drug. This resulted in slowly rising and highly variable antimalarial drug

concentrations in the whole population which were ideal for the selection of resistance. It may be no coincidence that chloroquine resistance arose in places where it was added to salt (27, 28).

*b) How MDA can reduce the de-novo selection of antimalarial drug resistance*

MDA *reduces* the risk of selecting de-novo resistance if it reduces the incidence of symptomatic malaria in the treated population. This correspondingly reduces resistance selection opportunities. It is generally agreed that MDA may be used to eliminate malaria (or in some instances to control an epidemic), but should not be part of routine control (29), so MDA should not be deployed in areas of high transmission (unless they are circumscribed geographically, and there is a realistic chance of eliminating malaria-e.g. an island). For example MDA proved effective in eliminating malaria from Aneityum in the South Pacific (11). Conversely MDA with pyrimethamine or sulphonamide-pyrimethamine combinations was deployed in several locations in Africa where transmission in and around the MDA area was high (30). Predictably it did not work and in some places resistance emerged. Effective MDA deployed in low transmission settings reduces the incidence of symptomatic malaria in the treated community. Each case of symptomatic malaria (parasite densities from 50 to >500,000/uL) will expose to antimalarial drugs between ten million and ten thousand billion malaria parasites which have not been contained by host-defence mechanisms (Figure 2). In contrast healthy individuals with asymptomatic malaria parasitaemia have already contained their infections (comprising one or more circulating genotypes), and may be well on the way to eliminating them. In the greater Mekong area geometric mean parasite densities in the blood of individuals with asymptomatic malaria have been estimated at approximately 5 parasites/uL in both falciparum and vivax malaria, which corresponds roughly to ten million parasites in the body of an adult (31). Thus patients with symptomatic malaria typically have parasite densities which are one thousand times or more higher than in asymptomatic individuals. That means that on average one patient with symptomatic malaria “contains” as many parasites (with as many mitotic divisions) as one thousand asymptomatic individuals. The hyperparasitaemic patient with 10% parasitaemia “contains” as many parasites as approximately one hundred patients with uncomplicated malaria and 100,000 individuals with asymptomatic parasitaemia (some malaria endemic countries in Asia and the Americas have less than 100,000 asymptomatic parasite carriers in the entire country!). The de-novo drug resistance selection opportunity is weighted even further towards the symptomatic patient by immunity, which the symptomatic patient lacks and asymptomatic individuals clearly have (7).

*c) Assessing the overall risk*

The overall risk assessment for selecting de-novo resistance selection with MDA depends on the sum of selection probabilities from treatment of asymptomatic and symptomatic individuals during and

after MDA versus the sum of selection probabilities from symptomatic patients if no MDA is deployed. Each has two components – the exposure of parasites to antimalarial drug during the treatment, and then the exposure of parasites which emerge from new inoculations during the drug's elimination phase. There is an additional consideration; if MDA eliminates malaria for a period sufficient to reduce the immunity of the population, and then malaria is reintroduced, then there may be a rebound such that there is more malaria for a period of time than there was before it started. This will give more opportunities for the selection of drug resistance. If different drugs are used for MDA and treatment then the balance of probabilities that resistance will emerge and be selected will also depend on the resistance probabilities for the individual drugs.

In terms of numbers of parasites exposed to drug the difference between MDA and no MDA is entirely dominated by the number of symptomatic infections (see example below). Effective MDA, which reduces transmission and thus incidence, exposes *much lower* parasite numbers to antimalarial drug than no MDA.

*Example (Figure 3)*

In a village of 500 people the prevalence of asymptomatic *P.falciparum* carriage is 20% (geometric mean parasite density 5000/mL corresponding to approximately 2.5 x $10^7$ parasites in the body of an adult, and proportionately less in children) (31). Half the population are children (average $10^7$parasites if asymptomatic).

Each year there are 500 malaria parasite inoculations (EIR =1/person/year; homogeneously distributed) one fifth of which result in illness; i.e. 100 symptomatic infections per year (geometric mean parasite density 5,000,000/mL corresponding to approximately 2.5 x $10^{10}$ parasites in the body of an adult, and proportionately less in children). Half the symptomatic infections are in children (average $10^{10}$ parasites).

Dihydroartemisinin-piperaquine is the current treatment (efficacy 95%), and it is also used for MDA (14, 21, ).

Only confirmed malaria is treated. Adherence to MDA is 80%, 10% of the population do not participate, and 10% take an incomplete course. There are no recrudescences following MDA, and falciparum malaria transmission and thus incidence falls by 80% over the subsequent two years.

The calculations below assume that $10^5$ parasites emerge from the liver following reinfection and there is a one month post-treatment selection window .

The total number of *P. falciparum* parasites *exposed to the antimalarial* over two years, (which relates to the resistance selection opportunities) are as follows:

**A. If no MDA is deployed**

1. Symptomatic malaria: acute illness: ~ $[2.25 \times 10^{10}] \times 100 \times 2$ = $4.5 \times 10^{12}$
2. Reinfections during drug elimination phase: ~ $10^5 \times 100 \times 0.083 \times 2$ = $1.7 \times 10^6$

**Total = $\mathbf{4.5 \times 10^{12}}$**

**B. If MDA is deployed**

1. Asymptomatic malaria: ~ $[2.25 \times 10^7] \times (500 \times 0.2)$ = $2.25 \times 10^9$
2. Symptomatic malaria: acute illness: ~ $[2.25 \times 10^{10}] \times 0.2 \times 100 \times 2$ = $9 \times 10^{11}$
3. MDA recipients: reinfection during elimination phase: ~ $10^5 \times 450 \times 0.083 \times 0.2 \times 100$ = $7.7 \times 10^7$
4. Symptomatics: Reinfection during elimination phase: ~ $10^5 \times 0.083 \times 0.2 \times 100 \times 2$ = $3.3 \times 10^5$

**Total = $\mathbf{9 \times 10^{11}}$**

*The importance of high malaria parasite burdens in de-novo resistance selection*

In considering de-novo antimalarial drug resistance selection we have to count the total numbers of malaria parasites exposed to selective drug concentrations *and* their individual probabilities of survival and subsequent effective multiplication to generate transmissible densities of gametocytes. Although the total number of drug-exposed parasites in the example above is five times less with MDA if the incidence of malaria is reduced, it does not necessarily mean selection opportunities are five times less. This is because the majority of malaria parasites in a correctly treated malaria infection are exposed to very high drug concentrations, much higher than the minimum inhibitory concentration of the most resistant mutant parasite, and with an ACT the parasites "see" two drugs (32). Unless the resistance mechanism confers an extremely high level of resistance and drug levels are low (because of poor drug quality, incorrect dosing, incomplete treatment, poor absorption or unusual pharmacokinetics), then for most patients there are no resistance selection opportunities at peak intra-host parasite densities. The very important exception to this is when the parasite numbers within a patient are very large (7). For example on the North-Western border of Thailand, before the recent decline in its efficacy fueled by artemisinin resistance, – the mefloquine-artesunate combination was over 95% efficacious in uncomplicated falciparum malaria, and remained so for over 15 years (33). However in hyperparasitaemic patients (>4% parasitaemia) the failure rate consistently approached 30% (i.e. over six times higher than in the majority of patients with lower densities). As hyperparasitaemia represents the upper end of the geometric distribution of parasite densities within people (7), the more people with symptomatic malaria there are, the more likely is hyperparasitaemia. For the reasons given above this suggests that prevention of high parasite burden infections is the main driver of the decreased risk of selecting antimalarial drug resistance with MDA.

What happens then in a dream scenario where all malaria infections are treated correctly, and the extreme case that there are no treatment failures at all? In this situation the only opportunity for the selection of resistance is in the low numbers of parasites which may emerge from the liver as a new infection is exposed to a selective window of concentrations following an antimalarial treatment (10, 23, 24). In this highly optimistic scenario it is clear that MDA provides a selective window in all individuals, whereas with no MDA it occurs only in symptomatic patients. In the example above with MDA there would be 450 such exposures in the MDA recipients plus 40 in symptomatic patients over two years versus 200 exposures in treated symptomatic patients without MDA. Thus in the "best case-perfect treatment" scenario MDA provides significantly more exposures than no MDA. But exposure does not equate directly with resistance selection. In many of the MDA exposures the individual would be "immune" and would therefore self-cure many of the newly acquired infections. These would not then generate transmissible densities of gametocytes. In contrast symptomatic patients have declared

themselves less immune, and therefore more likely to generate transmissible densities. In other words the per-parasite probabilities of survival of a newly acquired infection are much greater in the post treatment periods of the relatively small number of symptomatic patients. Even in this extreme "best case" of 100% therapeutic efficacy it is uncertain which would provide the greater de-novo resistance selection opportunity in the drug elimination phase. However as highly effective treatments do not cure all patients, and as the numbers of parasites exposed in symptomatic infections are so much greater than occur immediately following hepatic schizogony, it is probable that in the majority of circumstances effective MDA results in less de-novo resistance selection than no MDA.

**Does MDA encourage the spread of resistance?**

Resistance spreads when a drug resistant infection is acquired from elsewhere and is transmitted onwards with a greater probability than a sensitive infection (32). Resistance can worsen if further genetic changes occur which either affect the mechanism of resistance itself or result in increased fitness of the resistant parasites (compensatory mutations). Higher levels of resistance mean that an infection can establish itself in higher drug concentrations than in previous hosts. Amplification of resistance occurs when there is heterogeneity in antimalarial drug concentrations in the human population (as in variable underdosing or in post-treatment elimination profiles). This heterogeneity is reduced with effective MDA.

The reduced transmission and thus lower number of symptomatic malaria infections following effective MDA results in a lower number of opportunities for acquisition of resistant infections and thus onward spread. Although MDA is associated with a larger number of individual exposures in the antimalarial drug elimination phase because everyone receives the drug, most of the sporozoite inoculations during the elimination phase do not result in symptomatic infections. This is because of the combined effects of the drug and immunity. MDA would usually only be deployed if there was significant proportion of asymptomatic parasite carriage reflecting acquired immunity. As a result of this immunity some newly acquired infections may result in asymptomatic parasitaemia (which can transmit) but the majority self-cure offering limited opportunity for selection. As MDA is given to everyone at the same time there is homogeneity in the population's drug concentration profiles which reduces the opportunity for further amplification of resistance. This is because by the time an infection has transmitted from one MDA recipient and been through the vector mosquito the entire treated community has *lower* drug levels, so there can be no additional selection. This contrasts with the no MDA scenario where there are more symptomatic infections (occurring at random times) and thus more treatments. The consequent heterogeneity in drug levels provides more opportunities for a resistant infection to encounter selective drug levels. This difference in favour of MDA is likely to be

much greater if MDA is deployed in the period of the year with the lowest malaria transmission (i.e. the dry season). During this period the probability of acquiring an infection can be more than ten times lower than during the rainy season – so the probability of resistance selection in the post MDA period is reduced correspondingly. In contrast symptomatic malaria predominates in the wet season, so the treatment of symptomatic malaria provides post-treatment windows of selection when there is a greater probability of being bitten by anopheline mosquitos.

In summary if MDA is ineffective because of poor coverage, poor adherence, substantial migration or surrounding high transmission then the probability of selecting resistance may be increased , whereas if MDA is effective, resistance should be reduced.

**Conclusions**

MDA both increases and decreases factors contributing to the emergence and spread of antimalarial drug resistance and so can either increase or reduce the overall risk depending on this balance. Successful MDA which drives malaria to elimination clearly reduces the risk overall. Contrary to general opinion well conducted MDA with good adherence deployed during the dry season in areas of low seasonal transmission is likely to reduce the probability of selecting resistance. If the same drugs are used for both treatment and MDA then there is a race to eliminate before resistance jeopardizes the efficacy of the drugs and defeats the objective. This argues for eliminating earlier rather than later. Paradoxically delaying MDA deployment because of theoretical fears of resistance may therefore both create more resistance than if MDA had been deployed –and prevent its later use.

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Conflict of Interest section: No conflicts of interest

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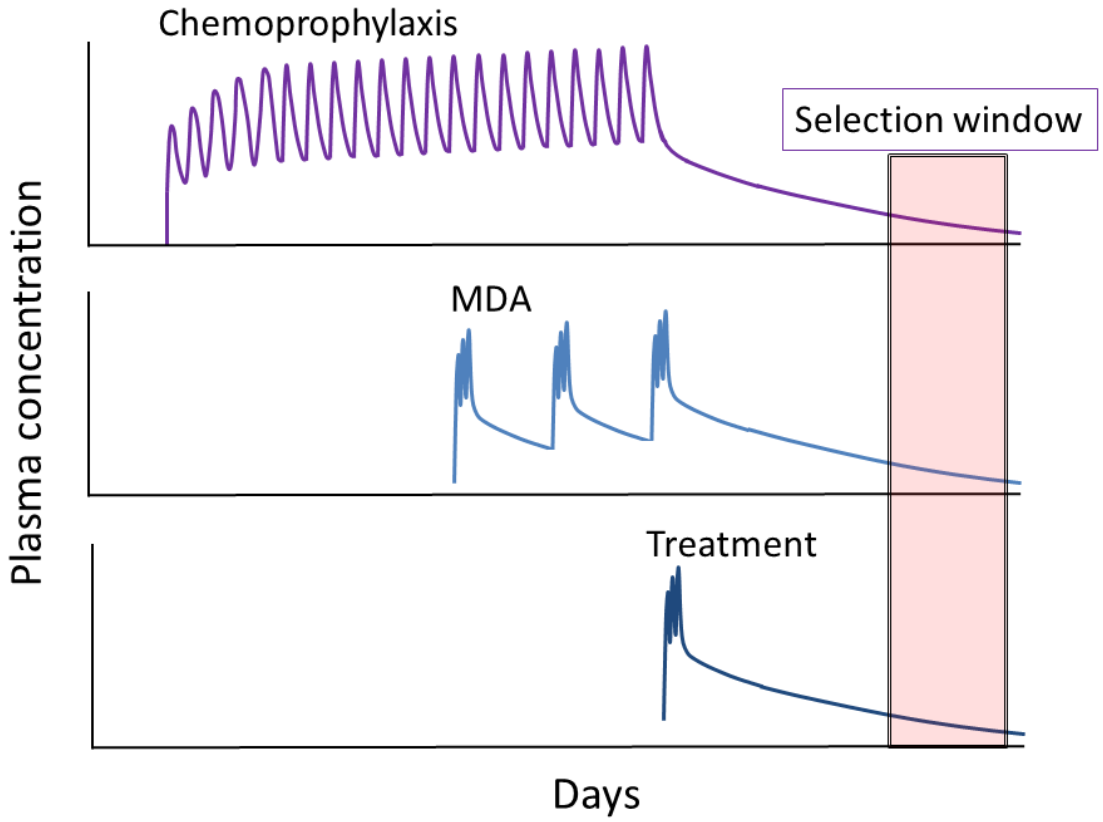
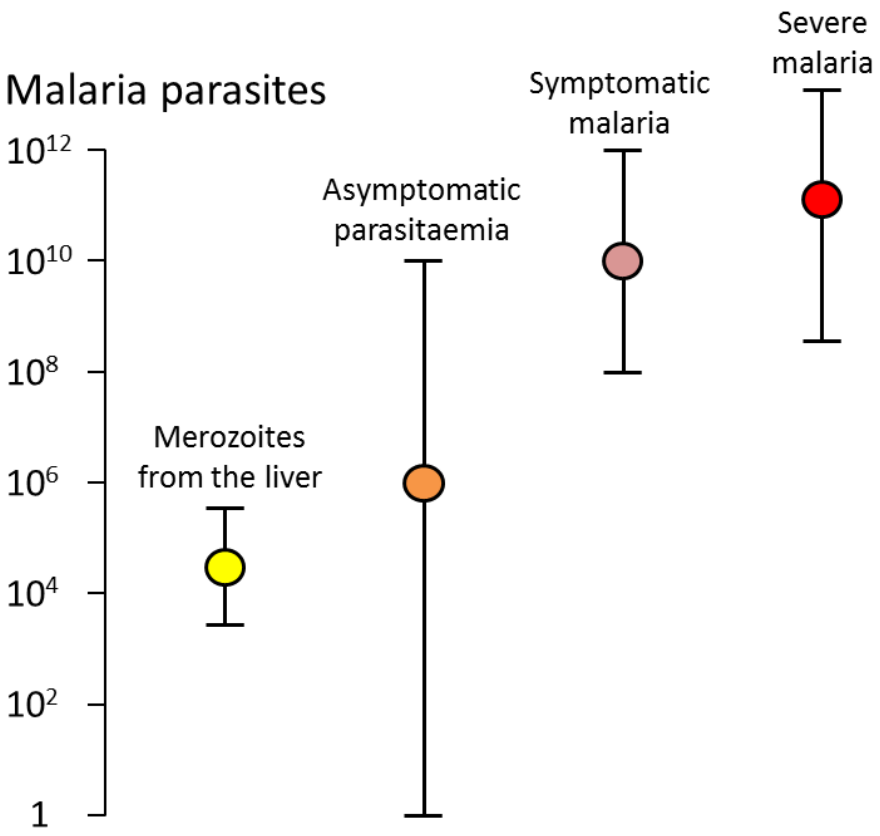
**Legend to Figures**

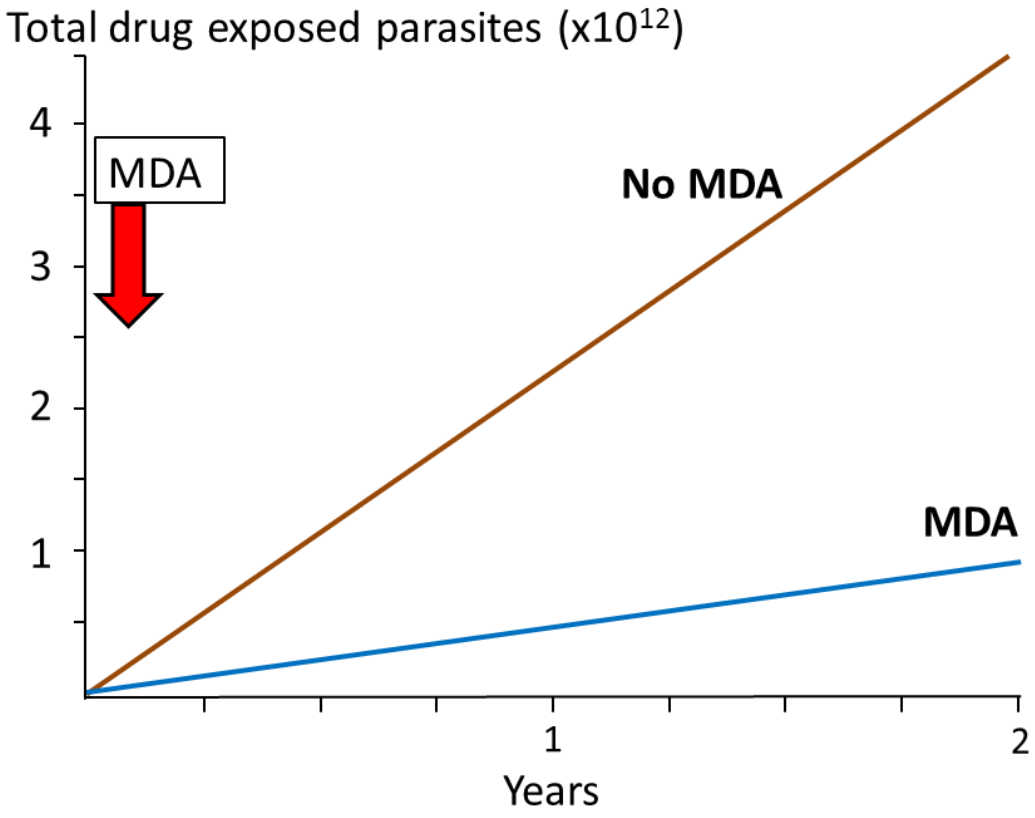
1. Plasma concentration profiles of a slowly eliminated antimalarial drug (e.g. piperaquine) with regular administration as in chemoprophylaxis (upper panel), monthly mass drug administration (3 rounds; middle panel), or a single treatment (lower panel). The selection window (box) in which resistant malaria parasites can survive but sensitive parasites are killed is the same for all three forms of drug administration.

2. Geometric mean (range) estimates of total malaria parasite numbers in the human body.

3. Total numbers of malaria parasites in the village in the worked example.




Malaria parasites
$10^{12}$
$10^{10}$
$10^{8}$
$10^{6}$
$10^{4}$
$10^{2}$
1
Merozoites from the liver
Asymptomatic parasitaemia
Symptomatic malaria
Severe malaria


Total drug exposed parasites ($x10^{12}$)
4
3
2
1
MDA
No MDA
MDA
1
2
Years