Optimum population-level use of artemisinin combination therapies: a modelling study

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Summary

Background **Artemisinin combination therapies (ACTs) are used worldwide as first-line treatment against confirmed or suspected *Plasmodium falciparum* malaria. Despite the success of ACTs at reducing the global burden of malaria, emerging resistance to artemisinin threatens these gains. Countering onset of resistance might need deliberate tactics aimed at slowing the reduction in ACT effectiveness. We assessed optimum use of ACTs at the population level, specifically focusing on a strategy of multiple first-line therapies (MFT), and comparing it with strategies of cycling or sequential use of single first-line ACTs.**

Methods **With an individual-based microsimulation of regional malaria transmission, we looked at how to apply a therapy as widely as possible without accelerating reduction of efficacy by drug resistance. We compared simultaneous distribution of artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine (ie, MFT) against strategies in which these ACTs would be cycled or used sequentially, either on a fixed schedule or when population-level efficacy reaches the WHO threshold of 10% treatment failure. The main assessment criterion was total number of treatment failures per 100 people per year. Additionally, we analysed the benefits of including a single non-ACT therapy in an MFT strategy, and did sensitivity analyses in which we varied transmission setting, treatment coverage, partner-drug half-life, fitness cost of drug resistance, and the relation between drug concentration and resistance evolution.**

Findings **Use of MFT was predicted to reduce the long-term number of treatment failures compared with strategies in which a single first-line ACT is recommended. This result was robust to various epidemiological, pharmacological, and evolutionary features of malaria transmission. Inclusion of a single non-ACT therapy in an MFT strategy would have substantial benefits in reduction of pressure on artemisinin resistance evolution, delaying its emergence and slowing its spread.**

Interpretation **Adjusting national antimalarial treatment guidelines to encourage simultaneous use of MFT is likely to extend the useful therapeutic life of available antimalarial drugs, resulting in long-term beneficial outcomes for patients.**

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Introduction

During the next decade, substantial public health effort and financial resources will be expended to eliminate malaria in as many parts of the world as possible.[1] In this endeavour, several antimalarial strategies will be used, including antimalarial treatment for clinically acute cases, antimalarial chemoprophylaxis in at-risk populations, insecticide-treated nets, household insecticide use, improved diagnostics, and expansion of health service delivery.[2] For some of these interventions, long-term diminishing returns as drug or insecticide resistance emerges and as mosquitoes adapt their behaviour to insecticide-treated nets and insecticide application are of concern. Efforts to maximise effects of elimination campaigns and to minimise the chances of an emergent drug or insecticide resistance phenomenon occurring during this period are important.[3] Such an event would seriously undermine the ambition and progress of malaria elimination programmes.

Since 2005, WHO has strongly endorsed first-line use of artemisinin-based combination therapies (ACTs) for uncomplicated *Plasmodium falciparum* malaria because of their safety and rapid action against asexual blood stages, including some transmission stages.[4,5] Additionally, WHO discouraged artemisinin monotherapy to reduce recrudescence rates and to decrease the probability of de-novo artemisinin resistance emerging in individual patients. The partner drug in a coformulated ACT is always eliminated more slowly than the rapidly eliminated artemisinin derivatives, providing protection during the course of treatment against de-novo emergence of an artemisinin-resistant genotype. For artemisinin resistance to emerge, a parasite must be capable of surviving exposure to artemisinin and the partner drug—a highly improbable event unless the infecting parasite population already carries resistance genes to the partner drug.

Despite these precautions aimed at preserving efficacy of artemisinin-based therapies, artemisinin resistance still warrants serious concern. A partly resistant, slow-clearing

Panel: Research in context

Evidence before this study

We searched PubMed combining the term "malaria OR plasmodium OR falciparum" with "treatment strategy" (22 results), "resistance management" (77 results), "multiple first" (seven results), "multiple drugs" (22 results), "two drugs" (92 results), and "drug distribution" (25 results), which yielded three publications in which mathematical models were used to compare different methods of distributing several available antimalarial therapies.

Added value of this study

The model presented here is an advance over these studies because it includes individual-level host detail, age-specific effects, explicit tracking of within-host parasite density, and drug-specific pharmacodynamics. Additionally, we validated the present model's behaviour against a range of field and clinical datasets to ensure that the model replicates well known clinical and epidemiological patterns of *Plasmodium falciparum* malaria.

Implications of all the available evidence

At national or regional levels, simultaneous use of multiple first-line artemisinin combination therapies should be recommended, because this approach will delay emergence and evolution of artemisinin-resistant parasites and partner-drug-resistant parasites.

P falciparum phenotype emerged in Cambodia in the 1980s or 1990s.[6,7] This phenotype was later seen on the border between Thailand and Myanmar[8] and in southern Vietnam near the Cambodian border,[9,10] and is now established in much of mainland southeast Asia.[10,11] Slow parasite clearance is strongly associated with a group of polymorphisms in the *P falciparum* kelch propeller domain.[6,10] When devising strategies to contain or extinguish this resistant genotype, the potential for stronger resistance and emergence of a fully artemisinin-resistant genotype in the next decade should also be considered.

Artemisinin pressure on parasites is likely to increase during the next decade for the following reasons: ACTs will remain the most commonly used antimalarial therapies; existing partner-drug resistance is likely to spread to areas where the corresponding ACTs are used; and artemisinin monotherapies are still likely to be used to some extent in contravention of strong WHO and national-level health policy recommendations. Additionally, in individual patients, underdosing with artemisinin-based drugs might be a concern because subtherapeutic doses create an environment favourable to fixation of drug-resistant genotypes.[12] Underdosing might occur as a result of substandard drugs,[13] insufficient absorption, poor adherence practices, or prescription of subtherapeutic doses, especially in hyperparasitaemic patients (who need higher doses than patients with lower parasite densities) and young children or pregnant women (who have low drug exposures).[12,14] For these reasons, additional measures should be taken to ensure that the evolutionary selection pressure for artemisinin-resistant genotypes is as low as possible for as long as possible.

A key biological principle underpinning potential strategies for slowing down evolution and spread of a novel mutant is that evolution occurs slowly in heterogeneous or variable environments.[15] Combination therapy takes advantage of this principle by introducing drug heterogeneity into a pathogen's environment and forcing the pathogen population to adapt to several new environmental features simultaneously. This principle can be applied at the population level, if a parasite encounters different drugs in different individuals. The two frequently explored approaches to achieve this effect are drug cycling—in which a single therapy is used population-wide for a specific amount of time before being replaced with a different therapy—and simultaneous distribution of several therapies in a population. Both strategies have been assessed with mathematical models for bacteria[16–18] and malaria,[19–22] and simultaneous distribution is generally more effective than drug cycling at delaying resistance evolution and keeping prevalence low for a longer period. One of the reasons is that, with a strategy of simultaneous distribution of different drugs, the parasite's environment is more variable than with a cycling strategy.[18,19] In this scenario, even if a de-novo resistant parasite were to emerge in a single host, it would have difficulty establishing itself in the population because the parasite's next host would have at least a 50% chance of not being treated with the same drug. This effect would be as strong in a cycling strategy only if the drugs were cycled in and out rapidly, on the order of the generation time of the infection.

We assessed optimum distribution of ACTs at the population level, specifically focusing on a strategy of multiple first-line therapies (MFT)[19]—in which therapies are simultaneously recommended as first-line and are prescribed to individual patients according to a random factor (eg, day of week or true randomisation)—and comparing it with strategies of cycling or sequential use of single first-line ACTs. We developed and validated an individual-based microsimulation, which is an advance over previous efforts to address this question because it accounts for key features of malaria epidemiology that affect patterns of resistance evolution: age-specific immune acquisition, biting rate heterogeneity, drug pharmacokinetics and pharmacodynamics, asexual parasite density, multiplicity of infection, and recombination.