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ANTIMALARIAL DRUG RESISTANCE, ARTEMISININ-BASED COMBINATION THERAPY, AND THE CONTRIBUTION OF MODELING TO ELUCIDATING POLICY CHOICES

SHUNMAY YEUNG, WIRICHADA PONGTAVORNPINYO, IAN M. HASTINGS, ANNE J. MILLS, AND NICHOLAS J. WHITE

Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Program, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Health Policy Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom; Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Abstract. Increasing resistance of *Plasmodium falciparum* malaria to antimalarial drugs is posing a major threat to the global effort to "Roll Back Malaria". Chloroquine and sulfadoxine-pyrimethamine (SP) are being rendered increasingly ineffective, resulting in increasing morbidity, mortality, and economic and social costs. One strategy advocated for delaying the development of resistance to the remaining armory of effective drugs is the wide-scale deployment of artemisinin-based combination therapy. However, the cost of these combinations are higher than most of the currently used monotherapies and alternative non-artemisinin–based combinations. In addition, uncertainty about the actual impact in real-life settings has made them a controversial choice for first-line treatment. The difficulties in measuring the burden of drug resistance and predicting the impact of strategies aimed at its reduction are outlined, and a mathematical model is introduced that is being designed to address these issues and to clarify policy options.

INTRODUCTION

The aim of this report is to provide an overview of antimalarial drug resistance with a particular emphasis on the place of artemisinin-based combination therapy (ACT) in the reduction of the burden of malaria. The difficulties in measuring the burden of drug resistance and predicting the impact of strategies aimed at its reduction are outlined. We aim to demonstrate how a bioeconomic model might be developed and deployed to address these issues and to clarify policy options.

Antimalarial drug resistance is now generally acknowledged to be one of the greatest threats to our ability to "Roll Back Malaria."[1,2] The situation is worsening, with the geographic spread of resistance widening to previously unaffected areas and a remorseless increase both in the prevalence and degree of drug resistance. Chloroquine-resistant *Plasmodium falciparum* now predominates in Southeast Asia, South America, and increasingly in Africa. Resistance to sulfadoxine-pyrimethamine (SP) is widespread in Asia and South America and is spreading in Africa.[3,4] Chloroquine and SP are affordable drugs at approximately US$0.10–0.20 per adult course, and their safety and efficacy as oral regimens means they have generally been readily accessible. When parasites began to show resistance to these drugs in Southeast Asia, the epicenter for multidrug-resistant *P. falciparum* malaria, they had to be replaced by the more expensive mefloquine. However, resistance soon developed to this compound, with resistance first being noted only six years after it was first deployed in Thailand in 1984, and spreading quickly thereafter. The efficacy of halofantrine, which shares cross-resistance with mefloquine, also decreased and even quinine has gradually become less effective over time (Figure 1).

Resistance to affordable drugs in Africa, which carries an estimated 90% of the burden of malaria, has reached critical levels. The continent faces the crucial issue of which drug regimen to switch to and when to make a switch. There is increasing acceptance that the ideal approach to antimalarial treatment is to use a combination of two or more drugs rather, than a single antimalarial drug, preferably with an artemisinin derivative as one of the partner drugs.[5] However, ACTs are relatively expensive, currently costing approximately US$1.20–3.50 per adult course. In addition, concerns about the practical difficulties in implementing any change in policy and the uncertainties about future costs, risks, and benefits, all make the decision of whether to switch, when to switch, and what drug regimen to switch to, a complex one.[6–8] In order for national governments, donor countries, and international institutions to make rational decisions on drug policy, there is a need to clarify how much of a burden antimalarial resistance causes currently, how much it is likely to cause in the future under different control strategies, and how much these strategies will cost and save.

Models are increasingly being used to help explore policy options such as these, where outcomes are uncertain and decisions complex.[9,10] They are ideally suited to exploring both biologic and economic influences on outcomes. Moreover, they can be used to produce the estimates of the cost-effectiveness of policy options which are now accepted to be a vital input to decision making in the health sector.[11,12]

ANTIMALARIAL DRUG RESISTANCE–THE BURDEN

The nature of the burden. The burden of disease caused by malaria and its consequences has been documented in terms of childhood mortality,[13] anemia,[14] maternal and infant morbidity and mortality,[15] neurologic disability,[16,17] and economic and social costs.[18,19] The burden caused specifically by antimalarial drug resistance is more difficult to quantify.[20] Recent estimates based on the best available data from Africa suggest that the demise of chloroquine is the "most plausible single factor contributing to the change in malaria specific mortality,"[21] which has been estimated to have at least doubled over the last 15 years.[22]

The actual relationships between therapeutic response to treatment and *ex vivo* measures such as resistance *in vitro* and the carriage of resistance genes is generally poorly defined, but of the drug, parasite, and host factors that contribute to therapeutic outcome, particularly important is the immunity of the host. Thus, in areas of high transmission, adults are relatively immune and tend to self cure irrespective of the

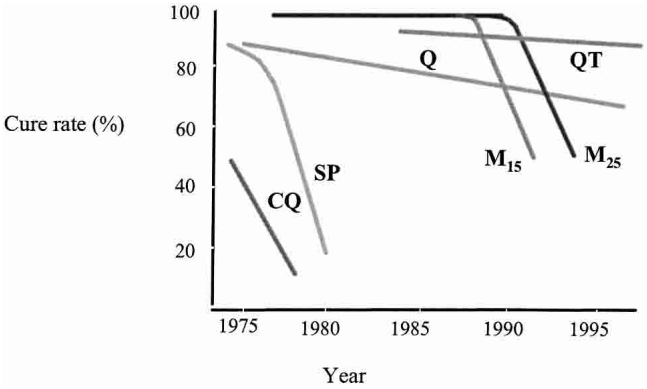

FIGURE 1. Drug efficacy in western Thailand. CQ = chloroquine; SP = sulfadoxine-pyrimethamine; Q = quinine; QT = quinine and tetracycline; M_{15} = mefloquine, 15 mg/kg; M_{25} = mefloquine, 25 mg/kg.

effectiveness of the drug or indeed whether an antimalarial drug is taken at all. Everyone has malaria parasites in their blood all the time, but usually at densities below that causing illness. The sensitivity of the parasite to the drug affects the clinical outcome more noticeably where the hosts are nonimmune and unable to control the infection themselves (i.e., patients of all ages in low transmission areas or young children in high transmission areas). In these circumstances, taking an ineffective drug can result in severe or protracted disease and even death. If an effective second-line drug is easily accessible, this impact may be limited although costs, particularly to the patient, may increase.[23] Unfortunately, however, effective second line drugs are often not readily available and therefore first line drug failure can lead directly to an increase in morbidity and mortality.

The burden of antimalarial drug resistance in terms of increased costs includes the direct cost of more expensive second- or third-line treatments and hospital admissions, the costs of seeking treatment, and the indirect costs of lost productivity.[18] In addition, there are broader costs at the household and macroeconomic levels[19] as well as intangible costs such as psychological stress and loss of confidence in a health system that fails to deliver a cure. Much of this burden falls on the poor, exacerbating already existing inequities, since the more expensive, effective antimalarials are accessible only to patients affluent enough to obtain them through informal sources, and remain out of reach to the majority of the rural poor who carry the largest burden of disease.

Measuring the burden. Measuring the impact of antimalarial drug resistance is difficult, and the impact may not be recognized until it is severe, especially in high transmission areas.[24] This is partly because routine health information systems grossly underestimate the magnitude of the problem.[25] Until the prevalent malaria parasites become completely resistant, patients will usually have an initial response to the drug, with a reduction in parasite numbers. However, as drug levels fall below the minimum inhibitory levels of the infecting resistant parasite in the individual patient, the parasite population once again begins to expand. By the time the parasite biomass increases back to a level causing symptoms, and is microscopically detectable, several days or weeks may have passed and the symptoms may not be associated with the initial illness, by either the patient or the health worker, and as a consequence may not be recorded as a treatment failure. This lack of reliable information is exacerbated by the fact that in many settings the majority of patients with malaria symptoms do not access the public sector where such information can be collected.[26]

Since routine health information systems cannot often be relied upon for accurate data on drug efficacy, there is a need for systematic surveillance and monitoring. Much effort has recently been put into setting up national and regional networks that use standardized methodology for monitoring *in vivo* drug efficacy.[27–29] In recent years, there has been a trend towards 14-day assessments in high transmission areas. Ideally, follow-up should be for at least 28 days, since failures do not become apparent within 14 days of taking treatment until drug resistance has reached very high levels and following patients up only until the 14th day results in a serious overestimation of the efficacy of failing drugs.[30] One of the arguments for the 14-day test was the difficulty in differentiating between recrudescence and reinfection, especially in areas of high transmission. Now that the genotypes of parasites in initial infections can be compared with those in any subsequent infections and it is therefore possible to differentiate confidently between reinfections and recrudescent infections, longer follow-up studies can and should be undertaken.

Reducing the burden. In considering possible strategies for the reduction of the burden of antimalarial drug resistance, it is useful to differentiate between the current burden of drug resistance and the potential burden in the future resulting from the continued emergence and spread of drug resistance. Central to achieving a reduction in both current and future burdens is an improvement in drug usage by patients and providers so that good quality drugs are available and taken at the correct dose and for a sufficient length of time to affect a radical cure and reduce the likelihood that partially resistant parasites will survive.

Improving drug use is most effective where the parasite is still sensitive to the drug. Where resistance has rendered the drug ineffective, the current burden of resistance can only be reduced by replacing the failing drug regimen with one that is effective. The difficulty lies in deciding which drug regimen to switch to, since the choice of drug or drug combination will determine the subsequent development of drug resistance.

Reducing the future burden of resistance requires that effective antimalarial drugs continue to be available in the future and requires the continuous search for and development of potential new antimalarial drugs[31,32] (http://www.mmv.org). However, the complete drug development process can take 10–15 years, making it imperative that the currently available drugs are deployed in a way most likely to maximize their lifespan by decreasing the likelihood that resistance will develop. The key strategy put forward to do this is to use available drugs in combination to prevent the emergence and spread of resistance.

THE EMERGENCE AND SPREAD OF ANTIMALARIAL DRUG RESISTANCE

The emergence of antimalarial drug resistance is dependent on the occurrence of a spontaneous genetic change (mutation or gene amplification) in a malaria parasite, which interferes with that parasite's susceptibility to a drug. A single mutation may be sufficient to confer almost complete resistance to

some drugs (e.g., atovaquone) or more usually there is a series of mutations that confer increasing tolerance of the parasite to increasing drug concentrations, as in the cases of pyrimethamine and chloroquine.[33]

However, for resistance to spread, the spontaneous occurrence of a mutation in itself is not sufficient. In the absence of the drug to which it is potentially resistant, a parasite with the resistant mutation does not have a survival advantage and therefore does not reproduce faster than the non-mutants. There may even be a survival disadvantage, a so-called fitness cost to having the mutation.[34] In the presence of the particular drug, the multiplication of the sensitive parasites is inhibited allowing the drug-resistant mutants to survive and multiply (i.e., selection), increasing the likelihood of transmission to the next host and therefore the spread of resistance.

Strategies for preventing spread. Once a drug-resistant mutant has arisen, preventing spread of resistance is difficult. Spread is facilitated by the exposure of malarial parasites to sub-therapeutic levels of antimalarial drugs, that kill sensitive parasites but allows parasites with a resistance mutation to survive and reproduce. Ensuring that drugs are taken in at a sufficient dose and for a sufficient duration reduces this risk. Drug pressure is higher where a drug with a long half-life is taken because the drug remains in the patient's blood at low levels for weeks, exposing any newly introduced malarial parasites to sub-therapeutic levels.[35] This is particularly likely to occur in high transmission areas where people are not only infected more frequently, but also take antimalarial drugs frequently whether or not they are have malaria. Theoretically, this form of drug pressure can be reduced by using drugs with a shorter half-life and by restricting the use of the first-line drug to patients with confirmed malaria: i.e., only treating those with a definitive diagnosis. There are downsides to both of these strategies that pit the long-term public health benefit against the benefit to the individual patient. Using drugs with short half-lives such as artesunate means that if they are used together with other rapidly eliminated drugs they need to be taken for a longer period resulting in poorer patient adherence and less likelihood of cure compared with drugs with longer half-lives such as mefloquine or SP, which can be taken over a three-day period or in a single dose. However, in combination with another effective drug, ACTs only require three days of treatment. Restricting usage of effective drugs to patients who have a definitive diagnosis of malaria would reduce access to cure to the most vulnerable communities because the availability and reach of diagnostic facilities is so poor. This would be expected to lead to an increase in current morbidity and mortality, a trade-off between current and future burden of disease, which is clearly unacceptable.

The use of rapid diagnostic tests that require minimal training and equipment may be a potential solution.[20] However, their cost of US $0.7 per test and the high levels of asymptomatic parasitemia and therefore false-positive results in areas of high transmission, limit the appropriateness of this technology to lower transmission areas. The cost-effectiveness of the diagnostic tests depends on their cost relative to that of the ACT and the positive predictive value of clinical diagnosis. For example, they are unlikely to be cost-effective when more than 50% of the patient group with a clinical diagnosis of malaria indeed does have an infection.

Strategies for preventing emergence. Because it is difficult to control antimalarial drug resistance once it has emerged, there is a need for strategies that prevent the rare event of initial emergence. Combinations of drugs which have different molecular targets delay the emergence of resistance. However, malaria control programs may be reluctant to adopt this strategy because until resistance emerges, there is no evident benefit to the more expensive combination treatment.

ARTEMISININ-BASED COMBINATION THERAPY

The rationale. The rationale for using drugs in combination is well established in the treatment of tuberculosis, infection with human immunodeficiency virus, and cancer. The probability of a parasite arising that is resistant simultaneously to two drugs with unrelated modes of action is the product of the per parasite mutation frequencies multiplied by the total number of parasites exposed to drugs.[36] Therefore, if the probability of a parasite being resistant to drug A is one in 10^9 and to drug B is one in 10^9 then the probability that a parasite will be simultaneously resistant to both is one in 10^{18}, representing a billion-fold reduction in probability. Mutations conferring resistance to artemisinins have never been documented and are therefore much less likely to occur than mutations to some other drugs such as SP.

Artemisinins are a particularly effective partner drug because they are more active than any other antimalarial, reducing the number of parasites by approximately 10^4 per asexual cycle[36] and therefore reducing the number of parasites that are exposed to the partner drug alone. In addition, artemisinins have broad stage specificity and can be used to treat severe as well as uncomplicated malaria. They inhibit the production of gametocytes and therefore have a potential to reduce transmission[37] and finally, to date, there has been no evidence of stable resistance either in therapeutic use or in experimental systems.

Artemisinins taken on their own as monotherapy must be taken for seven days for radical cure. However, adherence to seven-day regimens is extremely low and a three-day regimen is generally regarded as the maximum because most people discontinue treatment when they feel better usually after a couple of days, and this can result in late recrudescences with monotherapy. Used in combination with another effective drug, a three-day course is sufficient and better adhered to and has the important advantage of protecting these valuable drugs.[38]

The evidence. There is an increasing body of field evidence supporting the theoretical basis for ACTs, principally from the Thailand-Myanmar border and more recently from South Africa. In an area on the Thailand-Myanmar border, the widespread deployment of ACT was associated with a decreased incidence in malaria,[39] sustained effectiveness of the combination for more than 10 years, and an increase in mefloquine sensitivity *in vitro*.[40] These results were obtained despite artesunate being added to mefloquine when resistance to the latter was already widespread, a less than ideal scenario in terms of delaying antimalarial resistance. In KwaZulu-Natal in South Africa, the combined effect of switching from SP to the fixed combination of artemether-lumefantrine and residual spraying with DDT was associated with a decrease in cases of 78% and an increase in cure rate of 87% (Barnes K, unpublished data).

The argument against using ACTs. There are a number of concerns about widespread deployment of ACT,[41] the chief

one being cost. These combination therapies currently cost more than US$1 for an adult course (although this cost is decreasing), so for them to be widely deployed as first-line therapy, substantial subsidy will be required to ensure that they are available to everyone, including those who cannot afford the market price. A second concern is that by deploying the artemisinin derivatives now, we risk losing our most valuable antimalarial, a potentially catastrophic event. This is particularly a concern in many tropical country settings because the local capacity to deliver health care to the population is often inadequate, in part due to a chronic lack of resources. Under these circumstances, implementing a change in drug policy without addressing underlying problems with delivery is likely to result in low rates of coverage and the inappropriate use of the drugs.

Currently there is only one registered co-formulated ACT that is produced to internationally recognized good manufacturing practice standards; artemether-lumefantrine (Co-Artem®; Novartis International AG, Basel, Switzerland). This has the disadvantage of requiring a twice a day dose and needing to be taken with fat to ensure adequate absorption. Recently, a co-formulated product of dihydroartemisinin-piperaquine (Artekin®; Holleykin Pharmaceutical Co., Ltd., Guangzhou, Guandong, People's Republic of China) has been shown to be safe, effective, and acceptable in clinical trials.[42] It is currently available at about half the cost of artemether-lumefantrine in Cambodia, China, and Vietnam where it has been used extensively. However, the current product has not yet undergone the lengthy and costly regulatory process required for international approval, and it will therefore be several years before it can be more widely deployed unless this process can be hastened. Fixed artesunate-mefloquine and artesunate-amodiaquine co-formulated drugs are under development.

If any other artemisinin-based combination is used today, such as artesunate and mefloquine or artesunate and SP, then it must be given as two separate types of tablets and there is a risk that patients will take only the artemisinin derivative responsible for rapid symptom resolution and that this will only be taken for a few days. Not only will this result in treatment failures, but also it theoretically increases the risk of drug resistance emerging in the future. Specific strategies aimed at improving coverage and correct drug usage can go some ways to addressing these concerns, including blister packaging of drugs[43] and involvement of the informal sector in providing treatment.[44]

The policy dilemma. However, because of the costs, risks and uncertainties involved in switching to artemether-lumefantrine or a non–co-formulated ACT now, many countries are delaying the decision or choosing an interim option such as SP on its own, or a combination of two non-artemisinin drugs such as chloroquine and SP. Often this is already ineffective, or the likelihood is that it will only remain effective for a few years before drug resistance worsens further (as the components are available individually) rendering the combination ineffective. So in making this choice, it is assumed or hoped that an affordable co-formulated ACT will become available in the near future. Apart from concerns over efficacy, a disadvantage of such an approach is that it may result in two changes in drug policy within a potentially short space of time. Not only does each change require a major investment of scarce human and financial resources, but frequent policy change is likely to lead to confusion among the public and a loss of credibility of the policy makers.

In the meantime, artemisinins are already increasingly available and are being used on their own as monotherapy, especially in the informal sector, which is often a community's main source of treatment. For example, in Cambodia a recent survey showed that more than 80% of the patients with a malaria-like illness sought treatment in the informal sector where 37% of the antimalarials treatments obtained contained an artemisinin, but of these only 20% of these were taken in combination with mefloquine as recommended. (Yeung SM, unpublished data). This use of artemisinin derivatives as monotherapy is a major threat to the ACT strategy and the challenge is therefore to make sure that they are deployed in a way that is least likely to encourage the development of resistance by ensuring that they are always used in combination with another effective anti-malarial drug.

The policy implications of these potential risks and benefits are the subject of intense debate. Clearly, the decision of when to switch and what to switch to is a complex one. Many scientific, behavioral, economic, and political factors need to be taken into consideration. Within all of these areas, many uncertainties remain in key areas. To clarify these issues, we are developing a bioeconomic model of antimalarial drug resistance and combination therapy. The aim is to use the model for a cost-benefit analysis to explore the implications of policy decisions such as the timing of switches in relation to the existing levels of drug resistance, the coverage achieved by the policy change, and specific strategies aimed at increasing coverage. At the core of the overall model is a biologic model of the transmission of antimalarial drug resistance.

MODELING ANTIMALARIAL DRUG RESISTANCE

The model of anti-malarial resistance aims to describe malaria epidemiology and predict the effect of potential policy interventions based on sound representations of the underlying biology. The predictions in terms of the prevalence of malaria infections and the proportion of infections that are resistant are used to calculate future cost and effectiveness.

Previous mathematical models in malaria have tended to focus on intra-host dynamics, epidemiology, or drug resistance in isolation.[45–53] A more recent model by Hastings and others[35] explores the effect of pharmacokinetic and pharmacodynamic properties on resistance and allows resistance to evolve more realistically through gradually increasing drug tolerance. In this current model of antimalarial drug resistance, we aim to incorporate drug, epidemiologic, parasitologic, vectorial, host, behavioral, and economic factors based on available data.

Model outline. The model is a time iterative model where resistance occurs and develops in two stages as mentioned above: *de novo* emergence and spread. The model used throughout this paper focuses only on the spread of resistance, allowing assumptions about the emergence of resistance for different drugs and drug combinations to be specified or explored in more detail in a preceding emergence model that incorporates mutation or amplification frequencies and factors (such as immunity) likely to reduce per parasite probabilities of survival.

To start the model, a set of initial inputs is required. These inputs are described later in this report. The iteration starts with a population of humans with a specified total frequency of infections and a proportion of resistant infections. It is assumed that a single resistant parasite is capable of expanding and cause a resistant infection in the host and that this can be transmitted resulting in one or more resistant infections in the next iteration. Transmission occurs at random within the human host population and at the end of each iteration the total number of infections and the ratio of resistant and sensitive infections are obtained. These intermediate outputs are then fed back into the model so that the next iteration of the model is run with the updated infection frequencies and the updated immunity profile, which is described later in this report. The process is repeated until the user-defined time limit is reached, eradication is achieved, or resistance reaches 100% (Figure 2).

Immunity. Central to the model is the effect of host immunity on the fate of an inoculated infection, its subsequent transmission, and the development of resistance. The effects of immunity included in the model are a reduction in parasite density,[54] a reduction in the proportion of infections that are symptomatic,[55] an increase in likelihood of self cure and cure rate of treated infections,[56] and a reduction in the reproductive rate (due to a decrease in duration of infection and treatment failure).[57,58]

Host immunity affects the development of drug resistance in a number of ways, including a direct influence on the likelihood that an infected person will be symptomatic and will therefore seek treatment. The relationship between an oversimplified binary description of immunity (fully immune and fully non-immune) and the proportion of patients treated in a low and high transmission intensity area is shown in Figure 3.

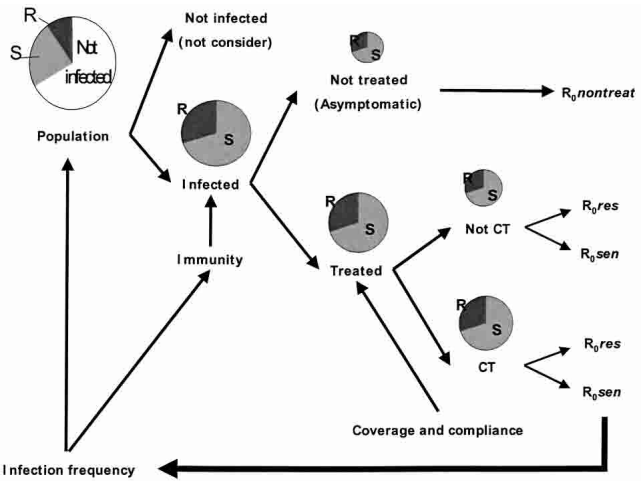

FIGURE 2. Simplified model structure simulating one iteration where immunity has been incorporated as a continuous factor. First, the infected population is divided into resistant (R or res) and sensitive (S or sens) infections. The proportion of infections that are treated is determined by the level of immunity, which depends on the transmission intensity. The proportion of infections treated with combination therapy (CT) and monotherapy (not CT) is varied as an input parameter. The reproductive rate (R_0) varies according to type of treatment and level of resistance and results in an increasing proportion of resistant infections in the next iteration. The outputs of the model are the predicted total number of malaria cases and the percentages of sensitive and resistant infections. nontreat = non-treated.

In a low transmission area (i.e., an entomologic inoculation rate [EIR] < 3), the level of immunity in the population is low and therefore the majority of patients will be symptomatic and seek treatment when they are infected with malaria. In contrast, in high transmission areas, the high level of immunity means the majority of the patients who are parasitemic are asymptomatic and therefore proportionally fewer of them seek treatment, exposing proportionally fewer parasites to drugs (although quantitatively there are more infected patients than in low transmission areas). In this situation, the selective pressure is lower because the transmission advantage of resistant infections is diluted by transmission from asymptomatic gametocyte carriers.

If patients are treated they can receive either combination therapy (CT) or monotherapy using one of the drugs in the combination (non-CT). In each population, transmission occurs both within and across the groups. Transmission is quantified by the basic reproductive rates (R_0). For sensitive infections, the reproductive rate is lower in treated infections than in untreated infections and lowest if the treatment received is an artemisinin-based CT. The rate of spread of resistance is determined by the ratio of the reproductive rates of the resistant infections compared with sensitive infections in each of the treatment groups. Initially, a relative reproductive rate of 4 for sensitive compared with resistant infections was used. This comes from a study[37] that showed that patients who had treatment failures following mefloquine carried gametocytes four times longer than patients with sensitive infections.

Incorporating immunity into the model. The mode of acquisition of immunity is complex and uncertain and whether age affects the rate of acquisition of immunity independent of malaria exposure is still questioned.[59,60] However, to make the model realistic, a function is required to incorporate the effects of infection frequency on immunity and the effects of changes in immunity need to be fed back into the model. In order to do this, immunity functions were constructed based on age stratified rates of parasitaemia, parasite density malaria morbidity and severe malaria at different transmission intensities. These functions are used at each iteration of the model to determine the parasite density, proportion of treated and non-treated infections, and the reproductive rates of each age group in relation to the values of the one-year old host who is assumed to be non-imune. As infection frequency changes over subsequent iterations of the model, the "immunity profile" of the population is also allowed to change, an "updating" that is made possible by adjusting the level of immunity in the immunity function used in the model according to the new transmission intensity.

Model inputs. The model requires the input of values for key parameters. Where these are measurable these values are taken from published data. However, where no data exists, these values have been derived from field observations and these assumptions are varied in the sensitivity analysis. The key initial inputs to the model are as follows: 1) Population size; 2) mutation rate or starting frequency of the mutation (1 in 10^9 to 1 in 10^{18}); 3) initial level of resistance to the non-artemisinin partner drug; 4) initial estimated EIR representing transmission intensity of the areas; 5) the basic reproductive rate (R_0) of a non-treated, sensitive infection, which ranges from 1 to 10; 6) the relative reproductive rates of treated infections for sensitive infections and resistant infec-

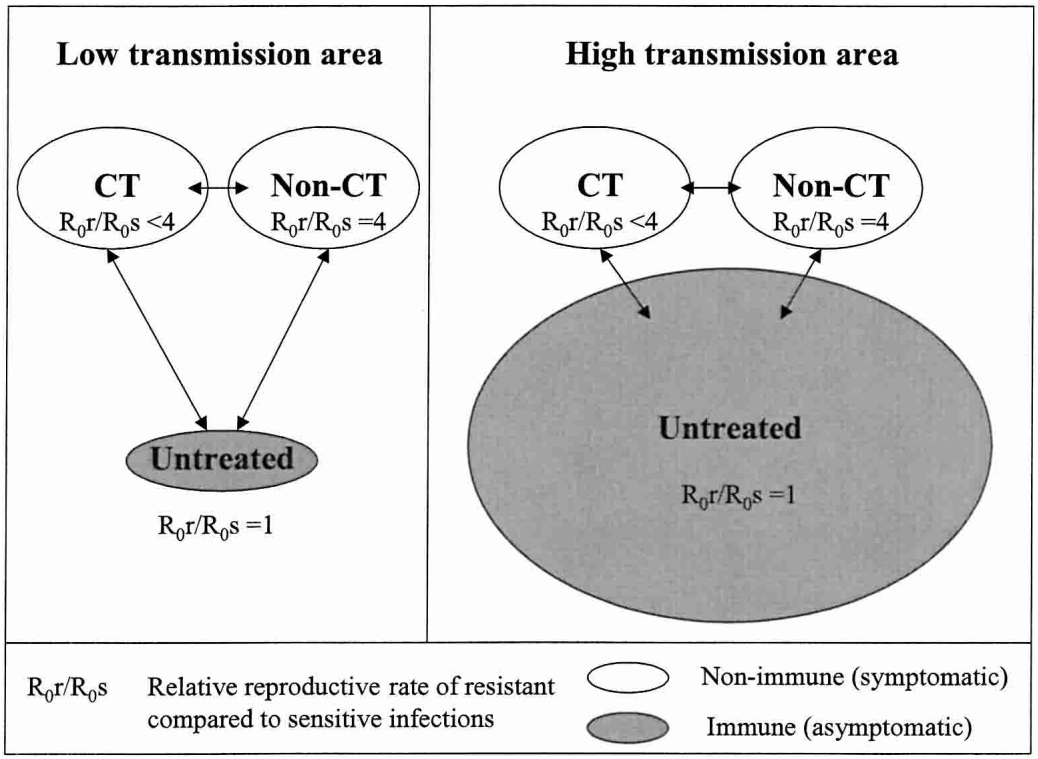

FIGURE 3. Different proportions of treated and non-treated patients in two extreme transmission intensity areas as determined by a binary description of immunity (fully immune and non-immune). The proportion of infections that are treated, and therefore the selective advantage of resistant infections, is greater in the low transmission settings. CT = combination therapy; Non-CT = non-combination therapy.

tions, which are all set in relation to this basic reproductive rate. (There are few data on which to base these rates. However, it is assumed that the reproductive rate of a sensitive infection that is treated with a non-artemisinin monotherapy is twenty times less than the basic reproductive rate. If it is treated with an artemisinin derivative, the reproductive rate is assumed to be much less because artemisinins reduce the parasite load much faster than other drugs and also prevent gametocytogenesis. The reproductive rate of treated resistant infections is assumed to be four times greater than treated sensitive infections.[37]); 7) there is assumed to be no fitness cost of carrying the resistant mutation. (This means that the R_0 is same for untreated infections whether they are sensitive or resistant infections; 8) Maximum parasite density assumed in a completely non-immune patient (10^9 to 10^{12} parasites per person); 9) Maximum proportion of infected patients receiving any antimalarial (50–100%); 10) the ACT coverage rate, i.e., proportion of antimalarial treatments received that are ACT (0–100%).

Using the model to work out cost-effectiveness. The epidemiologic model is then used as the basis for working out the long-term cost-effectiveness of ACTs under different implementation conditions. Taking a societal perspective, costs to both the patient and the provider are incorporated into the model.

Costs to the provider. One of the key concerns about using ACTs has been the increased cost of drug, so the cost of initial treatment with a first-line drug has been kept separate from the cost of failure (which increase as more cases fail due to increasing drug resistance). In addition to the cost of the antimalarial drug, the cost of the initial treatment to the public provider includes the cost of consultation and diagnosis and the inpatient costs for the small proportion of patients who require hospitalization. The cost of failure includes the cost of drugs that include second- and third-line drugs, the cost of consultation and diagnosis, the cost of inpatient care, and the cost of treating a number of specific complications such as severe anemia, cerebral malaria, renal failure, and low birth weight babies.

Cost to the patient. For patients attending public health facilities, the main costs are the direct costs of transport and food. It is assumed that consultation, diagnosis, and treatment are provided free. In reality, user fees are often charged, but as this does not represent a net change in overall societal costs; they are not included in the overall analysis and only given separately where appropriate. For patients receiving home treatment or attending informal sector providers for modern medicines, the direct costs paid by the patient for consultation, diagnosis, and treatment are included, as well as the cost of transport and food.

In addition to the direct costs, the indirect impact on the loss of productivity is estimated. This is presented both as actual number of lost days of productivity as well as the cost that this might represent. This is because of methodologic difficulties in estimating the latter associated with the time of year in relation to the agricultural calendar, family, and social context, etc.

Each outcome state from the biologic model is assigned likelihoods of cure and failure depending on level of resistance and adherence. Since the actual cure rates of non-adherers is unknown, estimates are derived using data from drug efficacy trials that studied drug regimens with shorter durations or lower drug doses than those currently recommended.

Over the period of the analysis, e.g., 10 years, the number of cases, cures, and failures and the total costs are summed. By varying the input parameters, the effect of using different drugs and drug combinations at different rates of coverage, the costs and effectiveness in terms of cases and costs averted can be compared. Furthermore, by incorporating the cost and effectiveness of specific strategies that alter coverage or adherence, the overall cost-effectiveness of changing drug policy and of specific implementation strategies can be compared. These could include pre-packaging drugs to increase adherence or increasing the proportion of treated cases who first have a definitive diagnosis.

DISCUSSION

Resistance to antimalarial drugs is resulting in avoidable morbidity, mortality, and financial losses. Urgent measures are needed now to reduce the current and future burden of disease. There is little justification for the continued use of ineffective drugs because effective drugs are currently available. The decisions of which drug regimen to change to, and how to implement the change in a way that maximizes potential benefit, are more difficult, but delaying a decision to switch because of these difficulties can only result in increased morbidity and mortality. Furthermore, delaying a switch to ACTs potentially puts at risk one of the key advantages of this strategy, which is to delay the emergence of resistance. The longer the decision is delayed, the more entrenched will become the unregulated use of the artemisinins and partner drugs as monotherapies. Partly because of the uncertainties, there is still significant reluctance to take action amongst potential funders and some national governments, both of whose commitment is essential for the success of any change in policy.

By developing a bioeconomic model that incorporates realistic drug, parasite, host immunity, behavioral, and economic factors, we hope to contribute a useful tool to this debate. The model is currently being refined so that key relationships are elucidated, particularly those relating to the relationships between carrying a resistant genotype, adherence to treatment, and outcome in terms of duration of illness and cure. To clarify the importance of uncertainties and the relative importance of such factors as coverage and adherence, extensive sensitivity analysis is being undertaken. The key objective is to produce a rational and transparent framework that can be used as a tool for the planning and evaluation of changes in drug policy and implementation strategies. To this end, in addition to making extensive use of data from the field in the model, we will be seeking to disseminate widely the initial model and to encourage its adaptation and application in different settings to maximize its robustness and credibility. It is hoped that through this process, the model will become a useful tool in supporting rational decision-making on the future deployment of ACT.

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Authors' addresses: Shunmay Yeung, Wirichida Pongtavornpinyo, and Nicholas J. White, Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Program, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand, Telephone: 66-2-246-0832, Fax: 66-2-246-7795, E-mails: shunmay.yeung@lshtm.ac.uk or shunmay@hotmail.com, pan@tropmedres.ac and nickw@tropmedres.ac. Ian M. Hastings, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom, Telephone: 44- 151-705-3183, Fax: 44-151-705-3371, E-mail: hastings@liverpool.ac.uk. Anne J, Mills, Health Economics and Financing Program, Department of Public Health and Policy, Health Policy Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom, E-mail: anne.mills@lshtm.ac.uk.

REFERENCES

1. Marsh K, 1998. Malaria disaster in Africa. *Lancet 352:* 924.
2. White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, Taylor TE, Newbold CI, Ruebush TK, Danis M, Greenwood BM, Anderson RM, Olliaro P, 1999. Averting a malaria disaster. *Lancet 353:* 1965–1967.
3. Roper C, Pearce R, Bredenkamp B, Gumede J, Drakeley C, Mosha F, Chandramohan D, Sharp B, 2003. Antifolate antimalarial resistance in southeast Africa: a population-based analysis. *Lancet 361:* 1174–1181.
4. Takechi M, Matsuo M, Ziba C, MacHeso A, Butao D, Zungu IL, Chakanika I, Bustos MD, 2001. Therapeutic efficacy of sulphadoxine/pyrimethamine and susceptibility *in vitro* of *P. falciparum* isolates to sulphadoxine-pyremethamine and other antimalarial drugs in Malawian children. *Trop Med Int Health 6:* 429–434.
5. World Health Organization, 2001. *Antimalarial Drug Combination Therapy*. Report of a WHO Technical Consultation. Geneva: World Health Organization. WHO/CDS/RBM/2001.35.
6. Fevre EM, Barnish G, 1999. Malaria-treatment policies: when and how should they be changed? *Ann Trop Med Parasitol 93:* 549–560.
7. Goodman CA, Coleman PG, Mills AJ, 1999. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet 354:* 378–385.
8. Bloland PB, Ettling M, 1999. Making malaria-treatment policy in the face of drug resistance. *Ann Trop Med Parasitol 93:* 5–23.
9. Rauner MS, 2002. Using simulation for AIDS policy modeling: benefits for HIV/AIDS prevention policy makers in Vienna, Austria. *Health Care Manag Sci 5:* 121–134.
10. Weinstein MC, Toy EL, Sandberg EA, Neumann PJ, Evans JS, Kuntz KM, Graham JD, Hammitt JK, 2001. Modeling for health care and other policy decisions: uses, roles, and validity. *Value Health 4:* 348–361.
11. Baltussen R, Leidl R, Ament A, 1999. Real world designs in economic evaluation. Bridging the gap between clinical research and policy-making. *Pharmacoeconomics 16:* 449–458.
12. Brennan A, Akehurst R, 2000. Modelling in health economic evaluation. What is its place? What is its value? *Pharmacoeconomics 17:* 445–459.
13. Snow RW, Craig M, Deichmann U, Marsh K, 1999. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bull World Health Organ 77:* 624–640.
14. Guyatt HL, Snow RW, 2001. The epidemiology and burden of *Plasmodium falciparum*-related anemia among pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg 64:* 36–44.
15. Steketee RW, Nahlen BL, Parise ME, Menendez C, 2001. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg 64:* 28–35.

16. Holding PA, Snow RW, 2001. Impact of *Plasmodium falciparum* malaria on performance and learning: review of the evidence. *Am J Trop Med Hyg 64:* 68–75.
17. Murphy SC, Breman JG, 2001. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. *Am J Trop Med Hyg 64:* 57–67.
18. Chima RI, Goodman CA, Mills A, 2003. The economic impact of malaria in Africa: a critical review of the evidence. *Health Policy 63:* 17–36.
19. Sachs J, Malaney P, 2002. The economic and social burden of malaria. *Nature 415:* 680–685.
20. Phillips M, Phillips-Howard PA, 1996. Economic implications of resistance to antimalarial drugs. *Pharmacoeconomics 10:* 225–238.
21. Snow RW, Trape JF, Marsh K, 2001. The past, present and future of childhood malaria mortality in Africa. *Trends Parasitol 17:* 593–597.
22. Trape JF, 2001. The public health impact of chloroquine resistance in Africa. *Am J Trop Med Hyg 64:* 12–17.
23. Goodman CA, Coleman PG, Mills A, 2000. *Economic Analysis of Malaria Control in Sub-Saharan Africa*. Geneva: World Health Organization. Global Forum for Health Research.
24. Hastings IM, 2001. Modelling parasite drug resistance: lessons for management and control strategies. *Trop Med Int Health 6:* 883–890.
25. Breman JG, 2001. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *Am J Trop Med Hyg 64:* 1–11.
26. McCombie SC, 1996. Treatment seeking for malaria: a review of recent research. *Soc Sci Med 43:* 933–945.
27. Hastings IM, 2001. Monitoring antimalarial drug resistance within National Malaria Control Programmes: the EANMAT experience. 2001. *Trop Med Int Health 6:* 891–898.
28. Bloland PB, Kazembe PN, Oloo AJ, Himonga B, Barat LM, Ruebush TK, 1998. Chloroquine in Africa: critical assessment and recommendations for monitoring and evaluating chloroquine therapy efficacy in sub-Saharan Africa. *Trop Med Int Health 3:* 543–552.
29. World Health Organization, 2001. *Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Falciparum Malaria*. Geneva: World Health Organization. WHO Guideline 2001 Draft.
30. White NJ, 2002. The assessment of antimalarial drug efficacy. *Trends Parasitol 18:* 458–464.
31. Enserink M, 2000. Malaria researchers wait for industry to join fight. *Science 287:* 1956–1958.
32. Ridley RG, 2002. Introduction. Antimalarial drug resistance: ramifications, explanations and challenges. *Microbes Infect 4:* 155–156.
33. Wellems TE, Plowe CV, 2001. Chloroquine-resistant malaria. *J Infect Dis 184:* 770–776.
34. Peters JM, Chen N, Gatton M, Korsinczky M, Fowler EV, Manzetti S, Saul A, Cheng Q, 2002. Mutations in cytochrome b resulting in atovaquone resistance are associated with loss of fitness in *Plasmodium falciparum*. *Antimicrob Agents Chemother 46:* 2435–2441.
35. Hastings IM, Watkins WM, White NJ, 2002. The evolution of drug-resistant malaria: the role of drug elimination half-life. *Philos Trans R Soc Lond B Biol Sci 357:* 505–519.
36. White N, 1999. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B Biol Sci 354:* 739–749.
37. Price RN, Nosten F, Luxemburger C, ter Kuile FO, Paiphun L, Chongsuphajaisiddhi T, White NJ, 1996. Effects of artemisinin derivatives on malaria transmissibility. *Lancet 347:* 1654–1658.
38. Nosten F, Luxemburger C, ter Kuile FO, Woodrow C, Eh JP, Chongsuphajaisiddhi T, White NJ, 1994. Treatment of multidrug-resistant *Plasmodium falciparum* malaria with 3-day artesunate-mefloquine combination. *J Infect Dis 170:* 971–977.
39. Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, McGready R, ter Kuile F, Looareesuwan S, White NJ, 2000. Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet 356:* 297–302.
40. Brockman A, Price RN, van Vugt M, Heppner DG, Walsh D, Sookto P, Wimonwattrawatee T, Looareesuwan S, White NJ, Nosten F, 2000. *Plasmodium falciparum* antimalarial drug susceptibility on the north-western border of Thailand during five years of extensive use of artesunate-mefloquine. *Trans R Soc Trop Med Hyg 94:* 537–544.
41. Bloland PB, Ettling M, Meek S, 2000. Combination therapy for malaria in Africa: hype or hope? *Bull World Health Organ 78:* 1378–1388.
42. Hien TT, Dolecek C, Mai PP, Dung NT, Truong NT, Thai LH, An DTH, Thanh TT, Stepniewska K, White NJ, Farrar J, 2003. Dihydroartemising-piperaquine against multidrug-resistant *Plasmodium falciparum* malaria in Vietnam: randomized clinical trial. *Lancet 363:* 18–22.
43. Shwe T, Lwin M, Aung S, 1998. Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar. *Bull World Health Organ 76:* 35–41.
44. Brugha R, Chandramohan D, Zwi A, 1999. Viewpoint: management of malaria–working with the private sector. *Trop Med Int Health 4:* 402–406.
45. Aron JL, 1982. Malaria epidemiology and detectability. *Trans R Soc Trop Med Hyg 76:* 595–601.
46. Aron JL, 1988. Mathematical modelling of immunity to malaria. *Math Biosci 90:* 385–396.
47. Cross AP, Singer B, 1991. Modelling the development of resistance of *Plasmodium falciparum* to anti-malarial drugs. *Trans R Soc Trop Med Hyg 85:* 349–355.
48. Curtis CF, Otoo LN, 1986. A simple model of the build-up of resistance to mixtures of anti-malarial drugs. *Trans R Soc Trop Med Hyg 80:* 889–892.
49. Dietz K, Molineaux L, Thomas A, 1974. A malaria model tested in the African savannah. *Bull World Health Organ 50:* 347–357.
50. Fine PEM, 1975. Superinfection—a problem in formulating a problem. *Trop Dis Bull 72:* 475–486.
51. Hastings IM, D'Alessandro U, 2000. Modelling a predictable disaster: the rise and spread of drug-resistant malaria. *Parasitol Today 16:* 340–347.
52. MacDonald G, 1950. The analysis of infection rates in diseases in which superinfection occurs. *Trop Dis Bull 47:* 907–914.
53. Ross R, 1911. *The Prevention of Malaria*. Second edition. London: Murray.
54. Buckling A, Read AF, 2001. The effect of partial host immunity on the transmission of malaria parasites. *Proc R Soc Lond B Biol Sci 268:* 2325–2330.
55. Bloland PB, Boriga DA, Ruebush TK, McCormick JB, Roberts JM, Oloo AJ, Hawley W, Lal A, Nahlen B, Campbell CC, 1999. Longitudinal cohort study of the epidemiology of malaria infections in an area of intense malaria transmission II. Descriptive epidemiology of malaria infection and disease among children. *Am J Trop Med Hyg 60:* 641–648.
56. Djimde AA, Doumbo OK, Traore O, Guindo AB, Kayentao K, Diourte Y, Niare-Doumbo S, Coulibaly D, Kone AK, Cissoko Y, Tekete M, Fofana B, Dicko A, Diallo DA, Wellems TE, Kwiatkowski D, Plowe CV, 2003. Clearance of drug-resistant parasites as a model for protective immunity in *Plasmodium falciparum* malaria. *Am J Trop Med Hyg 69:* 558–563.
57. Mayxay M, Chotivanich K, Pukrittayakamee S, Newton P, Looareesuwan S, White NJ, 2001. Contribution of humoral immunity to the therapeutic response in falciparum malaria. *Am J Trop Med Hyg 65:* 918–923.
58. White NJ, 1998. Why is it that antimalarial drug treatments do not always work? *Ann Trop Med Parasitol 92:* 449–458.
59. Baird JK, 1995. Host age as a determinant of naturally acquired immunity to *Plasmodium falciparum. Parasitol Today 11:* 105–111.
60. Taylor-Robinson AW, 2002. A model of development of acquired immunity to malaria in humans living under endemic conditions. *Med Hypotheses 58:* 148–156.