

Benefits of using multiple first-line therapies against malaria

Maciej F. Boni^{†§¶}, David L. Smith^{||†}, and Ramanan Laxminarayan^{†§}

[†]Resources for the Future, Washington, DC 20036; [‡]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; [§]Princeton Environmental Institute, Princeton, NJ 08544; and ^{||}Department of Zoology and [¶]Emerging Pathogens Institute, University of Florida, Gainesville, FL 32611

Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved June 30, 2008 (received for review May 13, 2008)

Despite the availability of many drugs and therapies to treat malaria, many countries' national policies recommend using a single first-line therapy for most clinical malaria cases. To assess whether this is the best strategy for the population as a whole, we designed an evolutionary-epidemiological modeling framework for malaria and compared the benefits of different treatment strategies in the context of resistance evolution. Our results show that the population-wide use of multiple first-line therapies (MFT) against malaria yields a better clinical outcome than using a single therapy or a cycling strategy where therapies are rotated, either on a fixed cycling schedule or when resistance levels or treatment failure become too high. MFT strategies also delay the emergence and slow the fixation of resistant strains (phenotypes), and they allow a larger fraction of the population to be treated without trading off future treatment of cases that may be untreatable because of high resistance levels. Earlier papers have noted that cycling strategies have the disadvantage of creating a less temporally variable environment than MFT strategies, making resistance evolution easier for the parasite. Here, we illustrate a second feature of parasite ecology that impairs the performance of cycling policies, namely, that cycling policies degrade the mean fitness of the parasite population more quickly than MFT policies, making it easier for new resistant types to invade and spread. The clinical benefits of using multiple first-line therapies against malaria suggest that MFT policies should play a key role in malaria elimination and control programs.

drug resistance | epidemiology | evolution | treatment strategies | cost of resistance

Prompt treatment with effective antimalarials is a crucial element of malaria control, but the effectiveness of antimalarial drugs can be seriously compromised by the evolution of drug resistance in the *Plasmodium* spp. that cause malaria. The evolution and worldwide spread of resistance to chloroquine (CQ) over the past 50 years (1) and the subsequent failure of sulfadoxine-pyrimethamine (SP) (1, 2) have created a crisis for many African nations and other malaria-endemic countries (3). A number of these countries have adopted the highly effective artemisinin-based combination therapies (ACTs) as their first-line therapy for uncomplicated malaria, but ACTs are not yet widely available. Extensive resistance has yet to be detected to artemisinin drugs, but there is concern that resistance could emerge and spread rapidly (4). Efforts to delay resistance to artemisinin have included a call to end production of artemisinin monotherapies and plans to subsidize ACTs to displace artemisinin monotherapies (5). As ACTs become available and affordable in the postchloroquine era, there will be a need to adopt sustainable treatment strategies that will further extend the useful therapeutic life of these and other new antimalarials.

Current and historical practice in Africa has been to recommend a single first-line therapy or drug (we use the terms interchangeably) for uncomplicated malaria and, when drug-resistance levels rise, to replace the officially recommended drug with a new one to which resistance has not yet emerged. In Kenya, for example, CQ was replaced by SP as the first-line treatment in 1998 and SP by artemether-lumefantrine (an ACT) during 2004–2006 on the basis

of high levels of resistance and treatment failure (6, 7). This “wait-and-switch” strategy burdens the surveillance networks and public health systems of developing countries and, as we show here, yields a suboptimal morbidity and mortality outcome. A more sustainable strategy would be to prospectively deploy existing antimalarials to minimize mortality and morbidity and delay resistance emergence and treatment failure for as long as possible.

In this study, we evaluate the use of multiple first-line therapies (MFT) in slowing the evolution of resistance. MFT is defined as a drug policy in which several therapies are made available in both the public and the private sectors, and patients and clinicians can choose which therapy to use. For most of the analysis presented here, we assume that the different first-line therapies are used in equal amounts in the host population; an important area of further study will be to determine how a particular drug-use distribution can be achieved in a given population. Just as combination therapies, wherein multiple drugs are coformulated into a single treatment, delay the evolution of resistance (8–15), deploying multiple therapies slows down resistance evolution compared with using a single therapy for the whole population. An MFT strategy with n drugs has two main benefits. First, it increases the variability of drugs in the parasite's environment, making it difficult for the parasite to adapt to any one part of the environment. If on every new infection, the parasite has a small chance of encountering the same drug it saw in its previous host, evolving resistance to any particular drug is difficult. Second, when using n drugs in equal amounts, the rate each drug is used is cut to $1/n$ of total use, thus reducing the overall selection pressure for resistance to that drug. Rationing treatment could achieve a similar reduction in selection pressure, but an MFT strategy reduces each drug's use without denying treatment. This must be balanced against the alternative of holding the drugs in reserve under a wait-and-switch policy; such comparisons have been done in the context of bacterial infections and antibiotic resistance (16–19), but malaria presents unique scientific and operational challenges. In making this comparison for malaria, we may be able to answer a question of historical interest: would CQ and SP still be useful if they had been deployed together? Today, the relevant policy question that requires attention is how to deploy the current ACTs to best effect.

We focus our analysis on the case when three different therapies are available, and we show that using more first-line therapies (*i*) significantly delays resistance emergence and treatment failure, (*ii*) slows the evolution of resistance, (*iii*) lowers the total clinical burden of malaria, and (*iv*) reduces the effect of the classic resistance-disease tradeoff, wherein treating a single case now and generating drug resistance may trade off with the ability to treat several cases in the future (20, 21). In addition, we show that MFT

Author contributions: M.F.B., D.L.S., and R.L. designed research; M.F.B. performed research; and M.F.B. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[¶]To whom correspondence should be addressed. E-mail: mboni@oucr.org.

This article contains supporting information online at www.pnas.org/cgi/content/full/0804628105/DCSupplemental.

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tiveness of drug treatment (30). The full set of equations and parameter values for our model is available in *SI Appendix*.

We let our model settle to the drug-sensitive strain's stable endemic equilibrium in the absence of drug treatment, and we evaluate the outcomes of deploying drugs in different ways. Minimizing resistance alone is a meaningless objective, because that is best achieved by not using any drugs, but the total amount of illness or death prevented over a fixed time period is a consistent measure of success that captures the value of both treating patients today and minimizing resistance levels in the future (20). Model results are usually sensitive to the length of the planning horizon; in general, the planning horizon should be chosen carefully, the main considerations being when new classes of drugs may become available and how long a particular treatment strategy will be financially and operationally sustainable. Here, we use a planning horizon of 20 years.

We consider four criteria for evaluating drug policies. The first is the average daily percentage of hosts who are experiencing a clinical case of malaria (daily percentage clinical, or DPC). Clinical case days are counted over the length of the treatment period and discounted at an annual rate of 3%. The second criterion is the total number of discounted clinical cases that remain untreated or receive a failing treatment (defined as treatment of a host whose parasites are resistant to the drugs being used). We call this the number of treatment failures (NTF) and present it in units per year per 100 population. NTF can be viewed as a proxy for mortality, whereas DPC can be viewed as a proxy for morbidity. Our last two criteria relate to the lifespan of the drugs being used: we measure the time until the total level of resistance has reached 5% ($T_{.05}$) and the time until the fraction of treatments failing has reached 10% ($T_{.10}^f$). The 5% resistance threshold is a danger zone for resistance evolution (32); 10% treatment failure is the World Health Organization-recommended level at which a national first-line therapy should be replaced (33). $T_{.10}^f$ determines the useful therapeutic life (UTL) of the drug(s) being deployed.

Results and Discussion

Using our four evaluation criteria, we compared a single, two, and three first-line therapies over a randomly sampled set \mathbf{P} of 5,000 parameter combinations spanning a range over the basic reproductive number ($1.1 \leq R_0 \leq 100$; see ref. 29), *de novo* mutation rate ($10^{-6} \leq \sigma_i \leq 10^{-1}$), fraction of clinical cases that are treated ($0.2 \leq f \leq 1.0$), the cost of resistance ($0.05 \leq s_i \leq 0.20$; see ref. 34), and the parasite population's inbreeding coefficient ($0.0 \leq F \leq 1.0$); drug-specific parameters are subscripted by i . Using three first-line therapies minimized failed treatments and overall clinical disease for 92.6% of the parameter combinations tested; this means that, without any knowledge of mutation rates or costs of resistance for particular resistant phenotypes, the odds are 14:1 that we would obtain a better clinical outcome by simply treating one-third of the population with drug 1, one-third with drug 2, and the final one-third with drug 3. When the σ_i are equal, an MFT strategy with three therapies is optimal under all four criteria 99.7% of the time (a single first-line therapy could be better in the comparisons on \mathbf{P} when σ_1 is low but σ_2 and σ_3 are high). See Fig. 2 for a typical picture of the dynamics of resistance evolution under single and multiple therapies.

In attempting to understand resistance evolution in a multidrug context, we must first understand the features of our system that have the most important effects of drug-resistance evolution in general.

One of the key epidemiological variables that drives resistance evolution in malaria is the fraction φ of infected hosts that have clinical malaria (Fig. 2 *Bottom*), because only hosts with symptoms receive drug treatment; the fraction φ is a measure of the selection pressure on the parasite population to evolve resistance. When φ is low, the high level of asymptomatic hosts causes natural selection to work against the resistant phenotypes, because competition

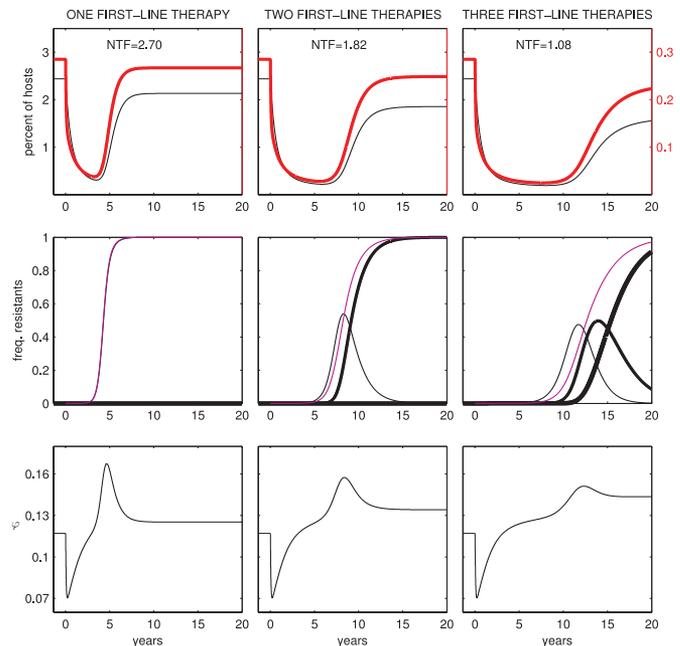


Fig. 2. Differences between single and multiple first-line therapies. Here, $R_0 = 3$, $s_i = 0.1$, $\sigma_i = 10^{-5}$, $f = 0.6$, and $F = 1.0$. System is started at its endemic equilibrium, and treatment is begun at time 0. (*Top*) Percentage of hosts undergoing a clinical episode of malaria (red line) and percentage of all hosts that are infected (black line); red axis labels correspond to red line. (*Middle*) Frequency of single- (thin black line), double- (medium black line), and triple-resistant strains (thick black line); a thicker line indicates more resistance. The magenta lines in the second row indicate the fraction of incident treated cases that receive a failing treatment. (*Bottom*) φ the fraction of infections that are currently in a clinical state and possibly being treated by drugs. As in a classic resistance epidemic, a quick initial decrease in disease prevalence and clinical cases is followed by a period of low prevalence, which is followed by a period when prevalence creeps back up almost to pretreatment levels; disease prevalence will not attain its full pretreatment level as long as there is some cost to resistance. The major difference among the treatment strategies is the pattern of fixation in the middle row. Here and in the model in general, resistance evolution begins later and occurs more slowly when more first-line therapies are used.

between sensitive and resistant parasites occurs in the absence of drugs among asymptomatic hosts; in addition, when φ is low, there is little selection pressure for resistance because of the low probability that an individual parasite will encounter a drug. The effect of a low fraction of hosts with clinical disease was hypothesized to explain the regional absence of the *dhfr* Leu-164 mutation, which confers antifolate resistance (35).

The influence of malaria transmission intensity on φ is one of two key relationships that drives the dynamics of our model. As R_0 increases, φ decreases because of an increased level of host immunity (Fig. 3 *Right*), which may help explain why resistance is more likely to arise in low transmission areas (36–38). The second relationship is that between R_0 and the equilibrium number of clinical cases \hat{C} (Fig. 3 *Left*); \hat{C} is maximized at an intermediate R_0 , because \hat{C} increases with higher prevalence but decreases with higher immunity, both of which increase with R_0 . This relationship between the clinical burden of malaria and the transmission intensity is in general agreement with field data (28, 39).

Increasing R_0 has two basic effects on resistance evolution: it shortens the parasites' generation time, thus making any type of evolution faster, and it lowers φ weakening the selection pressure for resistance. Fig. 3 *Right* shows how these two opposing effects balance. In general, decreasing R_0 when it is large will lead to earlier treatment failure and resistance emergence, as suggested elsewhere (40). In our model, this behavior is explained by an immunogenic mechanism (as opposed to a recombination mechanism in other

involved in switching therapies and maintaining a high level of surveillance (43). Moreover, cycling strategies are sensitive to the length of the cycling period and implementation delay (Fig. S1 in *SI Appendix*), and they may incur a higher level of treatment failure than noted in the modeling if there are delays in phasing out a failed first-line therapy. Note that the MFT strategy analyzed in this study is a nonadaptive strategy. In the context of the same surveillance networks available to cycling strategies, the clinical benefits of an adaptive MFT over cycling strategies could be much greater.

An important challenge in applying this type of theoretical work is that we will usually not know the *de novo* mutation rate to resistant strains (σ_r) or the resistant types' fitness cost of resistance (s_r), and we may have to rely on our best judgment to make a conservative but effective recommendation. Moreover, not all factors in malaria control—imperfect compliance with treatment regimens, delays in implementing policy switches, recommended use of second-line drugs, likely use of cheap but ineffective drugs such as chloroquine, varying levels of surveillance available to detect resistance or treatment failure—have been included in our model; model-influenced regional recommendations should take into account regional variations in drug-use patterns and malaria epidemiology.

The pharmacokinetic/pharmacodynamic (PK/PD) aspect of malaria treatment has also been omitted from the model presented here. In reality, some drugs remain in the system for days, whereas others linger for weeks. When designing MFT strategies, drugs with longer half-lives should be used more sparingly to distribute the drugs as uniformly as possible in the parasites' environment; this way, the parasite has the lowest probability of encountering the same drug twice in a row. More importantly, the increasing use of

ACTs makes it critical to analyze the effects of mismatched half-lives in combination therapies (4). The short half-life of the artemisinin component in ACTs may make it possible to use multiple ACTs in an MFT strategy, even though each therapy contains an artemisinin derivative. These suggestions should be evaluated with detailed within-host PK/PD modeling.

Our results suggest an important general principle for malaria treatment that holds across a broad parameter range and in other model formulations: compared with a single first-line therapy, multiple first-line therapies reduce total clinical cases and failed treatments, significantly delay resistance emergence and treatment failure, and slow resistance evolution once resistance emerges. Extrapolating our conclusions to use of multiple ACTs may yield even stronger results. Because resistance to the nonartemisinin partner drugs typically arises and spreads quite easily, the evolution of artemisinin resistance is likely to be followed in rapid succession by the evolution of resistance to all ACTs. Thus, in theory, the optimal strategy would be to deploy all available ACTs to reduce selection pressure on the partner drugs; protecting the partner drugs may extend the useful therapeutic lives of all ACTs. As new drugs are deployed, and as we are able to assess the levels of use in different countries, we should look toward identifying locations with drug-use patterns that would allow us to quantify the population-wide benefits of using multiple first-line therapies to treat malaria infections.

ACKNOWLEDGMENTS. We thank Hellen Gelband, Carl Bergstrom, and an anonymous referee for comments on an earlier version of this article. This work was funded primarily by Grant no. 44811 from the Bill and Melinda Gates Foundation. M.F.B. is also supported by National Institutes of Health/National Institute of General Medical Sciences Grant P50GM071508.

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