Averting a malaria disaster


Estimates for the annual mortality from malaria range from 0·5 to 2·5 million deaths. The burden of this enormous toll, and the concomitant morbidity, is borne by the world’s poorest countries. Malaria morbidity and mortality have been held in check by the widespread availability of cheap and effective antimalarial drugs. The loss of these drugs to resistance may represent the single most important threat to the health of people in tropical countries. Chloroquine has been the mainstay of antimalarial drug treatment for the past 40 years, but resistance is now widespread and few countries are unaffected.\(^1\) Pyrimethamine-sulfadoxine (PSD) is usually deployed as a successor to chloroquine. Both these antimalarials cost less than US$0·20 per adult treatment course, but the drugs required to treat multi-drug-resistant falciparum malaria (quinine, mefloquine, halofantrine) are over ten times more expensive and cannot be afforded by most tropical countries—especially those in Africa, where it is estimated that more than 90% of the world’s malaria deaths occur. Resistance to chloroquine is widespread across Africa and resistance to PSD is increasing.\(^1\) A health calamity looms within the next few years.\(^1\) As treatments lose their effectiveness, morbidity and mortality from malaria will inevitably continue to rise. Can this disaster be prevented? Can we really “roll back malaria”, as the new Director-General of WHO has demanded?\(^2\)

The rationale for combining drugs with independent modes of action to prevent the emergence of resistance was first developed in antituberculous chemotherapy.


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This approach has since been adopted for cancer chemotherapy, and, more recently, for the treatment of AIDS and early HIV-1 infection. To treat tuberculosis or AIDS with a single drug is no longer regarded as ethical. We believe the same principle should apply to the treatment of malaria. The calculation is simple. Resistance arises from mutations. The chance that a mutant will emerge that is simultaneously resistant to two different antimalarial drugs is the product of the mutation rates per parasite for the individual drugs, multiplied by the number of parasites in an infection that are exposed to the drugs. For example, if one in 10\(^5\) parasites are resistant to drug A and one in 10\(^5\) are resistant to drug B, and the genetic mutations that confer resistance are not linked, only one in 10\(^{10}\) parasites will be resistant simultaneously to both A and B. Most patients who are ill with malaria have between 10\(^5\) and 10\(^6\) parasites at presentation, and a biomass of more than 10\(^6\) parasites in a single person is physically impossible. In this example, therefore, most patients will have at least one parasite resistant to drug A, between 0·1% and 1·0% will have a parasite resistant to drug B, but a parasite simultaneously resistant to the two drugs would only occur about once every 10\(^{22}\) treatments (ie, less than once a century). Compared with sequential use of single drugs, which is current policy, combinations will thus impede the development of resistance substantially.

Artemisinin and its derivatives (artesunate, artether, dihydroartemisinin) are the most potent and rapidly acting of the antimalarial drugs. They reduce the infecting malaria parasite biomass by roughly 10000-fold per asexual (2-day) life cycle, combined with 100-fold to 1000-fold for other antimalarials.\(^3\) Artemisinin and its derivatives are remarkably well tolerated and, to date, no significant resistance has been reported either in clinical isolates or in laboratory experiments. Combinations of artemisinin, or one of its derivatives, with more slowly eliminated drugs such as mefloquine or lumefantrine (benflumetol) have proved highly effective, even against multidrug-resistant Plasmodium falciparum.\(^4\) On the northwestern border of Thailand, which harbours the most resistant P falciparum in the world, combination chemotherapy has halted the progression of mefloquine resistance. This is attributed to two factors. First, combinations ensure high cure rates because treatment for 3 days with an artemisinin derivative eliminates most of the infection, and the residuum of parasites remaining is exposed to maximum concentrations of the more slowly eliminated mefloquine.\(^5\) This residuum (a maximum of 10\(^5\) parasites or 0·000001% of the asexual parasites present initially) is all that is exposed to mefloquine alone. Thus, because of this rapid reduction in the parasite population within each patient, the selective pressure for the emergence of mutants with...
reduced mefloquine sensitivity is lessened substantially. Second, the artemisinin derivatives decrease gametocyte carriage by roughly 90%. Recrudescence (ie, resistant) infections are associated with increased gametocyte carriage rates, which provide a powerful selection pressure to the spread of resistance. This spread is prevented by the artemisinin derivatives. These benefits are particularly important in areas of low or unstable transmission where morbidity and mortality are high, and most malaria is treated. In this context, the antimalarial drugs are under intense selective pressure and resistance has, in the past, often developed rapidly. In areas of high transmission, where infections occur frequently, and are usually asymptomatic in older children and adults, the rapidly eliminated artemisinin derivative will not protect its more slowly eliminated partner during the elimination “tail” of declining blood concentrations. Infections newly acquired during this tail will therefore be under selection pressure. But, provided the patients with these infections are treated with the combination if they become symptomatic, and provided the combination partner retains some efficacy against any selected mutants, the infections will usually be cured and the resistant parasites will not be transmitted. The reduction in the risk of selecting resistant mutants in the primary symptomatic infection is not affected by the prevailing rate of malaria transmission. Thus, combinations should slow the evolution of drug resistance in all malarious areas.

There are additional benefits to artemisinin combinations. The rapid therapeutic response ensures that patients are able to return to school or work earlier and, in the unlikely event of complete resistance to the combination partner, a therapeutic response will still occur—ie, there will not be a high-grade or dangerous failure to respond to treatment. Thus, for several reasons, combination therapy with artemisinin or a derivative makes therapeutic sense.

Current practice is to deploy antimalarial drugs individually in sequence. When one drug fails, another is introduced. Unfortunately, there are few antimalarials and, as for many microbial pathogens, the evolution of resistance in P falciparum seems to be outstripping the development of new drugs. There are compelling reasons to believe that resistance to the available antimalarial drugs would be slowed or prevented by the addition of artemisinin or one of its derivatives, as has been the case with mefloquine. Combination of an artemisinin derivative with chloroquine and PSD in areas where partial sensitivity to these compounds is still retained should extend their useful life. So what are the objections to combination antimalarial chemotherapy?

**Will artemisinin resistance be encouraged?**

Some have argued that artemisinin derivatives are so effective in the management of severe malaria that they should be withheld from use in uncomplicated malaria in those areas where they are not needed, so as to protect them from the development of resistance. However, combination chemotherapy does protect the artemisinin derivatives from the development of resistance. If the drug is always used in combination with another unrelated antimalarial drug, then, provided they are at least partially susceptible to the second drug, parasites are never exposed to the antimalarial activity of the artemisinin derivative alone. Given the reassuring lack of resistance to date and the rapid elimination of these drugs such that subinhibitory (ie, selective) blood or plasma concentrations occur for only hours, resistance to this group of drugs will probably develop fairly slowly. Furthermore, artemisinin derivatives are already available in many countries, and their use is generally regulated poorly. Such use is already providing selective pressure to the emergence of resistance. If these drugs were used only in combination with other antimalarials, artemisinin resistance would develop much more slowly. This mutual protection will result in a longer useful lifespan for both components in combination antimalarial chemotherapy than if the two components were deployed in sequentially.

### Toxic effects

In animals, intramuscular injections of the oil-based compounds arteether and artether have induced an unusual and selective pattern of damage to certain brain-stem nuclei. This damage seems to result from sustained exposure of the central nervous system, which is a consequence of the very slow absorption of these drugs from the intramuscular site. By contrast, in animals, the therapeutic ratio is substantially larger after oral administration of these same drugs, and, for the water-soluble compounds, by any route of administration—presumably because of rapid absorption and elimination (T G Brewer, personal communication). There has been no evidence of any adverse neurological effects in a clinical experience extending to several million patients, detailed prospective studies in over 10,000 patients, and neurophysiological assessments in more than 300 individuals who have received multiple treatment courses (FN, TTH, unpublished). The artemisinin derivatives are well-tolerated antimalarials individually but combinations of drugs may lead to unexpected adverse effects. There is no evidence for serious adverse effects resulting from combinations of artemisinin derivatives with mefloquine, lumefantrine, and, in a small study with atovaquone-proguanil. However, studies of pharmacokinetics and tolerability are needed on combinations with other available antimalarials (particularly chloroquine, PSD, and amodiaquine), and also on the safety of combinations in pregnancy.

### Cost

Cost is usually the major factor that determines the use of antimalarial drugs. Combinations with artemisinin derivatives would, in general, be expected to double the treatment cost for individual patients. But increased short-term costs should result in overall savings in the longer term. If combination treatment translates into a 3–5 year extension in the useful lifespan of chloroquine, amodiaquine, or PSD (as it has done for mefloquine on the western border of Thailand), the overall cost would be less than that of deploying the next, more expensive alternatives (mefloquine, quinine). Since chloroquine and PSD are already failing in many areas, combination treatment would be expected to improve cure rates with a reduction in the morbidity (and therefore costs) associated with treatment failure. In areas of low transmission, use of the artemisinin derivatives may have the added benefit of reducing the incidence of malaria. In parts of Vietnam and Thailand, where these drugs...
have been used systematically, there has been a reduction in the incidence of falciparum malaria, thus saving lives and money.

Regulatory requirements
To ensure compliance with drug combinations, the individual components should ideally be formulated together in a single tablet or liquid preparation. However, such formulations would need the expensive pharmacokinetic, pharmacuent, and toxicological studies required for regulatory approval—and who will pay for these? A less satisfactory but simpler alternative initially would be to combine separate components in blister packs, as is done for the multiple-drug treatment of tuberculosis and leprosy. The successes of directly observed therapy in these infections may be relevant to antimalarial treatment. The use of combinations should be accompanied by new initiatives to facilitate compliance and to encourage dispensers and retailers to educate their patients on the need to complete a full course of treatment. Single-dose treatments should be monitored. More effective surveillance should also be encouraged in tropical countries, both to monitor efficacy and to document adverse reactions.

What is to be done?
Normally, the answer is more research, and more research is certainly required. However, with a concerted effort, this research could be completed within 2 years. Critical decisions often need to be taken with incomplete knowledge. Time is running out in Africa; four countries—Malawi, Kenya, Botswana, and South Africa—have already been forced to use PSD as their first-line antimalarial. When this happened in southeast Asia, high-level resistance developed within a few years and mefloquine had to be substituted. But there is so much more malaria in Africa and so much less money. For the vast majority who cannot afford a US$1 or more for antimalarial treatment, widespread resistance to PSD or its analogues will be a disaster. Time is short. In east Africa, parasites with up to three mutations in the DHFR gene, conferring antifolate resistance, are already prevalent in some areas. Acquisition of the 164 DHFR mutation, found in southeast Asia, would render PSD ineffective. The development of artemisinin resistance would also be a health-care catastrophe. We believe that both these disasters could be averted if the approach we have outlined were adopted widely. To buy 5 or 10 years’ extra life for the available affordable antimalarial drugs will allow time for new drugs to be developed and other interventions to be deployed. We recognise that there are formidable logistic and political barriers to rapid action on the scale required, but we believe that this is now the single most important issue for malaria in Africa. Our purpose in writing this paper has been to present this subject at the top of the agenda for every individual, organisation, and funding body concerned with the control of malaria.

References
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