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Editorial

Intermittent Preventive Treatment for Malaria in Sub-Saharan African: A Halfway Technology or a Critical Intervention?

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In what was a highly influential but is now, sadly, largely forgotten essay, the eminent medical scholar Lewis Thomas distinguished halfway technologies from high technologies. He noted that while halfway technologies are simultaneously sophisticated and primitive, they are carried out after the fact, and they are "the kind of thing that one must continue to do until there is a genuine understanding of the mechanisms involved in disease."[1,2] The notion of halfway technologies seems to apply fully to intermittent preventive therapy (as well as bednets) for malaria. On the other hand, Thomas characterized high technologies as "the most decisive technology of modern medicine," which in the context of malaria aims at the holy grail of a highly effective vaccine. Yet because we lack precise knowledge of mechanisms of anti-malarial immunity in humans, the silver bullet of the long-promised malaria vaccine remains elusive. This lesson applies fully today to the global context of malaria. We know that malaria causes poverty; that poverty causes malaria. It is generally agreed that until a highly efficacious and deployable vaccine to eradicate malaria becomes available, all means available must be used to ameliorate the effects of malaria on human populations. In the short run we must temporize, always looking towards more definitive interventions that include global malaria eradication.

The prospect of any highly effective, inexpensive, and easily administered intervention to reduce the public health burden of malaria is always attractive.[3] Recent years have seen the advent of intermittent preventive treatment (IPT) (also called intermittent presumptive therapy) in malaria as one approach. IPT is distinguished from frank malaria chemoprophylaxis by the periodic, scheduled use of inexpensive anti-malarial drugs to reduce the burden of malaria, in the context of other programmatic measures such as prenatal care and infant immunization. In contrast, systematic chemoprophylaxis is difficult to deploy effectively and comprehensively in malaria-endemic regions, so that integration of an intermediate method of chemoprophylaxis into ongoing programmatic measures is practical, if not ideal.

Unfortunately, parasite biology often seems to get in the way of what would seem to be important and sensible public health measures. The use of antimalarials to prevent malaria on a population basis—notably chloroquine and pyrimethamine—has been long recommended but logistically difficult to implement. Significant concerns are consistently raised about such measures selecting for drug resistance. One might have predicted–because of the rapid spread of resistance over the past decade–that IPT in pregnancy using the current standard sulfadoxine-pyrimethamine (SP) might be less effective throughout sub-Saharan Africa than when it was first implemented.

The article by Raman et al. published this month in the *Journal* supports this prediction.[4] These authors carried out comprehensive 5-year surveillance in southern Mozambique to investigate mutations in the SP protein targets of folic acid biosynthesis encoded by *Plasmodium falciparum dhfr* and *dhps* (dihydrofolate reductase and dihydropteroate synthase). In their systematic survey involving more than 2000 *P. falciparum* samples from 26 sentinel sites, SP resistance was shown to have spread rapidly throughout districts in southern Mozambique and to have become fixed in the parasite populations there. These findings add to the current body of knowledge indicating the need for new public health-based antimalarial strategies and bring into serious question the sustainability of any mass drug administration-based malaria control policy. Importantly, this study brings into question the conclusions of a recent pooled analysis of 6 randomized, placebo-controlled studies that stated "IPTi with sulfadoxine-pyrimethamine was safe and efficacious across a range of malaria transmission settings, suggesting that this intervention is a useful contribution to malaria control."[5] Rather, the more nuanced conclusions by Gosling et al. bring caution to the widespread implementation of SP-based IPT.[6]

As currently implemented, the administration of IPT is incorporated into prenatal care programs to ameliorate the panoply of adverse outcomes associated with *P. falciparum* infection during pregnancy. IPT is targeted not only at pregnant women (IPTp) but also infants (IPTi) and children in high malaria-transmission settings, which to date have been primarily in sub-Saharan Africa, in association with programs such as Expanded Access to Immunisation. Whether IPT should be used in low-transmission settings for both *P. falciparum* and *P. vivax* has been discussed, and has some theoretical advantages, especially considering that the lack of preexisting clinical immunity in such settings further complicates birth outcomes. The decision of where and under what transmission conditions to deploy IPT (whether among children or pregnant women) comes down to cost effectiveness arguments and subjective value judgments about where to deploy scarce resources amid concerns about selecting for drug resistant parasites.[7]

Drugs for IPT must fulfill a number of criteria.[8] Safety is paramount, given the long duration of treatment and the large scale of the intervention, and, indeed, serious adverse effects appear to be uncommon on a population basis.[5] The pharmacokinetics of the active components of optimal IPT drug combinations must be long enough to clear parasites while impairing the formation of resistance-bearing gametocytes and preventing the emergence of *de novo* resistance. Clinical trials have been interpreted as indicating a range of efficacy from "very"[5] to none.[6] A recent pooled analysis of 6 randomized, placebo-controlled

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clinical trials of sulfadoxine-pyrimethamine showed an overall protective efficacy of ~30% against episodes of clinical, symptomatic malaria, 38% against hospital admission associated with malaria parasitemia and 21% against anemia.[5] In this pooled analysis, SP-based IPTi did not significantly reduce mortality. Some have taken these conclusions as evidence that the SP-based IPT regimens ought to be continued, even in combination with an artemesinin compound.[9] A recent randomized, double-blind, placebo controlled trial testing the efficacy of IPTi failed to show efficacy of SP in areas of high resistance,[6] which is directly relevant to the data reported by Raman. Additional commentary has made the point that the WHO call for IPT based on SP seems to be less than fully justified.[10] Clearly, regardless of the approach, any drug treatment or prophylaxis policy ought to take account local parasite drug resistance patterns.

Policies regarding the deployment of specific antimalarial drugs are determined country-by-country at the ministerial level, and often require in-country clinical trials to demonstrate efficacy before changes in anti-malarial drug administration are made. This policy, while rational, is expensive and slow, and thus changes in anti-malaria drug implementation often lag behind the demonstration of drug resistance. We can hope that SP-sensitive *P. falciparum* might eventually return to regions where there might have been a "drug holiday" such as happened with chloroquine in Malawi.[11] However, given the ease with which *P. falciparum* becomes resistant to anti-folate drugs, the fixation of triple mutants within local parasite populations in Africa with no obvious loss of fitness, and the widespread use of anti-folates in HIV/AIDS in Africa, the lifespan of SP for any use in malaria, including IPT, is likely coming to an end. New drugs will have to be developed for this indication, as part of ongoing halfway technologies that will ameliorate but not eliminate malaria.

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