

Intermittent Preventive Treatment for Malaria in Infants: Moving Forward, Cautiously

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(See the brief report by Marks et al., on pages XXX–XX.)

The drug use strategy for malaria includes treatment for acute illness, chemoprophylaxis, and, more recently, intermittent preventive treatment (IPT) of asymptomatic persons. *Plasmodium falciparum* resistance to antimalarial drugs is the major challenge to these interventions [1]. The study by Marks et al. [2] is the first report of the appearance of highly resistant parasites after a single treatment dose of sulfadoxine-pyrimethamine (S-P) was given to infants at the time of immunization. The implications of this finding merit comment, because IPT for malaria in infants (IPTi) may soon become part of a package of preventive health strategies for children.

Each year >21 million children are born among a total population of 521 million persons living in areas of sub-Saharan Africa that are endemic for malaria [3]. The great majority of these newborns soon become highly vulnerable to the pervasive *P. falciparum*-bearing anopheline mosquitoes. The tremendous burden of malaria in young African children, particularly those between 6 and 23 months old, has

stimulated great interest in ways to protect them [1, 4]. Vector-control approaches (e.g., use of insecticide-treated bednets, spraying of dwellings with insecticide, use of larvicides, and environmental management) are very effective, but these measures must complement the repeated antimalarial drug treatments for the many febrile episodes that occur during early childhood.

IPT, which eliminates or reduces parasitemia during periods of vulnerability, has proven to be salutary for pregnant women during their last trimester, especially in preventing low birth weight [5]. After confirmatory studies, the World Health Organization now recommends this intervention [6]. The approach for IPT depends on synergy between the drug and host immunity—an immunity that infants lose when maternally derived protection wanes. A research consortium (information available at: <http://www/ipti-malaria.org>), funded by the Bill & Melinda Gates Foundation, is assessing if IPTi is efficacious and feasible. Early studies show a decreased incidence of malaria episodes and anemia in infants after S-P treatments given at 2, 3, and 9 months old or amodiaquine treatments given at 3, 5, and 7 months old [7, 8].

There is concern that treating largely asymptomatic individuals for malaria will lead to increased selection of drug-resistance mutations in parasites and a

higher frequency and intensity of parasitemias, with increased morbidity and mortality (the rebound effect) due to decreased acquired immunity [9–12]. Advancing technological methods to map drug resistance-associated mutations in *P. falciparum* recently made it possible to define drug-resistance profiles in parasites found in different areas [13]. Until now, no studies looked at such mutations in parasites from infants after they had received single-dose S-P.

Marks et al. show that the first *P. falciparum* infections after S-P treatment of 9-month-old aparasitemic infants near Kumasi, Ghana, were highly resistant to S-P [2]. In treated infants, parasites with 4 mutations in the genes encoding dihydropteroate synthase and dihydrofolate reductase—the targets, respectively, of sulfadoxine and pyrimethamine—appeared significantly earlier than they did in the placebo group. The prevalence of drug-resistant falciparum infections was higher in the treated group than in the placebo group from week 9 until week 26 after treatment. The prevalence of all infections was higher in the treated group during the same interval, although this difference was not significant, possibly because of the small sample size (28 and 35 infants in the treatment and placebo groups, respectively).

These results suggest a possible link between drug resistance and the rebound ef-

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fect. The half-lives of pyrimethamine and sulfadoxine are ~3 and ~5 days [14], respectively, with elimination occurring 3–4 weeks after treatment. In areas endemic for malaria, both treated and untreated children undergo a constant barrage of infectious mosquito bites, through which drug-resistant parasites, drug-sensitive parasites, or both are transmitted. Untreated, susceptible children frequently become ill and manifest infections that are sensitive or resistant to treatment, depending on the prevalence of drug-resistant parasites. Treated children are initially protected from infection, but this protection decreases as the drug concentration decreases (figure 1). Once the concentration dips below a threshold that is permissive for drug-resistant parasites to replicate, parasites emerging from the liver will enter red blood cells and multiply. Children inoculated with drug-resistant *P. falciparum* at ~2–3 weeks after S-P treatment (at the time of decreasing drug concentration) will present with drug-resistant parasites nearly simultaneously. If single-dose S-P is synchronizing the appearance of drug-resistant infections in the treatment group, this could lead to the rebound effect that has been observed in several studies [15, 16].

Rebound after extended, effective chemoprophylaxis is likely due to impaired

acquisition of immunity [17–20]. However, the rebound effect after single-dose S-P could be due to a high prevalence of drug-resistant parasites [15, 16]. Whether the rebound effect is observed after short-term protective treatment will depend on the prevalence of drug-resistant parasites in the community, the frequency of infectious bites, and the mode of action and pharmacokinetics of the drug used. If very few children receive infectious bites containing drug-resistant parasites during the time when drug concentrations are decreasing, then the appearance of simultaneous infections in the treated cohort will not occur. Similarly, any drug active against the liver stage of the parasite will prevent resistance-related rebound. This leads to additional constraints on the drug used for IPTi; the prevalence of drug resistance and the mode of action of the drug will influence both the efficacy of the intervention and the possibility of the rebound effect.

Marks et al. conclude: “The parasitological rebound effect observed in infants treated with single-dose S-P raises considerable concern, in particular on the background of the preexisting high levels of drug resistance—associated mutations.... One might assume that S-P in IPTi provides a disadvantage (development of drug-resistant strains), rather than a benefit

(prevention of disease).” Although sobering, these results should be interpreted cautiously: only 63 infants were followed, the treatment histories of these children before age 3 months are unknown, and the prevalence of resistance to S-P and other antimalarials in the community was not reported. Even so, Marks et al. provide experimental evidence that many concerns raised about IPTi are valid [10].

Careful monitoring of the clinical status of children and the drug-resistance profile of the parasites is necessary in IPT studies. In the study by Marks et al., the definition of “mild malaria” was arbitrary (temperature >38.0°C and parasitemia), and more precise definitions of the types of clinical malaria are needed when the rebound effect is being measured. Also needed are assessments of the pharmacokinetics of the drugs used in the target groups, because metabolism is likely to be affected by age and infection status. Although they will be challenging to design and implement, studies to address the impact of IPTi on the spread of drug-resistant parasites in the community should be undertaken. To separate the effect of selection pressure caused by IPTi from selection pressure caused by repeated treatments of febrile episodes in the same community, a different drug would, ide-

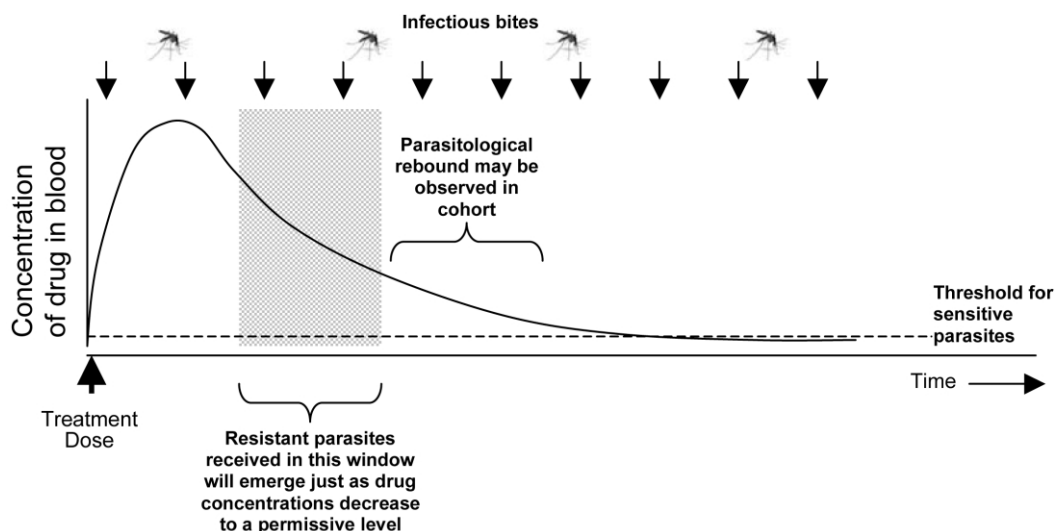


Figure 1. Schematic diagram of drug concentration and the appearance of drug-resistant parasites after single-dose preventive treatment for malaria

ally, be used for each intervention. IPTi programs must establish rigorous protocols to monitor drug resistance and the rebound effect, so that researchers would have the earliest possible warning of any adverse impact.

Because of increasing concern about resistance to chloroquine and S-P, many African countries are shifting to artemisinin combination therapy (ACT) for first-line treatment [3]. ACT is a good candidate for IPTi, particularly when artemisinin derivatives are coupled with drugs with long half-lives, such as piperaquine, because of their high efficacy and low probability of selecting for drug-resistant parasites [9]. Trials funded by the IPTi consortium are testing several combination therapies, including artesunate plus S-P and artesunate plus amodiaquine. ACT is just beginning to be used in young children. Although multiple doses are required and the costs are high, it is important to promptly assess these drugs for use in IPTi so that the best protection for individuals most vulnerable to malaria can be found.

Ultimately, reducing malaria transmission is the best solution for decreasing the malaria burden. Newer and better drugs, improved vector-control methods, and a vaccine will move us closer to solving the urgent problem of malaria in Africa and elsewhere. In the meantime, we must protect the drugs that are available to treat malaria by using them for prevention only after careful scrutiny of the possible impact.

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