Intermittent preventive therapy for malaria: progress and future directions

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Purpose of review

This review summarizes recent evidence regarding the efficacy of intermittent preventive treatment with focus on infancy (IPTi) and the rationale behind such a control strategy.

Recent findings

Pooled safety and efficacy analyses of all six trials of IPTi with sulfadoxine-pyrimethamine conducted between 1999 and 2007 have demonstrated a 30% protective efficacy against clinical malaria, a 24% protective efficacy against all-cause hospital admissions, a 37% protective efficacy against malaria-related hospital admissions, and a 15% protective efficacy against anemia, all in the first year of life. Rebound in malaria following discontinuation of the intervention has not been noted in pooled analyses of the IPTi trials.

Summary

Given the efficacy, excellent safety and tolerability of the intervention and the fact that it is inexpensive and easily deliverable if linked to the Expanded Programme on Immunization, IPTi-sulfadoxine-pyrimethamine appears to add a valuable tool to the malaria-control armamentarium in endemic areas of Africa. Routine monitoring of sulfadoxine-pyrimethamine efficacy will be required to guide future IPTi programme implementation. Variations of IPTi that target older children may be required for areas of Africa with highly seasonal malaria transmission.

Keywords

Africa, expanded programme on immunization, infants, intermittent preventive treatment, malaria

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Abbreviations

EPI	Expanded Programme on Immunization
IPT	intermittent preventive treatment
IPTc	intermittent preventive treatment delivered to children
IPTi	intermittent preventive treatment delivered to infants
IPTp	intermittent preventive treatment delivered to pregnant women
ITN	insecticide-treated mosquito net
SAE	serious adverse events

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Introduction

Plasmodium falciparum malaria continues to cause an enormous public health burden in Africa, killing an estimated 1 million children below 5 years of age annually [1]. The indirect death toll attributable to malaria is also high. Malaria is a major cause of anemia in pregnant women, infants and older children; anemia and malaria-associated sequelae may account for another 400 000 to 1.7 million deaths annually in Africa [2]. Until relatively recently, malaria control in Africa relied almost exclusively on attempting to deliver prompt and efficacious treatment to persons with symptomatic malaria. Since the African Summit on Roll Back Malaria held in Abuja in 2000 [3], there has been an increased emphasis on malaria prevention through the use of insecticide-treated mosquito nets (ITNs) [4] and, more recently, indoor residual spraying [5]. In addition, the strategy of intermittent preventive treatment (IPT) – the administration of treatment doses of antimalarials to a target population at regularly scheduled intervals – became an integral part of antenatal care practice in malarious areas to prevent the adverse consequences of malaria during pregnancy. Since then, the concept of IPT has been broadened to include infants (IPTi) [6•] and children (IPTc) [7••]. A number of trials [8,9,10•–13•] (Table 1) have now demonstrated the potential benefit of IPTi. Some of these were conducted under the auspices of the IPTi Consortium [14], which was formed to generate an evidence base on the safety and efficacy of IPTi upon which the World Health Organization (WHO) could base a decision on whether to recommend IPTi as an additional malaria control strategy [6•]. Here, we look into the potential role of this new intervention in Africa.

Why not chemoprophylaxis?

IPT is an attractive form of malaria control in pregnant women, infants, and children because giving limited

Table 1 Study characteristics of all six IPTi-sulfadoxine-pyrimethamine efficacy trials

Study parameter	Schellenberg *et al.* [6•,8]	Chandramohan *et al.* [9]	Macete *et al.* [10•]	Kobbe *et al.* [11•]	Grobusch *et al.* [12•]	Mockenhaupt *et al.* [13•]
Trial, country	Ifakara, Tanzania	Navrongo, Ghana	Manhica, Mozambique	Kumasi, Ghana	Lambaréné, Gabon	Tamale, Ghana
Recruitment year(s)	1999–2000	2000–2002	2002–2004	2003–2005	2004–2005	2003
EIR/year	29	418	38	400	50	NA
Transmission	Perennial	Highly seasonal	Perennial with seasonal peaks	Perennial	Perennial with seasonal peaks	Perennial with seasonal peaks
Incidence rate/year of clinical malaria in placebo group (all episodes)	0.43	1.0	0.55	1.29	0.22	0.88
In-vivo sulfadoxine-pyrimethamine resistance by day 14	31 (1999–2000)	22 (2004)	21 (2001)	NA	21 (2004)	14 (2002)
Use of bed nets, % placebo/sulfadoxine-pyrimethamine treated (untreated)	67/68	17/19	0/0 (14/15)	20/20 estimate (39/38)	5/5 (80/80)	<1%
Iron supplementation	Daily unsupervised from 2 to 6 months of age (2 mg/kg/day)	Twice weekly unsupervised for 1 month after each IPTi dose, (2.5 ml, 15 mg elemental iron)	None	None	None	None
Ages at dosing, months	2, 3, 9 (at time of DPT2, DPT3 and measles)	3, 4, 9, 12 (at time of DPT2, DPT3 & measles+extra at 12 months)	3, 4, 9 (at time of DPT2, DPT3 and measles)	3, 9, 15 (at time of DPT3 and measles+extra at 15 months)	3, 9, 15 (at time of DPT3 and measles+extra at 15 months)	3, 9, 15 (at time of DPT3 and measles +extra at 15 months)
Method and duration of follow up	PCD to 24 months of age (CSS at 12 and 18 months of age)	PCD to 24 months of age (CSS at 2, 9, 12 and 18 months of age)	PCD to 24 months of age (CSS at 12 and 24 months of age)	ACD monthly to 21 months of age and PCD	ACD monthly to 30 months of age and PCD	ACD every 3 months to 24 months of age and PCD
No. of children enrolled, placebo/active	351/350 = 701	1242/1243 = 2485	755/748 = 1503	535/535 = 1070	595/594 = 1189	600/600 = 1200
Study design	Individual randomization	Cluster randomization	Individual randomization	Individual randomization	Individual randomization	Individual randomization
EPI serology analysis		Measles, yellow fever	DTP, polio, hep B, measles			
Vit A supplementation	100 000 IU at time of measles vaccination	100 000 IU at 6 months of age, then every 6 months (not sure until what age)	100 000 IU starting at 6 months of age, once every 6 months up to 5 years of age	Every 6 months, and for treatment of measles (6–11 months = 100 000 IU; 12–59 months = 200 000 IU)	None	None

IPTi, intermittent preventive treatment delivered to infants; ACD, active case detection; PCD, passive case detection; EIR, entomological inoculation rate; CSS, cross-sectional surveys; DPT, diphtheria pertussis tetanus; EPI, Expanded Programme on Immunization.

treatment doses of antimalarial drugs may circumvent the problems associated with chemoprophylaxis. Chemoprophylaxis is effective at preventing clinical malaria [15] and mortality [16] among young children in endemic African settings. Among infants receiving weekly chemoprophylaxis with pyrimethamine plus dapsone for 1 year, however, the rates of severe anemia and malaria experienced after discontinuing chemoprophylaxis during the second year of life were higher than in those infants who never received chemoprophylaxis [15]; by 4 years of age these differences had essentially disappeared, however [17••]. A similar rebound in malaria morbidity was observed among Gambian children during the first year following discontinuation of weekly chemoprophylaxis with pyrimethamine plus dapsone given during the first 5 years of life [18]; no rebound in mortality was seen among these children. This so-called rebound effect is thought to be the result of a loss, or delay, in the acquisition of naturally acquired immunity due to a lack of exposure to parasites [15]. Chemoprophylaxis also poses logistical delivery problems, is costly, and might accelerate the spread of drug resistance through the use of sub-therapeutic – rather than treatment – doses of antimalarial drugs.

Evidence from pregnant women that intermittent preventive treatment is an efficacious and effective strategy

Multiple trials have now demonstrated that IPT delivered to pregnant women (IPTp) is successful at preventing adverse consequences of malaria during pregnancy, including placental parasitemia [19–21,22•], maternal anemia [20,21,23], and low birth weight [21]. Most trials have been conducted using two doses of sulfadoxine-pyrimethamine delivered at antenatal care visits during the second and third trimesters of pregnancy. Among HIV-positive pregnant women, there is now evidence from pooled studies that monthly dosing of IPTp-sulfadoxine-pyrimethamine results in less placental parasitemia and higher mean birth weights when compared with a two-dose regimen of IPTp-sulfadoxine-pyrimethamine [24••].

Programme effectiveness evaluations have demonstrated similar benefits of IPTp-sulfadoxine-pyrimethamine, likely because of the fact that a high percentage of women attend antenatal clinics in Africa, and sulfadoxine-pyrimethamine can be easily administered as directly observed therapy [25]. With IPTp-sulfadoxine-pyrimethamine was born the idea that treatment doses of an antimalarial drug, delivered at regular intervals to asymptomatic individuals already attending facility-based care, might prove to be a cost-effective platform for a new approach to malaria control.

Recent evidence regarding efficacy and effectiveness of intermittent preventive treatment delivered to infants

Results are now available from five additional trials of IPTi-sulfadoxine-pyrimethamine delivered alongside EPI vaccines across a range of malaria-transmission settings in Africa [9,10•–13•]. The IPTi Consortium has conducted pooled safety and efficacy analyses of all six trials of IPTi-sulfadoxine-pyrimethamine at 12 months of age (Breckenridge *et al.*; Aponte *et al.*, in preparation). These analyses have demonstrated a 30% protective efficacy against malaria, a 23% protective efficacy against all-cause hospital admissions, a 38% protective efficacy against malaria-related hospital admissions, and a 15% protective efficacy against anemia – all in the first year of life.

Overall evidence regarding safety and serologic interactions of IPTi-sulfadoxine-pyrimethamine with serologic response to Expanded Programme on Immunization antigens

Sulfadoxine-pyrimethamine has been extensively used in Africa over many years, and its safety in all age-groups and in later stages of pregnancy is well established [24••,26–28,29•]. Approximately 4000 infants received ~12 000 doses of IPTi-sulfadoxine-pyrimethamine in the six trials. The total number of deaths in the IPTi-sulfadoxine-pyrimethamine groups and in the control groups was similar, although the trials were not powered to measure the effect of IPTi on mortality (Breckenridge *et al.*, in preparation). There was one death in the six trials that was considered possibly attributable to sulfadoxine-pyrimethamine [11•]. Overall, there was a statistically significant 19% reduction in the risk of serious adverse events (SAE) among those receiving IPTi-sulfadoxine-pyrimethamine compared with placebo across all trials (pooled relative risk 0.82, 95% confidence interval 0.74–0.9). Only one trial [11•] noted skin reactions considered due to IPTi; two in the sulfadoxine-pyrimethamine group (both Stevens Johnson Syndrome), and one in the placebo group; all three infants recovered fully.

A committee convened by the WHO to investigate possible interactions between IPTi and the serological response to EPI vaccines found no difference in the geometric mean titer between the sulfadoxine-pyrimethamine and placebo groups for the following antigens: measles, diphtheria, pertussis, tetanus, polio, hepatitis B and yellow fever (limited results only for yellow fever). The committee concluded that IPTi-sulfadoxine-pyrimethamine delivered at the time of routine vaccination does not have an adverse impact on the serological responses to EPI vaccines when delivered alongside those vaccines.

How does intermittent preventive treatment delivered to infants work?

While the mechanism by which IPTi works is not known, several trials have reported that the period of greatest protective efficacy against malaria is in the 30 days following an IPTi dose, suggesting that the primary mechanism of action is prophylaxis [9,10•–13•]. This conclusion has also been supported by modeling exercises [30]. By decreasing the risk of a first malaria episode, IPTi may reduce the risk for subsequent episodes [31]. Additionally, sulfadoxine-pyrimethamine, when administered to uninfected infants in endemic areas who have maternal antibody against malaria and also still have fetal hemoglobin, may effectively prevent new blood-stage infections. Finally, as malaria episodes are not entirely prevented by IPTi, there may be an increase in subclinical infections among those receiving IPTi that may enhance the development of protective antibody responses [31].

Why has there not been a rebound observed with intermittent preventive treatment delivered to infants?

A possible rebound effect following termination of an IPTi intervention did not occur in the initial Tanzanian trial, which demonstrated a sustained protective efficacy of 36% against clinical malaria during the follow-up period from 10 to 24 months of age [31]. No rebound effect was reported from the Mozambiquan trial [10•] during follow-up until the age of 24 months. Chandramohan *et al.* [9] reported a 19% increase in high-density ($\geq$5000 parasites per microliter) malaria from 16 to 24 months of age, corresponding to 4–12 months after the last dose of IPTi, but did not identify any other evidence of rebound in terms of overall burden of clinical malaria, hospitalizations, or anemia. In the Kumasi and Tamale trials [11•,13•], rebound in anemia was seen in the second year of life but these effects were only seen in select subgroup analyses, and do not represent an overall pattern of rebound.

In the pooled analysis of the six trials, there was no significant rebound in episodes of clinical malaria, anemia, or all-cause hospital admissions or with parasites in the 5-month period after the IPTi schedule was finished. Based on the evidence to date, it seems that IPTi is not associated with a rebound effect as was seen in earlier chemoprophylaxis trials. It appears that while IPTi protects against clinical malaria and anemia, it does not interfere with the acquisition of natural immunity to *P. falciparum*. Further analysis of the results from extended follow-up of the IPTi trials may help to elucidate the complex interplay between various potential determinants of protection such as transmission intensity and the use of ITNs.

Is intermittent preventive treatment delivered to infants the appropriate strategy in all epidemiological settings in Africa?

While IPTi clearly appears to be a promising strategy for much of Africa where malaria transmission is stable and perennial, there are legitimate concerns about its role in areas with seasonal transmission. Chandramohan *et al.* [32•] have predicted the impact that IPTi might have in West Africa where transmission of malaria is often seasonal. These authors estimate that of the 18.6 million episodes of malaria expected annually in 10 West African countries, only 10% would be averted through an EPI-linked IPTi delivery mechanism. This estimate, lower than one would expect based on the efficacy results from published trials, is attributed to the low coverage with EPI vaccines, the highly seasonal nature of transmission in much of the sub-region, and the fact that the disease burden in such epidemiological settings is not necessarily concentrated in infancy. The authors suggest that alternative delivery strategies, such as IPTc (also labeled seasonal IPT by some), may be required.

In an area of intense, highly seasonal (5 months) malaria transmission in West Africa, however, IPTi delivered through EPI resulted in a 25% reduction in clinical malaria, a 40% reduction in hospital admissions for malaria, and a 35% reduction in hospital admissions for anemia [9], demonstrating that IPTi delivered through the EPI can be efficacious in such areas with up to a 5-month malaria transmission season.

To date, one published trial, conducted in Senegal [7••], in an area where the malaria season lasts for 3 months, examined the efficacy of seasonal IPT with sulfadoxine-pyrimethamine (single dose)+artesunate (single dose) given at monthly intervals for 3 months. This intervention resulted in an 86% protective efficacy against clinical malaria in children 2–59 months of age.

There are two primary concerns regarding IPTc or seasonal IPT as a potential malaria-control strategy. The first is whether such an approach – which does not build on an existing healthcare platform such as antenatal care clinics or EPI – is feasible and can be scaled up at reasonable cost outside of a trial setting to achieve the desired coverage levels. The second concern is whether the administration of multiple closely spaced doses of antimalarials during a short transmission season will completely impede the generation of natural immunity. If, in such settings, the strategy is coupled with aggressive transmission reduction through the use of ITNs, with the ultimate goal of actually interrupting transmission, then these concerns might be allayed.

Will intermittent preventive treatment with sulfadoxine-pyrimethamine continue to work as sulfadoxine-pyrimethamine fails for treatment?

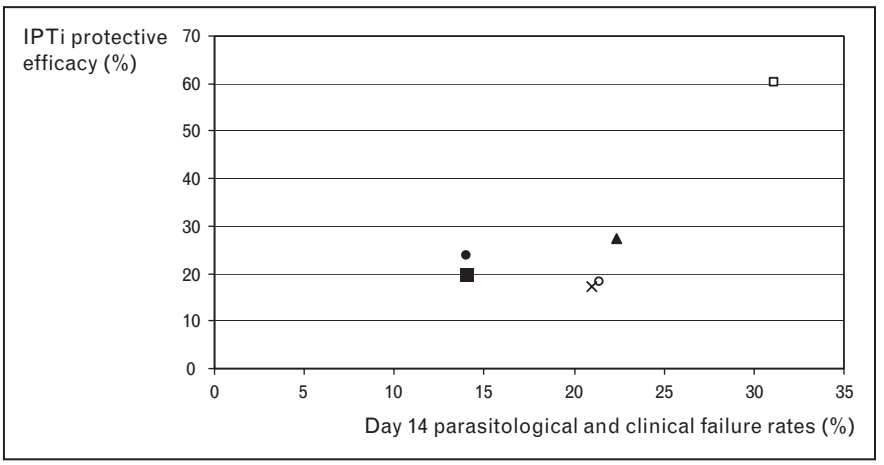
There are two concerns relating to IPT and drug resistance. First, how does the efficacy of an antimalarial when measured using the standard in-vivo measure of efficacy for treatment relate to the efficacy of IPT, that is, prevention? Second, what role does the administration of antimalarials to asymptomatic individuals have in the progression of parasite drug resistance?

Sulfadoxine-pyrimethamine, when used as first-line treatment for malaria, exerts a strong selection pressure on parasite populations, increasing the frequency of mutations associated with parasite resistance to sulfadoxine-pyrimethamine, namely those mutations found in DHFR and DHPS in the parasite folate pathway [33]. These mutations are associated with a reduction in the efficacy of sulfadoxine-pyrimethamine for the treatment of uncomplicated malaria in children less than 5 years old [34,35], and this rise in resistance has been well documented in in-vivo studies throughout the African continent including the IPTi study areas [36–40]. Many countries have therefore changed their recommended first-line antimalarial drug regimen for treating uncomplicated malaria to artemisinin combination therapy (ACT) [41]. When used for malaria prevention, however, sulfadoxine-pyrimethamine appears to continue to function despite high rates of resistant haplotypes and reduced efficacy in treatment of symptomatic malaria. In studies of IPTp, sulfadoxine-pyrimethamine was associated with a reduced risk of placental malaria and maternal anemia, and increased birth weight in areas where day-14 clinical and parasitologic failure rates were as high as 19–26% [24••].

In studies of IPTi, the lack of association between sulfadoxine-pyrimethamine preventive and treatment efficacy is illustrated in Fig. 1. At levels of at least 31% clinical and parasitologic failure with sulfadoxine-pyrimethamine, there does not appear to be a correlation between the protective efficacy of sulfadoxine-pyrimethamine used as IPTi and treatment efficacy. The mechanism of action of sulfadoxine-pyrimethamine may be different in the context of prevention as opposed to treatment. In the case of asymptomatic infections, sulfadoxine-pyrimethamine may be able to suppress lower levels of parasitemia despite the presence of resistant haplotypes. Studies examining this question are currently being undertaken in Tanzania and Gabon (ClinicalTrials.gov identifiers NCT00361114 and NCT00453856).

The second concern to policy makers is how the implementation of IPT-sulfadoxine-pyrimethamine will affect parasite resistance to sulfadoxine-pyrimethamine. There is no doubt that widespread use of sulfadoxine-pyrimethamine for treatment leads to selection of resistant parasites. Now that sulfadoxine-pyrimethamine monotherapy is no longer generally used as a first-line treatment antimalarial, the drug pressure on the parasite is substantially reduced, as is the primary concern of waning sulfadoxine-pyrimethamine efficacy for treatment of clinical malaria. The IPTi Consortium is currently examining the relationship between widespread use of sulfadoxine-pyrimethamine for IPTi and molecular markers of drug resistance in a community-randomized effectiveness trial of IPTi-sulfadoxine-pyrimethamine delivered to 12 000 infants a year in Tanzania; effects on drug resistance will be measured in all age groups of the population in the trial area.

Figure 1 IPTi protective efficacy up to 3 months after last dose compared with estimated *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine across six sites in Africa



□ Ifakara, Tanzania [6•,8]; ○ Manhica, Mozambique [10•]; ▲ Navrongo, Ghana [9]; × Lambaréné, Gabon [12•]; ■ Kumasi, Ghana [11•]; ● Tamale, Ghana [13•].

What are likely successor drugs beyond sulfadoxine-pyrimethamine for intermittent preventive treatment?

It is possible that rates of *P. falciparum* resistance to sulfadoxine-pyrimethamine will continue to rise to levels that will render IPTi with sulfadoxine-pyrimethamine less efficacious, although that scenario is by no means assured. Prudence dictates, however, that the safety and efficacy of alternative drugs to sulfadoxine-pyrimethamine be explored for use as IPT. Three trials, two in Africa and one in Oceania, exploring alternatives to sulfadoxine-pyrimethamine for IPTi are currently underway. One, in Kenya, is testing sulfadoxine-pyrimethamine (single dose)+artesunate (given over 3 days), amodiaquine (given over 3 days)+artesunate (given over 3 days), and chlorproguanil-dapsone (given over 3 days). Another, in Tanzania, is examining sulfadoxine-pyrimethamine (single dose), mefloquine (single dose) and chlorproguanil-dapsone (given over 3 days). The third trial in Papua New Guinea is testing sulfadoxine-pyrimethamine (single dose)+artesunate (given over 3 days), and sulfadoxine-pyrimethamine (single dose)+amodiaquine (given over 3 days).

Finding a replacement for sulfadoxine-pyrimethamine will not be easy as it has properties that make it ideal for IPT. It has a long half-life of at least 5 days [42]; it can be administered as a single dose, has few acute unpleasant side effects (such as vomiting) that might limit acceptability, and it is very inexpensive. In addition, the lack of a correlation between moderate levels of sulfadoxine-pyrimethamine treatment failure and IPTi efficacy, coupled with the lack of a rebound effect seen in the IPTi trials, may indicate that a drug like sulfadoxine-pyrimethamine that is 'leaky' or failing to completely clear parasitemia, is ideal for a preventive strategy such as IPT. Such a drug used preventively may actually function more like a vaccine, allowing extended exposure to parasites while preventing clinical illness and the associated counter-productive immunologic cascade.

Recent evidence from the pooled analyses suggests that the effect of IPTi is more related to intermittent chemoprophylaxis, rather than clearance of parasitemia. Therefore, the addition of short-acting drugs like artesunate to drugs such as sulfadoxine-pyrimethamine or amodiaquine, or the use of short-acting drugs alone, such as chlorproguanil-dapsone, are unlikely to yield promising results. Mefloquine, with its long half-life and ability to be administered as a single dose, is promising, although vomiting and other adverse effects may limit its acceptability when used for prevention. Dihydroartemisinin-piperaquine may also prove to be a viable candidate for IPT. There may be risks, however, associated with using a drug that has great promise as a first line in the treatment of symptomatic malaria simultaneously for mass prevention. In addition, it remains unclear if using a drug as efficacious and long-acting as dihydroartemisinin-piperaquine may result in sufficiently complete prevention of malaria to result in clinical rebound in the second year of life, due to the lack of exposure to parasites and resultant effect on limiting the development of natural immunity.

What other questions need to be answered?

Acceptance by caregivers and communities is critical for the successful uptake of any new intervention, which must also be cost-effective. A series of acceptability trials is currently being carried out at several IPTi Consortium sites. The first of these studies to be published showed that while there were some concerns related to the IPTi trial itself, the intervention was generally well accepted, did not affect perceptions of EPI, and was not misperceived as a malaria vaccine [43•]. A large-scale community effectiveness trial is underway in Tanzania, the results of which will elucidate how well the protective effect of IPTi holds when the intervention is scaled up programmatically. Results of this trial are expected in late 2007 or early 2008. A group of health economists are examining the cost effectiveness of IPTi. Preliminary data suggest that the cost per DALY averted is less than US$4 using IPTi-sulfadoxine-pyrimethamine, making this public-health intervention a very good investment by any measure (Hutton *et al.*, submitted for publication). UNICEF teams are currently conducting large-scale pilot implementation of IPTi-sulfadoxine-pyrimethamine involving over 300 000 infants in six African countries (Benin, Ghana, Madagascar, Malawi, Mali and Senegal). These pilot experiences will provide valuable lessons for programmers on how best to scale up IPTi if the strategy is ultimately adopted by National Malaria Control Programmes.

Conclusion

A solid evidence base demonstrated in a pooled analysis of 6 trials that IPTi-sulfadoxine-pyrimethamine provides a 30% protective efficacy against malaria, a 24% protective efficacy against all-cause hospital admissions, a 37% protective efficacy against malaria-related hospital admissions, and a 15% protective efficacy against anemia – all in the first year of life. Given the excellent safety and tolerability of sulfadoxine- pyrimethamine, and that the intervention is inexpensive and easily deliverable if linked to the EPI, IPTi appears to add a valuable tool to the malaria-control armamentarium. Variations of IPTi that target older children may be required for areas of Africa with highly seasonal malaria transmission. There is a need to be alert to the potential detrimental effect an increase in *P. falciparum* resistance to sulfadoxine-pyrimethamine might have on the efficacy of IPTi with sulfadoxine-pyrimethamine. This threat demands monitoring of the efficacy of IPTi with sulfadoxine-pyrimethamine and the prompt evaluation of other suitable antimalarial agents.

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Andrea Egan works for the Hospital Clinic Foundation (Barcelona) as the coordinator of the IPTi Consortium. She receives her salary from the Hospital Clinic Foundation, which receives the funds for her position from the Bill and Melinda Gates Foundation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 641–642).

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