

# Intermittent Preventive Antimalarial Treatment in Infants

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(See the article by Kobbe et al. on pages 16–25)

Intermittent preventive antimalarial treatment in infants (IPTi) involves the administration of a curative dose of an antimalarial drug to infants at the time of routine immunization, without determining whether the infant is parasitemic. This approach to the prevention of malaria in infants was tried first by Schellenberg et al. [1] in Ifakara, Tanzania, in 1999. They found that administration of sulfadoxine-pyrimethamine (SP) to infants when they presented for vaccination with diphtheria, pertussis, and tetanus or measles vaccines at 2, 3, and 9 months of age reduced the incidence of clinical attacks of malaria and anemia (packed cell volume, <25%) by 59% (95% CI, 41%–72%) and 50% (95% CI, 8%–73%), respectively. Remarkably, protection persisted throughout the second year of life, long after SP had disappeared from circulation [2]. A second trial conducted in Tanzania at approximately the same time found that administration of amodiaquine to infants at 3-month intervals during the first year of life had a similar impact on the incidence of clinical attacks of malaria and anemia [3]. These

very promising results led to the creation of the IPTi Consortium [4], whose brief is to determine the efficacy, safety, relation of efficacy to drug sensitivity, cost-effectiveness, and acceptability of this promising new approach to the prevention of malaria.

Since the results of the initial studies in Tanzania were reported, 5 additional trials of IPTi with SP have been completed, and the results of 3 of these studies have been published—the latest in this issue of *Clinical Infectious Diseases* [5–7]. Preliminary results from 2 other trials have been presented at open meetings. A large effectiveness trial of IPTi with SP is underway in southern Tanzania, and the United Nations Children's Fund is performing pilot implementation studies of IPTi with SP in several countries in Africa.

The carefully conducted study reported by Kobbe et al. [7] in this issue of *Clinical Infectious Diseases* was performed in the Ashanti region of central Ghana. Rainfall in the area is high, and malaria transmission occurs throughout the year, although with seasonal peaks. The entomological inoculation rate is estimated to be ~400 infectious bites per year. Local strains of *Plasmodium falciparum* are still moderately sensitive to SP. The design of this new trial did not mimic exactly that of the initial Tanzanian study, because SP was administered to infants aged 3, 9, and 15 months, and cases of malaria were detected predominantly through monthly home visits; in Ifakara, passive case detec-

tion was used. One thousand seventy infants were individually randomized to receive SP treatment or placebo, and the groups were matched at entry into the study. In infants and children aged 3–18 months (including the period 3 months after the last administration of IPTi), the protective efficacy of IPTi against first or single episodes of clinical malaria was 18% (95% CI, 4%–31%), and the protective efficacy of IPTi against all episodes of clinical malaria was 20% (95% CI, 11%–29%). No significant protection was observed against anemia (hemoglobin level, <7.5 g/dL) or hospital admission. No protection against clinical malaria or anemia was observed during an 8-month period starting 1 month after the final administration of IPTi (at 15 months of age). Significant protection was seen only after the administration of the first and second doses of IPTi.

The protective efficacy against all clinical attacks of malaria observed in this trial (20%) is comparable with that observed in 2 studies in northern Ghana (25% and 22%) (F. Mockenhaupt, personal communication) [5] and a trial in Mozambique (23%) [6]. In both studies in northern Ghana (1 of which was a cluster randomized trial), a significant effect on anemia was recorded (F. Mockenhaupt, personal communication) [5], but this was not found in Mozambique [6]. Thus, the 4 trials of IPTi with SP performed since the initial Tanzanian studies suggest that IPTi with SP provides 20%–25% pro-

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tection against clinical attacks of malaria during the first year of life, without any protection or major rebound effect occurring during the year after IPTi was administered, although there has been a trend towards an increase in anemia or high parasite density infections in some studies during the period after drug administration was stopped.

Why have subsequent trials failed to find the high level of protection observed in the first year of life and the persistence of protection observed in the second year of life recorded in the initial study in Ifakara, Tanzania? A major difficulty in trying to address this question is that it is not known how IPTi with SP achieves its protective effect. It is possible that the protective effect is predominantly because of the ability of SP to prevent the establishment of new blood-stage infections by producing inhibitory blood concentrations for ~4 weeks after administration of each dose (i.e., through chemoprophylaxis). An alternative possibility is that SP does not prevent new blood-stage infections but contains parasite density below the level needed to cause a clinical episode of malaria or anemia, while at the same time allowing sufficient parasite multiplication to induce a protective immune response. It is possible that low-density infections are more effective for inducing persistent immunity than clinical attacks. The findings in Ghana and Mozambique of ~25% protection efficacy against clinical attacks of malaria following administration of IPTi with SP 3 or 4 times during the first 12–18 months of life support the first hypothesis, with SP providing 3 or 4 months of prophylaxis. The persistence of protection observed in Ifakara after the first 4 weeks of drug administration and during the second year of life requires the involvement of more-complex mechanisms, probably including an effect on naturally acquired immunity.

Whatever its mode of action, why did IPTi with SP have such different effects in Tanzania than it had in Ghana and Mozambique? The simplest explanation for

the difference in efficacies between sites is that the high level of protection observed in Ifakara was a chance effect, with efficacy being found at the upper confidence limit for a true effect, somewhere between that found in Ifakara and elsewhere. However, 95% CIs for efficacy in the Ifakara trial and those obtained at the other sites do not overlap; thus, a chance effect is an unlikely explanation for the difference. Differences in the methods used for case ascertainment would be expected to have an impact on the number of cases prevented by IPTi in different trials (as has proved to be the case) but would be less likely to have an effect on the percentage reduction of cases or to account for persistence or absence of protection during the second year of life.

If modulating, rather than preventing, malaria infection is the key to the long-term efficacy of IPTi, then it would be anticipated that the impact of IPTi would be influenced strongly by the sensitivity of local strains of *P. falciparum* to SP, with persistent protection being most marked in situations where parasites were moderately resistant to SP. This was the case at Ifakara, where the parasitological failure rate in symptomatic children 14 days after the start of treatment was ~30%. However, similar levels of SP resistance were present in Mozambique and in Ghana at the time of the IPTi trials performed in these areas; thus, such a hypothesis seems to be an unlikely explanation for the differences observed between sites, unless SP resistance needs to be present within very tight margins to give persistent protection. Drug sensitivity studies among both symptomatic children and asymptomatic children are currently being conducted at some of the sites where trials of IPTi with SP have recently been performed, and the results of these studies may provide additional information on this important issue.

Finally, it is possible that the efficacy of IPTi against clinical attacks of malaria is influenced by the simultaneous use of other antimalarial control measures. Use

of insecticide-treated bednets was higher in Ifakara than at the other sites, and it is possible that this contributed to the high level of efficacy against clinical attacks of malaria observed in this trial. This would require that insecticide-treated bednets have a synergistic rather than just an additive effect to IPTi. How this might be achieved is uncertain, but it is possible that a reduction in malaria infections achieved through the use of an insecticide-treated bednet, combined with a reduction in the density of any breakthrough infections that is provided by IPTi, could be the optimum way of inducing long-lasting protective immunity.

In a similar manner, the effect of IPTi on anemia might be enhanced by coadministration of iron. Iron was administered in both the Ifakara study and the trial of IPTi in northern Ghana; both studies demonstrated a significant effect of IPTi on the incidence of anemia. Iron was not given in the studies in Mozambique and Ashanti, and these studies did not show an effect on anemia.

It seems likely that, in most epidemiological situations in Africa, IPTi with SP will give ~25% protection against clinical attacks of malaria during the first year of life. Is this sufficient to warrant a recommendation to implement IPTi with SP (an issue currently under review by the World Health Organization)? Protective efficacy of 25% does not sound impressive, but, because of the high prevalence of malaria throughout much of tropical Africa, a 25% reduction in the incidence of malaria during the first year of life could still represent a substantial reduction in mortality and severe morbidity caused by malaria. There is surprisingly little information on the proportion of cases of malaria that occur during the first year of life in Africa. However, data collected by the Severe Malaria in African Children Consortium from sites in Ghana, Kenya, Malawi, and The Gambia [8] suggest that ~20% of cases of severe malaria occur in infants aged <1 year and that the proportion of deaths in infants may be slightly

higher. In areas such as these, universal coverage with IPTi could potentially prevent ~5% of cases of severe malaria and malaria deaths. Studies sponsored by the IPTi Consortium have shown that IPTi with SP is safe, has no adverse effect on the immune response to routinely administered vaccines, and does not decrease use of Extended Program of Immunization services [9]. Preliminary analyses suggest that IPTi with SP is highly cost-effective. Thus, despite the relatively low level of protection achieved in recent studies, including the study by Kobbe et al. [7], a strong case can be made for implementation of IPTi with SP in some areas where malaria is endemic. However, such recommendation needs to be accompanied by 2 important caveats. The first concerns the use of SP for IPTi. Even if IPTi with SP achieves its effect primarily by modulating, rather than preventing, malaria infection, a level of resistance to SP must eventually be reached, at which time even modulation could not occur. It is not known what this level of resistance is—although it is likely to be higher than that required to cure symptomatic malaria infections—or how it should be measured. Standard *in vivo* studies of drug resistance conducted among symptomatic children may not be the most appropriate way of investigating the level of resistance of malaria to SP when used for IPTi. Investigations currently being performed by the IPTi Consortium should provide more information about the threshold level of SP resistance above which IPTi with SP is ineffective. It is necessary to have up-to-date information on the level of SP resistance in an area where it is proposed to implement IPTi and to allow an informed guess to be made of its likely efficacy, although, unfortunately, there are currently no firm

guidelines that can be used to predict success.

The critical threshold above which IPTi with SP will no longer be effective may already have been reached in some parts of Africa, although this situation may change if a switch of first-line treatment of symptomatic malaria to an artemisinin-based combination results in a substantial reduction in the use of SP. If SP cannot be used for IPTi, is there an alternative? If, as seems likely, a drug used for IPTi needs to have a long action, small-mefloquine and artesunate piperaquine are the most promising candidates. A trial that is currently in progress in Tanzania is evaluating the safety and efficacy of mefloquine when used for IPTi.

The second caveat with regard to the implementation of IPTi relates to the variability in the age distribution of malaria across Africa, determined by the intensity of malaria infection and by its seasonality. In large parts of Africa, including most countries of the Sahel and sub-Saharan where malaria is highly seasonal, only a small percentage of cases of severe or uncomplicated malaria occur in infants aged <1 year, and IPTi may not be an appropriate intervention in these areas. As the intensity of malaria transmission is reduced in other African countries through expanded use of insecticide-treated bednets and adoption of indoor residual spraying, the average age of children with malaria will increase, reducing the number of cases susceptible to prevention by IPTi. IPTi programs should not be implemented unless there is recent information from the proposed intervention area that a significant proportion of cases of malaria occur in infants and might thus be prevented by the intervention. Enthusiasm for IPTi should not disguise the fact that this in-

tervention, valuable though it may prove to be, will not prevent the  $\geq 80\%$  of cases of malaria in older children who need to be protected against this infection by other means.

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## References

1. Schellenberg D, Menendez C, Kahigwa E, et al. Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo controlled trial. *Lancet* **2001**;357:1471–7.
2. Schellenberg D, Menendez C, Aponte JJ, et al. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised placebo-controlled trial. *Lancet* **2005**;365:1481–3.
3. Massaga JJ, Kitua AY, Lemnge MM, et al. Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *Lancet* **2003**;361:1853–60.
4. Schellenberg D, Cisse B, Menendez C. The IPTi Consortium: research for policy and action. *Trends Parasitol* **2006**;22:296–300.
5. Chandramohan D, Owusu-Agyei S, Carneiro I, et al. Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana. *BMJ* **2005**;331:727–33.
6. Macete E, Aide P, Aponte JJ, et al. Intermittent preventive treatment for malaria control administered at the time of routine vaccinations in Mozambican infants: a randomized, placebo-controlled trial. *J Infect Dis* **2006**;194:276–85.
7. Kobbe R, Kreuzberg C, Adjei S, et al. A randomized controlled trial of intermittent preventive antimalarial treatment in infants. *Clin Infect Dis* **2007**;45:16–25 (in this issue).
8. Taylor T, Olola C, Valim C, et al. Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. *Trans R Soc Trop Med Hyg* **2006**;100:615–22.
9. Pool R, Munguambe K, Macete E, et al. Community response to intermittent preventive treatment delivered to infants (IPTi) through the EPI system in Manhiça, Mozambique. *Trop Med Int Health* **2006**;11:1670–8.