

Intermittent Preventive Treatment in Infants—Adjusting Expectations and Seeing Opportunity

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(See the article by Macete et al., on pages 276–85.)

Antimalarial drugs have long been used to treat acute cases of malaria, to cure infection, and to prevent disease progression, severe disease, and death. They have also been used to prevent illness (e.g., chemoprophylaxis) and to reduce transmission (e.g., mass drug administration coupled with vector control measures). With each preventive strategy, the balance of efficacy and long-term feasibility has led to progressively more focused use of the drug. That is, mass drug administration and broad use of chemoprophylaxis in a population have been reduced to targeted drug administration to fewer people and only specific groups or to shorter time intervals, to maximize benefits and to reduce costs, poor adherence, and the potential impact on drug resistance.

Among pregnant women in settings where malaria is endemic, who have long been a target population for chemoprophylaxis, studies have demonstrated that

a few treatment doses of a safe and efficacious antimalarial at intervals linked to routine antenatal clinic visits could produce a substantial reduction in rates of maternal anemia, placental parasite infection, and the attendant risk of low birth weight. This proactive and presumptive (not linked to symptoms or documentation of infection) use of treatment doses at a few specific intervals, which is known as “intermittent preventive treatment (IPT) during pregnancy,” has been widely adopted in many sub-Saharan African countries [1]. The concept of the time- and population-limited use of an antimalarial for a specific purpose and linked to existing routine health-care visits led to its evaluation in settings where malaria is highly endemic among infants, who have limited immunity to malaria and are at great risk of anemia and of rapid progression to severe disease and death. The demonstration by Schellenberg et al. [2] that IPT in infants (IPTi) with sulfadoxine-pyrimethamine (SP) at the time of routine immunization visits led to substantial reductions in illness and severe anemia was groundbreaking and rekindled the idea of the preventive use of antimalarials in young children. Results from an additional trial of IPTi with amodiaquine given at 3, 5, and 7 months of age provided equally promising results [3]. The IPTi Consortium, a group of experienced pub-

lic health scientists interested in understanding whether this approach could lead to an additional viable malaria-prevention strategy, was formed to identify the information needs and appropriate methods and studies that would clarify the value of IPTi [4].

The study reported in this issue of the *Journal of Infectious Diseases* by Macete et al. [5] is part of the first set of results from trials by the IPTi consortium that are centered on the safety and efficacy of IPTi with SP. These results come just 1 year after the promising results of the 2-year follow-up of the initial Tanzania study [6] and 6 months after an additional IPTi study in Ghana [7]. Although additional study results will be forthcoming, can we get a sense of where this is headed?

First, if the drug is not safe, this will all end very quickly. However, Macete et al. provide important evidence that the drug was well tolerated in infants and was not associated with adverse reactions or an adverse impact on laboratory measures and blood chemistry levels. Importantly, no adverse effects were observed on the immunogenicity of the Expanded Program of Immunization (EPI) vaccines that were administered concurrently. This is very encouraging as we await the review of these measures from the full set of studies, which will be critical in this assessment of safety.

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Table 1. Efficacy of intermittent preventive treatment in infants in Africa, from 4 completed trials.

Study parameter	Schellenberg et al. [2, 6]	Chandramohan et al. [7]	Macete et al. [5]	Massaga et al. [3]
Country	Tanzania	Ghana	Mozambique	Tanzania
Intervention drug	SP	SP	SP	AQ
Recruitment year(s)	1999–2000	2000–2002	2002–2004	1999
Entomological inoculation rate/year	29	418	38	405
Transmission	Perennial	Highly seasonal	Perennial with seasonal peaks	Holoendemic perennial
Incidence rate/year of clinical malaria in placebo group	0.36	1.02	0.43	2.19
Antimalarial drug resistance by day 14, % (drug) ^a	31 (SP)	22 (SP)	17 (SP)	3 (AQ)
Use of bed nets, placebo/intervention, %	76/79 ^{b,c}	17/19 ^c	14/15 ^c	30/32 ^d
Ages at dosing, months	2, 3, 9	3, 4, 9, 12	3, 4, 9	3, 5, 7 ^e
No. of children enrolled, placebo/active	351/350	1242/1243	755/748	145/146
Protective efficacy, % (95% CI)	By 12 months	By 15 months	By 12 months	By 9 months
Clinical malaria (all episodes)	62.3 (44.2–74.6)	24.8 (14.3–34.0)	22.6 (1.6–39.2)	64.7 (42.4–77.2) (No iron) 60.7 (35.9–75.9) (Iron)
Clinical malaria with high-density infection	67.8 (48.8–79.8)	23.6 (11.1–34.3)	26.4 (5.1–42.9)	72.4 (52.5–83.9) (No iron) 68.2 (46.5–81.1) (Iron)
All-cause hospital admissions	30.0 (8.1–46.6)	12.7 (–4.8 to 27.3)	19.0 (4.0–31.0)	59.9 (23.0–79.1) (No iron) 52.9 (12.4–74.7) (Iron)
All-cause severe anemia	50.3 (7.6–73.2)	35.5 (11.2–53.1) ^f	12.7 (–17.3 to 35.1)	71.2 (38.5–87.0) (Iron) 74.4 (43.4–88.4) (No iron)
Rebound effect	None: sustained effect (10–24 months)	Yes: more high-density parasitemia in children 16–24 months old. None for severe anemia.	None (10–24 months)	None (9–13 months). No extended follow-up data available after 13 months.

NOTE. AQ, amodiaquine; CI, confidence interval; SP, sulfadoxine-pyrimethamine.

^a Percentage of clinical and parasitological treatment failure by day 14 in symptomatic children <5 years old.

^b Modified from Schellenberg et al. [2] by including only children with known bed-net data.

^c Mostly untreated nets in the studies by Schellenberg et al. [2] and Chandramohan et al. [7]. Untreated nets only in the study by Macete et al. [5].

^d Insecticide-treated nets.

^e Not administered with routine vaccinations.

^f Children hospitalized with severe anemia.

What about efficacy? The growing spectrum of studies shows variations in efficacy (table 1). Just as we should not expect this intervention to solve all the problems of malaria in African children, we should not be surprised that the results will vary in different studies and settings. Per the IPTi Consortium plans and the standards for reporting on randomized controlled trials [4], Macete et al. report a predetermined set of outcomes. The episodes of malaria illness (with varying parasite density criteria), severe anemia, frequency of outpatient visits and hospital admissions, and other illness findings (e.g., respiratory symptoms, diarrheal illness, splenomegaly, and anemia during the short interval after dosing) were all recorded. The protective efficacy (PE) for clinical malaria with more or less strict criteria ranged from 22.2% to 26.4%. The PE estimate for severe anemia was 17%, but this result was not statistically significant; there was a statistically significant reduction in hospital admissions for anemia during the month after doses 1 and 2 of the antimalarial. There were significant reductions in all-cause hospital admissions (19%), and fewer health-care facility visits for children with respiratory symptoms or diarrhea were observed, during the month after the first or second dose. The authors refrain from discussing these nonmalaria findings, but similar observations for respiratory symptoms were made in the earlier trial by Schellenberg et al. [2], which may be consistent with efficacious use of a weak antibiotic (SP) in a preventive mode. Importantly, unlike the previous study in Ghana, there was no indication of a rebound effect within the year after the completion of the third dose.

However, some of the findings were not as dramatic as those of previous reports (table 1). So is this disappointing, or does it simply demonstrate the inherent variability of malaria and its interventions? That is, the studies differ somewhat in transmission intensity; transmission seasonality; timing of dosing of the drug (starting at age 2 vs. 3 months); timing of

the assessment of main end points (12 vs. 9 or 15 months); parasite resistance to the antimalarial drug; other illnesses or nutrient deficiencies affecting anemia; coverage with other malaria prevention and treatment interventions, such as iron supplementation and the use of (insecticide-treated) bed nets; and other features not measured or reported. Of interest, the SP study showing the greatest impact (in Tanzania) also had the highest coverage of bed nets. Furthermore, in the Ghana trial, the use of bed nets appeared to mitigate the effect of rebound malaria; but, in contrast to children without insecticide-treated nets, no rebound effect of high-parasite-density malaria was observed in children protected by the nets.

Nonetheless, the combined data from the 4 trials suggest that, across different investigations, with different transmission intensity and seasonality settings and even different drugs, there is substantial (albeit variable) protective efficacy of IPTi in altering the frequency of severe anemia, malaria illness, and hospital admissions. The initial enthusiasm associated with very high efficacy may be moderated with the lower protective efficacy seen in the more recent trials, but the efficacy remains and is not trivial.

Decisions about recommending the introduction of IPTi will come soon—the set of studies of the safety and efficacy of SP are expected to be formally reviewed this year. The efficacy and safety decisions derived from the individual studies and the combined analysis will offer a more complete picture for considering policy issues and next steps. The IPTi Consortium investigators will need to confront the evolving increase in antifolate resistance that could eventually preclude the use of SP. SP has a combination of features that may make it uniquely suitable for use as IPT: it is cheap, it has a relatively long half-life (3 days for pyrimethamine and 7 days for sulfadoxine), it is very well tolerated in young infants (unlike many other drugs), and it can be given as a single dose. The feasibility of the IPTi approach will benefit

greatly from linkage with immunization programs that provide a venue to achieve high coverage with directly observed therapy at a few key time points in an infant's life. This partnership with immunization programs makes it likely that IPTi with SP will be very cost-effective even if the efficacy turns out to be more modest than was suggested in the first study. Cost-effectiveness may be somewhat less favorable, although still substantial, if some of the alternative drugs are considerably more expensive and require multiday dosing that must be done in the home. The half-life of the drug may also need to be taken into consideration when estimating how the implementation of IPTi may affect the spread of drug-resistant parasites [8]. The IPTi Consortium is addressing these issues with studies of the safety, tolerability, and efficacy of other drugs with different half-lives and multiday regimens [4].

The sum of all this is the justification for having an IPTi Consortium. The public health community needs focused attention on important intervention strategies that are thoroughly probed by a set of studies that address the expected variations. The malaria-research community can benefit in many different ways from this example of a well-coordinated consortium of scientists with a comprehensive and targeted research agenda.

We have often expected too much from a single intervention. If IPTi is adopted, it will need to find its place within the scaling up of existing preventive interventions, such as insecticide-treated bed nets or indoor residual spraying. Currently, antimalarial drug use for young children in settings where malaria is endemic focuses on case management, which must rely on prompt recognition of illness and rapid action by families and health-care workers to respond to the illness. The proactive public health approach using IPTi builds on existing contacts with high-risk infants and appears to offer substantial improvement in their health. We will see, but this could be very helpful.

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